Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
November 9, 2022

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Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document
P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Preferred with Clinical Criteria: Listed on the Agency's Preferred Drug Lists but will require a prior authorization. Clinical criteria must be met in order to be approved.

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are preferred with clinical criteria, are non-preferred status, or if they required PA prior to the PDL.

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Accumulation Edit
Brand Limit Switchover
Dispense As Written Override
Early Refill
Ingredient Duplication
Maintenance Supply Opt Out
Maximum Unit/Max Cost Limitations
Short Acting Opioid Naïve Override
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-10 code(s) may be used. Use of ICD-10 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic, OTC or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic, OTC or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic, OTC or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, OTC, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Skeletal Muscle Relaxants

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must have also failed 30-day treatment trials with at least two prescribed and preferred skeletal muscle relaxants, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given if the patient has been on consecutive 60 day or greater treatment if the skeletal muscle relaxant being requested is for a chronic condition associated with muscle spasticity.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- For chronic conditions associated with muscle spasticity, approval may be given for up to 6 months initially and up to 12 months for renewal requests.

- For acute conditions associated with muscle spasms, approval may be given for up to a 10-day course of medication consistent with current maximum limits when criteria are met.

Electronic Prior Authorization (PA)

- Skeletal muscle relaxant agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Narcotic Analgesics

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

- For buprenorphine, Subutex® and/or Suboxone®, the patient must have a diagnosis of opioid dependence. Treatment must only be prescribed by a licensed physician who qualifies for a waiver under the Drug Addiction Treatment Act (DATA) and has notified the Center for Substance Abuse Treatment of the intention to treat addiction patients and has been assigned a DEA (X) number.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least 2 prescribed and preferred narcotic analgesics in this class, either generic, OTC, or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- For narcotic analgesics, medical justification must include documentation of therapeutic pain management failure with nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or aspirin and a complete pain evaluation in the medical record. Type of pain (acute vs chronic) and pain intensity (mild, moderate or severe) must be indicated in the Drug/Clinical Information section under Medical Justification. Medical justification may also include peer-reviewed literature, medical record documentation or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 3 months with initial and renewal requests unless one of the qualifying diagnoses is indicated, then approval may be given for up to 6 months. If the patient is a nursing home resident, approval may be given for up to 6 months for initial requests and up to 12 months for renewal requests.

Electronic Prior Authorization (PA)

- Not Applicable

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Selective Serotonin Agonists

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

- The request must be for acute treatment, not prophylactic therapy.

Prior Treatment Trials

- The patient must have failed 2-week treatment trials with at least two other prescribed and preferred selective serotonin agonists, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have been stable on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 6 months initially and up to 12 months for renewal requests.

Electronic Prior Authorization (PA)

- Selective serotonin agonists are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Antiemetic Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 3-day treatment trials with at least two prescribed antiemetics, to include promethazine or a preferred antiemetic agent, either generic, OTC or brand, within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Antiemetic agents are included in the electronic PA program.

- Through the Electronic PA program, allowances are made for patients with a cancer diagnosis to receive Emend®.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Proton Pump Inhibitors (PPI)

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record. Requests must indicate under the Clinical Information Section of the PA Request Form whether medication is for acute or maintenance therapy.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least 2 prescribed and preferred PPIs in this class, either generic, OTC, or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- For Prevpac®, the patient must have failed 2 treatment trials of at least 14 days each with lack of healing on an acid suppressor and 2 antibiotics, either generic, OTC or brand, within the past 6 months, or have a documented contraindication to all preferred agents in these classes.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

Uncomplicated Symptomatic GERD (Nonerosive Reflux Disease)

The patient must meet prior usage requirements. Empirical therapy with a PPI is an appropriate initial management strategy for patients with typical symptoms in the absence of alarm features. A diagnosis of GERD can be made based on a history of classic symptoms and favorable response to antisecretory therapy without further testing.

For acute therapy, approval may be given for up to 8 weeks.

For maintenance therapy, documentation of appropriate testing (endoscopy, manometry, ambulatory impedance-pH, catheter pH, or wireless pH monitoring) is required for patients who have not responded to an empirical trial of PPI therapy. Approval may be given for up to 12 months. After 12 months, approval will require documentation of persistent symptoms. Retesting is not required for maintenance therapy renewals.

Complicated GERD (Erosive Esophagitis)
The patient must have an appropriate diagnosis confirmed by testing (endoscopy) and meet prior usage requirements.

For acute therapy, approval may be given for up to 8 weeks. For patients who do not heal after 8 weeks, an additional 8 weeks may be approved.

For maintenance therapy, approval may be given for up to 12 months. Retesting is not required for maintenance therapy renewals.

Positive *H. pylori* Infections
The patient must have a diagnosis of *H. pylori* infection, confirmed by testing (breath test, blood test or tissue biopsy if endoscopic exam done) within the past 30 days, and duodenal ulcer disease, confirmed by testing within the past 12 months, and meet prior usage requirements.

For acute therapy, the patient may be approved for up to 14 days of combination therapy.

Gastric or Duodenal Ulcers
The patient must have an appropriate diagnosis confirmed by testing (barium contrast or double contrast radiography, or endoscopy) within the past 12 months and meet prior usage requirements.

For acute therapy, approval may be given for up to 8 weeks of therapy.

For maintenance of healed duodenal ulcers, maintenance therapy may be approved for up to 12 months (Prevacid®).

To reduce the risk of NSAID-associated gastric ulcers in patients at risk for developing a gastric ulcer who require the use of an NSAID, approval may be given for up to 12 weeks (Prevacid®) or 6 months (Nexium®) of therapy.

Barrett's Esophagus, Zollinger-Ellison Syndrome, or Other Pathological Hypersecretory Conditions
The patient must have an appropriate diagnosis confirmed by testing (barium contrast or double contrast radiography, or endoscopy).

For acute therapy, approval may be given for up to 12 months of treatment.

For maintenance therapy, approval may be given for up to 12 months. Retesting is not required for maintenance therapy renewals.

PA Timeframe Approval

- Approval may be given for up to 12 months for maintenance. Otherwise, please see above.

Electronic Prior Authorization (PA)

- Not Applicable

Verbal PA Requests

- PA requests that meet prior usage requirements for approval may be accepted verbally.

Anxiolytics/Sedatives/Hypnotics

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

- If the request is for Onfi® for a diagnosis of Lennox-Gastaut syndrome, the patient must also be ≥2 years of age, have a diagnosis by a pediatric neurologist and have failed 30-day treatment trials of valproic acid, lamotrigine, and topiramate within the past 6 months, or have a documented allergy or contraindication to all of those agents.

- If the request is for Onfi® for a diagnosis of intractable seizures, the patients must also have a diagnosis by a neurologist (diagnosis by a pediatric neurologist is required for patients <18 years of age) and have failed 30-day treatment trials with a minimum of four anti-convulsant medications within the past 6 months, or have a documented allergy or contraindication to other anti-convulsant medications.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 3 months for initial request and up to 6 months for renewal requests.

Electronic Prior Authorization (PA)

- Anxiolytic, sedative and hypnotic agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

November 9, 2022
1:00 p.m. – 3:00 p.m.

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1. Opening remarks……..……..……..……Chair
2. Approval of August 10, 2022 P&T Committee Meeting minutes……...…...……Chair
3. Pharmacy program update.....Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives
   (prior to each respective class review)
5. Pharmacotherapy class re-reviews….....UMass Clinical Pharmacy Services
   - Centrally Acting Skeletal Muscle Relaxants – AHFS 122004
   - Direct-Acting Skeletal Muscle Relaxants – AHFS 122008
   - GABA-Derivative Skeletal Muscle Relaxants – AHFS 122012
   - Skeletal Muscle Relaxants, Miscellaneous – AHFS 122092
   - Opiate Agonists – AHFS 280808
   - Opiate Partial Agonists – AHFS 280812
   - Selective Serotonin Agonists – AHFS 283228
   - Antiemetics, Antihistamines – AHFS 562208
   - Antiemetics, 5-HT3 Receptor Antagonists – AHFS 562220
   - Antiemetics, Neurokinin-1 Receptor Antagonists – AHFS 562232
   - Antiemetics, Miscellaneous – AHFS 562292
   - Proton-Pump Inhibitors – AHFS 562836
   - Calcitonin Gene-related Peptide (CGRP) Antagonists – AHFS 283212
   - Anxiolytics, Sedatives, and Hypnotics – Barbiturates – AHFS 282404
   - Anxiolytics, Sedatives, and Hypnotics – Benzodiazepines – AHFS 282408
   - Anxiolytics, Sedatives, and Hypnotics – Miscellaneous – AHFS 282492
   - Orexin Receptor Antagonists – AHFS 282440
6. New Drug Review Livtencity® (maribavir) ….....UMass Clinical Pharmacy Services
7. Results of voting announced…….....……...……..Chair
8. New Business……..……..……..Chair
   - Election of new Chair and Vice-Chair
9. Next meeting dates
   - February 8, 2023
   - May 3, 2023
   - August 2, 2023
   - November 8, 2023
10. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Centrally Acting Skeletal Muscle Relaxants
AHFS Class 122004
November 9, 2022

I. Overview

The centrally acting skeletal muscle relaxants are used to treat two different types of conditions: spasticity from upper motor neuron syndromes and muscular pain/spasms from peripheral musculoskeletal conditions. Spasticity can be defined as a velocity-dependent increase in muscle tone. This means that the faster the passive movement of the limb through its range of motion, the greater the increase in muscle tone.[1] Spasticity is associated with a number of central nervous system disorders, including stroke, multiple sclerosis, as well as brain and spinal cord injuries.[1] Because of the loss of inhibitory controls at the upper motor neuron level (brain or spinal cord), there is permanent ongoing or intermittent involuntary striated muscle contraction. This spasticity can severely limit functioning due to weakness, spasms, and loss of dexterity. The goal of therapy is to improve functioning as well as alleviate pain and facilitate activities of daily living.[2] Tizanidine is the only centrally acting skeletal muscle relaxant approved for the management of spasticity. It is a centrally acting α_2-adrenergic agonist and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons.[3]

All of the centrally acting skeletal muscle relaxants (with the exception of tizanidine) are approved to relieve discomfort associated with acute, painful musculoskeletal conditions.[4-10] Carisoprodol and chlorzoxazone act on the spinal cord and subcortical levels of the brain to depress polysynaptic neuron transmission. Carisoprodol is metabolized to meprobamate (an anxiolytic). Cyclobenzaprine is structurally related to the tricyclic antidepressants and acts primarily at the brain stem to reduce tonic somatic motor activity. The therapeutic effects of metaxalone and methocarbamol are thought to be due to general central nervous system depression.[4-10]

The centrally acting skeletal muscle relaxants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in August 2020.

Table 1. Centrally Acting Skeletal Muscle Relaxants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Carisoprodol	tablet	Soma®*	none†
Chlorzoxazone	tablet	Lorzone®	chlorzoxazone
Cyclobenzaprine	extended-release capsule*, tablet*	Amrix®*, Fexmid®*	cyclobenzaprine
Metaxalone	tablet	Skelaxin®*	metaxalone
Methocarbamol	injection, tablet	Robaxin®*	methocarbamol
Tizanidine	capsule, tablet	Zanaflex®*	tizanidine
Combination Products			
Codeine, carisoprodol, and aspirin	tablet	N/A	none†

*Generic is available in at least one dosage form or strength.
†Generic carisoprodol products were placed on prior authorization due to abuse potential through P&T and Drug Utilization Review.
PDL=Preferred Drug List.
N/A=Not available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the centrally acting skeletal muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Centrally Acting Skeletal Muscle Relaxants

Clinical Guideline	Recommendation(s)

National Institute for Clinical Excellence: **Low back pain and sciatica in over 16s: assessment and management (2016)**[11]
 	
Reaffirmed Dec 2020
	Pharmacological management of sciatica
	• Do not offer gabapentinoids, other antiepileptics, oral corticosteroids or benzodiazepines for managing sciatica as there is no overall evidence of benefit and there is evidence of harm.
	• Do not offer opioids for managing chronic sciatica.
	• If a person is already taking opioids, gabapentinoids or benzodiazepines for sciatica, explain the risks of continuing these medicines.
	• As part of shared decision making about whether to stop opioids, gabapentinoids or benzodiazepines for sciatica, discuss the problems associated with withdrawal with the person.
	• Be aware of the risk of harms and limited evidence of benefit from the use of non-steroidal anti-inflammatory drugs (NSAIDs) in sciatica.
	• If prescribing NSAIDs for sciatica:
	  ○ take into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age
	  ○ think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment
	  ○ use the lowest effective dose for the shortest possible period of time.
	
	Pharmacological management of low back pain
	• Consider oral NSAIDs for managing low back pain, taking into account potential differences in gastrointestinal, liver, and cardio-renal toxicity, and the person's risk factors, including age.
	• When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.
	• Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time.
	• Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated, or has been ineffective.
	• Do not offer paracetamol alone for managing low back pain.
	• Do not routinely offer opioids for managing acute low back pain.
	• Do not offer opioids for managing chronic low back pain.
	• Do not offer selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, or tricyclic antidepressants for managing low back pain.
	• Do not offer gabapentinoids or antiepileptics for managing low back pain.

American College of Physicians: **Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline (2017)**[12]	• Given that most patients with acute or subacute low back pain improve over time regardless of treatment, nonpharmacologic treatment with superficial heat, massage, acupuncture, or spinal manipulation should be used. If pharmacologic treatment is desired, select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants. • For patients with chronic low back pain, initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation. • In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients.

Clinical Guideline	Recommendation(s)
American Academy of Neurology/Child Neurology Society: **Practice Parameter: Pharmacologic Treatment of Spasticity in Children and Adolescents with Cerebral Palsy (2010)**[13] Reaffirmed July 2019	• For generalized spasticity that warrants treatment, diazepam should be considered for short-term treatment and tizanidine may be considered. • There are insufficient data to support or refute use of dantrolene, oral baclofen, or continuous intrathecal baclofen.
National Institute for Clinical Excellence: **Multiple sclerosis in adults: management (2014)**[14] Last updated Nov 2019	Spasticity • In people with multiple sclerosis (MS) assess and offer treatment for factors that may aggravate spasticity such as constipation, urinary tract or other infections, inappropriately fitted mobility aids, pressure ulcers, posture and pain. • Encourage people with MS to manage their own spasticity symptoms by explaining how doses of drugs can be adjusted within agreed limits. • Ensure that the person with MS: o has tried the drug at an optimal dose, or the maximum dose they can tolerate o stops the drug if there is no benefit at the maximum tolerated dose (but note any special precautions needed when stopping specific drugs) o has their drug treatment reviewed at least annually once the optimal dose has been reached. • Consider baclofen or gabapentin as a first-line drug to treat spasticity in MS depending on contraindications and the person's comorbidities and preferences. If the person with MS cannot tolerate one of these drugs consider switching to the other. • Consider a combination of baclofen and gabapentin for people with MS if: o individual drugs do not provide adequate relief or o side effects from individual drugs prevent the dose being increased. • Consider tizanidine or dantrolene as a second‑line option to treat spasticity in people with MS. • Consider benzodiazepines as a third‑line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms. • If spasticity cannot be managed with any of the above pharmacological treatments, refer the person to specialist spasticity services.
Department of Veteran Affairs/ Department of Defense Clinical Practice Guideline Working Group: **Management of Stroke Rehabilitation (2019)**[15]	• Diazepam and other benzodiazepines should be avoided during the stroke recovery period because this class of medication may interfere with cerebral functions associated with recovery of function after stroke, and these agents are likely to produce sedation which will compromise an individual's ability to participate effectively in rehabilitation. • Consider use of botulinum toxin, on its own, or in conjunction with oral medication for patients with focal spasticity that is painful, impairs function, reduces the ability to participate in rehabilitation or compromises proper positioning or skin care. • Intrathecal baclofen treatments may be considered for stroke patients with severe chronic lower extremity spasticity that cannot be effectively managed by other interventions.
Department of Veteran Affairs/ Department of Defense Clinical Practice Guideline	Pharmacologic Therapy • For patients with chronic low back pain, duloxetine is suggested. • For patients with low back pain, non-steroidal anti-inflammatory drugs (NSAIDs) are suggested. • For patients with low back pain, with or without radicular symptoms, there is

Clinical Guideline	Recommendation(s)
Working Group: **Clinical Practice Guideline For Diagnosis and Treatment of Low Back Pain (2022)**[16]	insufficient evidence to recommend for or against gabapentin or pregabalin. • For patients with low back pain, there is insufficient evidence to recommend for or against tricyclic antidepressants. • For patients with low back pain, there is insufficient evidence to recommend for or against topical preparations. • For patients with acute low back pain, there is insufficient evidence to recommend for or against a non-benzodiazepine muscle relaxant for short-term use. • For patients with chronic low back pain, offering a non-benzodiazepine muscle relaxant is not suggested. • For patients with low back pain, acetaminophen is not suggested. • For patients with low back pain, monoclonal antibodies are not suggested. • For patients with chronic low back pain, opioids are not suggested. • For patients with low back pain, with or without radicular symptoms, systemic corticosteroids (oral or intramuscular injection) are not suggested. • For patients with low back pain, benzodiazepines are not recommended.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the centrally acting skeletal muscle relaxants are noted in Table 3.

Table 3. FDA-Approved Indications for the Centrally Acting Skeletal Muscle Relaxants[3-10]

Indication	Single Entity Agents						Combination Products
	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine	Codeine, Carisoprodol and Aspirin
Painful Musculoskeletal Conditions							
Adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions	✔ †	✔	✔ †	✔	✔		✔ †
Spasticity							
Management of spasticity						✔	

†Should only be used for short periods (up to two or three weeks).

IV. Pharmacokinetics

The pharmacokinetic parameters of the centrally acting skeletal muscle relaxants are listed in Table 4. No relevant clinical information specific to the combination products was identified. Pharmacokinetic properties of the combination products would be in line with the properties of their individual components listed below.

Table 4. Pharmacokinetic Parameters of the Centrally Acting Skeletal Muscle Relaxants[3-10]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Carisoprodol	Not reported	Not reported	Liver	Not reported	8
Chlorzoxazone	100	Not reported	Liver	Renal (74)	1.1
Cyclobenzaprine	33 to 55	93	Liver	Renal (51)	ER: 32 IR: 18
Metaxalone	Not reported	Not reported	Liver	Not reported	8 to 9
Methocarbamol	~100	Not reported	Liver	Renal (40 to 50)	1 to 2
Tizanidine	40	30	Liver	Renal (60)	2

ER=extended-release, IR=immediate-release

V. Drug Interactions

Major drug interactions with the centrally acting skeletal muscle relaxants are listed in Table 5.

Table 5. Major Drug Interactions with the Centrally Acting Skeletal Muscle Relaxants[5]

Generic Name(s)	Interaction	Mechanism
Centrally acting skeletal muscle relaxants (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, tizanidine)	Benzodiazepines, barbiturates, opioid analgesics, sodium oxybate, and alcohol	Additive central nervous system and respiratory depression may occur when a centrally acting skeletal muscle relaxant is administered concomitantly with other central nervous system depressants.
Cyclobenzaprine	Duloxetine, milnacipran. nefazodone, sibutramine, venlafaxine	There is an increased risk of serotonin syndrome, therefore concomitant use is discouraged.
Cyclobenzaprine	Citalopram, escitalopram	There is an increased risk of serotonin syndrome, therefore concomitant use is discouraged.
Cyclobenzaprine	Fluoxetine	Cytochrome P450 2D6 hepatic enzymes are inhibited by fluoxetine and cyclobenzaprine may also be metabolized via this pathway. The combination of cyclobenzaprine and fluoxetine may increase the risk of QT prolongation due to inhibition of cyclobenzaprine metabolism.
Cyclobenzaprine	Tricyclic antidepressants	There is an increased risk of serotonin syndrome, therefore concomitant use is discouraged.
Cyclobenzaprine	Monoamine oxidase inhibitors	Cyclobenzaprine is closely related to the tricyclic antidepressants. Hypertensive crisis, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors.
Cyclobenzaprine	Tramadol	Concomitant administration of tramadol and cyclobenzaprine increases the risk of seizures.
Cyclobenzaprine	Verapamil	Concurrent use of cyclobenzaprine and verapamil may result in increased cyclobenzaprine exposure and

Generic Name(s)	Interaction	Mechanism
		increased risk of serotonin syndrome.
Tizanidine	Amiodarone	Amiodarone is a moderately potent inhibitor of CYP1A2-mediated metabolism of tizanidine. Concomitant use of amiodarone with tizanidine increases tizanidine exposure and the risk of excessive sedation and hypotension.
Tizanidine	Cimetidine	Cimetidine is a moderately potent inhibitor of CYP1A2-mediated metabolism of tizanidine. Concomitant use of cimetidine and tizanidine increases tizanidine exposure and the risk of excessive sedation and hypotension.
Tizanidine	Ciprofloxacin	Ciprofloxacin is a moderately potent inhibitor of CYP1A2-mediated metabolism of tizanidine. Concomitant use of ciprofloxacin with tizanidine potentiates tizanidine exposure and the risk of excessive sedation and hypotension.
Tizanidine	Famotidine	Tizanidine is primarily metabolized by the CYP1A2 isozyme. Although not studied, coadministration with famotidine, a CYP1A2 inhibitor, should be avoided due to the possibility of increased tizanidine exposure, which may result in excessive sedation and hypotension.
Tizanidine	Fluvoxamine	Concurrent administration of fluvoxamine, a potent CYP1A2 inhibitor, and tizanidine induced a profound increase in tizanidine bioavailability. The inhibition of CYP1A2-mediated tizanidine metabolism provokes clinically significant hypotension and alteration of consciousness.
Tizanidine	Mexiletine	Mexiletine is a moderately potent inhibitor of CYP1A2-mediated metabolism of tizanidine. Concomitant use of mexiletine with tizanidine increases tizanidine exposure and the risk of excessive sedation and hypotension.
Tizanidine	Norfloxacin	Norfloxacin is a moderately potent inhibitor of CYP1A2-mediated metabolism of tizanidine. Concomitant use of norfloxacin with tizanidine increases tizanidine exposure and the risk of excessive sedation and hypotension.
Tizanidine	Ofloxacin	Tizanidine is primarily metabolized by the CYP1A2 isozyme. Although not studied, coadministration with ofloxacin, a CYP1A2 inhibitor, should be avoided due to the possibility of increased tizanidine exposure, which may result in excessive sedation and hypotension.
Tizanidine	Oral contraceptives	Contraceptives are moderately potent inhibitors of CYP1A2-mediated metabolism of tizanidine. Concomitant use of contraceptives and tizanidine may increase the risk of excessive hypotension and sedation.
Tizanidine	Propafenone	Propafenone is a moderately potent inhibitor of CYP1A2-mediated metabolism of tizanidine. Concomitant use of propafenone with tizanidine increases tizanidine exposure and the risk of excessive sedation and hypotension.
Tizanidine	Ticlopidine	Ticlopidine is a moderately potent inhibitor of CYP1A2-mediated metabolism of tizanidine. Concomitant use of ticlopidine with tizanidine increases tizanidine exposure and the risk of excessive sedation and hypotension.
Tizanidine	Verapamil	Tizanidine is primarily metabolized by the CYP1A2 isozyme. Although not studied, coadministration with verapamil, a CYP1A2 inhibitor, should be avoided due to the possibility of increased tizanidine exposure, which may result in excessive sedation and hypotension.

Generic Name(s)	Interaction	Mechanism
Tizanidine	Zileuton	Tizanidine is primarily metabolized by the CYP1A2 isozyme. Although not studied, coadministration with zileuton, a CYP1A2 inhibitor, should be avoided due to the possibility of increased tizanidine exposure, which may result in excessive sedation and hypotension.

VI. Adverse Drug Events

The most common adverse drug events reported with the centrally acting skeletal muscle relaxants are listed in Table 6. There have been postmarketing reports of dependence, withdrawal, and abuse with prolonged use of carisoprodol.[6] Most cases have occurred in patients who have had a history of addiction or who used carisoprodol in combination with other drugs with abuse potential. However, there have been postmarketing adverse event reports of carisoprodol-associated abuse when used without other drugs with abuse potential. Withdrawal symptoms have been reported following abrupt cessation after prolonged use. No relevant clinical information specific to the combination products was identified. Adverse events of the combination products would be in line with the adverse events of their individual components listed below.

Table 6. Adverse Drug Events (%) Reported with the Centrally Acting Skeletal Muscle Relaxants[3-10]

Adverse Events	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine
Cardiovascular						
Arrhythmia	-	-	<1	-	-	✔
Bradycardia	-	-	-	-	✔	✔
Hypotension	✔	-	<1	-	✔	16 to 33
Palpitations	-	-	6	-	-	✔
Tachy-arrhythmia	-	-	<1	-	-	-
Tachycardia	✔	-	-	-	-	-
Sinus tachycardia	✔	-	-	-	-	-
Syncope	-	-	<1	-	✔	✔
Vasodilation	-	-	<1	-	-	✔
Ventricular extrasystoles	-	-	-	-	-	✔
Central Nervous System						
Agitation	✔	✔	<1	-	-	-
Amnesia	-	-	-	-	✔	-
Anxiety	-	-	<1	-	-	✔
Asthenia	-	-	1 to 3	-	-	41 to 78
Ataxia	✔	-	<1	-	✔	-
Confusion	✔	-	1 to 3	-	✔	-
Delirium	-	-	✔	-	-	-
Depression	✔	-	<1	-	-	✔
Dis-orientation	✔	-	✔	-	-	-
Dizziness	7 to 8	✔	3 to 19	✔	✔	16 to 45
Drowsiness	13 to 17	✔	✔	✔	✔	48 to 92
Dyskinesia	-	-	-	-	-	✔
Fatigue	✔	-	1 to 3	-	-	9 to 16
Hallucinations	-	-	<1	-	-	3
Headache	3 to 5	✔	1 to 17	✔	✔	✔
Impaired cognition	✔	-	-	-	-	-

Adverse Events	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine
Insomnia	✔	-	<1	-	✔	6 to 16
Irritability	✔	-	-	✔	-	-
Lethargy	✔	-	-	-	-	-
Lightheadedness	-	✔	-	-	✔	✔
Malaise	-	✔	-	-	-	-
Mania	-	-	✔	-	-	-
Migraine	-	-	-	-	-	✔
Nervousness	-	-	-	✔	-	✔
Over stimulation	-	✔	-	-	-	-
Paresthesia	-	-	<1	-	-	✔
Seizure	✔	-	<1	-	✔	-
Sedation	-	-	-	-	✔	48
Somnolence	-	-	1 to 100	-	-	38 to 92
Suicide attempt	-	-	-	-	-	✔
Syncope	✔	-	-	-	-	✔
Tremor	✔	-	0 to 6	-	-	✔
Vertigo	✔	-	-	-	✔	-
Weakness	✔	-	-	-	-	✔
Dermatological						
Allergic skin reactions	-	✔	<1	-	-	-
Anaphylaxis	-	-	<1	-	✔	-
Angioedema	-	-	<1	-	✔	-
Diaphoresis	-	-	-	-	-	✔
Ecchymosis	-	✔	-	-	-	-
Facial edema	-	-	<1	-	-	-
Flushing	✔	-	-	-	✔	-
Petechiae	-	✔	-	-	-	-
Pruritus	-	✔	<1	✔	✔	✔
Rash	-	✔	<1	✔	✔	✔
Skin eruptions	-	-	-	-	✔	-
Skin ulcer	-	-	-	-	-	✔
Urticaria	-	-	<1	-	✔	-
Endocrine and Metabolic						
Fever	-	-	-	-	✔	✔
Hypoglycemia	-	-	✔	-	-	-
Gastrointestinal						
Abdominal cramp/pain	-	-	-	-	-	✔

Adverse Events	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine
Anorexia	-	✔	<1	-	✔	-
Constipation	-	✔	1 to 3	-	-	<6
Diarrhea	-	✔	<1	-	-	<6
Dyspepsia	✔	✔	-	✔	✔	✔
Epigastric pain or discomfort	✔	-	✔	-	-	-
Flatulence	-	-	<1	-	-	-
Gastritis	-	-	<1	-	-	-
Hiccups	✔	-	-	-	-	-
Indigestion	-	-	4	-	-	-
Ileus	-	-	-	-	✔	-
Increased bowel activity	✔	-	-	-	-	-
Nausea	✔	✔	3 to 8	✔	✔	✔
Pharyngeal dryness	-	-	8	-	-	-
Tongue edema	-	-	<1	-	-	-
Vomiting	✔	✔	<1	✔	✔	✔
Xerostomia	-	-	6 to 58	-	-	49 to 88
Genitourinary						
Urine discoloration	-	✔	-	-	✔	-
Urinary frequency	-	-	<1	-	-	✔
Urinary retention	-	-	<1	-	-	✔
Hepatic						
Hepatotoxicity	-	✔	<1	-	-	5
Increased aspartate aminotransferase	-	-	-	-	-	5
Increased alanine aminotransferase	-	-	-	-	-	5
Jaundice	-	-	-	✔	✔	-
Hematologic						
Hemolysis	-	-	-	-	✔	-
Hemolytic anemia	-	-	-	✔	-	-
Leukopenia	✔	-	-	✔	✔	✔
Pancytopenia	✔	-	-	-	-	-
Musculoskeletal						
Back ache	-	-	-	-	-	✔
Dysarthria	-	-	<1	-	-	-
Muscular incoordination	-	-	-	-	✔	-
Muscular weakness	-	-	<1	-	-	-
Respiratory						
Bronchospasm	-	-	-	-	✔	-

Adverse Events	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine
Nasal congestion	-	-	-	-	✔	-
Special Senses						
Ageusia	-	-	✔	-	-	-
Blurred vision	-	-	3	-	✔	-
Conjunctivitis	-	-	-	-	✔	✔
Deafness	-	-	-	-	-	✔
Death	-	-	-	-	-	✔
Diplopia	-	-	<1	-	✔	-
Dysgeusia	-	-	1 to 6	-	-	-
Metallic taste	-	-	-	-	✔	-
Mydriasis	✔	-	-	-	-	-
Nystagmus	-	-	-	-	✔	-
Speech disorder	-	-	-	-	-	✔
Tinnitus	-	-	✔	-	-	✔
Visual impairment	✔	-	-	-	-	-

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the centrally acting skeletal muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Centrally Acting Skeletal Muscle Relaxants[3-10]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Carisoprodol	Painful musculoskeletal disorders: Tablet: 250 to 350 mg TID and QHS	Painful musculoskeletal disorders ≥16 years of age: Tablet: 250 to 350 mg TID and QHS	Tablet: 250 mg 350 mg
Chlorzoxazone	Painful musculoskeletal disorders: Tablet: 250 to 750 mg TID to QID	Safety and efficacy in children have not been established.	Tablets: 250 mg 375 mg 500 mg 750 mg
Cyclobenzaprine	Painful musculoskeletal disorders: Capsule (ER): 15 to 30 mg QD Tablet (IR): 5 to 10 mg TID	Painful musculoskeletal disorders: Capsule (ER): Safety and efficacy in children have not been established. Tablet (IR): ≥15 years of age: 5 to 10 mg TID	Capsule (ER): 15 mg 30 mg Tablet (IR): 5 mg 7.5 mg 10 mg
Metaxalone	Painful musculoskeletal disorders: Tablet: 800 mg TID to QID	Painful musculoskeletal disorders ≥12 years of age: Tablet: 800 mg TID to QID	Tablet: 400 mg 800 mg
Methocarbamol	Painful musculoskeletal disorders: Injection: 1 g every eight hours; maximum 3 g daily for no greater than three days Tablet: 750 mg every four hours, 1,000 mg QID or 1,500 mg TID	Painful musculoskeletal disorders Injection: Safety and efficacy in children have not been established. Tablet: ≥16 years of age: 750 mg every four hours, 1,000 mg QID or 1,500 mg TID	Injection: 100 mg/mL Tablet: 500 mg 750 mg
Tizanidine	Muscle spasticity: Capsule and tablet: 2 to 12 mg every six to eight hours; maximum, 36 mg in 24 hours	Safety and efficacy in children have not been established.	Capsule: 2 mg 4 mg 6 mg Tablet: 2 mg 4 mg
Combination Products			
Codeine, carisoprodol and aspirin	Painful musculoskeletal disorders: Tablet: one to two tablets QID	Safety and efficacy in children have not been established.	Tablet: 16-200-325 mg

ER=extended-release, IR=immediate-release, QD=once daily, QID=four times daily, QHS=at bedtime, TID=three times daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the centrally acting skeletal muscle relaxants are summarized in Table 8. Although skeletal muscle relaxants have been available for many years, there are limited head-to-head trials for the treatment of spasticity and musculoskeletal disorders.

Table 8. Comparative Clinical Trials with the Centrally Acting Skeletal Muscle Relaxants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Musculoskeletal Pain				
Serfer et al.[17] (2010) Carisoprodol 250 mg QID vs carisoprodol 350 mg QID vs placebo	DB, MC, RCT Adults with acute, painful muscle spasms of the lower back rated as moderate or severe	N=828 7 days	Primary: Patient-rated relief from starting backache and patient-rated global impression of change Secondary: Patient functional assessment according to the RMDQ	Primary: The carisoprodol 250 mg regimen was significantly more effective than placebo as assessed by both patient-rated relief from starting backache (P=0.0001) and patient-rated global impression of change (P=0.006). There were no significant differences between carisoprodol 250 or 350 mg. Secondary: Treatment with carisoprodol was associated with significantly greater improvements in RMDQ scores on days three and seven compared to placebo. No significant differences between carisoprodol 250 or 350 mg in effects on RMDQ were observed.
Rollings et al.[18] (1983) Carisoprodol 350 mg QID vs cyclobenzaprine 10 mg QID	DB, PC, RCT Patients 19 to 65 years of age with acute LBP of at least moderate intensity with muscle spasms of 7 days or less	N=78 7 days	Primary: Improvement in pain; muscle spasm and activity impairment; overall improvement for acute LBP Secondary: Not reported	Primary: Pain at baseline and day eight: Carisoprodol (70, 30); Cyclobenzaprine (74, 28) Muscle spasm at baseline and day eight: Carisoprodol (64, 22); Cyclobenzaprine (67, 25) Activity impairment at baseline and day eight: Carisoprodol (74, 32); cyclobenzaprine (76, 26) Overall improvement (very good to excellent) at end of treatment: Carisoprodol (70%) and cyclobenzaprine (70%). There were no differences between the treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Boyles et al.[19] (1983) Carisoprodol 350 mg QID vs diazepam 5 mg QID	DB, RCT Patients 19 to 65 years of age with acute LBP	N=80 7 Days	Primary: Improvement of pain, muscle stiffness, activity, sleep impairment, tension, and overall improvement Secondary: Not reported	Primary: Pain day seven – baseline: Carisoprodol (58); Diazepam (48) Muscle stiffness: Carisoprodol (59); Diazepam (42) Activity: Carisoprodol (58); Diazepam (41) Sleep impairment: Carisoprodol (52); Diazepam (40) Tension: Carisoprodol (51); Diazepam (38) Results were statistically significant for muscle stiffness, activity, tension and relief. Overall improvement (very good + excellent): Carisoprodol (70%); Diazepam (45%) Secondary: Not reported
Bragstad et al.[20] (1979) Chlorzoxazone 500 mg TID vs tizanidine 2 mg TID	DB, RCT Patients with acute LBP	N=27 7 Days	Primary: Pain, muscle tension, limitation of movement and overall effectiveness by patient Secondary: Not reported	Primary: Pain day seven – baseline: Tizanidine (2.29, 0.83); Chlorzoxazone (2.31, 0.73) Muscle tension: Tizanidine (2.57, 0.71); Chlorzoxazone (2.69, 0.44) Limitation of movement: Tizanidine (2.0, 1.0); Chlorzoxazone (2.15, 0.9) Overall effectiveness: Tizanidine (excellent=11; moderate/poor=3)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Chlorzoxazone (excellent=9; moderate/poor=3) Secondary: Not reported
Ralph et al.[21] (2008) Carisoprodol 250 mg TID and QHS vs placebo	DB, MC, PC, PG, RCT Patients with acute, painful muscle spasm of the lower back rated as moderate or severe in intensity were included	N=562 7 days	Primary: Patient-rated global impression of change and patient-rated relief from starting backache (day three). Secondary: RMDQ, time to improvement, patient-rated medication helpfulness, physician assessment of range of motion	Primary: Carisoprodol was significantly more effective than placebo for patient-rated global impression of change (2.24 vs 1.70; P<0.0001) and patient-rated relief from starting backache (1.83 vs 1.12; P<0.0001) on study day three. Significant differences were also found on treatment day seven in favor of carisoprodol (P<0.0001). Secondary: Patient-rated medication helpfulness was higher in the carisoprodol group than in the placebo group on days three and seven (P<0.0001). A greater improvement in RMDQ score was observed in the carisoprodol group than in the placebo group at days three and seven (P<0.0001). The median time to symptom improvement was earlier with carisoprodol (day three) compared to placebo (day six) P<0.0001. There was no difference between the treatment groups with regards to range of motion at day three or seven.
Hindle et al.[22] (1972) Carisoprodol 350 mg QID vs butabarbital 15 mg QID vs placebo	DB, MC, RCT Patients 18 to 70 years of age with acute LBP and acute lumbar strain and spasm	N=48 4 days	Primary: Pain, muscle spasm, interference with daily activities at baseline, day two and day four; number of patients with global improvement Secondary: Not reported	Primary: Pain (100 mm visual analog scale) at baseline, day two and day four: Carisoprodol (85.0, 33.0, 15.5); butabarbital (75.2, 58.7, 49.1); placebo (65.5, 58.5, 64.0). Carisoprodol was significantly better than butabarbital and placebo. Muscle spasm (4-point scale) at baseline, day two and day four: Carisoprodol (3.1, 2.4, 1.8); butabarbital (3.1, 2.8, 2.6); placebo (3.0, 2.9, 2.9). There was no significant difference between the groups. Interference with daily activities at baseline, day two and day four: Carisoprodol (3.7, 2.4, 1.8); butabarbital (3.3, 2.0, 2.7); placebo (3.1, 3.1, 3.4). Carisoprodol was significantly better than placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Number of patients with global improvement: Carisoprodol (12); butabarbital (2); placebo (2). Carisoprodol was significantly better than butabarbital and placebo. Secondary: Not reported
Borenstein et al.[23] (2003) <u>Study 1:</u> Cyclobenzaprine 5 mg TID vs cyclobenzaprine 10 mg TID vs placebo <u>Study 2:</u> Cyclobenzaprine 2.5 mg TID vs cyclobenzaprine 5 mg TID vs placebo	DB, MC, PC, PG, RCT Adults with acute, physician-rated moderate or moderately severe painful muscle spasm of the lumbar and/or cervical region	N=1,405 7 days	Primary: Patient-rated clinical global impression of change, medication helpfulness, and relief from starting backache on days three and seven Secondary: Physician's rating of muscle spasm	Primary: <u>Study 1</u> Patients receiving cyclobenzaprine 5 or 10 mg had significantly higher mean scores on all the primary efficacy measures compared to those receiving placebo (P≤0.001). There were no differences between the doses of cyclobenzaprine with regards to efficacy. <u>Study 2</u> Cyclobenzaprine 2.5 mg was better than placebo for the relief from starting backache on day three only; cyclobenzaprine 5 mg was better than placebo for patient-rated clinical global impression of change, medication helpfulness, and relief from starting backache at visit three or day seven only (all, P<0.03). Secondary: <u>Study 1</u> Mean changes in the physician rating of the severity of muscle spasm were greater for cyclobenzaprine 5 and 10 mg compared to placebo (P<0.001 and P=0.006, respectively). <u>Study 2</u> Mean changes in the physician rating of the severity of muscle spasm were greater for cyclobenzaprine 5 mg compared to placebo (P=0.03). Adverse events were reported in 54.1, 61.8, and 35.4% of patients receiving cyclobenzaprine 5 or 10 mg or placebo, respectively in study 1 and by 43.9, 55.9, and 35.4% of patients receiving cyclobenzaprine 2.5 or 5 mg or placebo, respectively in study 2.
Malanga et al.[24] (2009)	DB, RCT Adults with muscle	<u>Study 1</u> N=250	Primary: Patient's rating of medication	Primary: Significant improvements in patient's rating of medication helpfulness were reported for CER vs placebo (CER 30 mg, study 1; P=0.007, CER 15

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cyclobenzaprine ER (CER) 15 mg QD vs cyclobenzaprine ER (CER) 30 mg QD vs cyclobenzaprine IR (CIR) 10 mg TID vs placebo	spasm associated with neck or back pain	<u>Study 2:</u> N=254 14 days	helpfulness on a 5-point scale and physician's clinical global assessment Secondary: Safety assessments	mg, study 2; P=0.018) at day four. Improvements with CER were comparable to that of CIR. Significant improvements with CER 30 mg vs placebo were also seen at day four in study 1 for patient-rated global impression of change (P=0.008), relief of local pain (P=0.004), and restriction of movement (P=0.002). Secondary: Neither study reported differences between study groups on the physician's clinical global assessment. In both studies, daytime drowsiness was reported more frequently in the active treatment groups than the placebo groups. In general, daytime drowsiness was reported more frequently in the CIR groups than the CER groups.
Weil et al.[25] (2010) Cyclobenzaprine ER (CER) 15 mg QD vs cyclobenzaprine ER (CER) 30 mg QD vs cyclobenzaprine IR (CIR) 10 mg TID	Pooled analysis Adults with muscle spasm associated with neck or back pain	N=504 14 days	Primary: Patient's rating of medication helpfulness on a 5-point scale and physician's clinical global assessment Secondary: Safety assessments	Primary: Significantly greater improvements in patient's rating of medication helpfulness were reported with CER 15 and 30 mg vs placebo at day four (P<0.025). No differences were reported between groups in physician's clinical global assessment. Secondary: There was less reported daytime drowsiness with CER 15 and 30 mg than with CIR (P<0.05). Most adverse events were mild in intensity. The most common adverse events for all groups were dry mouth, constipation, dizziness, headache, and somnolence.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Childers el al.[26] (2005) Cyclobenzaprine 5 mg TID vs cyclobenzaprine 5 mg TID and ibuprofen 400 mg TID vs cyclobenzaprine 5 mg TID and ibuprofen 800 mg TID	MC, OL, PG Adults 18 to 65 years of age; with cervical or thoracolumbar pain and spasm for ≤14 days	N=867 7 days	Primary: Patient Global Impression of Change after seven days of treatment. Secondary: Patient Global Impression of Change after three days; patient-rated scales: (spasm intensity, functional disability, medication helpfulness for pain/spasm); responders after three and seven days	Primary: No significant differences were found in patients with combined neck/back or neck pain only in the seven-day Patient Global Impression of Change outcome. Secondary: No significant differences were found in patients with combined neck/back pain in the three-day Patient Global Impression of Change outcome Mean Patient Global Impression of Change was significantly different from 'no change' after three and seven days of therapy in all three treatment groups (P<0.001). All three treatment groups demonstrated significant improvements from baseline in spasm and pain from baseline after three and seven days (P<0.001 for all comparisons). There was no difference among the three treatment groups. Mean Percent Oswestry Disability Index scores improved from baseline to after three days and after seven days in all three treatment groups (P<0.001 for all comparisons). There was no difference among the three treatment groups. No significant differences were detected in medication helpfulness scores among the treatment groups after three and seven days of therapy.
Khwaja et al.[27] (2010) Cyclobenzaprine 5 mg TID as needed vs	DB, RCT Adults who presented to the emergency department with cervical strains from	N=61 7 days	Primary: A 100-mm visual analog scale marked "no pain" and "most pain" at the low and high ends, respectively,	Primary: In all three study groups, there was a significant reduction in pain scores over time (P<0.001). The changes in pain scores over time were similar among the three treatment groups. Compared to ibuprofen alone, the addition of cyclobenzaprine to ibuprofen did not result in better pain relief or earlier resumption of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ibuprofen 800 mg TID as needed vs cyclobenzaprine 5 mg and ibuprofen 800 mg TID as needed	a motor vehicle collision or fall within the past 24 hours		was used to assess pain severity 30 to 60 minutes after taking the morning dose of the assigned treatment Secondary: Not reported	normal daily activities in this study. Secondary: Not reported
Friedman et al.[28] (2019) Metaxalone 400 mg vs tizanidine 2 mg vs baclofen 10 mg vs placebo All regimens were to take 1 to 2 capsules 3 times daily as needed. All participants received 21 tablets of ibuprofen 600 mg, to be taken 3 times a day as	DB, PG, RCT Patients 18 to 64 years of age with nonradicular low back pain for ≤2 weeks were eligible if they had a score >5 on the RMDQ who presented to the emergency department (ED)	N=320 1 week	Primary: Improvement on the RMDQ between ED discharge and one week later Secondary: Pain intensity one week after ED discharge (severe, moderate, mild, or none)	Primary: At one-week follow-up, the mean RMDQ score of patients randomized to placebo improved by 11.1 points (95% CI, 9.0 to 13.3), baclofen by 10.6 points (95% CI, 8.6 to 12.7), metaxalone by 10.1 points (95% CI, 8.0 to 12.3), and tizanidine by 11.2 points (95% CI, 9.2 to 13.2). Secondary: At one-week follow-up, 30% of placebo patients (95% CI, 21 to 41%) reported moderate to severe low back pain versus 33% of baclofen patients (95% CI, 24 to 44%), 37% of metaxalone patients (95% CI, 27 to 48%), and 33% of tizanidine patients (95% CI, 23% to 44%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
needed.				
Friedman et al.[29] (2018) Methocarbamol 750 mg vs orphenadrine 100 mg vs placebo All regimens were to take 1 to 2 tablets 3 times daily as needed. All participants received 14 tablets of naproxen 500 mg, to be taken twice a day as needed.	DB, PG, RCT Patients 18 to 69 years of age with nonradicular low back pain for ≤2 weeks were eligible if they had a score >5 on the RMDQ who presented to the emergency department (ED)	N=240 1 week	Primary: Improvement on the RMDQ between ED discharge and one week later Secondary: Pain intensity one week after ED discharge (severe, moderate, mild, or none)	Primary: One week after the ED visit, patients randomized to placebo improved by a mean of 10.9 (95% CI, 8.9 to 12.9) RMDQ points while orphenadrine patients improved by 9.4 (95% CI, 7.4 to 11.5) and methocarbamol patients improved by 8.1 (95% CI, 6.1 to 10.1). The difference between orphenadrine and placebo was 1.5 RMDQ points (95% CI, −1.4 to 4.3) while the difference placebo and methocarbamol was 2.8 (95% CI, 0 to 5.7). Secondary: At one-week follow-up, 34% of placebo patients reported moderate to severe low back pain versus 33% of orphenadrine patients, and 39% of methocarbamol patients. Secondary outcomes were similar among the groups.
Hennies et al.[30] (1981) Tizanidine 4 mg TID vs diazepam 5 mg TID	DB, RCT Patients with acute LBP	N=30 7 Days	Primary: Pain improvement; daily activity improvement Secondary: Not reported	Primary: Number of cases with pain improvement on day three and seven: Tizanidine (13, 13); Diazepam (8, 11) Pain relief at end of trial: Tizanidine (77.4%); Diazepam (47.8%) Number of cases with daily activity improvement on day three and seven: Tizanidine (12, 13); Diazepam (10, 14) Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Spasticity				
Lapierre et al.[31] (1987) Tizanidine up to 36 mg vs placebo	DB, PC, PG, RCT Patients 18 to 60 years of age with multiple sclerosis and spasticity server enough to affect function	N=66 8 weeks	Primary: Resistance to passive stretch, muscle power, reflexes, clonus, EDSS score, ambulation index, upper extremities index, electro-physiological studies Secondary: Not reported	Primary: A statistically significant benefit in spastic muscle groups in the legs was found with tizanidine compared to placebo. A statistically significant reduction in hyperactive stretch reflexes and ankle clonus was found with tizanidine compared to placebo. No changes in functional status were detected. No statistically significant difference between tizanidine and placebo were found in any of the validated assessment methods. Secondary: Not reported
Smith et al.[32] (1994) Tizanidine 2 to 36 mg vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with multiple sclerosis	N=220 15 weeks	Primary: Muscle tone (Ashworth Scale); type and frequency of muscle spasms Secondary: Reflexes; clonus; spasms; muscle power; walking time, activities of daily living, global evaluation of efficacy	Primary: There were no significant differences in muscle tone using Ashworth Scores between tizanidine-treated patients and placebo-treated patients. Treatment with tizanidine resulted in a significantly greater reduction in spasms and clonus than placebo. Secondary: There were no significant differences between tizanidine and placebo in secondary end-points, except a better global efficacy and tolerability score with tizanidine.
UKTTG[33] (1994) Tizanidine up to 36 mg vs	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with multiple sclerosis	N=187 9 weeks	Primary: Muscle tone (Ashworth Scale) Secondary: Muscle power; EDSS score;	Primary: Muscle tone (Ashworth Scale) was significantly reduced with tizanidine compared to placebo (P=0.004). Tizanidine achieved a 20% mean reduction in muscle tone. Secondary: 71 and 50% of tizanidine-treated patients and placebo-treated patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			reflexes; clonus; spasm score; 8m walking time; motor skills and upper limb functions; activities of daily living; overall effect on function; efficacy and tolerability	reported subjective improvement without an increase in muscle weakness, respectively (P<0.005). There was no significant difference in EDSS, power grade, spasm score, pain score, or 8 meter walking time for patients receiving tizanidine compared to placebo. There was no improvement in activities of daily living depending on movement between tizanidine-treated patients and placebo-treated patients.
Nance et al.[34] (1994) Tizanidine up to 36 mg vs placebo	MC, PC, RCT Patients with spinal cord injury of >12 months	N=124 7 weeks	Primary: Muscle tone (Ashworth Scale); muscle strength; activities of daily living Secondary: Not reported	Primary: Patients receiving tizanidine had a significant reduction in muscle tone and frequency of spasms compared to placebo (P=0.0001). No significant changes in muscle strength or activities of daily living were demonstrated with tizanidine compared to placebo. Secondary: Not reported
Gelber et al.[35] (2001) Tizanidine up to 36 mg	MC, OL Patients who were a minimum of 6 months poststroke with significant spasticity	N=47 16 weeks	Primary: Muscle tone (Ashworth Scale); muscle strength; functional assessments; Pain and Functional Spasticity Questionnaires Secondary: Not reported	Primary: Tizanidine treatment significantly improved muscle tone (P<0.0001) with no decline in muscle strength. Tizanidine treatment resulted in a significant improvement in pain intensity (P=0.0375), quality of life (P=0.0001), and physician assessment of disability (P=0.0001). Secondary: Not reported
Bass et al.[36] (1988) Tizanidine up to 32 mg	DB, RCT, XO Patients with multiple sclerosis	N=66 11 weeks	Primary: Muscle tone and power; EDSS score; Pedersen functional	Primary: Physicians and physiotherapists found baclofen to be more effective than tizanidine (P<0.05). There was no significant difference between the baclofen and tizanidine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs baclofen up to 80 mg			disability scale; reflexes; clonus; overall evaluations of efficacy and tolerability Secondary: Not reported	treatment groups based on patient perception of efficacy. There were no significant differences in EDSS or muscle tone measures between the baclofen treatment group and the tizanidine treatment group. Secondary: Not reported
Eysette et al.[37] (1988) Tizanidine up to 24 mg vs baclofen up to 60 mg	DB, MC, RCT Patients 18 to 70 years of age suffering from chronic spasticity due to multiple sclerosis	N=100 8 weeks	Primary: Locomotor function; condition in bed and chair; spasms; tonic stretch reflex; clonus; power; bladder control Secondary: Not reported	Primary: Tizanidine and baclofen improved functional status of 80 and 76% of patients, respectively (P=NS). No significant differences were noted in spasms, tonic stretch reflex, clonus, power, or bladder control. Secondary: Not reported
Smolenski et al.[38] (1981) Tizanidine up to 36 mg vs baclofen up to 80 mg	DB, PG, RCT Hospitalized patients 42 to 73 years of age with multiple sclerosis	N=21 6 weeks	Primary: Muscle tone (Ashworth scale); EDSS score, spasm score, muscle power, global impression, side effects Secondary: Not reported	Primary: There was no significant difference in spastic state, spasms and clonus in baclofen-treated patients compared to tizanidine-treated patients. Muscle strength, bladder function and activities of daily living were improved more with tizanidine than baclofen. Tiredness was the most frequent side effect on tizanidine and muscle weakness on baclofen. Secondary: Not reported
Stien et al.[39] (1987) Tizanidine up to 36 mg	DB, RCT Seriously handicapped patients with multiple sclerosis	N=40 6 weeks	Primary: Muscle tone (Ashworth Scale); EDSS; Pedersen rating scales; overall impression	Primary: There was no significant difference in spastic state, spasms and clonus in baclofen-treated patients compared to tizanidine-treated patients. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs baclofen up to 90 mg			Secondary: Not reported	
Simpson et al.[40] (2009) Tizanidine (TZD) 2 to 36 mg/day vs botulinum neurotoxin (BoNT) administered IM vs placebo	DB, MC, RCT Adults with prior stroke or traumatic brain injury with spasticity of the wrist	N=60 18 weeks	Primary: Difference in change in wrist flexor modified Ashworth score Secondary: Not reported	Primary: BoNT produced greater tone reduction than TZD or placebo in finger and wrist flexors at week three (P<0.001 vs TZD; P<0.02 vs placebo) and six (P=0.001 vs TZD; P=0.08 vs placebo). BoNT was more effective than TZD in reducing tone and disfigurement in upper-extremity spasticity. Secondary: Not reported
Dai et al.[41] (2008) Tizanidine 0.3 to 0.5 mg/kg/day in 4 divided doses and botulinum type A 20 to 24 units/kg vs baclofen 10 to 15 mg/kg/day in 3 divided doses and botulinum type A 20 to 24 units/kg	RETRO Children 2 to 14 years of age with cerebral palsy and spastic equines foot deformity	N=30 12 weeks	Primary: Mean scores of Gross Motor Functional Measurement, Caregiver Questionnaire form, and the modified Ashworth scale for leg functional measurement and for leg spasticity assessment by a pediatric neurologist Secondary:	Primary: The mean Gross Motor Functional Measurement (76.63 vs 68.17; P<0.001) and Caregiver Questionnaire form scores (70.23 vs 66.59; P=0.03) for the tizanidine group were significantly higher as compared to the baclofen group. This study suggests that the combination of botulinum toxin type A with oral tizanidine is more effective than the combination of botulinum toxin type A and oral baclofen for spastic cerebral palsy. However, details about the frequency and types of side effects in the study were lacking. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	

Drug regimen abbreviations: QD=once daily, TID=three times daily, QID=four times daily, QHS=every night at bedtime
Study abbreviations: DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective
Miscellaneous abbreviations: EDSS=Expanded Disability Status Scale, ER=extended release, IM=intramuscular, IR=immediate release, LBP=low back pain, RMDQ=Roland-Morris Disability Questionnaire

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the Centrally Acting Skeletal Muscle Relaxants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Carisoprodol	tablet	Soma®*	$$$$$	$$$
Chlorzoxazone	tablet	Lorzone®	$$$$$	$
Cyclobenzaprine	extended-release capsule*, tablet*	Amrix®*, Fexmid®*	$$$$$	$
Metaxalone	tablet	Skelaxin®*	$$$$$	$
Methocarbamol	injection, tablet	Robaxin®*	$$$	$
Tizanidine	capsule, tablet	Zanaflex®*	$$$	$
Combination Products				
Codeine, carisoprodol and aspirin	tablet	N/A	N/A	$$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

All of the centrally acting skeletal muscle relaxants (with the exception of tizanidine) are approved to relieve discomfort associated with acute, painful musculoskeletal conditions.[3-10] Tizanidine is a short-acting agent that is approved for the management of spasticity.[3] Due to the short duration of action, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important.[3] All of the products are available in a generic formulation.

For the management of multiple sclerosis, guidelines recommend the use of tizanidine when treatment with baclofen or gabapentin is unsuccessful, or if adverse events are intolerable.[14] For the management of stroke rehabilitation, guidelines no longer recommend the use of tizanidine for spasticity resulting in pain.[15] Clinical trials have enrolled small numbers of patients and data to support the long-term use of tizanidine is limited.[31-41] However, tizanidine has consistently been found to be more effective than placebo.[31-33] There are limited studies directly comparing tizanidine to other antispasticity agents.[36-39,42-43]

The centrally acting skeletal muscle relaxants are effective for the treatment of musculoskeletal disorders, including the short-term symptomatic relief of non-specific low back pain. However, adverse events require that they be used with caution. Guidelines recommend the use of acetaminophen or nonsteroidal anti-inflammatory drugs as first-line therapy for the treatment of low back pain.[12,16] Skeletal muscle relaxants are not recommended for mild to moderate acute low back pain or for chronic use in subacute or chronic low back pain (other than acute exacerbations).[12] There is no compelling evidence to indicate that the centrally acting skeletal muscle relaxants differ in efficacy or safety for the treatment of low back pain.[18,24-25,28-29]

Adverse events are problematic with the centrally acting skeletal muscle relaxants, with drowsiness and dizziness being common with all of the agents. The prolonged use of carisoprodol has been associated with dependence, withdrawal, and abuse.[6] According to the prescribing information, carisoprodol and cyclobenzaprine should only be used for short periods of time (up to two or three weeks) because there is insufficient evidence to support prolonged use.[3-10] In addition, muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.[4-5,10] Tizanidine occasionally causes liver injury, most often hepatocellular in type.[3]

There is insufficient evidence to support that one brand centrally acting skeletal muscle relaxant is safer or more efficacious than another. Due to the potential risk of abuse, carisoprodol and carisoprodol containing products should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand centrally acting skeletal muscle relaxants within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand centrally acting skeletal muscle relaxant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Carisoprodol and carisoprodol containing products should not be placed in preferred status regardless of cost.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Direct-Acting Skeletal Muscle Relaxants
AHFS Class 122008
November 9, 2022

I. Overview

Dantrolene is the only direct-acting skeletal muscle relaxant that is currently available. It is approved for the management of spasticity, as well as for the prevention and treatment of malignant hyperthermia.[1-5] Spasticity can be defined as a velocity-dependent increase in muscle tone. This means that the faster the passive movement of the limb through its range of motion, the greater the increase in muscle tone.[6] Spasticity is associated with a number of central nervous system disorders including stroke, multiple sclerosis, cerebral palsy, as well as brain and spinal cord injuries.[6] Because of the loss of inhibitory controls at the upper motor neuron level (brain or spinal cord), there is permanent ongoing or intermittent involuntary striated muscle contraction. This spasticity can severely limit functioning due to weakness, spasms, and loss of dexterity. The goal of therapy is to improve functioning, as well as to alleviate pain and facilitate daily care activities.[7-8] While some treatments for spasticity act centrally on the spinal cord or brain stem, dantrolene acts directly on the skeletal muscles by inhibiting the release of calcium from the sarcoplasmic reticulum, which inhibits muscle contraction.[1-5]

Malignant hyperthermia is a life-threatening, genetically-based disorder that occurs in susceptible individuals after exposure to certain drugs, usually anesthetic agents.[9] It is hypothesized that exposure to the "trigger" drug elevates the level of calcium in the myoplasm and that dantrolene reestablishes a normal level of ionized calcium.[9]

The direct-acting skeletal muscle relaxants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Dantrolene is available in a generic formulation. This class was last reviewed in August 2020.

Table 1. Direct-Acting Skeletal Muscle Relaxants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dantrolene	capsule, injection	Dantrium®*, Ryanodex®, Revonto®*	dantrolene

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the direct-acting skeletal muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Direct-Acting Skeletal Muscle Relaxants

Clinical Guideline	Recommendation(s)
National Institute for Clinical Excellence: **Low back pain and sciatica in over 16s: assessment and management (2016)**[10] Reaffirmed Dec 2020	Pharmacological management of sciatica • Do not offer gabapentinoids, other antiepileptics, oral corticosteroids or benzodiazepines for managing sciatica as there is no overall evidence of benefit and there is evidence of harm. • Do not offer opioids for managing chronic sciatica. • If a person is already taking opioids, gabapentinoids or benzodiazepines for sciatica, explain the risks of continuing these medicines. • As part of shared decision making about whether to stop opioids, gabapentinoids or benzodiazepines for sciatica, discuss the problems associated with withdrawal with the person. • Be aware of the risk of harms and limited evidence of benefit from the use of non-steroidal anti-inflammatory drugs (NSAIDs) in sciatica. • If prescribing NSAIDs for sciatica:

Clinical Guideline	Recommendation(s)
	○ take into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age ○ think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment ○ use the lowest effective dose for the shortest possible period of time. <u>Pharmacological management of low back pain</u> • Consider oral NSAIDs for managing low back pain, taking into account potential differences in gastrointestinal, liver, and cardio-renal toxicity, and the person's risk factors, including age. • When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment. • Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time. • Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated, or has been ineffective. • Do not offer paracetamol alone for managing low back pain. • Do not routinely offer opioids for managing acute low back pain. • Do not offer opioids for managing chronic low back pain. • Do not offer selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, or tricyclic antidepressants for managing low back pain. • Do not offer gabapentinoids or antiepileptics for managing low back pain.
American College of Physicians: **Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline (2017)**[11]	• Given that most patients with acute or subacute low back pain improve over time regardless of treatment, nonpharmacologic treatment with superficial heat, massage, acupuncture, or spinal manipulation should be used. If pharmacologic treatment is desired, select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants. • For patients with chronic low back pain, initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation. • In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients.
American Academy of Neurology/Child Neurology Society: **Practice Parameter: Pharmacologic Treatment of Spasticity in Children and Adolescents with Cerebral Palsy (2010)**[12] Reaffirmed July 2019	• For generalized spasticity that warrants treatment, diazepam should be considered for short-term treatment and tizanidine may be considered. • There are insufficient data to support or refute use of dantrolene, oral baclofen, or continuous intrathecal baclofen.
National Institute for	<u>Spasticity</u>

Clinical Guideline	Recommendation(s)
Clinical Excellence: **Multiple sclerosis in adults: management (2014)**[13] Last updated Nov 2019	• In people with multiple sclerosis (MS) assess and offer treatment for factors that may aggravate spasticity such as constipation, urinary tract or other infections, inappropriately fitted mobility aids, pressure ulcers, posture and pain. • Encourage people with MS to manage their own spasticity symptoms by explaining how doses of drugs can be adjusted within agreed limits. • Ensure that the person with MS: o has tried the drug at an optimal dose, or the maximum dose they can tolerate o stops the drug if there is no benefit at the maximum tolerated dose (but note any special precautions needed when stopping specific drugs) o has their drug treatment reviewed at least annually once the optimal dose has been reached. • Consider baclofen or gabapentin as a first-line drug to treat spasticity in MS depending on contraindications and the person's comorbidities and preferences. If the person with MS cannot tolerate one of these drugs consider switching to the other. • Consider a combination of baclofen and gabapentin for people with MS if: o individual drugs do not provide adequate relief or o side effects from individual drugs prevent the dose being increased. • Consider tizanidine or dantrolene as a second‑line option to treat spasticity in people with MS. • Consider benzodiazepines as a third‑line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms. • If spasticity cannot be managed with any of the above pharmacological treatments, refer the person to specialist spasticity services.
Department of Veteran Affairs/ Department of Defense Clinical Practice Guideline Working Group: **Management of Stroke Rehabilitation (2019)**[14]	• Diazepam and other benzodiazepines should be avoided during the stroke recovery period because this class of medication may interfere with cerebral functions associated with recovery of function after stroke, and these agents are likely to produce sedation which will compromise an individual's ability to participate effectively in rehabilitation. • Consider use of botulinum toxin, on its own, or in conjunction with oral medication for patients with focal spasticity that is painful, impairs function, reduces the ability to participate in rehabilitation or compromises proper positioning or skin care. • Intrathecal baclofen treatments may be considered for stroke patients with severe chronic lower extremity spasticity that cannot be effectively managed by other interventions.
Department of Veteran Affairs/ Department of Defense Clinical Practice Guideline Working Group: **Clinical Practice Guideline For Diagnosis and Treatment of Low Back Pain (2022)**[15]	Pharmacologic Therapy • For patients with chronic low back pain, duloxetine is suggested. • For patients with low back pain, non-steroidal anti-inflammatory drugs (NSAIDs) are suggested. • For patients with low back pain, with or without radicular symptoms, there is insufficient evidence to recommend for or against gabapentin or pregabalin. • For patients with low back pain, there is insufficient evidence to recommend for or against tricyclic antidepressants. • For patients with low back pain, there is insufficient evidence to recommend for or against topical preparations. • For patients with acute low back pain, there is insufficient evidence to recommend for or against a non-benzodiazepine muscle relaxant for short-term use. • For patients with chronic low back pain, offering a non-benzodiazepine muscle relaxant is not suggested. • For patients with low back pain, acetaminophen is not suggested. • For patients with low back pain, monoclonal antibodies are not suggested. • For patients with chronic low back pain, opioids are not suggested. • For patients with low back pain, with or without radicular symptoms, systemic

Clinical Guideline	Recommendation(s)
	corticosteroids (oral or intramuscular injection) are not suggested. • For patients with low back pain, benzodiazepines are not recommended.
Association of Anaesthetists: **Malignant hyperthermia (2020)**[16]	• The principles of management of a malignant hyperthermia reaction are to immediately reverse the reaction and treat the consequences of the reaction. • Three approaches to reversing the malignant hyperthermia process should be applied together: eliminate the trigger agent; give intravenous dantrolene; and start active body cooling. • Activated charcoal filters should be available at all locations where general anaesthesia is administered. • The initial dose of dantrolene is 2 to 3 mg/kg with a further 1 mg/kg every five minutes until treatment goals are reached. • Dantrolene should be given until the $ETCO_2$ is < 6 kPa with normal minute ventilation and the core temperature is < 38.5°C.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the direct-acting skeletal muscle relaxants are noted in Table 3.

Table 3. FDA-Approved Indications for the Direct-Acting Skeletal Muscle Relaxants[1-5]

Indication	Dantrolene (Oral)	Dantrolene (Intravenous)
Malignant Hyperthermia		
Preoperatively to prevent or attenuate the development of signs of malignant hyperthermia in known, or strongly suspect, malignant hyperthermia susceptible patients who require anesthesia and/or surgery	✔	
Preoperatively, and sometimes postoperatively, to prevent or attenuate the development of clinical and laboratory signs of malignant hyperthermia in individuals judged to be malignant hyperthermia susceptible		✔ (Dantrium®)
Prevention of malignant hyperthermia in patients at high risk		✔ (Ryanodex®)
Management of the fulminant hypermetabolism of skeletal muscle characteristic of malignant hyperthermia crises in patients of all ages		✔ (Dantrium®)
Following a malignant hyperthermic crisis to prevent recurrence of the signs of malignant hyperthermia	✔	
Treatment of malignant hyperthermia in conjunction with appropriate supportive measures		✔ (Ryanodex®)
Spasticity		
To control the manifestations of clinical spasticity resulting from upper motor neuron disorders (e.g., spinal cord injury, stroke, cerebral palsy, or multiple sclerosis)	✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the direct-acting skeletal muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Direct-Acting Skeletal Muscle Relaxants[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Dantrolene	70	Significant (% not reported)	Liver	Renal (20)	9

V. Drug Interactions

Major drug interactions reported with the direct-acting skeletal muscle relaxants are listed in Table 5. Hyperkalemia and cardiac depression has been reported when dantrolene is coadministered with verapamil. Also, additive central nervous system and respiratory depression may occur when administered concomitantly with other central nervous system depressants.[3-5]

Table 5. Major Drug Interactions with the Direct-Acting Skeletal Muscle Relaxants[2]

Generic Name(s)	Interaction	Mechanism
Dantrolene	Barbiturates, benzodiazepines	Concurrent use may result in additive respiratory depression.
Dantrolene	Calcium Channel Blockers	Concurrent use of dantrolene and calcium channel blockers may result in severe hyperkalemia with cardiovascular collapse.
Dantrolene	Buprenorphine	Concurrent use of buprenorphine and dantrolene may result in increased risk of respiratory and CNS depression.
Dantrolene	Methadone	Concurrent use of dantrolene and methadone may result in

Generic Name(s)	Interaction	Mechanism
		increased risk of respiratory and CNS depression.
Dantrolene	Methotrexate	Concurrent use of dantrolene and methotrexate may result in an increased risk of methotrexate toxicity.

VI. Adverse Drug Events

The most common adverse drug events reported with the direct-acting skeletal muscle relaxants are listed in Table 6. The boxed warning for dantrolene is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Direct-Acting Skeletal Muscle Relaxants[1-5]

Adverse Events	Dantrolene
Cardiovascular	
Erratic blood pressure	✔
Heart Failure	✔
Pericarditis	✔
Phlebitis	✔
Tachycardia	✔
Central Nervous System	
Confusion	✔
Delirium	✔
Depression	✔
Dizziness	✔
Drowsiness	✔
Fatigue	✔
Giddiness	✔
Incoordination	✔
Insomnia	✔
Lightheadedness	✔
Nervousness	✔
Seizure	✔
Somnolence	✔
Vertigo	✔
Dermatological	
Abnormal hair growth	✔
Dermatosis	✔
Photosensitivity	✔
Rash	✔
Sweating	✔
Gastrointestinal	
Abdominal cramp/pain	✔
Anorexia	✔
Constipation	✔
Diarrhea	✔
Drooling	✔
Dysphagia	✔
Gastritis	✔
Gastrointestinal bleed	✔
Nausea	✔
Obstruction	✔
Vomiting	✔
Genitourinary	
Crystalluria	✔
Erectile dysfunction	✔

Adverse Events	Dantrolene
Incontinence	✔
Nocturia	✔
Urinary frequency	✔
Urinary retention	✔
Hematologic	
Aplastic anemia	✔
Leukopenia	✔
Lymphocytic lymphoma	✔
Thrombocytopenia	✔
Hepatic	
Hepatotoxicity	1
Musculoskeletal	
Back ache	✔
Myalgia	✔
Respiratory	
Dyspnea	✔
Respiratory depression	✔
Special Senses	
Diplopia	✔
Dysgeusia	✔
Epiphora	✔
Visual impairment	✔

✔ Percent not specified.

Table 7. Boxed Warning for Dantrolene[1]

WARNING
Dantrolene has a potential for hepatotoxicity; do not use in conditions other than those recommended. Symptomatic hepatitis (fatal and nonfatal) has been reported at various dose levels of the drug. The incidence reported in patients taking up to 400 mg/day is much lower than in those taking doses of 800 mg or more per day. Even sporadic short courses of these higher dose levels within a treatment regimen markedly increased the risk of serious hepatic injury. Liver dysfunction as evidenced by blood chemical abnormalities alone (liver enzyme elevations) has been observed in patients exposed to dantrolene for varying periods of time. Overt hepatitis has occurred at varying intervals after initiation of therapy, but has been most frequently observed between the third and 12th month of therapy. The risk of hepatic injury appears to be greater in females, in patients over 35 years of age, and in patients taking other medication(s) in addition to dantrolene. Use dantrolene only in conjunction with appropriate monitoring of hepatic function including frequent determination of aspartate aminotransferase or alanine transaminase. If no observable benefit is derived from the administration of dantrolene after a total of 45 days, discontinue therapy. Prescribe the lowest possible effective dose for the individual patient.

VII. Dosing and Administration

The usual dosing regimens for the direct-acting skeletal muscle relaxants are listed in Table 8.

Table 8. Usual Dosing Regimens for the Direct-Acting Skeletal Muscle Relaxants[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Dantrolene	Malignant hyperthermia: Capsule: Preoperatively, 4 to 8 mg/kg/day in three or four divided doses for one or two days prior to surgery; post crisis: 4 to 8 mg/kg/day orally in four divided	Malignant hyperthermia: Capsule: Preoperatively, 4 to 8 mg/kg/day in three or four divided doses for one or two days prior to surgery; post crisis, 4 to 8 mg/kg/day orally	Capsule: 25 mg 50 mg 100 mg Injection:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	doses for one to three days Injection: Treatment, 1 mg/kg as a continuous rapid intravenous push; continue until symptoms subside or 10 mg/kg cumulative dose has been reached; preoperatively, 2.5 mg/kg, starting approximately 1 to 1/4 hours before anticipated anesthesia and infused over approximately 1 hour; post crisis, start with 1 mg/kg or more as the clinical situation dictates Spasticity: Capsule: 25 to 100 mg orally three times daily	in four divided doses for one to three days Injection: Treatment, 1 mg/kg as a continuous rapid intravenous push; continue until symptoms subside or 10 mg/kg cumulative dose has been reached; preoperatively: 2.5 mg/kg, starting approximately 1 to 1/4 hours before anticipated anesthesia and infused over approximately 1 hour; post crisis, start with 1 mg/kg or more as the clinical situation dictates Spasticity: Capsule: 0.5 to 2 mg/kg orally three times daily	20 mg 250 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the direct-acting skeletal muscle relaxants are summarized in Table 9. Although skeletal muscle relaxants have been available for many years, there are limited head-to-head trials for the treatment of spasticity. No controlled trials were found in the peer-reviewed literature regarding the use of dantrolene for malignant hyperthermia.

Table 9. Comparative Clinical Trials with the Direct-Acting Skeletal Muscle Relaxants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Haslam et al.[7] (1974) Dantrolene (3 to 12 mg/kg/day) vs placebo	DB, PC, XO Children with spasticity	N=26 2 week treatment phase with 40 day follow-up	Primary: Spasticity grading scale and clinical evaluations Secondary: Not reported	Primary: Improvements in reflexes and scissoring were found with dantrolene compared to placebo (P<0.005 and P<0.05, respectively). There was no significant difference in clonus, muscle tone, spontaneous and passive range of motion with dantrolene compared to placebo. There was no significant difference in physical therapy activities and nursing evaluations with dantrolene compared to placebo. Secondary: Not reported
Joynt et al.[8] (1980) Dantrolene (4 to 12 mg/kg/day) vs placebo	DB, PC, PG, RCT Children 4 to 15 years of age with cerebral palsy	N=21 3 week treatment phase with 42 day follow-up	Primary: Muscle strength, range of motion; muscle tone, reflexes, clonus, spasms, physiologic measurements, activities of daily living, and adverse events Secondary: Not reported	Primary: There was no significant difference in muscle tone, muscle strength, range of motion, reflexes, clonus, spasms, or activities of daily living with dantrolene compared to placebo. Physiologic measurements were significantly improved with dantrolene compared to placebo (P<0.03). There was no significant difference in adverse events with dantrolene compared to placebo by visit three. Secondary: Not reported
Ketel et al.[17] (1984) Dantrolene	Phase 1: OL Phase 2: DB, PC, PG, RCT	Phase 1: N=18 Phase 2: N=14 Phase 3: N=13	Primary: Spasticity grading scale and activities of daily living	Primary: Phase 1: Spasticity was reduced in all 18 patients (no P values provided for measures).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(25 mg every 8 to 12 hours) vs placebo 1st phase: dantrolene 2nd phase: responders only 3rd phase: responders continued on dantrolene	Adults 48 to 78 years of age with stroke	Phase 1: 6 weeks Phase 2: 6 weeks Phase 3: 81 to 978 days	Secondary: Not reported	Phase 2: Improvements in spasticity grading scale were demonstrated with dantrolene compared to placebo (no P values provided). Phase 3: Dantrolene significantly reduced resistance and increased strength compared to placebo (P<.01 and P<.01, respectively). Adverse events occurred in 50% of dantrolene-treated patients compared to 5% of placebo-treated patients. Secondary: Not reported
Katrak et al.[18] (1992) Dantrolene (50 to 200 mg/day) vs placebo	DB, PC, XO Adults 35 to 85 years of age with stroke	N=38 14 weeks	Primary: Muscle tone; motor function scale; isokinetic dynamometric measurements; activities of daily living; adverse events Secondary: Not reported	Primary: There was no significant difference in muscle tone, motor function scale, or activities of daily living with dantrolene compared to placebo. Dantrolene improved of isokinetic measurements to a greater extent than placebo. Lethargy/drowsiness was reported in 45% of dantrolene-treated patients compared to 20% of placebo-treated patients (P=0.03). Slurred speech occurred in 19% of dantrolene-treated patients compared to no patients in the placebo group (P=0.01). Secondary: Not reported

Study abbreviations: DB=double-blind, OL=open label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 10. Relative Cost of the Direct-Acting Skeletal Muscle Relaxants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Dantrolene	capsule, injection	Dantrium®*, Ryanodex®, Revonto®*	$$$$$	$$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Dantrolene is the only direct-acting skeletal muscle relaxant that is currently available. It is approved for the management of spasticity, as well as for the prevention and treatment of malignant hyperthermia.[1-5] Dantrolene is available in a generic formulation.

For the management of multiple sclerosis, guidelines recommend dantrolene if treatment with baclofen or gabapentin is unsuccessful, or if adverse events are intolerable.[13,19] Clinical trials with dantrolene have been of short duration and enrolled small numbers of patients. However, dantrolene has consistently been found to be more effective than placebo.[7-8,17-18] There are limited studies directly comparing dantrolene to other antispasticity agents.[20]

Dantrolene is the treatment of choice for malignant hyperthermia.[16,20] When used, this treatment is emergent in nature and occurs in the inpatient or outpatient operative setting. Use of oral dantrolene for preoperative prophylaxis should be reserved for those patients with documented medical necessity.

Symptomatic hepatitis (fatal and nonfatal) has been reported with dantrolene.[3-5] The risk of hepatic injury appears to be greater in females, in patients >35 years of age, and in patients taking other medications in addition to dantrolene. If no observable benefit is observed after 45 days, treatment should be discontinued.[3-5]

Therefore, all brand direct-acting skeletal muscle relaxants within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand direct-acting skeletal muscle relaxant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of GABA-Derivative Skeletal Muscle Relaxants
AHFS Class 122012
November 9, 2022

I. Overview

Baclofen is the only gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxant that is currently available, and it is approved for the management of spasticity.[1-6] Spasticity can be defined as a velocity-dependent increase in muscle tone. This means that the faster the passive movement of the limb through its range of motion, the greater the increase in muscle tone. Spasticity is associated with a number of central nervous system disorders including stroke, multiple sclerosis, cerebral palsy, as well as brain and spinal cord injuries.[7] Because of the loss of inhibitory controls at the upper motor neuron level (brain or spinal cord); there is permanent ongoing or intermittent involuntary striated muscle contraction. This spasticity can severely limit functioning due to weakness, spasms and loss of dexterity. The goal of therapy is to improve functioning, as well as to alleviate pain and facilitate daily care activities.[8] Baclofen is an analog of GABA and inhibits both monosynaptic and polysynaptic reflexes at the spinal level to cause muscle relaxation.[1-6]

The GABA-derivative skeletal muscle relaxants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Baclofen is available in generic formulations. This class was last reviewed in August 2020.

Table 1. GABA-derivative Skeletal Muscle Relaxants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Baclofen	intrathecal injection*, oral granules, oral solution*, oral suspension, tablet*	Fleqsuvy®, Gablofen®*, Lioresal Intrathecal®, Lyvispah®	baclofen

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the GABA-derivative Skeletal Muscle Relaxants

Clinical Guideline	Recommendation(s)

National Institute for Clinical Excellence: **Low back pain and sciatica in over 16s: assessment and management (2016)**[9]
 	
Reaffirmed Dec 2020
	<u>Pharmacological management of sciatica</u>
	• Do not offer gabapentinoids, other antiepileptics, oral corticosteroids or benzodiazepines for managing sciatica as there is no overall evidence of benefit and there is evidence of harm.
	• Do not offer opioids for managing chronic sciatica.
	• If a person is already taking opioids, gabapentinoids or benzodiazepines for sciatica, explain the risks of continuing these medicines.
	• As part of shared decision making about whether to stop opioids, gabapentinoids or benzodiazepines for sciatica, discuss the problems associated with withdrawal with the person.
	• Be aware of the risk of harms and limited evidence of benefit from the use of non-steroidal anti-inflammatory drugs (NSAIDs) in sciatica.
	• If prescribing NSAIDs for sciatica:
	  ○ take into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age
	  ○ think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment

Clinical Guideline	Recommendation(s)
	○ use the lowest effective dose for the shortest possible period of time. Pharmacological management of low back pain • Consider oral NSAIDs for managing low back pain, taking into account potential differences in gastrointestinal, liver, and cardio-renal toxicity, and the person's risk factors, including age. • When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment. • Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time. • Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated, or has been ineffective. • Do not offer paracetamol alone for managing low back pain. • Do not routinely offer opioids for managing acute low back pain. • Do not offer opioids for managing chronic low back pain. • Do not offer selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, or tricyclic antidepressants for managing low back pain. • Do not offer gabapentinoids or antiepileptics for managing low back pain.
American College of Physicians: **Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline (2017)[10]**	• Given that most patients with acute or subacute low back pain improve over time regardless of treatment, nonpharmacologic treatment with superficial heat, massage, acupuncture, or spinal manipulation should be used. If pharmacologic treatment is desired, select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants. • For patients with chronic low back pain, initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation. • In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients.
American Academy of Neurology/Child Neurology Society: **Practice Parameter: Pharmacologic Treatment of Spasticity in Children and Adolescents with Cerebral Palsy (2010)[11]** Reaffirmed July 2019	• For generalized spasticity that warrants treatment, diazepam should be considered for short-term treatment and tizanidine may be considered. • There are insufficient data to support or refute use of dantrolene, oral baclofen, or continuous intrathecal baclofen.
National Institute for Clinical Excellence: **Multiple sclerosis in adults: management (2014)[12]**	Spasticity • In people with multiple sclerosis (MS) assess and offer treatment for factors that may aggravate spasticity such as constipation, urinary tract or other infections, inappropriately fitted mobility aids, pressure ulcers, posture and pain. • Encourage people with MS to manage their own spasticity symptoms by

Clinical Guideline	Recommendation(s)

Last updated Nov 2019	explaining how doses of drugs can be adjusted within agreed limits.
	• Ensure that the person with MS:
	  ○ has tried the drug at an optimal dose, or the maximum dose they can tolerate
	  ○ stops the drug if there is no benefit at the maximum tolerated dose (but note any special precautions needed when stopping specific drugs)
	  ○ has their drug treatment reviewed at least annually once the optimal dose has been reached.
	• Consider baclofen or gabapentin as a first-line drug to treat spasticity in MS depending on contraindications and the person's comorbidities and preferences. If the person with MS cannot tolerate one of these drugs consider switching to the other.
	• Consider a combination of baclofen and gabapentin for people with MS if:
	  ○ individual drugs do not provide adequate relief or
	  ○ side effects from individual drugs prevent the dose being increased.
	• Consider tizanidine or dantrolene as a second‑line option to treat spasticity in people with MS.
	• Consider benzodiazepines as a third‑line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms.
	• If spasticity cannot be managed with any of the above pharmacological treatments, refer the person to specialist spasticity services.

Department of Veteran Affairs/ Department of Defense Clinical Practice Guideline Working Group: **Management of Stroke Rehabilitation (2019)**[13]	• Diazepam and other benzodiazepines should be avoided during the stroke recovery period because this class of medication may interfere with cerebral functions associated with recovery of function after stroke, and these agents are likely to produce sedation which will compromise an individual's ability to participate effectively in rehabilitation. • Consider use of botulinum toxin, on its own, or in conjunction with oral medication for patients with focal spasticity that is painful, impairs function, reduces the ability to participate in rehabilitation or compromises proper positioning or skin care. • Intrathecal baclofen treatments may be considered for stroke patients with severe chronic lower extremity spasticity that cannot be effectively managed by other interventions.
Department of Veteran Affairs/ Department of Defense Clinical Practice Guideline Working Group: **Clinical Practice Guideline For Diagnosis and Treatment of Low Back Pain (2022)**[14]	Pharmacologic Therapy • For patients with chronic low back pain, duloxetine is suggested. • For patients with low back pain, non-steroidal anti-inflammatory drugs (NSAIDs) are suggested. • For patients with low back pain, with or without radicular symptoms, there is insufficient evidence to recommend for or against gabapentin or pregabalin. • For patients with low back pain, there is insufficient evidence to recommend for or against tricyclic antidepressants. • For patients with low back pain, there is insufficient evidence to recommend for or against topical preparations. • For patients with acute low back pain, there is insufficient evidence to recommend for or against a non-benzodiazepine muscle relaxant for short-term use. • For patients with chronic low back pain, offering a non-benzodiazepine muscle relaxant is not suggested. • For patients with low back pain, acetaminophen is not suggested. • For patients with low back pain, monoclonal antibodies are not suggested. • For patients with chronic low back pain, opioids are not suggested. • For patients with low back pain, with or without radicular symptoms, systemic corticosteroids (oral or intramuscular injection) are not suggested. • For patients with low back pain, benzodiazepines are not recommended.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxants are noted in Table 3.

Table 3. FDA-Approved Indications for the GABA-derivative Skeletal Muscle Relaxants[1-6]

Generic Name(s)	Baclofen
Alleviate signs and symptoms of spasticity resulting from multiple sclerosis	✔ †
Management of severe spasticity	✔ ‡

†Oral formulations.
‡Intrathecal injection.

IV. Pharmacokinetics

The pharmacokinetic parameters of the gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the GABA-derivative Skeletal Muscle Relaxants[1-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Baclofen (oral)	100	30	Liver	Renal (69 to 85)	3 to 7

V. Drug Interactions

There are no significant drug interactions reported with the gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxants.[1] Concurrent use of baclofen with other CNS depressants may result in risk of enhanced CNS depression.[1-3]

VI. Adverse Drug Events

The most common adverse drug events reported with the gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxants are listed in Table 5. The boxed warning for intrathecal baclofen is listed in Table 6.

Table 5. Adverse Drug Events (%) Reported with the GABA-derivative Skeletal Muscle Relaxants[1-6]

Adverse Events	Baclofen
Cardiovascular	
Arrhythmia	✔
Chest pain	✔
Deep vein thrombosis	✔
Dyspnea	✔
Hypotension	0 to 9
Palpitations	✔
Peripheral edema	✔
Syncope	✔
Central Nervous System	
Agitation	✔
Amnesia	✔
Catatonia	✔
Coma	✔
Confusion	1 to 11
Convulsions	1 to 5
Depression	✔
Disorientation	✔

Adverse Events	Baclofen
Dizziness	5 to 15
Drowsiness	10 to 63
Dysarthria	✔
Euphoria	✔
Excitement	✔
Fatigue	2 to 4
Hallucinations	✔
Headache	4 to 8
Impaired cognition	✔
Insomnia	2 to 7
Lethargy	✔
Lightheadedness	✔
Mania	✔
Paranoia	✔
Paresthesia	3 to 7
Psychosis	✔
Seizure	✔
Slurred speech	✔
Somnolence	6 to 21
Suicidal ideation	✔
Weakness	5 to 15
Dermatological	
Diaphoresis	✔
Flushing	✔
Pruritus	✔
Rash	✔
Urticaria	✔
Endocrine and Metabolic	
Elevated glucose	✔
Weight gain	✔
Gastrointestinal	
Abdominal cramp/pain	✔
Anorexia	✔
Bowel incontinence	✔
Constipation	2 to 6
Diarrhea	✔
Ileus	✔
Nausea	4 to 12
Vomiting	4 to 12
Xerostomia	1 to 3
Genitourinary	
Ejaculation dysfunction	✔
Impotence	✔
Urinary frequency	2 to 6
Urinary retention	1 to 2
Hepatic	
Increased aspartate aminotransferase	✔
Increased alanine aminotransferase	✔
Musculoskeletal	
Hypotonia	13 to 25
Muscle rigidity	✔
Muscular weakness	✔
Myalgia	✔
Respiratory	

Adverse Events	Baclofen
Aspiration pneumonia	✔
Bronchospasm	✔
Respiratory depression	✔
Nasal congestion	✔
Special Senses	
Blurred vision	✔
Diplopia	✔
Dysgeusia	✔
Miosis	✔
Mydriasis	✔
Tinnitus	✔
Other	
Accidental injury	1 to 3
Septicemia	✔
Meningitis	✔
Intracranial bleeding	✔
Subdural hemorrhage	✔

✔ Percent not specified.

Table 6. Boxed Warning for Intrathecal Baclofen[1]

WARNING
Abrupt discontinuation of intrathecal baclofen, regardless of the cause, has resulted in sequelae that include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, which in rare cases has advanced to rhabdomyolysis, multiple organ-system failure, and death. Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Advise patients and caregivers of the importance of keeping scheduled refill visits and educate them on the early symptoms of baclofen withdrawal. Give special attention to patients at apparent risk (e.g., spinal cord injuries at T-6 or above, communication difficulties, history of withdrawal symptoms from oral or intrathecal baclofen). Consult the technical manual of the implantable infusion system for additional post-implant clinician and patient information.

VII. Dosing and Administration

The usual dosing regimens for the gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the GABA-derivative Skeletal Muscle Relaxants[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Baclofen	Muscle spasticity: Intrathecal injection: initial screening dose, 50 µg; maintenance (spinal cord injury) dosages have ranged from 12 to 2,003 µg/day, (most patients, 300 to 800 µg/day); maintenance (cerebral origin spasticity) dosages have ranged from 22 to 1,400 µg/day (most patients require 90 to 700 µg/day) Oral: maintenance, 40 to 80 mg per	Muscle spasticity: Intrathecal injection: >4 years of age, 25 to 50 µg initial screening dose; after the first 24 hours, the daily dose should be increased slowly by 5 to 15% only once every 24 hours, until the desired clinical effect is achieved. Oral: safety and efficacy have not been established in	Intrathecal injection: 50 µg/mL 500 µg/mL 1,000 µg/mL 2,000 µg/mL Oral granules: 5 mg 10 mg 20 mg Oral solution:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	day divided in three or four doses	pediatric patients <12 years of age	5 mg/5 mL Oral suspension: 5 mg/mL Tablet: 5 mg 10 mg 20 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxants are summarized in Table 8. Although skeletal muscle relaxants have been available for many years, there are limited head-to-head trials for the treatment of spasticity.

Table 8. Comparative Clinical Trials with the GABA-derivative Skeletal Muscle Relaxants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Musculoskeletal Pain				
Sanders et al.[15] (2009) Baclofen 100 mg and spinal injection of 15 mg of 0.75% hyperbaric bupivacaine vs spinal injection of 15 mg of 0.75% hyperbaric bupivacaine with saline	DB, RCT Adults undergoing total knee arthroplasty	N=60 3 months	Primary: Total opioid consumption during the first 72 hours postoperatively and pain scores (evaluated at three months after the operation) Secondary: Not reported	Primary: The baclofen group used less morphine in the post-anesthesia care unit than the control group (5 vs 9.3 mg; P=0.04). At three months, fewer patients in the baclofen group reported pain than the control group (8/27 vs 19/29; P=0.009). Secondary: Not reported
Friedman et al.[16] (2019) Metaxalone 400 mg vs tizanidine 2 mg vs baclofen 10 mg	DB, PG, RCT Patients 18 to 64 years of age with nonradicular low back pain for ≤2 weeks were eligible if they had a score >5 on the RMDQ who presented to the emergency department (ED)	N=320 1 week	Primary: Improvement on the RMDQ between ED discharge and one week later Secondary: Pain intensity one week after ED discharge (severe, moderate, mild, or none)	Primary: At one-week follow-up, the mean RMDQ score of patients randomized to placebo improved by 11.1 points (95% CI, 9.0 to 13.3), baclofen by 10.6 points (95% CI, 8.6 to 12.7), metaxalone by 10.1 points (95% CI, 8.0 to 12.3), and tizanidine by 11.2 points (95% CI, 9.2 to 13.2). Secondary: At one-week follow-up, 30% of placebo patients (95% CI, 21 to 41%) reported moderate to severe low back pain versus 33% of baclofen patients (95% CI, 24 to 44%), 37% of metaxalone patients (95% CI, 27 to 48%), and 33% of tizanidine patients (95% CI, 23% to 44%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All regimens were to take 1 to 2 capsules 3 times daily as needed. All participants received 21 tablets of ibuprofen 600 mg, to be taken 3 times a day as needed.				
Spasticity				
Brar et al.[17] (1991) Baclofen 20 mg vs placebo	B, PC, XO Patients with multiple sclerosis and minimal to moderate spasticity	N=30 10 weeks	Primary: Muscle tone (Ashworth Scale score); Cybex II isokinetic unit; timed gait; patient questionnaire Secondary: Not reported	Primary: Treatment with baclofen significantly improved moderate quadriceps spasticity compared to placebo. Patients reported subjective improvements in function when treated with baclofen compared to placebo. Secondary: Not reported
Sachais et al.[18] (1977) Baclofen 60 to 80 mg vs placebo	DB, MC, RCT Patients with spasticity secondary to multiple sclerosis	N=106 5 weeks	Primary: Resistance to passive movement, spasms, degree of knee jerks, subjective patient report of spasms, clonus and function Secondary: Not reported	Primary: Baclofen improved symptoms of spasticity, resistance to passive joint movements, and tendon stretch reflexes compared to placebo. Patient self-evaluation showed a significant reduction in clonus. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Feldman et al.[19] (1978) Baclofen up to 80 mg vs placebo	DB, RCT, XO Patients 38 to 53 years of age with multiple sclerosis and any degree of spasticity	N=23 3 years	Primary: Daily spasm count; resistance to passive movement; clonus; Barthel score Secondary: Not reported	Primary: Baclofen significantly reduced frequency of spasms and clonus compared to placebo. Treatment with baclofen enabled patients to maintain functional status for prolonged periods compared to placebo. For more disabled patients, treatment with baclofen gave symptomatic relief of painful spasms and made immobility more tolerable vs placebo. Secondary: Not reported
Gerszten et al.[20] (1997) Baclofen intrathecal infusion	RETRO Patients with spastic cerebral palsy or traumatic brain injury who were ambulatory to some extent, either with or without assistive devices	N=24 52 months	Primary: Ambulation graded on four functional levels (community, household, non-functional, and non-ambulatory) Secondary: Not reported	Primary: Level of ambulation improved by one functional level in nine patients, did not change for 12 patients, and was worse in three patients. Gait was improved in 20 of 24 patients as assess by the patients or families. The overall functional improvement not directly related to ambulation was found to be improved in 20 patients, unchanged in two patients, and worse in two patients. Secondary: Not reported
Gilmartin et al.[21] (2000) Baclofen intrathecal infusion	MC, OL Patients 4 to 41 years of age with spastic cerebral palsy	N=51 39 months	Primary: Spasticity (Ashworth Scale score) Secondary: Not reported	Primary: Clinically significant spasticity relief in the lower extremities was demonstrated by a decrease in the average Ashworth Scale from 3.64 at baseline to 2.33 at six months, 2.15 at 12 months, and 1.90 at 39 months. A decrease in upper-extremity spasticity was demonstrated over the same time period, however not significantly. The average daily dose required to maintain therapeutic effect was titrated from 78 µg at implantation to 402 µg at 39 months. A total of 42 patients experienced adverse events. Most commons

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				adverse events were hypotonia (15%), seizures (no new onset, 9%), somnolence (9%), and nausea (4%) or vomiting (7%). Secondary: Not reported
Van Schaeybroeck et al.[22] (2000) Baclofen intrathecal infusion vs placebo	DB, PC, PRO Patients 8 to 55 years with spasticity of cerebral origin (primarily cerebral palsy)	N=8 2 years	Primary: Spasticity (Ashworth Scale score and visual analogue scale); spasms; pain; functional abilities Secondary: Not reported	Primary: Patients treated with intrathecal baclofen demonstrated a significant benefit compared to placebo Ashworth Scale scores were significantly lower than baseline with intrathecal baclofen compared to placebo. A reduction in visual analog scores was maintained during the intrathecal baclofen continuous infusion (P=0.03). Overall functional improvements were maintained and all patients reported a decrease in pain and better quality of life with intrathecal baclofen compared to placebo. Secondary: Not reported
Hoving et al.[23] (2009) Baclofen intrathecal infusion vs placebo	RCT Children with intractable, spastic cerebral palsy	N=17 6 months	Primary: Changes on visual analogue scale for individually formulated problems and the caregiver assistance scale of the Pediatric Evaluation of Disability Inventory self-care domain Secondary: Not reported	Primary: The visual analogue scale for individual problems improved by 4.0 in the baclofen group compared to 0.2 in the control group (P<0.001). Pediatric Evaluation of Disability Inventory scores did not change significantly among the treatment groups. Secondary: Not reported
Krach et al.[24] (2010)	RETRO	N=708	Primary: Survival	Primary: Survival after eight years was 92% in the baclofen group and 82% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Baclofen intrathecal infusion vs placebo	Adults and children with cerebral palsy	8 years	probabilities Secondary: Not reported	placebo group (P<0.001). After adjustment to account for recent trends in improved survival in cerebral palsy, eight-year survival in the placebo group was 88%, which was not significantly different from the baclofen group (P=0.073). Baclofen therapy does not increase mortality in individuals with cerebral palsy and may suggest an increase in life expectancy. Secondary: Not reported
Creamer et al.[25] (2018) SISTERS Baclofen intrathecal infusion and physiotherapy vs conventional medical management (CMM) with oral antispastic medications (a combination of oral antispastic medication, at least one of oral baclofen, tizanidine, diazepam or other benzodiazepines, or dantrolene; and physiotherapy)	MC, OL, RCT Patients 18 to 75 years of age with severe poststroke spasticity after 6 months active treatment (e.g., physiotherapy, botulinum toxin injection and oral medication)	N=60 6 months	Primary: Change in the average Ashworth Scale score in the lower extremities of the affected body side from baseline to month 6 Secondary: Safety	Primary: Intrathecal baclofen showed a greater improvement in Ashworth Scale score than CMM (mean Ashworth Scale score reduction, −0.99 (intrathecal baclofen) vs −0.43 (CMM); Hodges-Lehmann estimate, −0.667 (95.1% CI, −1.0000 to −0.1667); P=0.0140). Secondary: More patients reported adverse events while receiving intrathecal baclofen (24/25 patients, 96%; 149 events) compared with CMM (22/35, 63%; 77 events), although events were generally consistent with the known safety profile of intrathecal baclofen therapy.
Ordia et al.[26]	OL	N=59	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1996) Baclofen intrathecal infusion	Patients with severe spasticity of spinal cord origin refractory to oral baclofen or who experienced intolerable side effects	Variable duration	Rigidity (Ashworth Scale score) Secondary: Not reported	The mean Ashworth Scale score for rigidity decreased from 4.3 preoperatively to 1.4 (P<0.00005) with intrathecal baclofen. The spasm frequency score decreased from a mean of 3.6 to 0.5 (P<0.0005). Improvements in sleep, skin integrity, pain eradication, and activities of daily living were demonstrated with intrathecal baclofen. Secondary: Not reported
Meythaler et al.[27] (1997) Baclofen intrathecal infusion	OL Patients 17 to 39 with acquired brain injury, severe, progressive spasticity, and dystonia refractory to maximal medical therapy, which interfered with activities of daily living	N=11 3 months	Primary: Muscle tone (Ashworth Scale score) Secondary: Not reported	Primary: Lower-extremity Ashworth Scale scores decreased from 3.5 points before treatment to 2.2 points after three months of treatment (P<0.0001). The average lower-extremity spasm frequency scores decreased from 1.8 points before treatment to 0.2 points after three months of treatment (P<0.0001). The average upper-extremity Ashworth Scale scores decreased from 3.3 points before treatment to 1.9 points after three months of treatment (P=0.0033). The average upper extremity spasm score decreased from 1.8 points before treatment to 0.6 points after three months of treatment (P=0.0070). The biceps reflex score decreased from 2.7 points to 1.7 points after three months of treatment (P=0.0111). Significant reductions in joint contractures were noted in seven patients, and in five others there have been functional improvements in gait and transfers. Secondary: Not reported
Ward et al.[28] (2009) Baclofen	PRO Children with spasticity and/or	N=25 6 months	Primary: Attainment of individual goals measured with the	Primary: A clinically relevant and statistically significant increase in both the satisfaction and performance domains of the Canadian Occupational Performance Measure was demonstrated six months after the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
intrathecal infusion	dystonia		Canadian Occupational Performance Measure and goal attainment scaling Secondary: Modified Ashworth Scale for tone assessment of the lower limbs, Barry–Albright Dystonia scale for dystonia and the Health Utilities Index Mark (III) for health-related quality of life	implantation of the baclofen pump (P<0.001). The mean goal attainment scaling T-score was significantly higher at six months post implant (P<0.001). Seventy percent of the subjects achieved their goals at six months. Secondary: The Modified Ashworth Scale results showed significant reduction in muscle tone post-implant. The median score changed from 2.28 to 1.43 (P<0.05). The Barry–Albright Dystonia Score showed a reduction from an average of 28.67 to 15.75, much greater than the 25% improvement considered to be significant for this measurement tool. The Health Utilities Index Mark (III) did not show a statistically significant change post-implant; however, the results were slightly improved.
Brochard et al.[29] (2009) Baclofen intrathecal infusion	RETRO Children (mean age 15 years) with cerebral palsy who were able to walk with or without an assist device during physiotherapy sessions	N=7 16 months	Primary: Ashworth scale score, range of motion (hip, knee, ankle), Gillette functional assessment questionnaire, joint kinematics, spatiotemporal parameters and Gillette Gait Index Secondary: Not reported	Primary: The global Ashworth score reduced after baclofen from 3.04 points to 1.89 points (P<0.05). Spasticity of rectus femoris and adductor magnus decreased more (1.86 and 1.28 points, respectively) than hamstrings and triceps surae (0.71 and 0.85 points, respectively). The only significant difference in joint angle measurements was increased rectus femoris range from 101.43 to 118.57 (P=0.02). Gillette functional assessment questionnaire significantly improved from 6.1 to 7.1 (P=0.02). Mean gait speed, cadence, step time and stance phase duration did not change significantly. Mean step length significantly improved from 0.65m to 0.74m (P<0.05). After baclofen, there was a decrease in minimum hip flexion angle during stance phase from 19.82° to 8.30° (P<0.01) and a decrease in hip flexion angle at terminal stance from 32.25° to 21.58° (P=0.01). There was no significant difference in knee flexion angle at initial contact

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.08), maximal knee flexion angle during swing phase (P=0.055), maximal ankle dorsiflexion in stance phase (P=0.09), or coronal and frontal plane. Mean Gillette Gait Index improved from 554.50 to 489.25 (P=NS). Secondary: Not reported
Horn et al.[30] (2010) Baclofen intrathecal infusion	RETRO Adults with muscle hypertonia due to stroke, trauma, or anoxia	N=28 6 hours	Primary: Ashworth score, self-selected gait speed, and sagittal plane range of motions in hip, knee, and ankle joints Secondary: Not reported	Primary: A significant decrease in the mean Ashworth score on the more involved side (2.0 to 1.3) and an increase in gait speed (41 to 47cm/s) were noted at different intervals after baclofen. Ankle range of motion significantly increased on the more involved (13° to 15°; P<0.01) and less involved (22° to 24°; P<0.05) sides. Range of motion symmetry increased at the knee and ankle joints from 55 to 60% and from 59 to 63% on average, respectively, but decreased from 72 to 69% at the hip. Range of motion significantly improved, significantly worsened, or showed no significant change in 42, 34, and 24% of individual joints, respectively. Peak changes in range of motion tended to be statistically significant more often in the ankle (93%) than either the hip (75%) or the knee (75%) joint on the less involved side (P=0.06). Significant range of motion improvement, in comparison with significant range of motion worsening, also tended to be more frequent in the ankle (66%) than in the hip joint (48%) across the two sides combined (P=0.08). Range of motion worsening occurred more frequently at two hours after baclofen (60%), whereas range of motion improvement was more often seen later (65% at four hours and 60% at six hours; P<0.05). Secondary: Not reported
Brochard et al.[31] (2009)	RETRO	N=21	Primary: Ashworth Scale	Primary: The mean Ashworth score decreased by 1.4 points (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Baclofen intrathecal infusion	Ambulant children with cerebral palsy	5 to 75 months	score, Gillette Functional Assessment Questionnaire score, use of walking aids, and joint angle at which the stretch reflex was triggered Secondary: Not reported	The Gillette Functional Assessment Questionnaire score increased from 5.04 to 6.09 (P=0.0054). None of the four children who did not use a walking aid before intrathecal baclofen infusion required one after treatment. Seven children were able to use less supportive walking aids. After treatment, none of the children required walking aids that provided more support than those they previously used. Secondary: Not reported
Margetis et al.[32] (2014) Baclofen intrathecal infusion	OL, PRO Patients diagnosed with hereditary spastic paraplegia	N=14 Average follow-up of 25.8 months	Primary: Ashworth Scale score, Gillette Functional Assessment Questionnaire score Secondary: Not reported	Primary: All patients experienced a reduction in lower limbs' spasticity measured in the modified Ashworth scale from 2.6 (±0.8) to 0.7 (±0.9) (P=0.000). Walking ability was improved in the modified Gillette functional walking scale from 5.9 (±1.7) to 7.4 (±2.0) (P=0.001). The mean baclofen dose was 90 µg/24 hours and usually required a long titration period. There was no correlation in the spasticity and gait improvement with either the patient age or the baclofen dose. Secondary: Not reported
Kraus et al.[33] (2017) Baclofen intrathecal infusion	OBS, PRO Children with severe spastic cerebral palsy	N=13 60 months	Primary: Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD™) questionnaire, KINDL^{R} questionnaire (assesses quality of life in children), Modified Ashworth Scale score	Primary: The CPCHILD overall score significantly improved from a mean of 60 to a mean of 40 points (P<0.01). The KINDL overall score improved when comparing pre- and post-treatment values. Mean value before pump implantation was 69.87 points (range 33.3 to 87.5, SD 21.8) and mean value at follow-up was 77.5 points (range 68.8 to 100, SD 12.9). Although there was no statistical significance (P=0.448) in the overall score, three of the six dimensions (physical and mental wellbeing, self-esteem) improved significantly. Modified Ashworth Scale score decreased from a mean of 3.8 to 1.7 (P=0.03). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	
Loubser et al.[34] (1991) Stage 1: Baclofen intrathecal infusion Stage 2: Permanent programmable baclofen infusion pump	PC, PRO Patients with spinal cord injuries whose spasticity had been refractory to oral medications	Stage 1: N=9 5 days Stage 2: N=7 3 to 22 months	Primary: Ashworth Scale score and reflex scores; functional abilities; somatosensory and brainstem auditory evoked potentials Secondary: Not reported	Primary: <u>Stage 1</u> Mean Ashworth scale score decreased from 3.78 to 1.16 (P<0.001) and the mean reflex score decreased from 3.57 to 0.64 (P<0.001) with intrathecal baclofen. These values differed significantly from those with placebo (Ashworth scale score, -2.54; P<0.001, reflex score, -2.56; P<0.01). Objective improvements in functional abilities and independence were noted in eight patients. Somatosensory and brainstem auditory evoked potentials were unchanged with both treatment groups. Urodynamic evaluation revealed increased bladder capacity in three patients, while in four no change was observed. <u>Stage 2</u> Mean Ashworth scale score decreased from 3.79 to 2.00 (P<0.001) and mean reflex score decreased from 3.85 to 2.18 (P<0.001). Secondary: Not reported
Bresolin et al.[35] (2009) Baclofen 60 mg/day vs eperisone 300 mg/day	DB, RCT Adults with moderate to severe spastic palsy	N=80 6 weeks	Primary: Functional analysis (Pedersen's scale, muscular tone, joint range of motion, 10-meter walking time); physiological and pathological reflexes; and electromyography (Hmax/Mmax amplitude ratio and	Primary: Both eperisone and baclofen significantly improved functionality of lower limbs vs baseline (eperisone, –9.1%; P<0.01, baclofen, –8.3%; P<0.05), but only eperisone improved this parameter in the upper limbs (–7.8%; P<0.01 vs –6.3%; P=NS). Both drugs reduced muscular tone from week two. Only eperisone improved the joint range of motion (–32.5%; P<0.01 vs –14.6%; P=NS). Both treatments reduced the 10-meter walking time (eperisone, –20.2%; P<0.01, baclofen, –24.0%; P<0.01); this effect was evident at week two with eperisone only.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			the Wartenberg test) Secondary: Not reported	Both drugs improved reflexes. Eperisone and baclofen decreased the Hmax/Mmax amplitude ratio (eperisone, –30.0%; baclofen, –18.6%; P<0.01 for both). Secondary: Not reported
Bass et al.[36] (1988) Tizanidine up to 32 mg vs baclofen up to 80 mg	DB, RCT, XO Patients with multiple sclerosis	N=66 11 weeks	Primary: Muscle tone and power; EDSS score; Pedersen functional disability scale; reflexes; clonus; overall evaluations of efficacy and tolerability Secondary: Not reported	Primary: Physicians and physiotherapists found baclofen to be more effective than tizanidine (P<0.05). There was no significant difference between the baclofen and tizanidine treatment groups based on patient perception of efficacy. There were no significant differences in EDSS or muscle tone measures between the baclofen treatment group and the tizanidine treatment group. Secondary: Not reported
Eysette et al.[37] (1988) Tizanidine up to 24 mg vs baclofen up to 60 mg	DB, MC, RCT Patients 18 to 70 years of age suffering from chronic spasticity due to multiple sclerosis	N=100 8 weeks	Primary: Locomotor function; condition in bed and chair; spasms; tonic stretch reflex; clonus; power; bladder control Secondary: Not reported	Primary: Tizanidine and baclofen improved functional status of 80 and 76% of patients, respectively (P=NS). No significant differences were noted in spasms, tonic stretch reflex, clonus, power, or bladder control. Secondary: Not reported
Smolenski et al.[38] (1981) Tizanidine up to 36 mg vs	DB, PG, RCT Hospitalized patients 42 to 73 years of age with multiple sclerosis	N=21 6 weeks	Primary: Muscle tone (Ashworth scale); EDSS score, spasm score, muscle power, global impression, side effects	Primary: There was no significant difference in spastic state, spasms and clonus in baclofen-treated patients compared to tizanidine-treated patients. Muscle strength, bladder function and activities of daily living were improved more with tizanidine than baclofen. Tiredness was the most frequent side effect on tizanidine and muscle

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
baclofen up to 80 mg			Secondary: Not reported	weakness on baclofen. Secondary: Not reported
Stien et al.[39] (1987) Tizanidine up to 36 mg vs baclofen up to 90 mg	DB, RCT Seriously handicapped patients with multiple sclerosis	N=40 6 weeks	Primary: Muscle tone (Ashworth Scale); EDSS; Pedersen rating scales; overall impression Secondary: Not reported	Primary: There was no significant difference in spastic state, spasms and clonus in baclofen-treated patients compared to tizanidine-treated patients. Secondary: Not reported
Dai et al.[40] (2008) Tizanidine 0.3 to 0.5 mg/kg/day in 4 divided doses and botulinum type A 20 to 24 units/kg vs baclofen 10 to 15 mg/kg/day in 3 divided doses and botulinum type A 20 to 24 units/kg	RETRO Children 2 to 14 years of age with cerebral palsy and spastic equines foot deformity	N=30 12 weeks	Primary: Mean scores of Gross Motor Functional Measurement, Caregiver Questionnaire form, and the modified Ashworth scale for leg functional measurement and for leg spasticity assessment by a pediatric neurologist Secondary: Not reported	Primary: The mean Gross Motor Functional Measurement (76.63 vs 68.17; P<0.001) and Caregiver Questionnaire form scores (70.23 vs 66.59; P=0.03) for the tizanidine group were significantly higher as compared to the baclofen group. This study suggests that the combination of botulinum toxin type A with oral tizanidine is more effective than the combination of botulinum toxin type A and oral baclofen for spastic cerebral palsy. However, details about the frequency and types of side effects in the study were lacking. Secondary: Not reported

Study abbreviations: B=blinded, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=crossover
Miscellaneous abbreviations: EDSS=Expanded Disability Status Scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the GABA-derivative Skeletal Muscle Relaxants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Baclofen	intrathecal injection*, oral granules, oral solution*, oral suspension, tablet*	Fleqsuvy®, Gablofen®*, Lioresal Intrathecal®, Lyvispah®	$$$$$	$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Baclofen is the only gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxant that is currently available, and it is approved for the management of spasticity.[1-6] Baclofen is available in generic formulations.

For the management of multiple sclerosis, guidelines recommend initial treatment with baclofen or gabapentin for bothersome regional or global spasticity or spasms.[12] In clinical trials, baclofen has been shown to be an effective treatment option for muscular spasms due to multiple sclerosis, cerebral palsy and brain/spinal cord injuries.[15-40] It has consistently been found to be more effective than placebo; however, there are relatively few studies that directly compare baclofen to other antispasticity agents.[34-39]

Adverse events are problematic with skeletal muscle relaxants, with drowsiness and dizziness being common with all of the agents. Abrupt withdrawal of oral baclofen can lead to hallucinations and seizures. Serious sequelae (e.g., high fever, altered mental status, exaggerated rebound spasticity and muscle rigidity) may occur if intrathecal baclofen is abruptly discontinued.[1-6]

There is insufficient evidence to support that one brand GABA-derivative skeletal muscle relaxant is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand GABA-derivative skeletal muscle relaxants within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand gamma aminobutyric acid (GABA)-derivative skeletal muscle relaxant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skeletal Muscle Relaxants, Miscellaneous
AHFS Class 122092
November 9, 2022

I. Overview

Orphenadrine and orphenadrine-aspirin-caffeine combination tablet are the only miscellaneous skeletal muscle relaxants currently available, and they are approved for the symptomatic relief of pain associated with acute musculoskeletal disorders.[1-3] Orphenadrine is an indirect skeletal muscle relaxant with central atropine-like effects. Although the exact mechanism of action has not been fully established, it may exert a beneficial effect due to its analgesic properties; orphenadrine does not directly relax tense skeletal muscles.[1-3]

The miscellaneous skeletal muscle relaxants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Orphenadrine is available in a generic formulation. This class was last reviewed in August 2020.

Table 1. Skeletal Muscle Relaxants, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Orphenadrine	injection, extended-release tablet	N/A	orphenadrine
Orphenadrine, aspirin, and caffeine	tablet	Norgesic Forte®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous skeletal muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skeletal Muscle Relaxants, Miscellaneous

Clinical Guideline	Recommendation(s)
National Institute for Clinical Excellence: **Low back pain and sciatica in over 16s: assessment and management (2016)**[4] Reaffirmed Dec 2020	Pharmacological management of sciatica • Do not offer gabapentinoids, other antiepileptics, oral corticosteroids or benzodiazepines for managing sciatica as there is no overall evidence of benefit and there is evidence of harm. • Do not offer opioids for managing chronic sciatica. • If a person is already taking opioids, gabapentinoids or benzodiazepines for sciatica, explain the risks of continuing these medicines. • As part of shared decision making about whether to stop opioids, gabapentinoids or benzodiazepines for sciatica, discuss the problems associated with withdrawal with the person. • Be aware of the risk of harms and limited evidence of benefit from the use of non-steroidal anti-inflammatory drugs (NSAIDs) in sciatica. • If prescribing NSAIDs for sciatica: o take into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age o think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment o use the lowest effective dose for the shortest possible period of time. Pharmacological management of low back pain

Clinical Guideline	Recommendation(s)
	• Consider oral NSAIDs for managing low back pain, taking into account potential differences in gastrointestinal, liver, and cardio-renal toxicity, and the person's risk factors, including age. • When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment. • Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time. • Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated, or has been ineffective. • Do not offer paracetamol alone for managing low back pain. • Do not routinely offer opioids for managing acute low back pain. • Do not offer opioids for managing chronic low back pain. • Do not offer selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, or tricyclic antidepressants for managing low back pain. • Do not offer gabapentinoids or antiepileptics for managing low back pain.
American College of Physicians: **Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline (2017)**[5]	• Given that most patients with acute or subacute low back pain improve over time regardless of treatment, nonpharmacologic treatment with superficial heat, massage, acupuncture, or spinal manipulation should be used. If pharmacologic treatment is desired, select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants. • For patients with chronic low back pain, initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation. • In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients.
Department of Veteran Affairs/ Department of Defense Clinical Practice Guideline Working Group: **Clinical Practice Guideline For Diagnosis and Treatment of Low Back Pain (2022)**[6]	Pharmacologic Therapy • For patients with chronic low back pain, duloxetine is suggested. • For patients with low back pain, non-steroidal anti-inflammatory drugs (NSAIDs) are suggested. • For patients with low back pain, with or without radicular symptoms, there is insufficient evidence to recommend for or against gabapentin or pregabalin. • For patients with low back pain, there is insufficient evidence to recommend for or against tricyclic antidepressants. • For patients with low back pain, there is insufficient evidence to recommend for or against topical preparations. • For patients with acute low back pain, there is insufficient evidence to recommend for or against a non-benzodiazepine muscle relaxant for short-term use. • For patients with chronic low back pain, offering a non-benzodiazepine muscle relaxant is not suggested. • For patients with low back pain, acetaminophen is not suggested. • For patients with low back pain, monoclonal antibodies are not suggested. • For patients with chronic low back pain, opioids are not suggested. • For patients with low back pain, with or without radicular symptoms, systemic corticosteroids (oral or intramuscular injection) are not suggested. • For patients with low back pain, benzodiazepines are not recommended.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous skeletal muscle relaxants are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skeletal Muscle Relaxants, Miscellaneous[1-3]

Indication	Orphenadrine	Orphenadrine, aspirin, and caffeine
Adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute painful musculoskeletal conditions	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous skeletal muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skeletal Muscle Relaxants, Miscellaneous[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Orphenadrine	95	Not reported	Liver	Renal (60)	13 to 20

V. Drug Interactions

Major drug interactions with the miscellaneous skeletal muscle relaxants are listed in Table 5.

Table 5. Major Drug Interactions with the Skeletal Muscle Relaxants, Miscellaneous[2]

Generic Name(s)	Interaction	Mechanism
Orphenadrine	Opiate agonists	Concurrent use may result in increased risk of paralytic ileus; increased risk of respiratory and CNS depression.
Orphenadrine	Buprenorphine	Concurrent use may result in increased CNS depression.
Orphenadrine	Sodium oxybate	Concurrent use may result in increased CNS depression.
Orphenadrine	Zolpidem	Concurrent use may result in increased CNS depression.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous skeletal muscle relaxants are listed in Table 6. Orphenadrine has been chronically abused for its euphoric effects, and the mood elevating effects may occur at therapeutic doses.[1-3] Adverse events associated with orphenadrine-aspirin-caffeine are those seen with aspirin and caffeine or those usually associated with mild anticholinergic agents, including orphenadrine, as listed below.[3]

Table 6. Adverse Drug Events (%) Reported with the Skeletal Muscle Relaxants, Miscellaneous[1-3]

Adverse Events	Orphenadrine
Cardiovascular	
Palpitations	✔
Tachycardia	✔
Central Nervous System	
Agitation	✔
Confusion	✔

Adverse Events	Orphenadrine
Dizziness	✔
Drowsiness	✔
Dyskinesia	✔
Euphoria	✔
Hallucinations	✔
Headache	-
Light-headedness	✔
Syncope	✔
Tremor	✔
Weakness	-
Dermatological	
Flushing	✔
Pruritus	✔
Urticaria	✔
Endocrine and Metabolic	
Hypoglycemia	✔
Gastrointestinal	
Abdominal distension	✔
Constipation	✔
Fecal impaction	✔
Gastrointestinal hemorrhage	-
Nausea	✔
Obstruction	✔
Vomiting	✔
Xerostomia	✔
Genitourinary	
Urinary hesitancy	✔
Urinary retention	✔
Hematologic	
Aplastic anemia	✔
Musculoskeletal	
Myasthenia gravis	✔
Special Senses	
Blurred vision	✔
Mydriasis	✔
Increased ocular tension	✔

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous skeletal muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Skeletal Muscle Relaxants, Miscellaneous[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Orphenadrine	Painful musculoskeletal disorders: Injection: 60 mg which may be repeated every 12 hours; oral form should be used for maintenance Tablet (ER): 100 mg twice daily	Safety and efficacy in children have not been established.	Injection: 30 mg/mL Tablet (ER): 100 mg

Orphenadrine, aspirin, and caffeine	Painful musculoskeletal disorders: Tablet: One-half to one tablet three to four times daily	Safety and efficacy in children have not been established.	Tablet: 50-770-60 mg

ER=extended-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous skeletal muscle relaxants are summarized in Table 8. Although skeletal muscle relaxants have been available for many years, there are limited head-to-head trials in the treatment of musculoskeletal disorders.

Table 8. Comparative Clinical Trials with the Skeletal Muscle Relaxants, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gold et al.[7] (1978) Orphenadrine 100 mg BID vs phenobarbital 32 mg BID vs placebo	DB, PC, RCT Patients with acute LBP and muscle spasms and limited work/daily activities	N=60 7 days	Primary: Reduced pain at two days; overall improvement at two days Secondary: Not reported	Primary: <u>Reduced pain at two days:</u> Orphenadrine (9/20); phenobarbital (3/20); placebo (4/20). Orphenadrine was significantly better than phenobarbital and placebo. <u>Overall improvement at two days:</u> Orphenadrine (7/20); phenobarbital (3/20); placebo (0/20). Orphenadrine was significantly better than placebo. Secondary: Not reported
Klinger et al.[8] (1988) Orphenadrine IV 60 mg vs placebo	DB, PC, RCT Patients 14 to 62 years of age with acute LBP and muscle spasms	N=80 Single dose study	Primary: Number of patients with self-assessment of pain as none, slight, moderate, or severe (45 minutes after injection); physician's assessment of spasm; global improvement Secondary: Not reported	Primary: <u>Self-assessment of pain (none, slight, moderate, or severe):</u> Orphenadrine was more effective at relieving pain (5, 30, 5, 0) according to patient self-assessment compared to placebo (0, 4, 31, 5). According to the physician's assessment of spasm, 95% of orphenadrine-treated patients were better after a single injection compared to 10% of placebo-treated patients (orphenadrine significantly better than placebo). 92% of orphenadrine-treated patients experienced global improvement compared to 12% of placebo-treated patients (orphenadrine significantly better than placebo). Secondary: Not reported
Tervo et al.[9] (1976)	DB, PC, RCT	N=25	Primary: Mean duration of	Primary: Treatment with orphenadrine significantly reduced the mean duration of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Orphenadrine 60 mg IM followed by orphenadrine 35 mg and acetaminophen (450 mg) 2 tablets TID vs saline IM followed by paracetamol (450 mg) 2 tablets TID	Patients with acute LBP	7 days	disability; subjective impressions of the treatments Secondary: Objective clinical examinations (gait, sitting posture, scoliosis, spinal flexion, muscle spasm, Lasegue)	disability by 8.6 days compared to 12.9 days with placebo. There was no significant differences between orphenadrine and acetaminophen treated patients and acetaminophen alone patients with regards to subjective impressions of the treatments. Secondary: There was no significant difference in the objective clinical examinations between the two treatment groups (gait, sitting posture, scoliosis, spinal flexion, muscle spasm, Lasegue).
Hoivik et al.[10] (1983) Orphenadrine 35 mg and acetaminophen (450 mg) 1 tablet TID vs placebo	DB, PC, PG, RCT Patients suffering from pain due to tension of the cervical and upper thoracic musculature	N=44 7 days	Primary: Pain using visual analogue scale Secondary: Not reported	Primary: Orphenadrine and acetaminophen significantly relieved pain compared to placebo. The combination of orphenadrine and acetaminophen produced significant pain relief by the second day of treatment compared to placebo. Secondary: Not reported
Friedman et al.[11] (2018) Orphenadrine 100 mg vs methocarbamol 750 mg	DB, PG, RCT Patients 18 to 69 years of age with nonradicular low back pain for ≤2 weeks were eligible if they had a score >5 on the RMDQ who presented to	N=240 1 week	Primary: Improvement on the RMDQ between ED discharge and one week later Secondary: Pain intensity one week after ED	Primary: One week after the ED visit, patients randomized to placebo improved by a mean of 10.9 (95% CI, 8.9 to 12.9) RMDQ points while orphenadrine patients improved by 9.4 (95% CI, 7.4 to 11.5) and methocarbamol patients improved by 8.1 (95% CI, 6.1 to 10.1). The difference between orphenadrine and placebo was 1.5 RMDQ points (95% CI, −1.4 to 4.3) while the difference placebo and methocarbamol was 2.8 (95% CI, 0 to 5.7). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All regimens were to take 1 to 2 tablets 3 times daily as needed. All participants received 14 tablets of naproxen 500 mg, to be taken twice a day as needed.	the emergency department (ED)		discharge (severe, moderate, mild, or none)	At one-week follow-up, 34% of placebo patients reported moderate to severe low back pain versus 33% of orphenadrine patients, and 39% of methocarbamol patients. Secondary outcomes were similar among the groups.

Drug regimen abbreviations: BID=twice daily, TID=three times daily, IV=intravenous, IM=intramuscular
Study abbreviations: DB=double-blind, LBP=low back pain, OL=open-label, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial, RMDQ= Roland-Morris Disability Questionnaire

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the Skeletal Muscle Relaxants, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Orphenadrine	injection, extended-release tablet	N/A	N/A	$
Orphenadrine, aspirin, and caffeine	tablet	Norgesic Forte®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

Orphenadrine and orphenadrine-aspirin-caffeine combination tablet are the only miscellaneous skeletal muscle relaxants currently available, and they are approved for the symptomatic relief of pain associated with acute musculoskeletal disorders.[1-3] Orphenadrine is available in a generic formulation.

Guidelines on the treatment of low back pain recommend acetaminophen or nonsteroidal anti-inflammatory drugs as first-line therapy.[4-6] Skeletal muscle relaxants are considered a second-line treatment option in select cases of moderate to severe acute low back pain. They are also considered a second- or third-line option for acute exacerbations of chronic low back pain, acute radicular pain syndromes, and acute post-surgical situations. They are not recommended for mild to moderate acute low back pain or for chronic use in subacute or chronic low back pain (other than acute exacerbations).[6] Clinical trials have demonstrated that orphenadrine is an effective treatment option for musculoskeletal disorders.[1-3,7-11]

Adverse events are problematic with skeletal muscle relaxants, with drowsiness and dizziness being common with all of the agents. Orphenadrine has been chronically abused for its euphoric effects, and the mood elevating effects may occur at therapeutic doses.[1-3]

Therefore, all brand miscellaneous skeletal muscle relaxants within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous skeletal muscle relaxant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Opiate Agonists
AHFS Class 280808
November 9, 2022

I. Overview

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of damage." Chronic pain is further defined as "pain which persists past the normal time of healing," generally lasting ≥3 months.[1] Pain is a subjective experience that is unique to the individual.[2] There are numerous etiologies of pain, and successful pain management can be difficult to achieve.

Opioids exert their effect by binding to receptors are widely distributed within the brain, spinal cord, and gastrointestinal tract. Binding and activation of the mu opioid receptor produces a variety of pharmacologic effects, including analgesia, euphoria, dysphoria, respiratory depression, somnolence, decreased gastrointestinal motility, histamine release, and physical dependence.[3] In addition to binding to the mu receptor, tapentadol inhibits norepinephrine reuptake, while tramadol inhibits both norepinephrine and serotonin reuptake.[4-6] The opiate agonists have no ceiling to their analgesic effect; the degree of analgesia is only limited by dose-related adverse events.[4-7] They are available in a variety of dosage forms as single entity agents, as well as in combination with acetaminophen, aspirin, butalbital, caffeine, and ibuprofen. Acetaminophen, aspirin, and ibuprofen are non-opiate analgesics. Butalbital is a barbiturate, which has anxiolytic and muscle relaxant properties. Caffeine is an analgesic adjuvant, as well as a central nervous system stimulant.[4-6] Apadaz® (benzhydrocodone/acetaminophen) is indicated for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Benzhydrocodone is a prodrug of hydrocodone and benzoic acid and is rapidly converted into hydrocodone and benzoic acid after oral administration.[6]

Opioid abuse, misuse, dependence, and overdose are significant health problems in the United States.[8,9] In response to this growing issue, many organizations have released strategies for mitigating prescription drug abuse, with the Food and Drug Administration (FDA), Centers for Medicare and Medicaid Services (CMS), and Centers for Disease Control and Prevention (CDC) all addressing opioid use in recent communications.[8-10]

The FDA has developed an action plan to take steps toward reducing the impact of opioid abuse on American families and communities. These actions include expanding the use of advisory committees, developing warnings and safety information for labeling of immediate-release (IR) opioids, strengthening postmarket requirements, updating the scope of the existing Risk Evaluation and Mitigation Strategy (REMS) program, expanding access to abuse-deterrent formulations to discourage abuse, supporting improved overdose and pain treatments, and reassessing the risk-benefit approval framework for opioid use.[8] Class-wide labeling changes for all extended-release and long-acting (ER/LA) opioid analgesics occurred in April 2014, addressing the risks of misuse, abuse, hyperalgesia, addiction, overdose, death, and neonatal opioid withdrawal syndrome.[11] On March 22, 2016 the FDA announced required class-wide safety labeling changes for IR opioid pain medications. Among the changes, the FDA requires a new boxed warning about the serious risks of misuse and abuse, which can lead to addiction, overdose, and death.[12]

In January 2016, CMS released an informational bulletin addressing prescription opioid overdoses, misuse, and addiction. The purpose of the bulletin was to highlight strategies for preventing opioid-related harms.[9] CMS emphasizes that methadone accounts for a disproportionate share of opioid-related overdoses and deaths, and encourages states to consider additional steps to reduce the use of methadone prescribed for pain relief. The pharmacokinetic and pharmacodynamic parameters of methadone make it a complex medication to prescribe for pain relief.[9] Of note, its elimination half-life is longer than its duration of analgesic action, there is high interpatient variability in absorption, metabolism, and relative analgesic potency, it is retained in the liver with repeat dosing, and it has a narrow therapeutic index.[13,14] CMS recommends removing methadone from preferred drug lists and limiting its use only to patients for whom treatment with other pain medications is ineffective.[9]

On March 18, 2016 the CDC published guidelines for prescribing opioids for chronic pain. This guideline provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and/or end-of-life care.[10] This guideline states that nonpharmacologic and nonopioid pharmacologic therapies are preferred for chronic pain. When opioid therapy is initiated for chronic pain, IR opioids should be used before ER/LA agents. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received IR opioids daily for at least a one-week duration. The guideline states that methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for chronic pain. Methadone should not be the first choice for an ER/LA opioid.[10]

In May 2010, the FDA notified healthcare providers about an increased risk of suicide with tramadol. Deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other central nervous system-active drugs.[15] An additional safety communication regarding the risks of using tramadol in children aged 17 years and younger was released in September 2015.[16] In 2017, the FDA announced labeling changes to tramadol-including products which include a contraindication to treating pain in children under 12 years of age, a contraindication to use in children under 18 years of age to treat pain after surgery to remove the tonsils and/or adenoids, a warning against use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, and a warning to restrict use in mothers who are breastfeeding.[17] In January 2018, the FDA announced that they are requiring safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18. They are also requiring the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the Boxed Warning of the drug labels for prescription cough and cold medicines containing codeine or hydrocodone.[18] An FDA Drug Safety Communication was also released on April 2019 regarding harm reported from sudden discontinuation of opioid pain medicines and requiring label changes to guide prescribers on gradual, individualized tapering.[19]

The opiate agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation, with the exception of tapentadol and tramadol-celecoxib. This class was last reviewed in August 2020. The sustained-release opiate agonists, with the exception of fentanyl transdermal patch, morphine sustained-release, tapentadol extended-release, and tramadol extended-release, are not included in this review; the remaining sustained-release agents are included in the Alabama Medicaid Prior Authorization Program, which is outside of the Preferred Drug Program.

Table 1. Opiate Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Alfentanil	injection^	N/A	alfentanil
Codeine	tablet	N/A	codeine
Fentanyl	buccal lozenge, buccal tablet, injection, transdermal patch	Actiq®*, Fentora®*	fentanyl
Hydromorphone	injection, liquid, rectal suppository, tablet	Dilaudid®*	hydromorphone
Levorphanol	tablet	N/A	levorphanol
Meperidine	injection, solution, tablet	Demerol®*	meperidine
Methadone	injection, oral concentrate, solution, tablet	Methadose®*	methadone
Morphine	epidural, injection, rectal suppository, solution, tablet	Duramorph®, Infumorph®	morphine
Oliceridine	injection^	Olinvyk®	none
Oxycodone	capsule, oral concentrate, solution, tablet	Oxaydo®, Roxicodone®*	oxycodone
Oxymorphone	tablet	N/A	oxymorphone

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Remifentanil	injection^	Ultiva®*	none
Sufentanil	injection^, sublingual tablet applicator^	Dsuvia®	sufentanil
Tapentadol	extended-release tablet, tablet	Nucynta®, Nucynta ER®	none
Tramadol	extended-release capsule, extended-release tablet, tablet	Conzip ER®*, Ultram®*	tramadol
Combination Products			
Benzhydrocodone and acetaminophen	tablet	Apadaz®*	benzhydrocodone and acetaminophen
Codeine and acetaminophen	solution, tablet	N/A	codeine and acetaminophen
Codeine, butalbital, acetaminophen, and caffeine	capsule	N/A	codeine, butalbital, acetaminophen, and caffeine
Codeine, butalbital, aspirin, and caffeine	capsule	Fiorinal With Codeine®*	codeine, butalbital, aspirin, and caffeine
Dihydrocodeine, acetaminophen, and caffeine	capsule	N/A	dihydrocodeine, acetaminophen, and caffeine
Hydrocodone and acetaminophen	solution, tablet	Lortab®*, Verdrocet®*	hydrocodone and acetaminophen
Hydrocodone and ibuprofen	tablet	Xylon®*	hydrocodone and ibuprofen
Opium and belladonna	rectal suppository	N/A	opium and belladonna
Oxycodone and acetaminophen	tablet	Percocet®*	oxycodone and acetaminophen
Tramadol and acetaminophen	tablet	Ultracet®*	tramadol and acetaminophen
Tramadol and celecoxib	tablet	Seglentis®	none

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the opiate agonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Opiate Agonists

Clinical Guideline	Recommendation(s)
National Comprehensive Cancer Network: **Adult Cancer Pain (2022)**[20]	• The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization (WHO) which suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a "weak opioid," such as codeine, and then to a "strong opioid," such as morphine. • The pain management algorithm distinguishes three levels of pain intensity, based on a 0 to 10 numerical rating scale: severe pain (8 to 10), moderate pain (4 to 7) and mild pain (1 to 3). • Pain associated with oncology emergency should be addressed while concurrently treating the underlying condition. General principles of opioid treatment

Clinical Guideline	Recommendation(s)
	• Periodically review prescription drug monitoring program databases. • Consider documentation of opioid and controlled substance agreement. • Dose and titrate with caution in patients with risk factors such as decreased renal/hepatic function, chronic lung disease, upper airway compromise, sleep apnea, and poor performance status. • The appropriate opioid dose is the lowest dose that relieves the patient's pain and maximizes function throughout the dosing interval without causing unmanageable adverse effects. • Generally, oral route is most common; however, other routes can be considered as indicated to maximize patient comfort. • Calculate dosage increase based upon total opioid dose (around the clock/scheduled and as needed) taken in the previous 24 hours and increase both around-the-clock and as-needed dose as required. The rapidity of dose escalation should be related to the severity of the symptoms, expected analgesic onset and duration, and ability to monitor during dose titration. • According to Food and Drug Administration (FDA) guidelines, when higher doses of analgesic are needed, switch from preparations of opioid combined with other medications (such as aspirin and acetaminophen) to a pure opioid preparation to allow optimized titration of both agents. • Steady state drug levels will be achieved when a stable drug dose has been routinely administered for a period equal to five times the drug elimination half life. • Consider opioid rotation if pain is inadequately controlled and further dose titration is limited by adverse effects. Other indications for switching to a different opioid include: out-of-pocket costs, limitations based on formularies, or change in a patient's condition (e.g., dysphagia, nothing by mouth status, initiation of tube feeding, renal/hepatic function). • Patient evaluations should include the routine assessment of risk factors for aberrant use of pain medications. • Educate the patients and caregivers about safe use, storage, and disposal of opioids. • Use caution when combining opioid medications with other medications that have a sedating effect (e.g., benzodiazepines). • Consider pain or palliative care consult. <u>Principles of maintenance opioid therapy</u> • For continuous pain, it is appropriate to give pain medication on a regular schedule with supplemental doses for breakthrough pain. • Add extended-release or long-acting formulation to provide background analgesia for control of chronic persistent pain controlled on stable doses of short-acting opioids. Initial range for converting to long-acting opioid would be 50 to 100% of the daily requirement, depending on expected pain natural history. • When using methadone as a long-acting opioid, a short-acting opioid should also be provided for breakthrough pain. • Increase the dose of regularly scheduled opioid if patient persistently needs doses of as-needed opioids or when dose of around-the-clock opioid fails to relieve pain at peak effect or at end of dose. • Breakthrough pain may require additional doses of opioid for pain not relieved by regular schedule of long-acting opioid. • Allow rescue use of short-acting opioids at doses of 10 to 20% of the 24-hour total of long-acting or regularly scheduled oral opioid dose up to every three to four hours as needed. Titrate rescue dose as needed. • Consider rapidly acting transmucosal fentanyl in opioid-tolerant patients for brief episodes of incident pain not relieved by traditional immediate-release opioids and not attributed to inadequate dosing of around-the-clock opioids. • Continue to monitor patients for opioid adverse effects and patients/family for abnormal patterns of opioid use that may suggest aberrant drug use and/or

Clinical Guideline	Recommendation(s)
	diversion. • Consider potential drug interactions. Principles of opioid dose reduction • Consider opioid dose reduction by 10 to 20% when possible; situations that may warrant dose reduction include: o Patient never or rarely needs breakthrough analgesic. o Completion of acute pain event or response to cancer-directed therapies. o Improvement of pain control through use of non-opioid pain management therapies. • If patient is experiencing unmanageable adverse effects and pain is ≤3 (mild), consider downward dose titration by approximately 10 to 25% and re-evaluate. Close follow-up is required to make sure that the pain does not escalate, and that the patient does not develop symptoms of withdrawal. If patient has rapid clinical deterioration (e.g., marked sedation due to sepsis), temporary opioid dose reduction by 50 to 75% may be necessary. • If pain is worsened with increasing dose, consider opioid-induced hyperalgesia; opioid dose reduction or rotation with attention to other pain therapies may be indicated. Opioids and Risk Evaluation and Mitigation Strategy (REMS) • Opioids are the principal analgesics for moderate to severe pain, yet opioids pose risks to patients and society. • Responding to the "public health crisis of addiction, misuse, abuse, overdose, and death," the FDA established REMS programs for all potent opioid products. Provider and patient education are the principal recommendations of proposed opioid REMS programs. • REMS programs are currently in place for all opioid analgesics. • It is important for prescribers to be aware of the range of opioid use patterns to detect any potential aberrant behaviors. • Patients receiving treatment for addiction should be encouraged to continue with therapy and pain management should be carried out in coordination with an addiction specialist. Strategies to maintain patient safety and minimize the risk of opioid misuse and abuse during chronic opioid use • Use caution when combining opioid medications with other medications that have a sedating effect (e.g., benzodiazepines). • Risk assessment prior to treatment is recommended, although current assessment tools have not been validated in the setting of cancer care and clinical judgment should be exercised. • Education regarding the potential risks and benefits of opioid therapy; educate regarding not sharing opioids with family members or friends. • Educate regarding safe manipulation, storage, and disposal of controlled substances. • Risk mitigation for all patients receiving opioid analgesics o Consider prescribing naloxone for administration by caregivers as needed for patients taking opioids who are at high risk for respiratory depression and sedation. o Pain medication diaries are recommended for patients to document the dose and/or number of tablets and the date and time taken. o Pill counts may be used at outpatient visits or by home health/hospice to assist in correct use of medication. o Urine drug testing at baseline and during treatment should be considered to help document opioid analgesic adherence, detect illegal drug use, and identify

Clinical Guideline	Recommendation(s)
	opioid diversion. • High-risk patients who exhibit one or more opioid misuse and abuse risk factors may benefit from additional education and support services. Behavioral and cognitive-behavioral interventions may increase a patient's ability to implement problem-solving strategies and reduce the impact of modifiable risk factors. o Increase frequency of outpatient visits to weekly, if possible, and/or reduce quantity of drug prescribed per prescription. o Consider earlier referral to interventional pain specialists to maximize non-opioid options for pain control. o Consider referral to interdisciplinary team including an addiction specialist. o Counsel high-risk patients that continuation of opioid therapy is contingent upon appropriate, safe use of prescribed analgesics. o Consider utilizing programmable electronic medication dispensers. <u>Management of pain in opioid-naïve patients</u> • Opioid-naïve patients (those not chronically receiving opioid therapy on a daily basis) should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support, as well as patient and family education. • Opioid-naïve patients experiencing mild pain should first consider non-opioids and adjuvant therapies, unless these are contraindicated due to adverse effects or potential drug interactions. • For opioid-naïve patients whose pain intensity is moderate/severe at presentation, non-opioids and adjuvant therapies should be initiated as appropriate with short-acting opioids as needed. If four or more doses are needed per day consistently, consider addition of long-acting opioid. For persistent pain, initiate regular schedule of opioid with rescue dose as needed. • Opioid-naïve patients experiencing acute, severe pain or pain crisis, consider hospital or inpatient hospice admission to achieve patient-specific goals for comfort and function. <u>Management of pain in opioid-tolerant patients</u> • Opioid-tolerant patients are those chronically taking opioids on a daily basis. According to the FDA, opioid-tolerant patients "are those who are taking at least 60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, or an equianalgesic dose of another opioid for one week or longer." • Patients should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support, as well as patient and family education. • Opioid-tolerant patients experiencing mild pain should first consider non-opioids and adjuvant therapies, unless these are contraindicated due to adverse effects or potential drug interactions. Re-evaluate need for opioids and reduce if appropriate. • Opioid-tolerant patients experiencing moderate pain should receive non-opioids and adjuvant therapies as appropriate with short-acting opioids as needed. Titrate short-acting opioid, with the goal of increasing daily dose by 30 to 50%. If four or more doses are needed per day consistently, consider addition of long-acting opioid. For persistent pain, initiate regular schedule of opioid with rescue dose as needed. • For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission to achieve patient-specific goals for comfort and function. <u>Opioid prescription, titration, and maintenance</u> • Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). An individual approach should be used to determine opioid starting dose, frequency, and titration in order

Clinical Guideline	Recommendation(s)
	to achieve a balance between pain relief and medication adverse effects. • Pure agonists (such as morphine, oxycodone, oxymorphone, and fentanyl) are the most commonly used medications in the management of cancer pain. • The short half-life opioid agonists (morphine, hydromorphone, fentanyl, and oxycodone) are preferred because they can be more easily titrated than the long half-life opioids (methadone and levorphanol). • In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice. Oral administration is preferred. • Morphine, hydromorphone, hydrocodone, oxymorphone, and codeine should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. • Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid-tolerant patients. It is usually the drug of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance. • Individual variations in methadone pharmacokinetics make using this agent in cancer pain difficult. Methadone should be started at lower-than-anticipated doses and slowly titrated upwards with provision of adequate short acting breakthrough pain medications during the titration period. • Meperidine, mixed agonist-antagonists (e.g., butorphanol, pentazocine), and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain, especially in patients with impaired renal function or dehydration. • The least invasive, easiest and safest route of administration should be provided to ensure adequate analgesia. Oral administration is preferred for chronic opioid therapy. The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences adverse events associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect in comparison with oral dosing.
American Society of Interventional Pain Physicians: **Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain (2012)**[21]	• Once medical necessity is established, opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid side effects. • Up to 40 mg of morphine equivalent is considered as a low dose, 41 to 90 mg of morphine equivalent as a moderate dose, and greater than 91 mg of morphine equivalent as a high dose. • In reference to long-acting opioids, titration must be carried out with caution, and overdose and misuse must be avoided. • The long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amendable to short-acting or moderate doses of long-acting opioids, as there is no significant difference between long-acting and short-acting opioids for their effectiveness or adverse effects. • Methadone and buprenorphine are recommended for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. • It is essential to monitor for side effects and manage them appropriately, including discontinuation of opioids if indicated. • A trial of opioid rotation may be considered for patients experiencing intolerable adverse events or inadequate benefit despite dose increases. • Chronic opioid therapy may be continued, with continuous adherence monitoring, in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects.

Clinical Guideline	Recommendation(s)
European Society for Medical Oncology: **Management of Cancer Pain in Adult Patients (2018)[22]**	• The intensity of pain and the treatment outcomes should be assessed regularly and consistently using the visual analog scale or numerical rating school using the question: 'What has been your worst pain in the last 24 hours? • Observation of pain-related behaviors and discomfort is indicated in patients with cognitive impairment to assess the presence of pain. • The assessment of all components of suffering, such as psychosocial distress, should be considered and evaluated. • Patients should be informed about pain and pain management and should be encouraged to take an active role in their pain management. • The onset of pain should be prevented by means of around-the-clock administration, taking into account the half-life, bioavailability and duration of action of different drugs. • Analgesics for chronic pain should be prescribed on a regular basis and not on an 'as required' schedule. • The oral route of administration of analgesic drugs should be advocated as the first choice. • Treatment of mild pain (WHO Step 1 analgesics): o Analgesic treatment should start with drugs indicated by the WHO analgesic ladder appropriate for the severity of pain (Acetaminophen or NSAIDs). o There is no significant evidence to support or refute the use of paracetamol alone or in combination with opioids for mild to moderate pain. o There is no significant evidence to support or refute the use of NSAIDs alone or in combination with opioids for mild to moderate pain. • Treatment of mild to moderate pain (WHO Step 2 analgesics): o For mild to moderate pain, weak opioids such as tramadol, dihydrocodeine and codeine can be given in combination with non-opioid analgesics. o As an alternative to weak opioids, low doses of strong opioids could be an option, although this recommendation is not currently part of WHO guidance. o There is no evidence of increase in adverse effects from the use of low-dose strong opioids instead of the standard step 2 approach with weak opioids. • Treatment of moderate to severe pain (WHO Step III analgesics): o The opioid of first choice for moderate to severe cancer pain is oral morphine. o The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3. o The average relative potency ratio of oral to subcutaneous morphine is between 1:2 and 1:3. o Morphine is most commonly used in severe pain and oral administration is the preferred route. o Hydromorphone and oxycodone are an alternative to oral morphine. o Transdermal fentanyl and transdermal buprenorphine should be reserved for patients whose opioid requirements are stable. They are usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance to morphine and patients with poor compliance. o Fentanyl and buprenorphine (via the transdermal or intravenous route) are the safest opioids in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate < 30 mL/min). o A different opioid should be considered in the absence of adequate analgesia (despite opioid dose escalation) or in the presence of unacceptable opioid side effects. o The subcutaneous route is simple and effective for the administration of morphine, diamorphine and hydromorphone and it should be the first-

Clinical Guideline	Recommendation(s)
	choice alternative route for patients unable to receive opioids by oral or transdermal routes. o Intravenous infusion should be considered when subcutaneous administration is contraindicated (peripheral edema, coagulation disorders, poor peripheral circulation and need for high volumes and doses). o Intravenous administration is an option for opioid titration when rapid pain control is needed. • Management of opioid side effects o Laxatives must be routinely prescribed for both the prophylaxis and the management of opioid-induced constipation. o The use of naloxone in association with oxycodone or methylnaltrexone to control opioid-induced constipation may be considered. o Naloxegol has been shown to be highly effective in opioid-induced constipation, but, to date, there is no specific reported experience in the cancer population. o Metoclopramide and antidopaminergic drugs should be recommended for treatment of opioid-related nausea/vomiting. o Psychostimulants (e.g. methylphenidate) to treat opioid-induced sedation are only advised when other methods to treat this have been tried (e.g. rationalize all medication with a sedative side effect). o Mu receptor antagonists (e.g. naloxone) must be used promptly in the treatment of opioid-induced respiratory depression. • Break-through cancer pain o Immediate-release opioids should be used to treat break-through cancer pain that is opioid-responsive and for which background cancer pain management has been optimized. o Transmucosal fentanyl formulations (oral, buccal, sublingual and intranasal) have a role in unpredictable and rapid-onset break-through cancer pain. o There are indications for standard normal-release oral opioids (e.g. morphine) that include a slow-onset break-through cancer pain or a pre-emptive administration of oral opioids 30 minutes before a predictable break-through cancer pain triggered by known events.
National Opioid Use Guideline Group: **Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain (2017)**[23]	<u>Initiation and dosing of opioids in patients with chronic noncancer pain</u> • When considering therapy for patients with chronic non-cancer pain, optimize non-opioid pharmacotherapy and non-pharmacological therapy rather than initiate a trial of opioids. • For patients with chronic noncancer pain, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized nonopioid therapy, add a trial of opioids rather than continue therapy without opioids. • For patients with chronic noncancer pain with an active substance use disorder, the use of opioids is not recommended. • For patients with chronic noncancer pain with an active psychiatric disorder whose nonopioid therapy has been optimized, and who have persistent problematic pain, stabilize the psychiatric disorder before a trial of opioids is considered. • For patients with chronic noncancer pain with a history of substance use disorder, whose nonopioid therapy has been optimized, and who have persistent problematic pain, continue nonopioid therapy rather than a trial of opioids. • For patients with chronic noncancer pain who are beginning long term opioid therapy, restrict the prescribed dose to <90 mg morphine equivalents daily. <u>Rotation and tapering of opioids, for patients with chronic noncancer pain</u> • For patients with chronic noncancer pain who are currently using opioids, and have persistent problematic pain and/or problematic adverse effects, rotate to other opioids.

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	• For patients with chronic noncancer pain who are currently using ≥90 mg morphine equivalents of opioids per day, taper opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy. • For patients with chronic noncancer pain who are using opioids and experiencing serious challenges in tapering, utilize a formal multidisciplinary program. <u>Best practice statements</u> • Acquire informed consent prior to initiating opioid use for chronic non-cancer pain. A discussion about potential benefits, adverse effects, and complications will facilitate shared-care decision making regarding whether to proceed with opioid therapy. • Monitor chronic non-cancer pain patients using opioid therapy for their response to treatment, and adjust treatment accordingly. • Clinicians with chronic non-cancer pain patients prescribed opioids should address any potential contraindications and exchange relevant information with the patient's general practitioner (if they are not the general practitioner) and/or pharmacists. <u>Expert guidance statements</u> • Dangers of overdose and diversion both mandate not prescribing large doses of opioids at one time. • In patients with continuous pain including pain at rest, clinicians can prescribe controlled release opioids both for comfort and simplicity of treatment. Activity related pain may not require sustained release treatment and opioid therapy may be initiated with immediate release alone. • Available studies yield conflicting results regarding the consequences of the concomitant use of opioids and sedatives such as benzodiazepines. The pharmacology suggests that sedatives and opioids would enhance the depressant effect of the other, worsening the balance of harms vs. benefits and increasing the risk of cognitive effects, falls, motor vehicle accidents and drug-related death, though the supporting evidence is unavailable. The expert perspective is that opioids and benzodiazepines should very rarely be prescribed together. • Patients with opioid-induced sleep apnea should be advised of the associated health risks, and particularly the risks of operating a motor vehicle. Clinicians may have a statutory duty to report to governmental licensing authorities. There are three main treatment approaches available to clinicians managing patients with opioid-induced sleep disordered breathing: o Reduce opioid dose without specific treatment for sleep apnea. o Provide specific treatment for sleep apnea without reducing opioid dose. o Reduce opioid dose and provide specific treatment for apnea. • As there is a high prevalence of secondary hypogonadism in this patient population, clinicians treating men using chronic opioid therapy should consider an evaluation for hypogonadism. Clinicians should advise patients who are diagnosed with opioid-induced hypogonadism regarding the potential short-term adverse effects, including reduced sexual function, amenorrhea, fatigue, mood changes and the long-term risk of osteoporosis. Patients should be offered opioid tapering as the initial strategy to correct hypogonadism. If opioid tapering is unsuccessful or declined, clinicians may offer testosterone supplementation therapy. • Risk mitigation o Systematic reviews found only low or very low quality evidence regarding strategies intended to reduce the adverse impact of opioid prescribing. o A baseline urine drug screen may be useful for patients currently receiving or being considered for a trial of opioids. Clinicians may repeat urine drug screening on an annual basis and more frequently if the patient is at elevated risk or in the presence of any aberrant drug-related behaviors.

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	○ Approximately 30% of urine drug screening will demonstrate aberrant results, largely because of prescribed opioid non-detection and tetrahydrocannabinol. ○ A written treatment agreement may be useful in structuring a process of informed consent around opioid use, clarifying expectations for both patient and physician, and providing clarity regarding the nature of an opioid trial with endpoints, goals, and strategies in event of a failed trial. ○ When available and affordable, tamper-resistant formulations may be used to reduce the risks of altering the intended delivery system (i.e., from oral to nasal or intravenous injection). They do not reduce the most common mode of misuse (oral ingestion), but are less favored by people who misuse opioids by any route. ○ When prescribing fentanyl or other drugs dispensed in a transdermal patch preparation, it may be advisable to ask patients to return used patches to the pharmacy when presenting for the next dispensing. ○ Clinicians may provide naloxone to patients receiving opioids for chronic pain who are identified as at risk due to high dose, medical history, or comorbidities.
Veterans Affairs/ Department of Defense: **Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (2017)[24]**	<u>Initiation and Continuation of Opioids</u> • Initiation of long-term opioid therapy for chronic pain is not recommended. • Alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments are recommended. • When pharmacologic therapies are used, nonopioids are recommended over opioids. • If prescribing opioid therapy for patients with chronic pain, a short duration is recommended. • Note: Consideration of opioid therapy beyond 90 days requires reevaluation and discussion with patient of risks and benefits. • For patients currently on long-term opioid therapy, ongoing risk mitigation strategies, assessment for opioid use disorder, and consideration for tapering when risks exceed benefits are recommended. • Long-term opioid therapy for pain in patients with untreated substance use disorder is not recommended. • For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering are recommended. • The concurrent use of benzodiazepines and opioids is not recommended. • Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate. • Long-term opioid therapy for patients <30 years of age secondary to higher risk of opioid use disorder and overdose is not recommended. • For patients <30 years of age currently on long-term opioid therapy, close monitoring and consideration for tapering when risks exceed benefits are recommended. • In general, no single opioid or opioid formulation is preferred over the others. <u>Risk Mitigation</u> • Implementing risk mitigation strategies upon initiation of long-term opioid therapy is recommended, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include: ○ Ongoing, random urine drug testing (including appropriate confirmatory testing). ○ Checking state prescription drug monitoring programs.

Clinical Guideline	Recommendation(s)
	○ Monitoring for overdose potential and suicidality. ○ Providing overdose education. ○ Prescribing of naloxone rescue and accompanying education. • Assess suicide risk when considering initiating or continuing long-term opioid therapy and intervene when necessary. • Evaluate benefits of continued opioid therapy and risk for opioid-related adverse events at least every three months. <u>Type, Dose, Follow-up, and Taper of Opioids</u> • If prescribing opioids, prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits is recommended. Note: There is no absolutely safe dose of opioids. • As opioid dosage and risk increase, more frequent monitoring for adverse events including opioid use disorder and overdose is recommended. Note: ○ Risks for opioid use disorder start at any dose and increase in a dose dependent manner. ○ Risks for overdose and death significantly increase at a range of 20 to 50 mg morphine equivalent daily dose. • Opioid doses over 90 mg morphine equivalent daily dose is not recommended for treating chronic pain. • Note: For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate for tapering to reduced dose or to discontinuation. • Prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy is not recommended. • Tapering to reduced dose or to discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits is recommended. • Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns. • Individualize opioid tapering based on risk assessment and patient needs and characteristics. • Note: There is insufficient evidence to recommend for or against specific tapering strategies and schedules. • Interdisciplinary care that addresses pain, substance use disorders, and/or mental health problems for patients presenting with high risk and/or aberrant behavior is recommended. • Offer medication assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder. Note: See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. <u>Opioid Therapy for Acute Pain</u> • Alternatives to opioids are recommended for mild-to-moderate acute pain. • Use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain is suggested. • If take-home opioids are prescribed, immediate-release opioids are recommended at the lowest effective dose with opioid therapy reassessment no later than three to five days to determine if adjustments or continuing opioid therapy is indicated. • Note: Patient education about opioid risks and alternatives to opioid therapy should be offered.
Veterans Affairs/ Department of Defense: **Clinical Practice Guideline for Management of Substance Use**	<u>Opioid use disorder- pharmacotherapy</u> • For patients with opioid use disorder, offering one of the following medications considering patient preferences is recommended: ○ Buprenorphine/naloxone ○ Methadone in an Opioid Treatment Program • For patients with opioid use disorder, offering extended-release naltrexone is suggested.

Clinical Guideline	Recommendation(s)
Disorders (2021)[25]	• There is insufficient evidence to recommend any one of the different FDA-approved formulations or routes of delivery of buprenorphine over another. • There is insufficient evidence to recommend for or against oral naltrexone for the treatment of opioid use disorder. Opioid use disorder- psychosocial interventions • For patients receiving medication treatment for opioid use disorder, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused Medical Management. • For patients with opioid use disorder for whom opioid use disorder pharmacotherapy is contraindicated, unacceptable, or unavailable, there is insufficient evidence to recommend for or against any specific psychosocial interventions. Opioid use disorder- stabilization and withdrawal • For patients with opioid use disorder, we recommend against withdrawal management, without planned ongoing pharmacotherapy treatment, due to high risk of relapse and overdose. • For patients with opioid use disorder for whom opioid withdrawal management is indicated, buprenorphine/naloxone (in any setting) or methadone or buprenorphine/naloxone (in inpatient or accredited opioid treatment programs) are suggested. • For patients with opioid use disorder for whom withdrawal management is indicated and for whom methadone and buprenorphine are contraindicated, unacceptable, or unavailable, we suggest offering clonidine or lofexidine as a second-line agent for opioid withdrawal management.
Center for Substance Abuse Treatment: **Medications for Opioid Use Disorder (TIP 63) (2021)[26]**	Introduction to Medications for Opioid Use Disorder (OUD) Treatment • Increasing opioid overdose deaths, illicit opioid use, and prescription opioid misuse constitute a public health crisis. • OUD medications reduce illicit opioid use, retain people in treatment, and reduce risk of opioid overdose death better than treatment with placebo or no medication. • Only physicians; nurse practitioners; physician assistants; and, until October 1, 2023, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives can prescribe buprenorphine for OUD. They must get a federal waiver to do so. • Only federally certified, accredited opioid treatment programs (OTPs) can dispense methadone to treat OUD. OTPs can administer and dispense buprenorphine without a federal waiver. • Any prescriber can offer naltrexone. • OUD medication can be taken on a short- or long-term basis, including as part of medically supervised withdrawal and as maintenance treatment. • Patients taking medication for OUD are considered to be in recovery. • Several barriers contribute to the underuse of medication for OUD. Addressing Opioid Use Disorder in General Medical Settings • All healthcare practices should screen for alcohol, tobacco, and other substance misuse (including opioid misuse). • Validated screening tools, symptom surveys, and other resources are readily available. • When patients screen positive for risk of harm from substance use, practitioners should assess them using tools that determine whether substance use meets diagnostic criteria for a substance use disorder (SUD). • Thorough assessment should address patients' medical, social, SUD, and family histories. • Laboratory tests can inform treatment planning.

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	• Practitioners should develop treatment plans or referral strategies (if onsite SUD treatment is unavailable) for patients who need SUD treatment. Medications for Opioid Use Disorder • OUD medications are safe and effective when used appropriately. • OUD medications can help patients reduce or stop illicit opioid use and improve their health and functioning. • Pharmacotherapy should be considered for all patients with OUD. Opioid pharmacotherapies should be reserved for those with moderate-to-severe OUD with physical dependence. • Patients with OUD should be informed of the risks and benefits of pharmacotherapy, treatment without medication, and no treatment. • Patients should be advised on where and how to get treatment with OUD medication. • Doses and schedules of pharmacotherapy must be individualized. • There are three FDA-approved medications used to treat OUD, including the mu-opioid receptor partial agonist buprenorphine, the mu-opioid receptor full agonist methadone, and the mu-opioid receptor antagonist naltrexone. Extended-release naltrexone (XR-NTX) is FDA approved to prevent relapse in patients who have remained opioid abstinent for sufficient time. o Methadone retains patients in treatment and reduces illicit opioid use more effectively than placebo, medically supervised withdrawal, or no treatment. o XR-NTX has demonstrated efficacy in reducing return to illicit opioid use, increasing treatment retention, and reducing opioid craving compared with placebo or no medication. o XR-NTX initiated prior to release from controlled environments (e.g., jails, prisons, residential rehabilitation programs) may be useful in preventing return to opioid use after release. o The oral formulation of naltrexone is not widely used to treat OUD because of low rates of patient acceptance and high rates of nonadherence leading to a lack of efficacy. o Buprenorphine is effective in retaining patients in treatment and reducing illicit opioid use. o Buprenorphine is a partial agonist with a ceiling effect on opioid activity. Hence, it is less likely than methadone and other full agonists to cause respiratory depression in an accidental overdose. o Currently, no empirical data indicate which patients will respond better to which OUD medications. All patients considering treatment should be educated about the effectiveness, risks, and benefits of each of the three OUD medications, treatment without medication, and no treatment. Partnering Addiction Treatment Counselors with Clients and Healthcare Professionals • Many patients taking OUD medication benefit from counseling as part of treatment. • Counselors play the same role for clients with OUD who take medication as for clients with any other SUD. • Counselors help clients recover by addressing the challenges and consequences of addiction. • OUD is often a chronic illness requiring ongoing communication among patients and providers to ensure that patients fully benefit from both pharmacotherapy and psychosocial treatment and support. • OUD medications are safe and effective when prescribed and taken appropriately. • Medication is integral to recovery for many people with OUD. Medication usually produces better treatment outcomes than outpatient treatment without medication. • Supportive counseling environments for clients who take OUD medication can promote treatment and help build recovery capital.

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention: **CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016 (2016)[10]**	This guideline provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. <u>Determining when to initiate or continue opioids for chronic pain</u> • Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic and nonopioid pharmacologic therapies, as appropriate. o Several nonopioid pharmacologic therapies (including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and selected antidepressants and anticonvulsants) are effective for chronic pain. o In particular, acetaminophen and NSAIDs can be useful for arthritis and low back pain. Selected anticonvulsants such as pregabalin and gabapentin can improve pain in diabetic neuropathy and post-herpetic neuralgia. Pregabalin, gabapentin, and carbamazepine are FDA-approved for treatment of certain neuropathic pain conditions, and pregabalin is FDA-approved for fibromyalgia management. • Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety. • Before starting and periodically during opioid therapy, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy as well as patient and clinician responsibilities for managing therapy. <u>Opioid selection, dosage, duration, follow-up, and discontinuation</u> • When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release (IR) opioids instead of extended-release/long-acting (ER/LA) opioids. o ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, oxymorphone, hydrocodone, and morphine. o Recommendations cannot be offered at this time related to use of abuse-deterrent formulations. o Methadone has been associated with a disproportionate number of overdose deaths relative to the frequency with which it is prescribed for chronic pain. Methadone should not be a first-line agent for an ER/LA opioid for pain management. o ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received IR opioids daily for at least one week. • When opioids are initiated, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dose, should carefully reassess evidence of individual benefits and risks when increasing doses to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing doses to ≥90 MME/day or carefully justify a decision to titrate doses to ≥90 MME/day. • Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of IR opioids and should not prescribe a quantity greater than needed for the expected duration of pain considered severe enough to require opioids. Three days or less is often sufficient; more than seven days is rarely needed. • Clinicians should evaluate benefits and harms with patients within one to four

Clinical Guideline	Recommendation(s)
	weeks of starting opioid therapy for chronic pain or a dose escalation. Clinicians should evaluate the benefits and harms of continued therapy with patients every three months or more frequently, as clinically warranted. If the benefits do not outweigh the harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower doses or taper and discontinue opioids. <u>Assessing risk and addressing harms of opioid use</u> • Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate strategies into the management plan to mitigate risks, including the consideration of naloxone prescribing when factors that increase the risk for opioid overdose are present (e.g., a history of overdose, history of substance use disorder, higher opioid doses (≥50 MME/day), or concurrent benzodiazepine use). • Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving other opioid doses or dangerous combinations that may put him or her at high risk for overdose. Clinicians should review PDMP data when initiating opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every three months. • When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drug use. • Clinicians should avoid prescribing opioid pain medications and benzodiazepines concurrently whenever possible. • Clinicians should offer or arrange evidence-based treatment options (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the opiate agonists are noted in Tables 3 to 6. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Agent Opiate Agonists (Drugs A-M)[4-6]

Indication	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine
Analgesia							
For obstetrical analgesia					✔ ‡		
Management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain		✔ *					
Management of pain in patients where an opioid analgesic is appropriate and alternate treatments are inadequate			✔	✔	✔ ‡§	✔ ‡	✔
Management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time and for which alternative treatment options are inadequate						✔ ‖	✔ #
Management of persistent, moderate to severe chronic pain in opioid-tolerant patients when a continuous, around-the-clock opioid analgesic is required for an extended period of time, and the patient cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids		✔ †					
Management of mild to moderate pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate	✔						
Epidural or intrathecal management of pain without attendant loss of motor, sensory, or sympathetic function							✔ **
Anesthesia							
For analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period as the need arises		✔ ‡					
Narcotic analgesic supplement in general or regional anesthesia		✔ ‡					
For administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia		✔ ‡					
For use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures		✔ ‡					
Preoperative medication					✔ ‡		

Indication	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine
Support of anesthesia					✔ ‡		
Detoxification/Dependence							
For detoxification treatment of opioid addiction (heroin or other morphine-like drugs)						✔ ¶	
For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services						✔ ¶	
For use in temporary treatment of opioid dependence in patients unable to take oral medication						✔ ‡	

*Buccal formulation.
†Transdermal formulation.
‡Injection formulation.
§Oral formulations.
‖ Oral solution and tablet formulations (5 to 10 mg only).
¶ Oral concentrate, oral solution, and tablet formulations.
# Sustained-release tablet.
**Epidural formulation.

Table 4. FDA-Approved Indications for the Single Agent Opiate Agonists (Drugs N-Z)[4-6]

Indication	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Analgesia				
For obstetrical analgesia		✔ *		
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults			✔ †	✔ †
Management of moderate to severe chronic pain or neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time			✔ †	
Management of acute and chronic moderate to severe pain in patients where an opioid analgesic is appropriate and for which alternative treatments are inadequate	✔			
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate		✔	✔	✔
Anesthesia				
Preoperative medication		✔ *		
Support of anesthesia		✔ *		
Miscellaneous				
Relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular dysfunction		✔ *		

*Injection formulation.
†Extended-release formulation.

Table 5. FDA-Approved Indications for the Combination Opiate Agonists (Drugs A-H)[4-6]

Indication	Benzhydrocodone and Acetaminophen	Codeine and Acetaminophen	Codeine, Butalbital, Acetaminophen and Caffeine	Codeine, Butalbital, Aspirin and Caffeine	Dihydrocodeine, Acetaminophen and Caffeine	Hydrocodone and Acetaminophen	Hydrocodone and Ibuprofen
Analgesia							
Management of mild to moderate pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate		✔					
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate					✔	✔	
Management of short-term (no more than 14 days) acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	✔						
Short-term (≤10 days) management of acute pain							✔
Headache							
Management of the symptom complex of tension (or muscle contraction) headache when nonopioid analgesic and alternative treatments are inadequate			✔	✔			

Table 6. FDA-Approved Indications for the Combination Opiate Agonists (Drugs I-Z)[4-6]

Indication	Opium and Belladonna	Oxycodone and Acetaminophen	Tramadol and Acetaminophen	Tramadol and celecoxib
Analgesia				
Management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate				✔
Management of pain severe enough to require opioid treatment and for which alternative treatment options are inadequate		✔		
Relief of moderate to severe pain associated with ureteral spasms not responsive to nonopioid analgesics and to space intervals between injections of opiates	✔			
Short-term (≤5 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate			✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the opiate agonists are listed in Table 7. Pharmacokinetic properties of the combination products not listed in the table below would be in line with the properties of their individual components listed in the table below.

Table 7. Pharmacokinetic Parameters of the Opiate Agonists[4-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents/Components					
Codeine	Oral: well absorbed	7 to 25	Liver (extensive)	Renal (90)	2.5 to 3.5
Dihydrocodeine	21	Not reported	Not reported	Renal (35)	3.4 to 4.5
Fentanyl	Buccal: 50 to 76 SL: 54 TD: 92	80 to 86	Liver	Renal (7)	Injection: <4 SL: 5 to 12 TD: 20 to 27
Hydrocodone*	Not reported	19 to 45	Liver	Renal (6 to 20)	3.8 to 4.5
Hydromorphone	24	8 to 27	Liver (95)	Renal (75)	Injection: 2.3 ER: 11
Levorphanol	Rapid	40 to 50	Liver	Not reported	11 to 16
Meperidine	Oral: variable	65 to 80	Liver	Renal (0.5 to 5.2)	3 to 8 Active metabolite: 20 to 48
Methadone	Oral: 36 to 100	85 to 90	Liver	Renal (21)	8 to 59
Morphine	Buccal: 50 Oral: 20 to 40 TD: 75	20 to 36	Liver	Renal (90)	1.5 to 2.0
Oxycodone	60 to 87	45	Liver	Renal (19)	3.5 to 5.6
Oxymorphone	10	10 to 12	Liver	Renal (1 to 2)	Injection: 1.3 Oral: 7 to 9
Tapentadol	32	20	Liver (97)	Renal (99)	4 to 5
Tramadol	IR: 75 ER: 85 to 95	20	Liver	Renal (30)	IR: 5.6 to 6.7 ER: 6.5 to 10.0
Combination Products					
Opium and belladonna	Not reported	Not reported	Not reported	Not reported	Not reported

ER=extended-release, IR=immediate-release, SL=sublingual, TD=transdermal
*Apadaz has met the bioequivalence criteria for hydrocodone AUC and C_{max} to other immediate-release hydrocodone combination products. Benzhydrocodone was not detectable in plasma after oral administration in clinical studies, indicating that exposure to benzhydrocodone was minimal and transient.

V. Drug Interactions

Major drug interactions with the opiate agonists are listed in Table 8.

Table 8. Major Drug Interactions with the Opiate Agonists[5]

Generic Name(s)	Interaction	Mechanism
Opiate agonists (benzhydrocodone, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine,	Naltrexone	Naltrexone may decrease or attenuate the pharmacologic effects of opiate agonists. Coadministration of naltrexone and opiate agonists may precipitate withdrawal symptoms in individuals who are physically dependent on opioid drugs.

Generic Name(s)	Interaction	Mechanism
methadone, morphine, opium and belladonna, oxycodone, oxymorphone, tapentadol, tramadol)		
Opiate agonists (benzhydrocodone, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone, tapentadol, tramadol)	Barbiturate anesthetics	The combination of barbiturate anesthetics and opiate agonists may result in increased respiratory and central nervous system depressive effects. Additive pharmacologic effects may produce increased clinical effects.
Opiate agonists (benzhydrocodone, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone, tapentadol, tramadol)	CNS depressants	The combination of CNS depressants and opiate agonists may result in increased respiratory and central nervous system depressive effects.
Opiate agonists (benzhydrocodone, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone, tapentadol, tramadol)	Monoamine oxidase inhibitors	Concurrent use may result in increased risk of serotonin syndrome and/or potentiation of opioid effects.
Opiate agonists (benzhydrocodone, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone, tapentadol, tramadol)	Safinamide	Concurrent use of safinamide and opioids may result in increased risk of serotonin syndrome.
Opiate agonists (benzhydrocodone, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone, tapentadol, tramadol)	Serotonin reuptake inhibitors	Toxic effects of serotonin reuptake inhibitors may be increased, resulting in development of serotonin syndrome.
Opiate agonists (benzhydrocodone,	Sodium oxybate	Concurrent use of sodium oxybate and opiate agonists may result in an increase in sleep duration and central

Generic Name(s)	Interaction	Mechanism
codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone, tapentadol, tramadol)		nervous system depression. Pharmacologic effects of sodium oxybate and opiate agonists may be additive.
Opiate agonists (codeine, fentanyl, methadone, oxycodone, tramadol)	Azole antifungal agents	Pharmacologic effects and adverse reactions of opiates may be increased due to inhibition of CYP3A4 metabolism by azole antifungals.
Opiate agonists (codeine, fentanyl, oxycodone, tramadol)	Human immuno-deficiency virus protease inhibitors	Human Immunodeficiency Virus protease inhibitors may increase plasma concentrations and pharmacologic effects of opiate agonists. Severe respiratory depression may occur. Inhibition of cytochrome P450 3A4 isoenzymes by Human Immunodeficiency Virus protease inhibitors may decrease the metabolic elimination of opiate agonists.
Opiate agonists (codeine, fentanyl, methadone, oxycodone, tramadol)	Macrolide and related antibiotics	Inhibition of opiate agonist metabolism (CYP 3A4) by macrolide and related antibiotics may increase opiate plasma concentrations, increasing the pharmacologic effects and toxicity.
Opium and belladonna	Phenothiazines	The antipsychotic effectiveness of phenothiazines may be decreased by opium/belladonna. Additive central and peripheral anticholinergic effects and decreased Phenothiazines bioavailability have been proposed.
Acetaminophen	Isoniazid	Isoniazid may increase the toxic effects of acetaminophen. The mechanism of this interaction is unknown.
Acetaminophen	Anticoagulants	The hypoprothrombinemic effects of anticoagulants may be increased by acetaminophen in a dose-dependent manner. Bleeding may occur, especially when acetaminophen use exceeds 2,000 mg daily or is prolonged for several days.
Aspirin	Celecoxib	Aspirin and celecoxib may cause additive adverse effects when co-administered. An increased rate of gastrointestinal ulceration or other complications may occur. Additive toxicity may occur.
Aspirin	Clopidogrel	The risk of life-threatening bleeding such as intracranial or gastrointestinal hemorrhage may be increased in high-risk patients with transient ischemic attack or ischemic stroke when given the combination of clopidogrel with aspirin.
Aspirin	Direct thrombin inhibitors	Use of direct thrombin inhibitors with aspirin may increase the risk of bleeding. Inhibition of the clotting cascade by multiple mechanisms may increase the risk of bleeding.
Aspirin	Anticoagulants	The use of anticoagulants with aspirin may increase the risk of bleeding, especially gastrointestinal bleeding. However, when low-dose aspirin is used with anticoagulants, the therapeutic benefit may outweigh the risk of minor bleeding.
Aspirin	Heparin and factor Xa inhibitors	The risk of bleeding in heparin and factor Xa inhibitors treated patients may be increased by aspirin due to additive anticoagulant effects.
Aspirin	Methotrexate	Therapeutic and toxic effects (bone marrow depression,

Generic Name(s)	Interaction	Mechanism
		hepatotoxicity) of methotrexate may be increased by concurrent use of aspirin. Aspirin may inhibit renal excretion of methotrexate and displace it from plasma protein binding sites.
Aspirin	Nonsteroidal anti-inflammatory drugs	Regular use of nonsteroidal anti-inflammatory drugs may decrease the antiplatelet effects of aspirin. Reduced antiplatelet efficacy in patients with underlying cardiovascular risk may occur. Additionally, the potential for gastrointestinal side effects, including bleeding, may be increased with regular use of full-dose aspirin.
Butalbital	Anticoagulants	Butalbital may decrease the hypoprothrombinemic effects of anticoagulants. Induction of hepatic microsomal enzymes by butalbital may increase the metabolism of anticoagulants. Butalbital may decrease the gastrointestinal absorption of dicumarol.
Butalbital	Estrogens	Butalbital may decrease the pharmacologic effects of estrogens with potential subsequent reductions of contraceptive or non-contraceptive estrogen efficacy. Butalbital may increase hepatic metabolism of estrogens.
Butalbital	Corticosteroids	Pharmacologic effects of corticosteroids may be decreased with possible exacerbation of the disease being treated. Induction of hepatic microsomal enzymes by butalbital may increase the metabolic elimination of corticosteroids.
Butalbital	Theophyllines	Pharmacologic effects of theophyllines may be decreased by butalbital. Decreased theophylline plasma concentrations, possibly with a suboptimal therapeutic response, may occur. Hepatic metabolism of theophyllines may be increased by butalbital.
Celecoxib	ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).
Celecoxib	Corticosteroids	Concomitant use of corticosteroids with celecoxib may increase the risk of GI ulceration or bleeding.
Celecoxib	Diuretics	Concurrent use of diuretics and NSAIDs may result in reduced diuretic effectiveness and possible nephrotoxicity.
Celecoxib	NSAIDs and Salicylates	Concurrent use of celecoxib and NSAIDs and salicylates may result in increased risk of bleeding.
Celecoxib	Tricyclic antidepressants, Serotonin norepinephrine reuptake inhibitors, Selective serotonin reuptake inhibitors	Concurrent use of NSAIDs and these agents may result in an increased risk of bleeding.
Celecoxib	Capecitabine	Concurrent use of capecitabine and celecoxib may result in increased celecoxib exposure that persists for at least seven days after capecitabine discontinuation.
Celecoxib	Cyclosporine	Concurrent use of cyclosporine and nonsteroidal antiinflammatory agents may result in an increased risk of cyclosporine nephrotoxicity.
Celecoxib	Lithium	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The

Generic Name(s)	Interaction	Mechanism
		mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Celecoxib	Methotrexate	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). Celecoxib has no effect on methotrexate pharmacokinetics.
Celecoxib	Pemetrexed	Concomitant use of celecoxib and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Fentanyl	Amiodarone	Profound bradycardia, sinus arrest, and hypotension have occurred.
Fentanyl	Diltiazem, verapamil	Diltiazem may increase plasma concentrations of fentanyl, increasing the potential for enhanced pharmacologic effects and toxicity. Inhibition of cytochrome P450 3A4 isoenzyme by diltiazem may decrease the metabolic elimination of fentanyl.
Fentanyl	Mifepristone	Concurrent use of fentanyl and mifepristone may result in increased fentanyl exposure and risk of adverse events.
Fentanyl	Nicardipine, nifedipine	Concurrent use of fentanyl and nicardipine/ nifedipine may result in severe hypotension.
Fentanyl	Nefazodone	Plasma concentrations and pharmacologic effects of fentanyl may be increased by nefazodone. Inhibition of cytochrome P450 3A4 metabolism by nefazodone may decrease the metabolic elimination of fentanyl.
Ibuprofen	Anticoagulants	The use of anticoagulants with ibuprofen may increase the risk of bleeding. Ibuprofen may impair platelet function and irritate the gastrointestinal mucosa leading to an increased risk of hemorrhage.
Ibuprofen	Heparin and factor Xa inhibitors	The risk of bleeding in heparin and factor Xa inhibitors treated patients may be increased by ibuprofen due to additive anticoagulant effects.
Ibuprofen	Methotrexate	Plasma concentrations and toxic effects of methotrexate may be increased by ibuprofen. Severe toxicity characterized by bone marrow suppression, nephrotoxicity and mucositis has occurred in patients receiving ibuprofen high-dose methotrexate chemotherapy.
Ibuprofen	Salicylates	Regular use of ibuprofen may decrease the antiplatelet effects of salicylates. Reduced antiplatelet efficacy in patients with underlying cardiovascular risk may occur. Additionally, the potential for gastrointestinal side effects, including bleeding, may be increased with regular use of full-dose aspirin.
Ibuprofen	Cyclosporine	Combination therapy with cyclosporine and ibuprofen may increase the probability and severity of renal impairment. Plasma concentrations of cyclosporine and ibuprofen may be increased.
Ibuprofen	Lithium	Pharmacologic effects of lithium may be increased. Elevated lithium serum concentrations and toxicity characterized by gastrointestinal symptoms, polyuria, muscular weakness, lethargy, and tremor may occur.
Ibuprofen	Loop diuretics	Diuretic effects of loop diuretics may be decreased by

Generic Name(s)	Interaction	Mechanism
		ibuprofen. Sodium retention and hypervolemia may occur. Ibuprofen may decrease natriuresis and diuresis of loop diuretics by inhibiting the synthesis of renal prostaglandins.
Ibuprofen	Thienopyridines	Use of ibuprofen with thienopyridines may increase the risk of bleeding. Ibuprofen-induced alteration in gastric mucosal function coupled with inhibition of platelet aggregation by thienopyridines may further increase the risk of gastrointestinal bleeding compared to ibuprofen alone.
Ibuprofen	Tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, SSRIs	Concurrent use of ibuprofen and certain antidepressants may result in an increased risk of bleeding.
Meperidine	Human immuno-deficiency virus protease inhibitors	Cardiac, hematologic, neurologic (seizures), or other potentially serious toxicities are listed in the manufacturer's package labeling when meperidine and human immunodeficiency virus protease inhibitors are coadministered. The mechanism is unknown.
Meperidine	Phenothiazines	Excessive or prolonged central nervous system depression, respiratory depression and hypotension may occur, when phenothiazines and meperidine are used concomitantly.
Methadone	Benzodiazepines	The synergistic effects of opioids and benzodiazepines may increase the risk of sedation and life-threatening respiratory depression, especially with overdosage.
Methadone	Class IA and IC antiarrhythmics	Co-administration of methadone and class IA and IC antiarrhythmics may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease. Methadone inhibits cardiac potassium channels and prolongs the QT interval. This may become significant with larger doses and in combination with other drugs that may also prolong the QT interval, such as class IA and IC antiarrhythmics.
Methadone	Class III antiarrhythmics	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when class III antiarrhythmics are co-administered with methadone. Pharmacologic effects of class III antiarrhythmics and methadone on electrical conduction of the heart may be additive.
Methadone	Dofetilide	Co-administration of methadone and dofetilide may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease. Methadone inhibits cardiac potassium channels and prolongs the QT interval. This may become significant with larger doses and in combination with other drugs that may also prolong the QT interval, such as dofetilide.
Methadone	Dronedarone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades

Generic Name(s)	Interaction	Mechanism
		de pointes, should be considered when dronedarone is co-administered with methadone. Pharmacologic effects of dronedarone and methadone on electrical conduction of the heart may be additive.
Methadone	H-1 antagonists	Co-administration of methadone and H-1 antagonists may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease. Methadone inhibits cardiac potassium channels and prolongs the QT interval. This may become significant with larger doses and in combination with other drugs that may also prolong the QT interval, such as H-1 antagonists.
Methadone	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and methadone. QT interval effects of each agent may be additive.
Methadone	Quinolones	Co-administration of methadone and quinolones may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease. Additionally, ciprofloxacin may increase pharmacologic effects of methadone. Methadone inhibits cardiac potassium channels and prolongs the QT interval. This may become significant with larger doses and in combination with other drugs that may also prolong the QT interval, such as quinolones.
Methadone	Efavirenz	Efavirenz may decrease pharmacologic effects and plasma concentrations of methadone. Induction of hepatic cytochrome P450 3A4 isoenzymes by efavirenz may increase the metabolic elimination of methadone.
Methadone	Human immuno-deficiency virus protease inhibitors	Human immunodeficiency virus protease inhibitors may decrease the pharmacologic effects and plasma concentrations of methadone. Induction of CYP2B6 by human immunodeficiency virus protease inhibitors may increase the metabolic elimination of methadone.
Methadone	Hydantoins	Serum concentrations and pharmacologic effects of methadone may be decreased by hydantoins. Methadone withdrawal signs (abdominal cramping, rhinorrhea, lacrimation, chills, and tremulousness) may occur. Hydantoins may induce the hepatic metabolism of methadone.
Methadone	Monoamine oxidase inhibitors-type B agents	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering methadone to patients receiving monoamine oxidase inhibitors -type B specific agents. The mechanism of this interaction is unknown.
Methadone	Nevirapine	Nevirapine may decrease the plasma concentrations of methadone. Induction of cytochrome P450 3A4 isoenzymes by nevirapine may increase the metabolic elimination of methadone.
Methadone	Nucleoside reverse transcriptase inhibitors	Plasma concentrations and pharmacologic effects of nucleoside reverse transcriptase inhibitors may be decreased by methadone. The mechanism of this interaction is unknown.

Generic Name(s)	Interaction	Mechanism
Methadone	Risperidone	Concurrent use of methadone and risperidone may result in precipitation of opioid withdrawal symptoms in opioid-dependent patients; increased risk of QT prolongation.
Methadone	Thioridazine	Concurrent use of methadone and thioridazine may result in increased risk of QT-interval prolongation.
Methadone	Ziprasidone	Concurrent use of methadone and ziprasidone may result in increased risk of QT-interval prolongation and increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Tramadol	Serotonin–norepinephrine reuptake inhibitors and serotonin reuptake blockers	Co-administration of Serotonin–norepinephrine reuptake inhibitors and serotonin reuptake blockers with tramadol may result in the development of serotonin syndrome (e.g., agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering).
Tramadol	Atypical antipsychotics	Increased risk of seizures is listed in the manufacturer's package labeling as a possibility when tramadol and atypical antipsychotics are coadministered. The mechanism of this interaction is unknown.
Tramadol	Cyclobenzaprine	Increased risk of seizures is listed in the manufacturer's package labeling as a possibility when tramadol and cyclobenzaprine are coadministered. The mechanism of this interaction is unknown.
Tramadol	Molindone	Use of tramadol with molindone may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	Phenothiazines	Use of tramadol with phenothiazines may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	Tricyclic antidepressants	Use of tramadol with tricyclic antidepressants may increase the risk of seizures. The mechanism of this interaction is unknown.

VI. Adverse Drug Events

The most common adverse drug events reported with the opiate agonists are listed in Tables 9 to 11. Adverse events of the combination products not listed in the tables below would be in line with the properties of their individual components. The boxed warnings for the opiate agonists are listed in Tables 12 to 25.

Table 9. Adverse Drug Events (%) Reported with the Opiate Agonists (Drugs A-M)[4-6]

Adverse Events	Benzhydro-codone	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Cardiovascular									
Abnormal ECG	-	-	-	-	-	-	-	-	✔
Angina	-	-	-	<1	-	-	-	-	-
Arrhythmia	-	-	-	-	-	-	✔	-	✔
Atrial fibrillation	-	-	-	-	-	-	-	-	-
Bigeminal rhythms	-	-	-	-	-	-	-	-	✔
Bradycardia	✔	✔	-	✔	✔	✔	✔	✔	✔
Cardiac arrest	✔	✔	-	✔	✔	✔	✔	✔	✔
Cardiomyopathy	-	-	-	-	-	-	-	-	✔
Chest pain	-	-	-	✔	-	-	-	-	-
Circulatory collapse	✔	✔	-	✔	✔	✔	-	✔	✔
Deep thrombophlebitis	-	-	-	✔	-	✔	-	-	-
Extrasystoles	-	-	-	-	-	✔	✔	-	✔
Faintness	-	✔	-	-	-	✔	-	-	✔
Flushing	-	✔	-	✔	-	✔	✔	✔	✔
Heart failure	-	-	-	-	-	✔	-	-	✔
Hypertension	✔	-	-	✔	✔	✔	-	-	✔
Hypotension	✔	✔	-	✔	✔	✔	✔	✔	✔
Myocardial ischemia	-	-	-	-	-	-	-	-	✔
Orthostatic hypotension	-	-	-	-	-	-	-	-	✔
Palpitation	-	-	-	✔	-	✔	✔	✔	✔
Peripheral vascular disorder	-	-	-	✔	-	-	-	-	-
Phlebitis	-	-	-	-	-	-	-	✔	✔
Prolonged QT interval	-	-	-	-	-	-	-	-	✔
Shock	-	-	-	-	-	-	-	✔	✔
Syncope	-	✔	-	✔	-	✔	✔	✔	✔
Tachycardia	-	✔	-	✔	-	✔	✔	✔	✔
Torsade de pointes	-	-	-	-	-	-	-	-	✔
Vascular disorder	-	-	-	✔	-	-	-	-	-
Vasodilation	-	-	-	≤4	-	-	-	-	✔
Ventricular fibrillation	-	-	-	-	-	-	-	-	✔
Ventricular tachycardia	-	-	-	-	-	-	-	-	✔
Central Nervous System									
Abnormal coordination	-	-	-	≥1	-	-	-	-	-

Adverse Events	Benzhydro-codone	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Abnormal dreams	-	-	✔	✔	-	✔	-	-	-
Abnormal gait	-	-	-	1 to 5	-	✔	-	-	-
Abnormal thinking	-	-	-	1 to 2	-	-	-	-	-
Acute brain syndrome	-	-	-	✔	-	-	-	-	-
Addiction	✔	-	✔	-	✔	-	✔	-	-
Agitation	-	✔	-	✔	-	✔	-	✔	✔
Amnesia	-	-	-	✔	-	-	-	-	-
Anxiety	✔	✔	-	3 to 15	✔	✔	-	-	-
Aphasia	-	-	-	✔	-	-	-	-	-
Asthenia	-	-	-	0 to 38	-	-	-	-	-
Cerebral ischemia	-	-	-	✔	-	-	-	-	-
Central nervous system stimulation	-	-	-	-	-	-	✔	-	-
Coma	✔	-	✔	-	✔	-	✔	-	-
Confusion	✔	-	✔	10 to 13	✔	✔	✔	-	✔
Convulsion	-	✔	-	0 to 2	-	-	✔	✔	✔
Depersonalization	-	-	-	✔	-	-	-	-	-
Depression	✔	-	-	2 to 10	✔	✔	✔	-	-
Disorientation	-	✔	-	-	-	✔	✔	✔	✔
Dizziness	✔	✔	✔	3 to 17	✔	✔	-	✔	✔
Drowsiness	✔	>10	✔	-	✔	✔	✔	-	✔
Dysphoria	✔	✔	-	-	✔	✔	-	✔	✔
Emotional lability	-	-	-	✔	-	-	-	-	-
Euphoria	✔	✔	-	3 to 10	✔	✔	-	✔	✔
Fear	✔	✔	-	-	✔	✔	-	-	-
Hallucinations	-	✔	✔	3 to 10	-	✔	-	✔	✔
Headache	6	✔	✔	3 to 20	6	✔	-	✔	✔
Hemiplegia	-	-	-	✔	-	-	-	-	-
Hostility	-	-	-	✔	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	-	✔	-	-
Hypertonia	-	-	-	✔	-	-	-	-	-
Hypesthesia	-	-	-	✔	-	✔	-	-	-
Hypokinesia	-	-	-	✔	-	-	✔	-	-
Hypotonia	-	-	-	✔	-	-	-	-	-
Impairment of performance	✔	✔	✔	-	✔	✔	-	-	-
Incoordination	-	-	-	✔	-	✔	-	✔	-
Increased intracranial pressure	-	-	-	-	-	✔	-	-	-
Insomnia	✔	✔	-	1 to 10	✔	✔	✔	-	✔
Lethargy	✔	✔	-	-	✔	✔	✔	✔	-
Lightheadedness	✔	✔	-	-	✔	✔	-	-	✔
Mental clouding	✔	✔	-	-	✔	✔	-	-	-

Adverse Events	Benzhydro-codone	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Migraine	✔	-	-	✔	✔	-	-	-	-
Mood changes	✔	✔	-	-	✔	✔	-	✔	-
Myoclonic movements	-	-	-	1 to 4	-	-	-	✔	-
Nervousness	-	-	-	1 to 10	-	✔	✔	-	-
Paranoid reaction	-	-	-	✔	-	-	-	-	-
Paresthesia	✔	-	-	✔	✔	✔	-	-	-
Personality disorder	-	-	-	-	-	-	✔	-	-
Shivering	-	-	-	✔	-	-	-	-	-
Sedation	✔	✔	-	3 to 20	✔	✔	-	✔	✔
Speech disorder	-	-	-	✔	-	-	-	-	-
Stupor	✔	-	-	1 to 4	✔	-	-	-	-
Subdural hematoma	-	-	-	✔	-	-	-	-	-
Suicide attempt	-	-	-	-	-	-	✔	-	-
Tremor	-	-	-	1 to 2	-	✔	-	✔	-
Twitching	-	-	-	-	-	-	-	✔	-
Vertigo	-	-	-	✔	-	-	-	-	-
Weakness	-	✔	-	-	-	✔	-	✔	✔
Withdrawal syndrome	-	-	✔	-	-	-	✔	-	-
Dermatological									
Alopecia	-	-	-	✔	-	-	-	-	-
Application-site reactions	-	-	-	1 to 10	-	-	-	-	-
Exfoliative dermatitis	-	-	-	✔	-	-	-	-	-
Herpes zoster	-	-	-	✔	-	-	-	-	-
Injection site pain/reaction	-	-	-	-	-	✔	✔	-	-
Itching	-	✔	-	1 to 10	-	✔	✔	-	✔
Localized skin reaction	-	-	-	✔	-	-	-	-	-
Pruritus	✔	-	✔	-	✔	✔	-	✔	✔
Pustules	-	-	-	✔	-	-	-	-	✔
Rash	✔	-	-	1 to 8	✔	✔	✔	✔	✔
Skin discoloration	-	-	-	✔	-	-	-	-	-
Skin ulcer	-	-	-	✔	-	-	-	-	-
Sweating	✔	✔	-	-	✔	✔	✔	✔	✔
Urticaria	-	-	-	✔	-	✔	✔	✔	✔
Vesiculobullous rash	-	-	-	✔	-	-	-	-	-
Wheal/flare	-	-	-	-	-	✔	-	-	✔
Endocrine and Metabolic									
Acidosis	-	-	-	✔	-	-	-	-	-
Antidiuretic effect	-	-	-	-	-	✔	-	-	✔
Amenorrhea	-	-	-	-	-	-	-	-	✔
Cyanosis	-	-	-	-	-	-	-	✔	-
Hypercalcemia	-	-	-	✔	-	-	-	-	-

Adverse Events	Benzhydro-codone	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Hyperglycemia	-	-	-	✔	-	-	-	-	-
Hypocalcemia	-	-	-	✔	-	-	<1	-	-
Hypoglycemia	✔	-	-	✔	✔	-	-	-	-
Hypokalemia	-	-	-	✔	-	-	-	✔	✔
Hypomagnesemia	-	-	-	✔	-	-	-	✔	✔
Hyponatremia	-	-	-	✔	-	-	-	-	-
Hypoproteinemia	-	-	-	✔	-	-	-	-	-
Gastrointestinal									
Abdominal distention	-	-	-	✔	-	-	-	-	-
Abdominal pain	✔	-	✔	1 to 10	✔	✔	✔	-	✔
Anorexia	-	✔	-	-	-	✔	-	-	✔
Biliary spasm	-	✔	-	-	-	-	✔	✔	✔
Cheilitis	-	-	-	✔	-	-	-	-	-
Colon hemorrhage	-	-	-	✔	-	-	-	-	-
Constipation	✔	>10	✔	3 to 20	✔	✔	-	✔	✔
Cramps	-	-	-	-	-	✔	-	-	✔
Dry mouth	✔	✔	✔	1 to 10	✔	✔	✔	✔	✔
Diarrhea	✔	-	✔	3 to 10	✔	✔	-	-	-
Dyspepsia	✔	-	-	3 to 10	✔	-	✔	-	-
Dysphagia	-	-	-	✔	-	✔	-	-	-
Eructation	-	-	-	✔	-	-	-	-	-
Esophageal stenosis	-	-	-	✔	-	-	-	-	-
Esophagitis	-	-	-	✔	-	-	-	-	-
Fecal impaction	-	-	-	✔	-	-	-	-	-
Fecal incontinence	-	-	-	✔	-	-	-	-	-
Flatulence	-	-	-	✔	-	-	-	-	-
Gastritis	-	-	-	✔	-	-	-	-	-
Gastroenteritis	✔	-	-	✔	✔	-	-	-	-
Gastrointestinal disorder	-	-	-	✔	-	-	-	-	-
Gastrointestinal hemorrhage	-	-	-	✔	-	-	-	-	-
Gingivitis	-	-	-	✔	-	-	-	-	-
Glossitis	-	-	-	✔	-	-	-	-	✔
Gum hemorrhage	-	-	-	✔	-	-	-	-	-
Heartburn	✔	-	-	-	✔	-	-	-	-
Hepatorenal syndrome	-	-	-	✔	-	-	-	-	-
Ileus	-	-	-	-	-	✔	-	-	-
Increased biliary tract pressure	-	✔	-	1 to 4	-	-	-	-	-
Jaundice	-	-	-	✔	-	-	-	-	-
Liver tenderness	-	-	-	✔	-	-	-	-	-
Mouth ulceration	-	-	-	✔	-	-	-	-	-
Nausea	✔	✔	✔	10 to 45	✔	✔	✔	✔	✔

Adverse Events	Benzhydro-codone	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Oral moniliasis	-	-	-	✔	-	-	-	-	-
Periodontal abscess	-	-	-	✔	-	-	-	-	-
Rectal disorder	-	-	-	✔	-	-	-	-	-
Rectal hemorrhage	-	-	-	✔	-	-	-	-	-
Stomatitis	-	-	-	✔	-	-	-	-	-
Tooth caries	-	-	-	✔	-	-	-	-	-
Tooth disorder	-	-		✔	-	-	-	-	-
Vomiting	✔	✔	✔	6 to 31	✔	✔	✔	✔	✔
Weight loss	-	-	-	✔	-	-	-	-	-
Genitourinary									
Amenorrhea	-	-	-	-	-	-	-	-	✔
Antidiuretic effect	-	✔	-	-	-	✔	-	✔	✔
Bladder pain	-	-	-	✔	-	-	-	-	-
Bladder spasm	✔	-	-	-	✔	✔	-	-	-
Breast neoplasm	-	-	-	✔	-	-	-	-	-
Breast pain	-	-	-	✔	-	-	-	-	-
Decreased libido/potency	-	✔	-	✔	-	-	-	-	✔
Dysuria	-	-	-	✔	-	✔	-	-	-
Hematuria	-	-	-	✔	-	-	-	-	-
Hydronephrosis	-	-	-	✔	-	-	-	-	-
Impotence	-	-	-	✔	-	-	-	-	-
Kidney failure	-	-	✔	✔	-	-	✔	-	-
Kidney pain	-	-	-	✔	-	-	-	-	-
Nephritis	-	-	✔	-	-	-	-	-	-
Nocturia	-	-	-	✔	-	-	-	-	-
Oliguria	-	-	-	✔	-	-	-	-	-
Polyuria	-	-	-	✔	-	-	-	-	-
Scrotal edema	-	-	-	✔	-	-	-	-	-
Spasm of vesical sphincters	-	✔	-	-	-	✔	-	-	-
Ureteral spasm	✔	✔	-	-	✔	-	-	-	-
Urinary frequency	-	-	-	-	-	✔	-	-	-
Urinary hesitancy	-	✔	-	-	-	✔	-	-	✔
Urinary incontinence	-	-	-	✔	-	✔	-	-	-
Urinary retention	✔	✔	-	1 to 10	✔	✔	-	✔	✔
Urinary tract infection	-	-	-	✔	-	-	-	-	-
Urinary urgency	-	-	-	✔	-	-	-	-	-
Urination impaired	-	-	-	✔	-	-	-	-	-
Vaginal hemorrhage	-	-	-	✔	-	-	-	-	-
Vaginitis	-	-	-	✔	-	-	-	-	-
Hematologic									
Agranulocytosis	✔	-	-	-	✔	-	-	-	-

Adverse Events	Benzhydro-codone	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Anemia	✔	-	-	✔	✔	-	-	-	-
Bleeding time increased	-	-	-	✔	-	-	-	-	-
Ecchymosis	-	-	-	✔	-	-	-	-	-
Hemoglobin disease	-	-	-	✔	-	-	-	-	-
Leukopenia	-	-	-	✔	-	-	-	-	-
Leukocytosis	-	-	-	✔	-	-	-	-	-
Lymphadenopathy	-	-	-	✔	-	-	-	-	-
Lymphedema	-	-	-	✔	-	-	-	-	-
Lymphoma-like reaction	-	-	-	✔	-	-	-	-	-
Pancytopenia	-	-	-	✔	-	-	-	-	-
Thrombocytopenia	✔	-	-	✔	✔	-	-	-	✔
Laboratory Test Abnormalities									
Alanine transaminase increased	-	✔	-	-	-	-	-	-	-
Aspartate aminotransferase increased	-	✔	-	-	-	-	-	-	-
Musculoskeletal									
Arthralgia	-	-	-	✔	-	-	-	-	-
Arthritis	-	-	-	✔	-	-	-	-	-
Back pain	-	-	-	✔	-	-	-	-	-
Bone disorder	-	-	-	✔	-	-	-	-	-
Chest wall rigidity	-	-	-	-	-	-	-	-	-
Joint disorder	-	-	-	✔	-	-	-	-	-
Leg cramps	-	-	-	✔	-	-	-	-	-
Muscle tremor	-	-	-	✔	-	-	-	-	-
Myalgia	-	-	-	✔	-	-	-	-	-
Myasthenia	-	-	-	✔	-	-	-	-	-
Myopathy	-	-	-	✔	-	-	-	-	-
Neck pain	-	-	-	✔	-	-	-	-	-
Neck rigidity	-	-	-	-	-	-	-	-	-
Pathological fracture	-	-	-	✔	-	-	-	-	-
Skeletal muscle movement	-	-	-	-	-	-	-	-	-
Synovitis	-	-	-	✔	-	-	-	-	-
Tendon disorder	-	-	-	✔	-	-	-	-	-
Weakness	-	-	-	-	-	-	-	✔	✔
Respiratory									
Asthma	-	-	-	✔	-	-	-	-	-
Bronchitis	-	-	-	✔	-	-	-	-	-
Cough	-	-	-	✔	-	-	-	-	-
Dyspnea	✔	-	-	2 to 22	✔	✔	-	✔	-
Epistaxis	-	-	-	✔	-	-	-	-	-
Hemoptysis	-	-	-	✔	-	-	-	-	-

Adverse Events	Benzhydro-codone	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Hiccoughs	-	-	-	✔	-	-	-	-	-
Hyperventilation	-	-	-	✔	-	✔	-	-	-
Laryngospasm	-	-	-	✔	-	✔	-	-	-
Lung disorder	-	-	-	✔	-	-	-	-	-
Pharyngitis	-	-	-	3 to 10	-	-	-	-	-
Pleural effusion	-	-	-	✔	-	-	-	-	-
Pneumonia	-	-	-	✔	-	-	-	-	-
Pneumothorax	-	-	-	✔	-	-	-	-	-
Pulmonary edema	-	-	-	-	-	-	-	-	✔
Pulmonary embolus	-	-	-	✔	-	-	-	-	-
Respiratory arrest	-	✔	-	✔	-	✔	-	✔	✔
Respiratory depression	✔	✔	✔	✔	✔	✔	-	✔	✔
Respiratory disorder	-	-	-	✔	-	-	-	-	-
Respiratory insufficiency	-	-	-	✔	-	-	-	-	-
Rhinitis	-	-	-	✔	-	-	-	-	-
Sinusitis	-	-	-	✔	-	-	-	-	-
Sputum increased	-	-	-	✔	-	-	-	-	-
Stertorous breathing	-	-	-	✔	-	-	-	-	-
Suppressed cough reflex	-	✔	-	-	-	-	-	-	-
Other									
Abnormal vision	-	-	-	0 to 3	-	-	✔	-	-
Abscess	-	-	-	✔	-	-	-	-	-
Accidental injury	-	-	-	0 to 9	-	-	-	-	-
Allergic reaction	✔	✔	✔	✔	✔	✔	-	-	-
Amblyopia	-	-	-	✔	-	-	-	-	-
Anaphylaxis	-	-	-	✔	-	-	-	✔	✔
Ascites	-	-	-	✔	-	-	-	-	-
Blurred vision	-	-	-	✔	-	-	-	-	-
Bone pain	-	-	-	✔	-	-	-	-	-
Cataracts	-	-	-	✔	-	-	-	-	-
Cellulitis	-	-	-	✔	-	-	-	-	-
Chills	-	-	-	✔	-	✔	-	-	-
Conjunctivitis	-	-	-	✔	-	-	-	-	-
Death	-	-	-	-	-	-	-	-	✔
Dehydration	-	-	-	✔	-	-	-	-	-
Diaphoresis	-	-	-	-	-	-	-	-	✔
Diplopia	-	-	-	✔	-	-	✔	-	-
Dry eyes	-	-	-	✔	-	-	-	-	-
Dysgeusia	-	-	-	✔	-	-	-	-	-
Ear disorder	-	-	-	✔	-	-	-	-	-
Ear pain	-	-	-	✔	-	-	-	-	-

Adverse Events	Benzhydro-codone	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Edema	-	-	-	✔	-	-	-	-	✔
Eye hemorrhage	-	-	-	✔	-	-	-	-	-
Fever	-	-	-	✔	-	-	-	-	-
Flu syndrome	-	-	-	✔	-	-	-	-	-
Fungal infection	-	-	-	✔	-	-	-	-	-
Hyperacusis	-	-	-	✔	-	-	-	-	-
Infection	-	-	-	✔	-	-	-	-	-
Lacrimation disorder	-	-	-	✔	-	-	-	-	-
Malaise	-	-	-	✔	-	-	-	-	-
Miosis	-	✔	-	✔	-	✔	-	-	✔
Nystagmus	-	-	-	✔	-	✔	-	-	-
Pain	-	-	-	✔	-	-	-	-	-
Pelvic pain	-	-	-	✔	-	-	-	-	-
Sepsis	-	-	-	✔	-	-	-	-	-
Shock	-	✔	-	-	-	✔	✔	✔	✔
Taste perversion	-	-	-	✔	-	✔	-	-	-
Tinnitus	-	-	-	✔	-	-	-	✔	-
Transitory deafness	-	-	-	✔	-	-	-	-	-
Viral infection	-	-	-	✔	-	-	-	-	-
Visual disturbances	-	✔	-	✔	-	✔	✔	✔	✔

✔ Percent not specified.
- Event not reported.

Table 10. Adverse Drug Events (%) Reported with the Opiate Agonists (Drugs M-Z)[4-6]

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Cardiovascular					
Abnormal ECG	-	-	-	-	<1
Arrhythmia	-	-	-	-	-
Atrial fibrillation	✔	-	-	-	-
Bradycardia	✔	-	✔	<1	<1
Cardiac arrest	✔	✔	-	-	-
Chest pain	✔	-	-	-	-
Circulatory depression/collapse	✔	✔	-	-	-
Congestive heart failure	-	<3	-	-	-
Extrasystoles	✔	-	-	-	-
Faintness	✔	-	-	-	-
Heart failure	-	-	-	-	-
Hypertension	✔	✔	✔	<1	<1
Hypotension	✔	1 to 5	✔	<1	<1

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Myocardial infarction	-	-	-	-	<1
Myocardial ischemia	-	-	-	-	<1
Orthostatic hypotension	-	✔	-	-	<1
Palpitation	✔	<3	-	-	<1
Pallor	✔	-	-	-	-
Peripheral edema	3 to 10	-	-	-	<1
Presyncope	-	-	-	<1	-
ST suppression	-	<1	-	-	-
Suicidal tendency	-	-	-	-	<1
Syncope	✔	-	-	<1	<1
Tachycardia	✔	<3	✔	<1	<1
Vasodilation	✔	<3	-	-	1 to 5
Central Nervous System					
Abnormal dreams	✔	✔	-	1	<1
Abnormal gait	✔	✔	-	-	<1
Abnormal thinking	✔	-	-	-	<1
Agitation	✔	<1	-	<1	<1
Amnesia	✔	-	-	-	<1
Anxiety	✔	✔	✔	1	1 to 5
Asthenia	✔	6	-	-	6 to 12
Ataxia	✔	-	-	<1	-
Attention disturbances	-	-	-	<1	-
Central nervous system stimulation	-	-	✔	-	7 to 14
Cognitive dysfunction	-	-	-	-	<1
Coma	✔	-	-	-	-
Concentration difficulty	-	-	-	-	<1
Confusion	✔	1 to 5	✔	1	1 to 5
Consciousness decreased	-	-	-	<1	-
Convulsion	✔	<1	-	-	<1
Coordination abnormal	-	-	-	<1	-
Delirium	✔	-	-	-	-
Depression	✔	<1	✔	-	<1
Disorientation	✔	<1	✔	<1	<1
Dizziness	6	2 to 13	7 to 18	24	10 to 33
Drowsiness	9 to >10	<5 to 23	9 to 19	-	7 to 25
Dysphoria	-	✔	-	-	-
Emotional lability	-	<1	-	-	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Euphoria	✔	1 to 5	✔	<1	1 to 5
Hallucinations	-	<1	✔	<1	<1
Headache	<2 to >10	7 to 14	7 to 12	<1	4 to 32
Insomnia	✔	1 to 5	✔	2	2 to 11
Irritability	-	✔	-	<1	<1
Lethargy	✔	✔	✔	1	-
Lightheadedness	✔	-	-	-	-
Memory impairment	-	-	-	<1	-
Migraine	-	<3	-	-	<1
Nervousness	-	1 to 5	✔	<1	1 to 5
Paresthesia	✔	✔	-	<1	<1
Personality disorder	-	<3	-	-	-
Restlessness	-	-	✔	<1	-
Serotonin syndrome	-	-	-	-	<1
Sedation	✔	23	✔	<1	16 to 25
Seizure	✔	-	-	<1	<1
Sleep disorder	-	-	-	-	<1
Somnolence	-	-	-	15	-
Speech disorder	-	<1	-	-	<1
Stupor	-	<1	-	-	-
Suicide	-	-	-	-	<1
Tremor	✔	<3	-	1	<1
Twitching	-	1 to 5	-	-	26 to 33
Vertigo	✔	<1	-	-	-
Weakness	✔	-	✔	-	-
Withdrawal syndrome	✔	<1 to 5	-	<1	-
Dermatological					
Cellulitis	-	-	-	-	<1
Dry skin	✔	-	<1	-	-
Exfoliative dermatitis	-	-	<1	-	-
Flushing	-	-	✔	1	-
Hyperhidrosis	-	✔	-	3	-
Itching/pruritus	✔	✔	13	-	8 to 11
Pruritus	✔	✔	8 to 15	3 to 5	3 to 12
Rash	✔	✔	1 to 5	1	1 to 5
Stevens-Johnson Syndrome	-	-	-	-	<1
Sweating	✔	✔	5	-	6 to 9

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Toxic epidermal necrolysis	-	-	-	-	<1
Urticaria	✔	-	<3	<1	<1
Vesicles	-	-	-	-	<1
Wheal/flare	✔	-	-	-	1 to 5
Endocrine and Metabolic					
Gout	-	-	<3	-	-
Hyperglycemia	-	✔	<3	-	-
Menstrual disorder	-	-	-	-	<1
Metabolic acidosis	-	-	-	-	-
Gastrointestinal					
Abdominal distention	-	-	<10	-	-
Abdominal pain	3 to 10	✔	✔	<1	1 to 5
Abnormal liver function tests	✔	-	-	-	✔
Anorexia	✔	✔	1 to 5	-	1 to 5
Appetite increased	-	-	<1	-	-
Biliary spasm	✔	✔	✔	-	-
Cholecystitis	-	-	-	-	<1
Cholelithiasis	-	-	-	-	<1
Colonic motility increased	✔	-	-	-	-
Constipation	9 to >10	5 to 23	4 to 28	8	9 to 46
Cramps	✔	-	✔	-	-
Diverticulitis	-	-	-	-	<1
Dry mouth	✔	✔	6	4	5 to 10
Diarrhea	3 to 10	✔	1 to 5	<1	5 to 10
Dyspepsia	✔	✔	1 to 5	2	1 to 13
Dysphagia	✔	-	<1	-	<1
Eructation	-	-	<1	-	-
Flatulence	-	-	<1	-	1 to 5
Gastric emptying decreased	-	-	-	<1	-
Gastritis	-	✔	1 to 5	-	-
Gastroenteritis	✔	-	-	-	-
Gastrointestinal disorder	-	-	<1	-	-
Gastrointestinal hemorrhage	-	-	-	-	✔
Hepatic failure	-	-	-	-	✔
Hepatitis	-	-	-	-	✔
Ileus	✔	✔	<1	-	-
Intestinal obstruction	✔	-	-	-	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Nausea	7 to >10	11 to 23	19 to 33	30	15 to 40
Rectal disorder	✔	-	-	-	-
Stomatitis	-	-	<1	-	<1
Taste perversion	-	-	-	-	<1
Toxic megacolon	✔	✔	-	-	-
Vomiting	2 to >10	4 to 21	9 to 16	18	5 to 17
Weight loss	✔	-	-	-	<1
Genitourinary					
Abnormal ejaculation	✔	-	-	-	-
Amenorrhea	✔	-	<1	-	-
Antidiuretic effect	-	✔	<1	-	-
Dysmenorrhea	-	-	-	-	<1
Dysuria	✔	✔	<1	-	<1
Fecal impaction	-	-	-	-	<1
Gastroenteritis	-	-	-	-	<1
Gastrointestinal bleeding	-	-	-	-	<1
Hematuria	-	-	<1	-	<1
Impotence	✔	-	-	-	-
Libido decreased	-	-	<1	<1	<1
Menopausal symptoms	-	-	-	-	1 to 5
Menstrual disorder	-	-	-	-	<1
Pollakiuria	✔	-	-	-	-
Polyuria	-	-	<1	-	-
Proteinuria	-	-	-	-	<1
Spasm of vesical sphincters	✔	-	-	-	-
Ureteral spasm	✔	✔	-	-	-
Urinary frequency	-	-	-	-	1 to 5
Urinary hesitancy	✔	✔	-	<1	-
Urinary retention	✔	✔	-	-	1 to 5
Urinary tract infection	✔	-	-	1	-
Urination impaired	-	-	-	-	-
Hematologic					
Anemia	✔	-	-	-	<1
Hemoglobin decreased	-	-	-	-	<1
Lymphadenopathy	-	-	<1	-	-
Thrombocytopenia	✔	-	-	-	<1
Hepatic					

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Hepatic steatosis	-	-	-	-	-
Hepatitis	-	-	-	-	<1
Hepatocellular injury	-	-	-	-	-
Hepatomegaly	-	-	-	-	-
Jaundice	-	-	-	-	-
Liver dysfunction	-	-	-	-	-
Liver failure	-	-	-	-	<1
Laboratory Test Abnormalities					
Alanine transaminase increased	-	-	-	<1	<1
Aspartate aminotransferase increased	-	-	-	<1	<1
Creatinine increased	-	-	-	-	<1
Hyperglycemia	-	-	-	-	<1
Musculoskeletal					
Arthralgia	✔	-	<3	1	-
Arthritis	-	-	<3	-	-
Dysarthria	-	-	-	<1	-
Hypertonia	-	-	-	-	1 to 5
Hypotonia	-	<1	-	-	-
Involuntary muscle contractions	-	-	-	<1	-
Muscle cramps	-	-	-	-	<1
Muscle spasms	✔	-	-	-	<1
Muscle twitching	✔	-	-	-	<1
Myalgia	-	-	<3	-	<1
Weakness	✔	-	✔	<1	-
Respiratory					
Bronchitis	-	-	<3	-	1 to 5
Bronchospasm	-	-	-	-	<1
Cough	-	✔	<3	<1	1 to 5
Dyspnea	✔	✔	1 to 5	<1	1 to 5
Epistaxis	-	-	<3	-	-
Hiccoughs	-	-	1 to 5	-	-
Hypoxia	✔	-	<3	-	-
Laryngospasm	✔	-	<3	-	-
Lung disorder	-	-	<3	-	-
Pharyngitis	-	-	-	1	-
Pneumonia	-	-	-	-	<1
Pulmonary edema	-	-	-	-	<1

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Pulmonary embolus	-	-	-	-	<1
Respiratory arrest	✔	-	-	-	-
Respiratory depression	✔	✔	-	<1	-
Rhinitis	-	-	<3	-	-
Sinusitis	-	-	<3	-	1 to 5
Other					
Abnormal vision	-	-	<1	-	-
Abscess	✔	-	-	-	<1
Accidental injury	-	-	<3	-	<1
Allergic laryngeal edema	-	✔	-	-	-
Allergic laryngospasm	-	✔	-	-	-
Allergic reaction	-	✔	<3	<1	<1
Amblyopia	-	<3	-	-	-
Anaphylaxis	✔	-	<1	-	<1
Angioedema	-	-	-	-	<1
Appendicitis	-	-	-	-	<1
Back pain	-	-	<3	-	-
Blurred vision	-	✔	-	-	-
Bone pain	-	-	<3	-	-
Cataracts	-	-	-	-	<1
Chills	✔	-	<3	-	-
Deafness	-	-	-	-	<1
Deep thrombophlebitis	-	<3	-	-	-
Dehydration	✔	-	<3	-	-
Diplopia	✔	✔	-	-	-
Dry eyes	-	-	-	-	<1
Ear infection	-	-	-	-	<1
Ear pain	-	-	-	<1	-
Edema	✔	-	-	<1	<1
Eye edema	-	-	-	-	-
Eye hemorrhage	✔	-	-	-	-
Flank pain	-	-	<3	-	-
Flu syndrome	✔	-	-	-	-
Fracture	-	-	<3	-	-
Fungal infection	-	-	<3	-	-
Hemorrhage	-	<3	-	-	-
Herpes simplex	-	-	<3	-	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Hypersensitivity	-	-	-	<1	<1
Hypoesthesia	-	-	-	<1	-
Infection	✔	-	-	1	-
Joint stiffness	-	-	-	-	<1
Malaise	✔	-	-	-	1 to 5
Miosis	✔	✔	-	-	-
Night sweats	-	-	-	-	<1
Nystagmus	✔	-	-	-	-
Pain	-	-	<3	-	-
Pancreatitis	-	-	-	-	<1
Pharyngolaryngeal pain	-	-	-	<1	-
Phlebitis	✔	-	-	-	-
Sepsis	✔	-	<3	-	-
Serotonin syndrome	-	-	-	-	<1
Shock	✔	-	✔	-	-
Taste perversion	✔	-	<1	-	-
Tinnitus	-	-	<1	-	<1
Visual disturbances	✔	-	-	<1	<1

✔ Percent not specified.
- Event not reported.

Table 11. Adverse Drug Events (%) Reported with the Combination Opiate Agonists[4-6]

Adverse Events	Opium and Belladonna
Cardiovascular	
Palpitation	✔
Central Nervous System	
Asthenia	✔
Dizziness	✔
Drowsiness	✔
Seizure	✔
Somnolence	✔
Dermatological	
Pruritus	✔
Urticaria	✔
Gastrointestinal	
Constipation	✔
Dry mouth	✔
Dyspepsia	✔
Nausea	✔
Vomiting	✔
Genitourinary	
Urinary retention	✔
Respiratory	
Respiratory depression	✔
Other	
Blurred vision	✔

✔ Percent not specified.

Table 12. Boxed Warning for Acetaminophen-Containing Products[6]

WARNING
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product.

Table 13. Boxed Warning for Codeine- and Dihydrocodeine-Containing Products[6]

WARNING
Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

Table 14. Boxed Warning for Benzhydrocodone and Hydrocodone Containing Products[4]

WARNING
Addiction, abuse, and misuse Benzhydrocodone/hydrocodone exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing, and monitor all patients regularly for the development of these behaviors and conditions. **Opioid analgesic risk evaluation and mitigation strategy** To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the FDA has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to health care providers. Health care providers are strongly encouraged to complete a REMS-compliant education program and counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products, emphasize to patients and their caregivers the importance of reading the Medication Guide every time

WARNING
it is provided by their pharmacist, and consider other tools to improve patient, household, and community safety. **Life-threatening respiratory depression** Serious, life-threatening, or fatal respiratory depression may occur with use of these agents. Monitor for respiratory depression, especially during initiation or following a dose increase. **Accidental ingestion** Accidental ingestion of these agents, especially by children, can result in a fatal overdose. **Neonatal opioid withdrawal syndrome** Prolonged use of these agents during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. **Cytochrome P450 3A4 interaction** The concomitant use of these agents with all CYP-450 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used CYP-450 3A4 inducer may result in an increase in hydrocodone plasma concentrations. Monitor patients receiving these agents and any CYP-450 3A4 inhibitor or inducer for signs of respiratory depression or sedation. **Risks from concomitant use with benzodiazepines or other CNS depressants** Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of hydrocodone/acetaminophen and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Table 15. Boxed Warning for Transdermal Fentanyl[6]

WARNING
Addiction, abuse, and misuse: Fentanyl exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing fentanyl, and monitor all patients regularly for the development of these behaviors or conditions. **Life-threatening respiratory depression**: Serious, life-threatening, or fatal respiratory depression may occur with use of fentanyl, even when used as recommended. Monitor for respiratory depression, especially during initiation of fentanyl or following a dose increase. Because of the risk of respiratory depression, fentanyl is contraindicated for use as an as-needed analgesic, in nonopioid tolerant patients, in acute pain, and in postoperative pain. **Accidental exposure**: Deaths due to a fatal overdose of fentanyl have occurred when children and adults were accidentally exposed to fentanyl, including an intact Ionsys device or the hydrogel component in Ionsys, through contact with skin or contact with mucous membranes. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure. **Neonatal opioid withdrawal syndrome**: Prolonged use of fentanyl during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. **Cytochrome P450 3A4 interaction**: The concomitant use of fentanyl with all cytochrome P450 (CYP-450) 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong

WARNING
adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving fentanyl and any CYP3A4 inhibitor or inducer. **Risks from concomitant use with benzodiazepines or other CNS depressants**: Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of fentanyl and benzodiazepine or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation. **Exposure to heat (Duragesic only)**: Exposure of the fentanyl application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds may increase fentanyl absorption and has resulted in fatal overdose of fentanyl and death. Patients wearing fentanyl systems who develop fever or increased core body temperature due to strenuous exertion are also at risk for increased fentanyl exposure and may require an adjustment in the dose of fentanyl to avoid overdose and death.

Table 16. Boxed Warning for Hydromorphone Oral[6]

WARNING
Hydromorphone immediate release: Hydromorphone is a potent Schedule II controlled opioid agonist. Schedule II opioid agonists have the highest potential for abuse and risk of producing respiratory depression. Alcohol, other opioids, and CNS depressants (sedative-hypnotics) potentiate the respiratory depressant effects of hydromorphone, increasing the risk of respiratory depression that might result in death. **Hydromorphone extended release**: **Addiction, abuse, and misuse**: Hydromorphone extended release (ER) exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing hydromorphone ER, and monitor all patients regularly for the development of these behaviors or conditions. **Life-threatening respiratory depression**: Serious, life-threatening, or fatal respiratory depression may occur with use of hydromorphone ER. Monitor for respiratory depression, especially during initiation of hydromorphone ER or following a dose increase. Instruct patients to swallow hydromorphone ER tablets whole; crushing, chewing, or dissolving tablets can cause rapid release and absorption of a potentially fatal dose of hydromorphone. **Accidental ingestion**: Accidental ingestion of even 1 dose, especially in children, can result in a fatal overdose of hydromorphone. **Neonatal opioid withdrawal syndrome**: Prolonged use during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. **Risk of medication errors (oral solution)**: Ensure accuracy when prescribing, dispensing, and administering. Dosing errors due to confusion between mg and mL can result in accidental overdose and death. R**isk from concomitant use with benzodiazepines or other CNS depressants**: Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of hydromorphone and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Table 17. Boxed Warning for Hydromorphone Injection[6]

WARNING
Risk of Medication Errors Hydromorphone hydrochloride injection (high potency formulation) is a more concentrated solution of hydromorphone than hydromorphone hydrochloride injection, and is for use in opioid-tolerant patients only. Do not confuse hydromorphone hydrochloride injection (high potency formulation) with standard parenteral formulations of hydromorphone hydrochloride injection or other opioids, as overdose and death could result. **Addiction, Abuse, and Misuse** Hydromorphone hydrochloride injection (high potency formulation) exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing hydromorphone hydrochloride injection (high potency formulation) and monitor all patients regularly for the development of these behaviors and conditions. **Life-Threatening Respiratory Depression** Serious, life-threatening, or fatal respiratory depression may occur with use of hydromorphone hydrochloride injection (high potency formulation). Monitor for respiratory depression, especially during initiation of hydromorphone hydrochloride injection (high potency formulation) or following a dose increase. **Neonatal Opioid Withdrawal Syndrome** Prolonged use of hydromorphone hydrochloride injection (high potency formulation) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. **Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants** Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. • Reserve concomitant prescribing of hydromorphone hydrochloride (high potency formulation) and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. • Limit dosages and durations to the minimum required. • Follow patients for signs and symptoms of respiratory depression and sedation. .

Table 18. Boxed Warning for Methadone[6]

WARNING
Addiction, abuse, and misuse: Methadone exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing methadone, and monitor all patients regularly for the development of these behaviors or conditions. **Life-threatening Respiratory Depression**: Serious, life-threatening, or fatal respiratory depression may occur; has been reported during initiation and conversion of patients to methadone, and even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and methadone should only be prescribed by health care providers who are knowledgeable in the use of methadone for detoxification and maintenance treatment of opioid addiction. Monitor for respiratory depression, especially during initiation of methadone or following a dose increase. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect, especially during the initial dosing period. **Life-threatening QT Prolongation**: QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Closely monitor patients for changes in cardiac rhythm

WARNING
during initiation and titration of methadone. **Neonatal opioid withdrawal syndrome**: Neonatal opioid withdrawal syndrome is an expected and treatable outcome of use of methadone during pregnancy. Neonatal opioid withdrawal syndrome may be life-threatening if not recognized and treated in the neonate. The balance between the risks of neonatal opioid withdrawal syndrome and the benefits of maternal methadone use may differ based on the risks associated with the mother's underlying condition, pain, or addiction. Advise the patient of the risk of neonatal opioid withdrawal syndrome so that appropriate planning for management of the neonate can occur. **Accidental ingestion**: Accidental ingestion of methadone, especially in children, can result in a fatal overdose of methadone. **Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction**: For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration. When used for the treatment of opioid addiction in detoxification or maintenance programs, methadone should be dispensed only by opioid treatment programs (and agencies, or practitioners or institutions by formal agreement with the program sponsor) certified by the substance abuse and mental health services administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of drug supply, revocation of program approval, and injunction precluding program operation. **Cytochrome P450 interaction**: The concomitant use of methadone with all cytochrome P450 (CYP-450) 3A4, 2B6, 2C19, 2C9, or 2D6 inhibitors may result in an increase in methadone plasma concentrations, which could cause potentially fatal respiratory depression. In addition, discontinuation of concomitantly used CYP450 3A4, 2B6, 2C19, or 2C9 inducers may also result in an increase in methadone plasma concentration. Follow patients closely for respiratory depression and sedation, and consider dosage reduction with any changes of concomitant medications that can result in an increase in methadone levels. **Risks from concomitant use with benzodiazepines or other CNS depressants**: Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of methadone and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Table 19. Boxed Warning for Morphine Injection[6]

WARNING
Risks with Neuroaxial Administration INFUMORPH: Because of the risk of severe adverse reactions when INFUMORPH is administered by the epidural or intrathecal route of administration, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial (single) test dose and, as appropriate, for the first several days after catheter implantation. DURAMORPH: Single-dose neuraxial administration may result in acute or delayed respiratory depression up to 24 hours. Because of the risk of severe adverse reactions when DURAMORPH is administered by the epidural or intrathecal route of administration, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose. **Life-Threatening Respiratory Depression** INFUMORPH: Serious, life-threatening, or fatal respiratory depression may occur with use of INFUMORPH. Monitor for respiratory depression, especially during initiation of INFUMORPH or following a dose increase. Patients must be observed in a fully equipped and staffed environment for at least 24 hours after each test dose and, as indicated, for the first several days after surgery. DURAMORPH: Serious, life-threatening, or fatal respiratory depression may occur with use of

DURAMORPH. Monitor for respiratory depression, especially during initiation of DURAMORPH or following a dose increase. Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid IV administration may result in overdosing.

Addiction, Abuse, and Misuse
INFUMORPH/DURAMORPH exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing, and monitor all patients regularly for the development of these behaviors and conditions.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of INFUMORPH/DURAMORPH during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of INFUMORPH/DURAMORPH and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Table 20. Boxed Warning for Morphine Oral[4]

WARNING

Ethanol use (extended-release capsules)
Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking morphine extended-release (ER) capsules. The coingestion of alcohol with morphine may result in increased plasma levels and a potentially fatal overdose of morphine.

Addiction, abuse, and misuse
Morphine exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing morphine and monitor all patients regularly for the development of these behaviors and conditions.

Life-threatening respiratory depression
Serious, life-threatening, or fatal respiratory depression may occur with use of morphine. Monitor for respiratory depression, especially during initiation of morphine or following a dose increase. Swallow morphine ER formulations whole; ER capsule contents may be sprinkled on applesauce and swallowed immediately without chewing. Crushing, chewing, or dissolving the tablets or contents within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine.

Neonatal opioid withdrawal syndrome
Prolonged use of morphine during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Accidental ingestion
Accidental ingestion of even one dose of morphine, especially by children, can result in a fatal overdose of morphine.

Risks from concomitant use with benzodiazepines or other CNS depressants
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in

WARNING
profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of morphine and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation. **Risk of medication errors (oral solution)** Ensure accuracy when prescribing, dispensing, and administering morphine sulfate oral solution. Dosing errors due to confusion between mg and mL, and other morphine solutions of different concentrations, can result in accidental overdose and death.

Table 21. Boxed Warning for Oxycodone[4]

WARNING
Addiction, abuse, and misuse Oxycodone exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing oxycodone and monitor all patients regularly for the development of these behaviors or conditions. **Life-threatening respiratory depression** Serious, life-threatening, or fatal respiratory depression may occur with use of oxycodone. Monitor for respiratory depression, especially during initiation of oxycodone or following a dose increase. Instruct patients to swallow oxycodone ER tablets whole; crushing, chewing, or dissolving oxycodone ER tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone**.** **Accidental ingestion** Accidental ingestion of even one dose of oxycodone, especially by children, can result in a fatal overdose of oxycodone. **Neonatal opioid withdrawal** Prolonged use of oxycodone during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. **Cytochrome P450 3A4 interaction** The concomitant use of oxycodone with all cytochrome P450 (CYP-450) 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used CYP3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving oxycodone and any CYP3A4 inhibitor or inducer. **Risks from concomitant use with benzodiazepines or other CNS depressants** Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of oxycodone and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation. **Risk of medication errors (oral solution)** Ensure accuracy when prescribing, dispensing, and administering oxycodone oral solution. Dosing errors due to confusion between mg and mL, and other oxycodone oral solutions of different concentrations can result in accidental overdose.

Table 22. Boxed Warning for Oxymorphone[4]

WARNING

Addiction, abuse, and misuse
Oxymorphone exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing oxymorphone, and monitor all patients regularly for the development of these behaviors and conditions.

Life-threatening respiratory depression
Serious, life-threatening, or fatal respiratory depression may occur with use of oxymorphone. Monitor for respiratory depression, especially during initiation of oxymorphone or following a dose increase. Instruct patients to swallow oxymorphone extended-release ER tablets whole; crushing, chewing, or dissolving oxymorphone (ER) tablets can cause rapid release and absorption of a potentially fatal dose of oxymorphone.

Accidental ingestion
Accidental ingestion of even 1 dose of oxymorphone, especially by children, can result in a fatal overdose of oxymorphone.

Neonatal opioid withdrawal syndrome
Prolonged use of oxymorphone during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Interaction with alcohol
Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking oxymorphone. The coingestion of alcohol with oxymorphone may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

Risks from concomitant use with benzodiazepines or other CNS depressants
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of oxymorphone and benzodiazepine or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Table 23. Boxed Warning for Tapentadol[4]

WARNING

Addiction, abuse, and misuse
Tapentadol exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing tapentadol, and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening respiratory depression
Serious, life-threatening, or fatal respiratory depression may occur with use of tapentadol. Monitor for respiratory depression, especially during initiation of tapentadol or following a dose increase. Instruct patients to swallow tapentadol ER tablets whole; crushing, dissolving, or chewing tapentadol ER can cause rapid release and absorption of a potentially fatal dose of tapentadol.

Accidental ingestion
Accidental ingestion of even 1 dose of tapentadol, especially by children, can result in a fatal overdose of tapentadol.

Neonatal opioid withdrawal syndrome
Prolonged use of tapentadol during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Interaction with alcohol (extended release)
Patients must not consume alcoholic beverages or take prescription or nonprescription medications that contain alcohol while taking tapentadol ER. The coingestion of alcohol with tapentadol ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.

Risks from concomitant use with benzodiazepines or other CNS depressants
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of tapentadol and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Table 24. Boxed Warning for Tramadol[4]

WARNING

Addiction, abuse, and misuse
Tramadol exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing tramadol, and monitor all patients regularly for the development of these behaviors and conditions.

Life-threatening respiratory depression
Serious, life-threatening, or fatal respiratory depression may occur with use of tramadol. Monitor for respiratory depression, especially during initiation of tramadol or following a dose increase. Instruct patients to swallow tramadol capsules and tablets intact, and not to split, break, chew, crush, or dissolve the contents of the capsules or tablets to avoid exposure to a potentially fatal dose of tramadol

Accidental ingestion
Accidental ingestion of even one dose of tramadol, especially by children, can result in a fatal overdose of tramadol.

Ultra-rapid metabolism of tramadol and other risk factors for life-threatening respiratory depression in children
Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases occurred following tonsillectomy and/or adenoidectomy; in at least 1 case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP-450 2D6 polymorphism. Tramadol is contraindicated in pediatric patients <12 years and in pediatric patients <18 years following tonsillectomy and/or adenoidectomy. Avoid the use of tramadol in pediatric patients 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol.

Neonatal opioid withdrawal syndrome
Prolonged use of tramadol during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

CYP-450 interaction
The effects of concomitant use or discontinuation of CYP3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of CYP3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1.

Risks from concomitant use with benzodiazepines or other CNS depressants
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of tramadol and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Table 25. Boxed Warning for Tramadol-Celecoxib[4]

WARNING
WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; CARDIOVASCULAR THROMBOTIC EVENTS; GASTROINTESTINAL BLEEDING, ULCERATION, AND PERFORATION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS ADDICTION, ABUSE, AND MISUSE SEGLENTIS exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing SEGLENTIS and monitor all patients regularly for the development of these behaviors and conditions. OPIOID ANALGESIC RISK EVALUATION AND MITIGATION STRATEGY (REMS) To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to • complete a REMS-compliant education program, • counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products, • emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and • consider other tools to improve patient, household, and community safety. LIFE-THREATENING RESPIRATORY DEPRESSION Serious, life-threatening, or fatal respiratory depression may occur with use of SEGLENTIS. Monitor for respiratory depression, especially during initiation of SEGLENTIS. ACCIDENTAL INGESTION Accidental ingestion of even one dose of SEGLENTIS, especially by children, can be fatal. CARDIOVASCULAR THROMBOTIC EVENTS • Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction, and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. • SEGLENTIS is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. GASTROINTESTINAL BLEEDING, ULCERATION, AND PERFORATION NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious (GI) events. ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFETHREATENING RESPIRATORY DEPRESSION IN CHILDREN Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism. SEGLENTIS is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Avoid the use of SEGLENTIS in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol.

NEONATAL OPIOID WITHDRAWAL SYNDROME
Prolonged use of SEGLENTIS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES
The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with SEGLENTIS requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1.

RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of SEGLENTIS and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit treatment to the minimum duration.
- Follow patients for signs and symptoms of respiratory depression and sedation.

VII. Dosing and Administration

The usual dosing regimens for the opiate agonists are listed in Table 26.

Table 26. Usual Dosing Regimens for the Opiate Agonists[4-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Codeine	Analgesia: Solution, tablet: 15 to 60 mg every four to six hours	Safety and efficacy in children have not been established.	Tablet: 15 mg 30 mg 60 mg
Fentanyl	Analgesia: Buccal lozenge: initial, 200 µg; titrate as necessary; maximum, two doses per breakthrough pain episode; wait at least four hours before treating another episode of breakthrough pain Buccal tablet: initial, 100 µg; maximum, two doses per breakthrough pain episode; may repeat dosing after 30 minutes for a single episode of breakthrough pain; wait at least four hours before treating another episode of breakthrough pain; titrate as necessary Injection: 50 to 100 µg IM or slow IV Transdermal patch: dose should	Analgesia: Buccal lozenge: ≥16 years of age, initial, 200 µg; titrate as necessary; maximum, two doses per breakthrough pain episode; wait at least four hours before treating another episode of breakthrough pain Injection: ≥12 years of age: 50 to 100 µg IM or slow IV; two to 12 years of age, 2 to 3 µg/kg Transdermal patch: ≥2 years of age, dose should be based on individual need; one patch is to be applied every 72 hours; however, some may require application of every 48 hours rather than	Buccal lozenge: 200 µg 400 µg 600 µg 800 µg 1,200 µg 1,600 µg Buccal tablet: 100 µg 200 µg 400 µg 600 µg 800 µg Injection: 50 µg/mL Transdermal patch: 12 µg/hr 25 µg/hr 37.5 µg/hr

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	be based on individual need; one patch is to be applied every 72 hours; however, some may require application of every 48 hours rather than every 72 hours	every 72 hours	50 µg/hr 62.5 µg/hr 75 µg/hr 87.5 µg/hr 100 µg/hr
Hydromorphone	Analgesia: Injection: 1 to 2 mg SC or IM every two to three hours, if given IV, inject 0.2 to 1 mg slowly over at least two to three hours. Liquid: 2.5 to 10 mg every three to six hours as directed Rectal suppository: one suppository (3 mg) inserted every six to eight hours Tablet: 2 to 4 mg every four to six hours as necessary	Safety and efficacy in children have not been established.	Injection: 0.5 mg/0.5 mL 1 mg/mL 2 mg/mL 4 mg/mL 10 mg/mL Liquid: 1 mg/mL Rectal suppository: 3 mg Tablet: 2 mg 4 mg 8 mg
Levorphanol	Analgesia: Tablet: 1 to 2 mg every six to eight hours	Safety and efficacy in children have not been established.	Tablet: 2 mg 3 mg
Meperidine	Analgesia: Injection: 50 to 150 mg IM or SC every three to four hours as necessary Solution, tablet: 50 to 150 mg every three to four hours as necessary	Analgesia: Injection: 1.1 to 1.8 mg/kg (0.5 to 0.8 mg/lb) IM or SC up to the adult dose every three to four hours as necessary Solution, tablet: 1.1 to 1.8 mg/kg (0.5 to 0.8 mg/lb) up to the adult dose, every three to four hours as necessary	Injection: 25 mg/0.5 mL 25 mg/mL 50 mg/mL 75 mg/mL 75 mg/1.5 mL 100 mg/mL 100 mg/2 mL Solution: 50 mg/5 mL Tablet: 50 mg
Methadone	Analgesia: Oral concentrate, solution, tablet: 2.5 to 10 mg every eight to 12 hours as necessary Detoxification: Oral concentrate, solution, tablet: initial, 20 to 30 mg to suppress withdrawal symptoms; individualize and adjust dose as tolerated and required up to 120 mg/day	Safety and efficacy in children have not been established.	Injection: 10 mg/mL Oral concentrate: 10 mg/mL Solution: 5 mg/5 mL 10 mg/5 mL Tablet: 5 mg 10 mg 40 mg
Morphine	Analgesia: Injection: 5 to 20 mg SC or IM every four hours	Analgesia: Injection: >6 months, 0.1 to 0.2 mg/kg every four hours	Injection: 0.5 mg/mL 1 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Solution, tablet: 5 to 30 mg every four hours Rectal suppository: 10 to 20 mg every four hours		2 mg/mL 4 mg/mL 5 mg/mL 8 mg/mL 10 mg/mL 25 mg/mL 30 mg/30 mL 50 mg/mL 150 mg/30 mL Rectal suppository: 5 mg 10 mg 20 mg 30 mg Solution 10 mg/5 mL 20 mg/5 mL 100 mg/5 mL Tablet: 15 mg 30 mg
Oxycodone	Analgesia: Capsule, oral concentrate, solution, tablet: 5 to 15 mg every four to six hours	Safety and efficacy in children have not been established.	Capsule: 5 mg Oral concentrate: 20 mg/mL Solution: 5 mg/5 mL Tablet: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg
Oxymorphone	Analgesia: Tablet: 10 to 20 mg every four to six hours	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Tapentadol	Analgesia: Tablet (IR): 50 to 100 mg every four to six hours Tablet (ER): individualize based on prior analgesic treatment; for opioid to naïve patients, initial, 50 mg twice daily	Safety and efficacy in children have not been established.	Tablet (IR): 50 mg 75 mg 100 mg Tablet (ER): 50 mg 100 mg 150 mg 200 mg 250 mg
Tramadol	Analgesia: Capsule (ER): initial, 100 mg	Analgesia: Tablet (IR): ≥16 years of	Capsule (ER): 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	once daily; titrate by 100 mg increments every five days Tablet (ER): 100 to 300 mg daily Tablet (IR): 50 to 100 mg every four to six hours	age, 50 to 100 mg every four to six hours	200 mg 300 mg Tablet (ER): 100 mg 200 mg 300 mg Tablet (IR): 50 mg
Combination Products			
Benzhydrocodone and acetaminophen	Analgesia: Tablet: one to two tablets every four to six hours as needed for pain; do not use >14 days	Safety and efficacy in children have not been established.	Tablet: 4.08-325 mg 6.12-325 mg 8.16-325 mg
Codeine and acetaminophen	Analgesia: Solution: 15 mL every four hours as needed Tablet: 0.5 to two tablets every four hours	Analgesia: Solution: ≥12 years of age, 15 mL every four hours as needed Tablet: ≥12 years of age, 0.5 to 1 mg codeine/kg/dose every four to six hours (10 to 15 mg acetaminophen/kg/dose every four hours)	Solution: 12-120 mg/5 mL 30-300 mg/12.5 mL Tablet: 15-300 mg 30-300 mg 60-300 mg
Codeine, butalbital, acetaminophen, and caffeine	Headache: Capsule: one or two capsules every four hours	Headache: Capsule: ≥12 years of age, one or two tablets or capsules every four hours	Capsule: 30-50-300-40 mg 30-50-325-40 mg
Codeine, butalbital, aspirin, and caffeine	Headache: Capsule: one or two capsules every four hours	Headache: Capsule: ≥12 years of age, one or two tablets or capsules every four hours	Capsule: 30-50-325-40 mg
Dihydrocodeine, acetaminophen, and caffeine	Analgesia: Capsule: two capsules every four hours	Safety and efficacy in children have not been established.	Capsule: 16-320.5-30 mg
Hydrocodone and acetaminophen	Analgesia: Tablet: one to two every four to six hours; hydrocodone 2.5 to 10 mg; acetaminophen 300 to 325 mg), one every four six hours Solution: 15 mL every four to six hours; 10-300 mg/15 mL solution, 11.25 mL every four to six hours	Analgesia: Solution: ≥2 years of age, Weight-based dosing which corresponds to an average individual dose of 0.27 mL/kg	Solution: 2.5-108 mg/5 mL 5-217 mg/10 mL 7.5-325 mg/15 mL 10-300 mg/15 mL Tablet: 2.5-325 mg 5-300 mg 5-325 mg 7.5-300 mg 7.5-325 mg 10-300 mg 10-325 mg
Hydrocodone and ibuprofen	Analgesia: Tablet: one tablet every four to six hours	Analgesia: Tablet: ≥16 years of age, one tablet every four to six hours	Tablet: 5-200 mg 7.5-200 mg 10-200 mg
Opium and	Analgesia:	Safety and efficacy in	Rectal suppository:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
belladonna	Rectal suppository: one suppository inserted one to two times per day	children have not been established.	30-16.2 mg 60-16.2 mg
Oxycodone and acetaminophen	Analgesia: Tablet: one to two tablets every six hours	Safety and efficacy in children have not been established.	Tablet: 2.5-325 mg 5-300 mg 5-325 mg 7.5-300 mg 7.5-325 mg 7.5-500 mg 10-300 mg 10-325 mg 10-650 mg
Tramadol and acetaminophen	Analgesia: Tablet: two tablets every four to six hours	Safety and efficacy in children have not been established.	Tablet: 37.5-325 mg
Tramadol and celecoxib	Analgesia: Tablet: two tablets every 12 hours	Safety and efficacy in children have not been established.	Tablet: 44-56 mg

IM=intramuscular, IR=immediate-release, IV=intravenous, SC=subcutaneous, ODT=orally disintegrating tablet, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the opiate agonists are summarized in Table 27.

Table 27. Comparative Clinical Trials with the Opiate Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Acute Pain				
Drendel et al.[27] (2009) Codeine-APAP suspension 1 mg/kg/dose (codeine component) vs ibuprofen suspension 10 mg/kg/dose	AC, DB, RCT Children 4 to 18 years of age with a closed fracture of the radius, ulna, or humerus	N=336 72 hours after ED discharge	Primary: Failure of study medication as defined by use of a rescue analgesic Secondary: Pain scores, adverse events, and satisfaction	Primary: The proportion of treatment failures for children receiving ibuprofen (20.3%) was lower than that for codeine-APAP (31.0%), although not statistically significant. Secondary: The total mean pain scores for day zero to day three were 1.6 for children receiving ibuprofen and 1.6 for children receiving codeine-APAP. At the end of the study, 27.5% of the children said they would not use codeine-APAP again compared to only 10.0% of the children who took ibuprofen (95% CI, 7.3 to 28.3). The primary reason associated with dissatisfaction in children receiving codeine-APAP was taste. There was no significant difference in analgesic failure and pain scores among children with an arm fracture receiving ibuprofen or codeine-APAP.
Best et al.[28] (2017) Intervention group (codeine 60 mg, APAP 1,000 mg, and ibuprofen 400 mg) vs control group (APAP 1,000 mg and ibuprofen 400	DB, PC, RCT Patients undergoing the surgical removal of at least one impacted mandibular third molar requiring bone removal	N=131 3 days	Primary: Postoperative pain assessed using the visual analog scale every three hours (while awake) for the first 48 hours after surgery Secondary: Pain globally assessed using a questionnaire on day three after	Primary: The control and intervention groups did not differ in their pain during the first 48 hours after mandibular third molar surgery. Secondary: The two groups did not differ in their global ratings of postoperative pain.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg)			surgery	
Rauck et al.[29] (2012) Fentanyl sublingual spray (100 to 1,600 µg) vs placebo Fentanyl sublingual spray was titrated up to 1,600 µg until an effective dose was reached. After titration to an effective dose of fentanyl sublingual spray, patients received ten doses of study medication (seven contained fentanyl and three were placebo).	DB, MC, OL, PC, RCT Adult patients with cancer, experiencing persistent cancer or treatment-related pain of no more than moderate severity, receiving ≥60 mg oral morphine, 30 mg oxycodone or 8 mg oral hydromorphone/ day or 25 µg transdermal fentanyl/hour or equivalent	N=130 10 BTP episodes	Primary: $SPID_{30}$ Secondary: $TOTPAR_{30}$, global evaluation of study medication at 30 minutes	Primary: The mean (SE) $SPID_{30}$ score was 640.3 (47.8) for fentanyl sublingual spray and 399.6 (40.8) for placebo; corresponding to a mean treatment difference of 240.7 (37.8) (P<0.0001). A significant difference in SPID values for episodes treated with fentanyl compared to placebo was seen as early as five minutes and maintained for up to 60 minutes. After 30 minutes, 79.3% of patients showed greater improvement with fentanyl sublingual spray compared to placebo (P<0.0001). Secondary: TOTPAR scores from five to 60 minutes were significantly greater in episodes treated with fentanyl sublingual spray compared to episodes treated with placebo (P<0.0001 for all time points). The $TOTPAR_{30}$ score in episodes treated with fentanyl sublingual spray was 78.3 compared to 61.0 in episodes treated with placebo (P<0.0001). After 30 minutes, the global evaluation of treatment effectiveness score was 2.8 for fentanyl sublingual spray compared to 2.0 for placebo (P<0.0001). This significant difference was maintained at 60 minutes as well.
Rauck et al.[30] (2010) Fentanyl buccal film 200 µg vs	DB, MC, PC, RCT, XO Patients ≥18 years of age with pain associated with cancer or cancer treatment, receiving	N=151 Up to 14 days or 9 BTP episodes	Primary: $SPID_{30}$ Secondary: SPID at five, 10, 15, 45, and 60 minutes post dose, pain intensity	Primary: Mean±SEM $SPID_{30}$ values for fentanyl buccal film treated BTP episodes were significantly greater than for placebo treated BTP episodes (47.9±3.9 vs 38.1±4.3; P=0.004). Secondary: SPID values for buccal film fentanyl treated BTP episodes were significantly greater than for placebo from 15 minutes through 60 minutes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Patients were provided with a titration kit consisting of five units each of 200, 400, 600, 800 and 1,200 µg doses of fentanyl buccal film. After titration to an effective dose of fentanyl buccal film, patients received nine doses of study medication (six contained fentanyl and three were placebo). If adequate pain relief was not experienced after 30 minutes, patients were instructed to use their usual BTP medication if needed.	stable opioid therapy equivalent to 60 to 1,000 mg/day of oral morphine or 50 to 300 µg/hour of transdermal fentanyl, that had one to four BTP episodes/day despite persistent opioid therapy and who achieved at least partial relief from opioid therapy		difference, pain relief, global satisfaction	post dose (all P<0.05). The mean pain intensity differences and pain relief for fentanyl treated BTP episodes were significantly greater (improved) than for placebo treated BTP episodes beginning at 30 minutes post dose (P<0.05). There was a significantly greater percentage of BTP episodes with a 33 or 50% decrease in pain with buccal film fentanyl compared to placebo starting at 30 minutes post dose (P<0.01). The percentage of BTP episodes when rescue medication was required was significantly lower when treated with buccal film fentanyl (30.0%±3.5%) than when treated with placebo (44.6%±4.4%; P=0.002). More patients rated their overall satisfaction with buccal film fentanyl as 'good', 'very good' or 'excellent' compared to placebo and fewer patients rated their overall satisfaction with buccal film fentanyl as 'poor' or 'fair' compared to placebo. The overall satisfaction with the study drug was greater with fentanyl buccal film compared to placebo (mean score, 2.0 vs 1.5; P<0.001). The most commonly reported adverse events included nausea (9.9%), vomiting (9.9%), and headache (1.2%). Twenty-three patients (15.3%) experienced a serious adverse event. None of the serious adverse events (including four deaths) were considered study drug-related.
Portenoy et al.[31] (2006) Fentanyl buccal tablet	PC, RCT, XO Adults with chronic cancer pain receiving 60 to	N=123 Duration not reported	Primary: $SPID_{30}$ Secondary: Pain relief and pain	Primary: The mean (±SD) $SPID_{30}$ was 3.00 (±0.12) vs 1.80 (±0.14) for fentanyl buccal tablet compared to placebo (P<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Enrolled patients began with an OL titration phase to identify an effective dose of fentanyl buccal tablet ranging from 100 to 800 µg. After titration to an effective dose of fentanyl buccal tablet, patients received ten doses of study medication (seven contained fentanyl and three were placebo).	1,000 mg/day of oral morphine or equivalent or 50 to 300 µg/hour of transdermal fentanyl for at least one week who experienced one to four episodes of BTP per day		intensity difference scores, TOTPAR, global medication performance assessment, need for supplemental medication, proportion of episodes in which there were ≥33 or ≥50% improvement in pain intensity scores	The mean pain relief and pain intensity difference scores were significantly higher in the fentanyl group compared to the placebo group at each time point (P<0.003 at 15 minutes for both; P<0.0001 for all other time points for both). TOTPAR scores were significantly higher in the fentanyl group compared to the placebo group at all time points (P<0.0001 for all). At 30 minutes after treatment, 48% of fentanyl treated patients had ≥33% improvement in pain intensity score compared to 29% of placebo patients (P<0.0001). At the same time point, 24% of fentanyl treated patients had ≥50% improvement in pain intensity score compared to 16% of placebo patients (P=0.0023). A significant difference in clinical improvement (≥33%) between the two groups was seen as early as 15 minutes (P=0.045). Global performance assessment ratings showed that fentanyl received a significantly higher satisfaction rating than placebo at both 30 and 60 minutes (P<0.0001 for both). Supplemental medication was needed in 23% of episodes treated with fentanyl compared to 50% of episodes treated with placebo (RR, 0.47; 95% CI, 0.37 to 0.60). Two percent of patients withdrew from the study because of application site ulcers of the oral mucosa deemed by the investigators to be related to the study drug.
Slatkin et al.[32] (2007) Fentanyl buccal tablet Patients were provided with a titration kit consisting of 100, 200, 400, 600, and 800 µg doses of fentanyl buccal	DB, PC, RCT, XO Patients 18 to 80 years of age with a histologically documented diagnosis of a malignant solid tumor or a hematologic malignancy causing cancer-related pain, a life expectancy ≥2	N=125 Up to 4 weeks	Primary: $SPID_{60}$ Secondary: Pain intensity at 0, five, 10, 15, 30, 45, 60, 90 and 120 minutes post dose; the percentage of BTP episodes with an improvement in pain intensity scores from	Primary: The $SPID_{60}$ values were significantly greater for BTP episodes treated with fentanyl buccal tablet compared to BTP episodes treated with placebo (mean±SE, 9.70±0.63 vs 4.90±0.50; P<0.0001). There were no clinically meaningful differences in $SPID_{60}$ in terms of the different underlying pain pathophysiologies (nociceptive, neuropathic, or mixed). Secondary: As assessed by pain intensity difference, there was a greater reduction in pain intensity following buccal tablet fentanyl than placebo at 10 minutes (0.9 vs 0.5; P<0.0001). The difference in pain intensity difference between the two treatments increased at subsequent time points up to 90 minutes post dose and then was maintained through two hours (P<0.0001 for each

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tablet. The starting dose and subsequent titration doses were specified in the protocol based on the medications the patient was using to treat BTP immediately before study enrollment. If adequate pain relief was not experienced after 30 minutes, patients were instructed to use their usual BTP medication if needed. After titration to an effective dose of fentanyl buccal tablet, patients were given ten randomly ordered treatment units (seven buccal tablet fentanyl units and three placebo units) in the form of identical tablets.	months; the use of a fixed-dose, around-the-clock opioid regimen for persistent pain (oral morphine ≥60 mg/day, transdermal fentanyl ≥25 µg/hour, or an equivalent dose of an alternative opioid for ≥7 days), an average pain intensity pain <7 (11 point numerical scale) for their persistent pain during the 24 hours before consent, a report of one to four BTP episodes/day while taking around-the-clock opioids and the use of an opioid to treat BTP that is at least partially effective		baseline ≥33 and ≥50% post dose; pain relief; TOTPAR at 60, 90 and 120 minutes post dose; and proportion of BTP episodes that required the use of supplemental medication	time point). A clinically significant improvement in pain intensity scores from baseline ≥33% occurred in a larger proportion of BTP episodes treated with fentanyl buccal tablet compared to BTP episodes treated with placebo at 10 minutes (16 vs 10%; P=0.007), 15 minutes (29 vs 14%; P<0.0001) and 30 minutes (51 vs 26%; P<0.0001). The differential increased through 60 minutes and was maintained over the two hour observation period (P<0.0001 for each subsequent time point). The difference in the proportion of BTP episodes with an improvement in pain intensity ≥50% following buccal tablet fentanyl or placebo was also significant at 10 minutes (7 vs 4%; P=0.033), 15 minutes (18 vs 8%; P<0.0001), and 30 minutes (38 vs 15%; P<0.0001), and continued to increase through two hours (P<0.0001). Pain relief was significantly better with fentanyl buccal tablet compared to placebo as early as 10 minutes (0.815 vs 0.606; P<0.0001); the differential increased over time up to 90 minutes and was maintained for two hours (P<0.0001 for each time point). Similarly, TOTPAR values were significantly better (P<0.0001) following fentanyl buccal tablet compared to placebo at 60, 90, and 120 minutes post dose. Supplemental medication was used for 53/493 (11%) BTP episodes treated with buccal tablet fentanyl compared to 67/223 (30%) episodes treated with placebo (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Zeppetella et al.[33] (2010) Fentanyl buccal tablet vs placebo Combined analysis of patients previously enrolled in Portenoy et al and Slatkin et al. After titration to an effective dose of fentanyl buccal tablet, patients were given ten randomly ordered treatment units (seven fentanyl buccal tablet units and three placebo units) in the form of identical tablets.	DB, PC, RCT Patients ≥18 years of age with a histologically documented diagnosis of a malignant solid tumor or hematological malignancy who were experiencing persistent cancer-related pain and BTP, and who were receiving maintenance opioid therapy for ≥1 week prior to screening	N=150 Duration not reported	Primary: Pain intensity, pain relief, global medication performance, use of rescue medication Secondary: Safety and tolerability	Primary: A greater effect was seen on the proportion of the BTP episodes with ≥33 or ≥50% improvement in pain intensity from baseline in the patients administering fentanyl buccal tablet compared to patients administering placebo, starting at the 15 minute time point and continuing to evaluation at 60 minutes (P<0.0001 at each time point). At 30 minutes, 59% of the episodes treated with fentanyl buccal tablet and 36% treated with placebo had a ≥2 point improvement in pain intensity, with the relative proportions increasing at 45 minutes to 74 and 44%, respectively (P<0.0001 at each time point). The percentage of BTP episodes with at least moderate pain relief also showed a difference, favoring fentanyl buccal tablet over placebo from 15 minutes (P=0.0004). At 30 minutes, 47% of the patients who took fentanyl buccal tablet had a least moderate pain relief compared to 28% who took placebo (P<0.0001). Respective differences favoring fentanyl buccal tablet over placebo were maintained at 45 minutes (64 vs 34%; P<0.0001) and at 60 minutes (69 vs 39%; P<0.0001). At 60 minutes, the mean global medication performance score for fentanyl buccal tablet was 2.1 and 1.2 for placebo (P value not reported). Patients were three times more likely to resort to rescue medication for a placebo-treated BTP episode (40 vs 17%; OR, 3.22; 95% CI, 2.43 to 4.28; P value not reported). Secondary: The adverse events noted were generally typical of those experienced by patients with cancer who take potent opioids. Most were classified as either mild or moderate in intensity and were transitory. The most common adverse events were nausea and dizziness.
Lennernäs et al.[34] (2010) Sublingual fentanyl tablet 100 µg	DB, MC, RCT, XO Adult patients with cancer pain that were regularly experiencing at least	N=38 Duration unknown	Primary: Pain intensity difference Secondary: Global assessment	Primary: A significant overall improvement in pain intensity difference was seen in the fentanyl 400 µg group compared to the placebo group (P<0.0001) with the effect first becoming significant after 15 minutes (P=0.005). However, a significant difference was not seen in the 100 or 200 µg groups compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sublingual fentanyl tablet 200 µg vs sublingual fentanyl tablet 400 µg vs placebo Patients received one dose of placebo and one of each of the three doses of fentanyl sublingual tablet in random order for four episodes. Treatment periods were separated by a washout period of at least one day.	four episodes of BTP over a period of 14 days and were receiving a fixed-schedule opioid regimen equivalent to 30 to 1,000 mg/day oral morphine or 25 to 300 µg transdermal fentanyl		of treatment (none, mild, moderate or excellent), need for rescue medication	Secondary: Nine patients reported treatment with fentanyl 400 µg as excellent compared to three with placebo (P=0.0146). Five and three patients taking fentanyl 100 and 200 µg, respectively rated treatment as excellent. Significantly fewer patients taking fentanyl 400 µg required rescue medications compared to patients taking placebo (P=0.001). Eleven and ten patients required a rescue medication with the 100 and 200 µg doses, respectively (P values not reported).
Rauck et al.[35] (2009) Fentanyl sublingual tablet 100 to 800 µg vs	DB, MC, PC, RCT Patients ≥17 years of age with stable cancer related pain, experiencing one to four episodes of BTP per day and receiving 60 to	N=131 10 BTP episodes 12 month safety phase	Primary: $SPID_{30}$ Secondary: Pain intensity difference and pain relief scores	Primary: The mean $SPID_{30}$ in episodes treated with sublingual fentanyl tablets was 49.5 compared to 36.6 in episodes treated with placebo (P=0.0004). The significant difference in SPID score was maintained at 60 minutes (P=0.0002). Secondary: Treatment of BTP episodes with sublingual fentanyl tablets showed greater improvements in pain intensity difference scores compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Fentanyl sublingual tablet was titrated up to 800 µg until an effective dose was reached.	1,000 mg oral morphine per day, transdermal fentanyl 50 to 300 µg per hour or equivalent			placebo at ten minutes after treatment administration (P=0.0055) and was maintained up to 60 minutes. In addition, pain relief scores were significantly greater in episodes treated with sublingual fentanyl tablets compared to placebo at ten minutes (P=0.0490). This significant difference was maintained up to 60 minutes. Among patients treated with sublingual fentanyl tablets, 11.2% required rescue medication compared to 27.4% in the placebo group. (P values not reported). During the safety phase, the most common treatment-emergent adverse events were nausea, vomiting, headache and somnolence.
Zecca et al.[36] (2017) Fentanyl sublingual tablet 100 µg vs subcutaneous morphine 5 mg	DB, DD, RCT Patients with pain due to advanced cancer; current pain ≥6 on a 0 to 10 numerical rating scale; average pain intensity score ≤4 of 10 in the previous 24 hours; stable opioid treatment in the previous 3 days; daily opioid consumption within a range of 20 to 120 mg oral morphine equivalent daily dose	N=114 30 minutes post-administration	Primary: Average of pain right now scores at 10, 20, and 30 minutes (AVP_30) Secondary: Analgesic efficacy at 60 min, proportion of patients needing a second dose of opioid, proportion of patients who expressed a preference for each of the two administration routes, adverse events	Primary: Pretreatment mean pain intensity was 7.5 in both groups. Mean AVP_30 was 5.0 and 4.5, respectively, for fentanyl and morphine, with a between-group difference of −0.49 and a 95% CI of −1.10 to 0.09, which includes the noninferiority margin. Secondary: Between-group difference at 60 minutes was slightly reduced (−0.36; 95% CI, −1.0 to 0.3), but the 95% estimate still did not indicate superiority of one of the two drugs over the other. Patients taking fentanyl more frequently received a second analgesic drug dose after 30 min (51% vs 37%; risk difference, −13%). Sublingual route of administration was preferred by 93% of patients (95% CI, 86 to 97%), with a slight difference by treatment (91% in fentanyl and 95% in morphine). No patients reported serious adverse events.
Portenoy et al.[37] (2010) Fentanyl nasal spray 100 to 800	DB, MC, PC, RCT, XO Adult patients with cancer experiencing	N=114 10 BTP episodes	Primary: Patient-averaged, $SPID_{30}$ Secondary:	Primary: The mean (±SD) $SPID_{30}$ score was 6.57 (±4.99) for fentanyl nasal spray and 4.45 (±5.51) for placebo; corresponding to a mean treatment difference of 2.12 (±3.91) (95% CI, 1.21 to 3.03; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg vs placebo Fentanyl nasal spray was titrated up to 800 µg until the patient received adequate pain relief for each BTP episode. After titration to an effective dose of fentanyl nasal spray, patients received ten doses of study medication (seven contained fentanyl and three were placebo).	at least one to four BTP episodes daily, who were also receiving fixed-dose opioids for pain at a total daily dose equivalent to 60 mg of oral morphine		Patient-averaged, summed pain intensity difference scores, patient-averaged, mean differences in pain relief, TOTPAR score, clinically meaningful reduction in pain intensity (≥2), need for additional rescue medication, patient acceptability scores	Secondary: The mean pain intensity score for patient-averaged fentanyl-treated episodes was significantly different from that for placebo-treated episodes at the five minute time point (P=0.03), and the difference in pain intensity was sustained over the 10, 15, 30, 45, and 60 minute evaluation time points. Patient-averaged mean differences in pain relief and TOTPAR scores were also significant at 10 minutes and at all measured time-points to 60 minutes. A total of 49% of those treated with fentanyl had a clinically meaningful reduction in pain intensity at 15 minutes (P<0.001) and 63% had the same degree of pain relief by 30 minutes. The cumulative SPID scores demonstrated that a significantly higher percentage of patients reported a mean reduction in SPID score ≥2 after fentanyl administration vs placebo administration at each evaluation from 10 to 60 minutes post-treatment dose. Overall, 90.6% of episodes treated with fentanyl nasal spray compared to 80.0% of episodes treated with placebo did not require an additional rescue medication within 60 minutes of breakthrough treatment (P<0.001). The overall mean patient-averaged acceptability assessment score was significantly greater for the fentanyl treatment vs placebo at 30 minutes post-treatment (2.63 vs 2.01; P<0.0001) and at 60 minutes post-treatment (2.73 vs 2.02; P<0.0001).
Taylor et al.[38] (2010) Fentanyl nasal spray 100 to 800 µg vs placebo Fentanyl nasal spray was titrated	DB, MC, PC, RCT, XO Adult patients with cancer experiencing at least one to four BTP episodes daily, who were also receiving fixed-dose opioids for pain at a total daily dose equivalent to 60 mg of oral morphine	N=114 10 BTP episodes	Primary: Pain intensity score, SPID score, pain relief score Secondary: Overall patient satisfaction, satisfaction with speed of relief and reliability of nasal spray, ease of use and convenience of	Primary: Fentanyl nasal spray significantly decreased pain intensity (≥1 point reduction) at all time intervals (five, 10, 15, 30, 45 and 60 minutes) compared to placebo (P<0.05 at 5 minutes, P<0.0001 at all other intervals). A significant meaningful reduction in pain intensity (≥2 point reduction) was first observed at 10 minutes in 32.9% of fentanyl patients compared to 24.5% of placebo patients (P<0.05) and increased to include 50.8% of fentanyl patients at 30 minutes (P<0.0001 vs placebo). Significant differences were also observed between fentanyl and placebo treated patients in the number of episodes with ≥2 point reduction in SPID score from 10 to 60 minutes (P<0.01). In addition, the number of episodes with pain relief score changes ≥1 point and ≥2 points was significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
up to 800 µg until the patient received adequate pain relief for each BTP episode. After titration to an effective dose of fentanyl nasal spray, patients received ten doses of study medication (seven contained fentanyl and three were placebo). Patients could take a maximum of four doses per day with at least four hours between doses.			nasal spray	higher in the fentanyl group compared to placebo from 10 to 60 minutes (P<0.0001 and P<0.001, respectively). Secondary: Significantly more patients in the fentanyl group reported a higher overall satisfaction score and satisfaction with speed of relief and reliability compared to placebo (P<0.0001 for all). A total of 68.5 and 69.9% of patients using fentanyl reported they were either satisfied or very satisfied with ease of use and convenience of the nasal spray, respectively.
Mercadante et al.[39] (2016) Fentanyl pectin nasal spray vs oral morphine	RCT, XO Cancer patients with pain receiving ≥60 mg of morphine equivalents/day and presenting with ≤3 episodes of BTP/day	N=53 167 BTP episodes	Primary: Number of patients who found a benefit with study medications at the different point intervals (treatment was considered unsuccessful if the pain decrease was ≤33% of background pain intensity) Secondary:	Primary: Pain intensity significantly changed with both drugs (P<0.0005). The statistical difference found between the two groups was observed at 15 minutes post-dose, but not at 30 minutes post-dose (P=0.018 and P=0.204, respectively). In a greater number of episodes treated with fentanyl nasal spray, there was a pain decrease ≥33% in comparison with oral morphine after 15 and 30 minutes (76.5 vs 32.8%, and 89 vs 54.9%, respectively; P<0.0005). Secondary: The mean (SD) pain difference at 15 minutes post-dose between fentanyl and morphine were 3.24 (1.7) and 2.70 (1.2), respectively, whereas the mean (SD) summed pain intensity difference calculated 30 minutes after dosing of fentanyl and morphine were 4.87 (1.7) and 4.54 (1.5), respectively. The difference was significant (P<0.0005) at 15 minutes vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Patient-averaged summed pain intensity difference calculated 30 minutes after dosing	30 minutes and between treatment groups (P=0.019). Of patients who received both treatments (45 patients), 26 and 11 patients preferred fentanyl and morphine, respectively. Eight patients did not provide any preference.
Christie et al.[40] (1998) Fentanyl transmucosal lozenge 200 µg vs fentanyl transmucosal lozenge 400 µg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode using one Fentanyl transmucosal lozenge unit. On each study day, as many as 4 units could be taken sequentially (one every 30 minutes) for up to two BTP	DB, dose titration, MC, RCT Adult patients with cancer using transdermal fentanyl for persistent pain	N=62 Duration not reported	Primary: Pain intensity, pain relief, and global satisfaction compared to usual BTP medication Secondary: Dosing requirements	Primary: Pain scores following fentanyl transmucosal on successful days were compared to pain scores on baseline days following usual BTP medication. Scores at zero minutes were not significantly different for the two groups. At 15, 30 and 60 minutes, transmucosal fentanyl produced markedly lower pain intensity scores and higher pain relief scores than the usual BTP medication (P≤0.0002 for each analysis). At 30 minutes, the mean±SD difference between pain intensity scores following usual BTP medication and transmucosal fentanyl was 1.6±1.9. Pain intensity difference values at 15, 30, and 60 minutes were significantly better following transmucosal fentanyl (P≤0.001). The 0 to 15 minute pain intensity difference values for transmucosal fentanyl was >2.5 times larger compared to the usual BTP medication (2.35 vs 0.91; P=0.0001), which is consistent with a faster onset of action. Also, transmucosal fentanyl produced a pain relief score at 15 minutes that was >2 times higher compared to the usual BTP medication (1.90 vs 0.82; P=0.001). At 30 minutes, the mean±SD difference between values following each treatment was 0.95±1.20. Global satisfaction ratings were significantly higher following transmucosal fentanyl compared to usual BTP medication (2.6 vs 2.0; P=0.0001). Secondary: Of the 62 patients enrolled, 47 (76%) were successfully titrated to a unit dose of transmucosal fentanyl that effectively treated their BTP. Four patients were unable to control their BTP with the highest transmucosal fentanyl dose of 1,600 µg and 11 patients withdrew from the trial; six of these withdrawals were due to a side effect.

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episodes/day. Patients' usual BTP medication included codeine, hydrocodone, hydromorphone, morphine, oxycodone, propoxyphene, tramadol, or no medication.				Patients who found a successful dose of transmucosal fentanyl were titrated to a mean dose of approximately 600 µg, with no statistically significant difference in the final dose between the patients who began with 200 µg and those who began with 400 µg (667 vs 825 µg, respectively; P=0.58).
Farrar et al.[41] (1998) Fentanyl transmucosal lozenge 200 µg vs placebo Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode. After titration to an effective dose of fentanyl transmucosal lozenge, patients	DB, MC, PC, RCT, XO Patients ≥18 years of age with cancer who had sufficient pain to require at least the equivalent of 60 mg/day of oral morphine or 50 µg/hour transdermal fentanyl, and had ≥1 BTP episode/day for which they took additional opioids	N=89 Duration not reported	Primary: Pain intensity, pain relief, and use of rescue medication at 15 minute intervals over a 60 minute period Secondary: Not reported	Primary: Transmucosal fentanyl produced significantly larger changes in pain intensity and better pain relief than placebo at all time points (two-sided P<0.0001). Episodes of BTP treated with placebo required the use of rescue medication more often than episodes treated with transmucosal fentanyl (34 vs 15%; RR, 2.27; 95% CI, 1.51 to 3.26; P<0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
were given ten randomly ordered treatment units (seven fentanyl transmucosal lozenge units and three placebo units) in the form of identical lozenges. If adequate pain relief was not achieved with a single dose of transmucosal fentanyl after 30 minutes, patients were instructed to take a dose of their usual BTP medication. Patients' usual BTP medication included hydrocodone, hydromorphone, morphine, oxycodone, and other medications.				
Hanks et al.[42] (2004) Fentanyl transmucosal lozenge 200 µg	MC, OL Patients stabilized on a long-acting opioid (60 to 1,000 mg/day of oral	N=57 Duration not reported	Primary: SPID and TOTPAR up to 60 minutes Secondary:	Primary: SPID values were significantly higher following transmucosal fentanyl compared to conventional medication at all time points (P<0.001 for all). Transmucosal fentanyl produced better pain relief scores than conventional medication beginning at the 15 minute time point (1.49 vs 0.89; P<0.001) and continuing at the 30, 45, and 60 minute time points

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode using one transmucosal fentanyl unit. Patients had access to their usual BTP medication. The majority of patients were using IR morphine as their usual BTP medication. If adequate pain relief was not achieved with a single dose of fentanyl transmucosal lozenge after 30 minutes, patients were instructed to take a dose of their usual BTP medication. The efficacy of their usual BTP	morphine, 50 to 300 µg/hour of transdermal fentanyl, or 8 to 135 mg/day of oral hydromorphone) for ≥3 days prior to enrollment, but experiencing up to four BTP episodes/day, and achieving at least partial relief from BTP using conventional medication		Not reported	(P<0.001 at all time points). TOTPAR values were also significantly higher at each time point evaluated (P<0.001 for all). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medication was documented in a run-in phase and patients then changed to fentanyl transmucosal lozenge.				
Payne et al.[43] (2001) Fentanyl transmucosal lozenge Patients had participated in a previous short-term titration trial of fentanyl transmucosal lozenge (Christie et al., Portenoy et al., and Farrar et al.). Patients began the study at the fentanyl transmucosal lozenge doses that they had found to be effective in the previous titration trials in which they participated.	MC, OL Patients requiring either a scheduled oral opioid regimen equivalent to 60 to 1,000 mg/day of oral morphine or 50 to 300 µg/hour of transdermal fentanyl for control of persistent pain, experiencing ≥1 BTP episode/day, and achieving at least partial relief of BTP by use of an opioid in the past	N=151 1 to 423 days	Primary: Number of successfully treated BTP episodes, global satisfaction rating, side effects Secondary: Not reported	Primary: Ninety-two percent of BTP episodes were considered successful (defined as a BTP episode for which a patient felt that they had achieved satisfactory pain relief using one transmucosal fentanyl unit [i.e., no additional rescue medication for the episode]). The number of patients dropped substantially from months five to eight (N=53) to months nine to 12 (N=19) and months >12 (N=8). Therefore, though the percentage of BTP episodes treated successfully with transmucosal fentanyl dropped from 90 to 85% after month nine, the declining sample size makes it difficult to determine whether this is an actual decrease in efficacy. Mean global satisfaction ratings were consistently above three, indicating 'very good' to 'excellent' relief. The satisfaction ratings also remained consistent over time. Common adverse events associated with transmucosal fentanyl were somnolence (9%), constipation (8%), nausea (8%), dizziness (8%), and vomiting (5%). Six patients discontinued therapy due to a transmucosal fentanyl-related adverse event. There were no reports of abuse and no concerns about the safety of the drug raised by patients or families. Secondary: Not reported
Minkowitz et al.[44]	EMC, OL	N=269	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2016) Fentanyl sublingual spray (100 to 1600 µg)	Patients ≥18 years of age and experiencing pain that was being managed with an around-the-clock opioid yet were experiencing ≤4 BTP episodes daily and were opioid-tolerant (i.e., receiving ≥60 mg/day oral morphine or an equivalent dose of another opioid for ≥1 week). Patients could be new or had successfully completed the final visit of a DB RCT.	90 days	Adverse events Secondary: Laboratory parameters, patient satisfaction	Of the 269 patients who entered the maintenance period, 163 (60.6%) completed the study; the primary reason for discontinuation was an adverse event (22.3%). Nausea (13%), vomiting (12%), and somnolence (10%) were the most common adverse events during the titration period, whereas malignant neoplasm progression (24%), vomiting (16%), and peripheral edema (12%) were the most common adverse events observed during the maintenance period. Secondary: During the titration and maintenance periods, laboratory values, vital signs, and physical examination findings generally remained within normal limits, or with minor changes from baseline. Shifts in liver enzymes from normal to elevated occurred in a small percentage of patients. On all domains of the Treatment Satisfaction Questionnaire for Medication, patients reported stable or improved levels of satisfaction from the start of the titration period to the end of the maintenance period. At the start of the titration period, 46% of patients were satisfied, very satisfied, or extremely satisfied with the effectiveness of the supplemental analgesic they had typically been using to manage BTP; this rate increased to a high of 87% satisfaction with the effectiveness of fentanyl sublingual spray at the second maintenance period visit and was reported at 84% at the final visit. More patients reported adverse events associated with their previously utilized BTP treatment (45%) than with fentanyl sublingual spray (20 to 28%). The percentage of patients who rated global satisfaction with their current treatment as satisfied, very satisfied, or extremely satisfied was 50% at the start of the titration period and 86% at the final visit.
Portenoy et al.[45] (1999) Fentanyl transmucosal lozenge 200 µg vs fentanyl	DB, dose titration, MC, RCT Adult patients with cancer-related pain who were receiving a scheduled oral opioid regimen equivalent to 60 to 1,000 mg of oral	N=65 Duration not reported	Primary: Pain intensity, pain relief, global assessment of drug performance Secondary: Not reported	Primary: For the 48 patients who were successfully titrated to an effective dose of transmucosal fentanyl, the mean pain intensity immediately before the dose of transmucosal fentanyl was approximately 6 on the 0 to10 numerical scale. After 60 minutes, the pain intensity averaged 1.5. The reduction in pain intensity during the 0 to 15 minute time period after the dose was 56% of the total pain intensity decline. Mean pain relief scores at 15 minutes and 30 minutes after the transmucosal fentanyl dose were 2.1 (‘moderate’ pain relief) and 2.5

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
transmucosal lozenge 400 µg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode using one fentanyl transmucosal lozenge unit. On each study day, as many as four units could be taken sequentially (one every 30 minutes) for up to two BTP episodes/day between 0700 to 1600 hours. Patients' usual BTP medication was used to treat all other BTPs on these study days.	morphine/day, experienced ≥1 BTP episode per day between 0700 to 1600 hours on the three days immediately preceding screening, and achieved at least partial relief of this BTP by the use of an oral opioid rescue dose			('moderate' to 'lots' of pain relief), respectively. The global performance of the transmucosal fentanyl during the two successful treatment days was 2.9 on the 0 to 4 verbal rating scale. With the exception of a single pain intensity difference recorded at the 60 minute time point, there were no significant differences between patients randomized to the 200 vs 400 µg starting doses in any of these outcome variables. Secondary: Not reported
Davies et al.[46] (2011) Fentanyl nasal spray	DB, DD, MC, XO Patients with a diagnosis of cancer, who were receiving fixed-schedule	N=110 10 BTP episodes	Primary: Pain intensity score, SPID, pain relief score, TOTPAR, onset of clinically	Primary: After ten minutes, fentanyl nasal spray had greater pain intensity difference scores and a higher proportion of episodes showing clinically meaningful pain relief compared to morphine IR (P<0.05 for both). After 15 minutes, 52.3% of patients taking fentanyl had a TOTPAR score ≥33% compared to 43.5% of patients taking morphine (P<0.01). This significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs morphine IR Fentanyl nasal spray was titrated up to 800 µg until the patient reached an effective dose that treated two consecutive BTP episodes. After titration to an effective dose, ten episodes of BTP were randomly treated with fentanyl nasal spray and encapsulated placebo or morphine IR and nasal spray placebo (five episodes of each).	opioid regimens at a total daily dose ≥60 mg/day oral morphine or equivalent and one to four episodes per day of moderate to severe cancer BTP		meaningful pain relief (≥2 point reduction in pain intensity score), patient acceptability score (overall satisfaction, satisfaction with speed of relief and satisfaction with reliability), adverse events Secondary: Not reported	difference was maintained until 60 minutes. Patient-averaged acceptability assessment scores were greater for fentanyl nasal spray than for morphine for all questions at 30 minutes (P<0.01) and 60 minutes (P <0.01). More treatment-emergent adverse effects were reported to be associated with fentanyl than with morphine. Only eight patients (six fentanyl and two morphine) experienced adverse effects that resulted in discontinuation of the drug (P values not reported). Secondary: Not reported
Fallon et al.[47] (2011) Fentanyl nasal spray 100 to 800 µg vs morphine IR	DB, DD, MC, RCT, XO Adult patients with cancer that were receiving fixed-schedule opioid regimens at a total daily dose equivalent to ≥60 mg/day oral	N=110 10 BTP episodes	Primary: Pain intensity difference after 15 minutes Secondary: Patient- and episode-averaged pain intensity difference, SPID, pain intensity	Primary: The mean (±SD) pain intensity difference score after 15 minutes was 3.02 (±0.21) for fentanyl nasal spray compared to 2.69 (±0.18) for morphine IR (P<0.05). Fentanyl nasal spray had significantly greater pain intensity difference scores compared to morphine IR from 15 minutes through 60 minutes after initial dose (P <0.05). Secondary: After treatment of BTP, fentanyl nasal spray treated episodes had significantly lower pain intensity scores compared to morphine IR treated episodes from 30 minutes through 60 minutes (P<0.05). In addition,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fentanyl nasal spray was titrated up to 800 µg until the patient received adequate pain relief for each BTP episode. IR morphine dose was determined as one-sixth of the total daily oral morphine dose equivalent of the patient's background opioid medication. After titration to an effective dose, ten episodes of BTP were randomly treated with fentanyl nasal spray and encapsulated placebo or IR morphine and nasal spray placebo (five episodes of each).	morphine and experiencing one to four BTP episodes per day		score, pain relief score, TOTPAR score, onset of analgesia (≥1 point reduction in pain intensity and pain relief), onset of clinically meaningful pain relief (≥2 point reduction in pain intensity and pain relief or 33% reductions in pain intensity and SPID), need for rescue medication	patient-averaged pain relief scores were significantly higher from 30 minutes through 60 minutes in patients who took fentanyl nasal spray compared to morphine IR (P≤0.005). Patient-averaged mean difference in TOTPAR were significant from 15 minutes through 60 minutes (P<0.05) favoring fentanyl nasal spray. The proportion of patients experiencing onset of analgesia and clinically meaningful pain relief was significantly greater in the fentanyl nasal spray group compared to the morphine IR group as early as five minutes and ten minutes, respectively (P<0.05 for both). There was no significant difference in the proportion of patients requiring rescue medication within 60 minutes between fentanyl nasal spray and morphine IR. More treatment emergent adverse events occurred in patients using fentanyl nasal spray (P value not reported). Of the 14 serious adverse events reported, 12 occurred following treatment with fentanyl nasal spray.
Mercadante et al.[48] (2015) Fentanyl buccal tablets	MC, RCT, XO Cancer patients with pain receiving ≥60 mg or more of oral morphine	N=81 263 episodes of BTP	Primary: Changes in pain intensity, and the number of episodes with a decrease in pain intensity of	Primary: Pain intensity significantly changed with both drugs (P=0.0005). A statistical difference between the two groups was observed at 15 minutes and 30 minutes (P<0.0005). There was a pain decrease of ≥33% in a higher number of episodes treated with fentanyl in comparison with morphine after 15 and 30 minutes (76.5 vs 32.8%, and 89 vs 54.9%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oral morphine	equivalents per day and presenting with ≤3 episodes of BTP per day		≥33% and ≥50%, recorded 15 and 30 minutes after study medication Secondary: Number of episodes in which patients reported adverse effects attributed to study medication, level of satisfaction with the treatments	respectively). The difference was significant (P<0.0005). Similar differences were found for the decrease in pain intensity of ≥50% after 15 and 30 minutes (52.3 vs 11.4%, and 75 vs 45.8%, respectively). Secondary: In both groups, an increase in intensity of nausea/vomiting was found at 30 minutes, but adverse effects after study drug administration were never severe (2 to 3 on the verbal scale). No statistical differences between the two groups were found at any time interval. Of patients who received both treatments, 44 and 20 patients preferred fentanyl and morphine, respectively. Four patients did not provide any preference.
Webster et al.[49] (2013) Fentanyl buccal tablet vs oxycodone IR <u>OL extension:</u> Fentanyl buccal tablet vs any traditional short-acting opioid (SAO) deemed appropriate by their treating physician	AC, DB, RCT, XO, followed by OL extension Patients 18 to 80 years of age with ≥3 month history of chronic pain, opioid tolerant (taking ≥60 mg/day of morphine equivalent, average pain intensity of ≤6 on an 11-point scale, and experiencing one to four episodes of BTP daily with at least partial relief with opioids	N=211 Two DB phases of 10 BTP episodes OL: 12 weeks	Primary: Difference in pain intensity (0 to 10 numeric scale) before and 15 minutes after medication Secondary: Pain response	Primary: During the double-blind treatment periods, the mean (standard deviation) PID score was significantly greater after fentanyl buccal tablet administration (0.88 [1.20]) than after immediate-release oxycodone (0.76 [1.13]; P<0.001). The mean PID also was significantly greater after fentanyl buccal tablet administration compared with immediate-release oxycodone beginning as early as 10 minutes postdose (P=0.01), and a significant difference was maintained through 60 minutes (P<0.001). Secondary: Mean values of patient assessments of pain response were significantly greater after fentanyl buccal tablet administration than after immediate-release oxycodone administration beginning at 15 minutes (P=0.04) and at all subsequent time points (P<0.01). Patients preferred fentanyl buccal tablet (47%) over oxycodone (35%); 18% had no preference. Patients and clinicians reported consistently better functional improvement and satisfaction with fentanyl buccal tablet vs short-acting opioids (P<0.05).
Ding et al.[50]	DB, RCT	N=56	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2016) Fentanyl PCA vs oxycodone PCA (potency ratio 1:60)	Patients 40 to 70 years of age undergoing elective gastric laparotomy	48 hours	Numeric rating scores (0 to 10) Secondary: Adverse events, respiratory rate, patient satisfaction	Numeric rating scores at rest was significantly lower in the oxycodone group at 30 minutes, 12, 24, and 48 hours after operation (P<0.05, respectively) and numeric rating scores upon movement was significantly lower in the oxycodone group at 30 minutes, 12 hours after the surgery (P=0.04, 0.01, respectively). Secondary: The percentage of patients experienced at least one adverse event were higher in oxycodone group than in fentanyl group, but the differences were not significant (33.3 vs 27.6%, P=0.64). No statistically significant differences between patients administered oxycodone and fentanyl were observed with regard to respiratory rate and no one reported respiratory depression in both groups. The overall satisfaction with pain management was rated by patients at 48 hours after the surgery, and there was no statistically significant difference between the groups (P=0.15).
Kim et al.[51] (2017) Fentanyl PCA vs oxycodone PCA (potency ratio 1:75)	DB, RCT Patients 18 to 65 years of age undergoing laparoscopic supracervical hysterectomy	N=127 48 hours	Primary: Numeric rating score (0 to 10) at 30 minutes post-op Secondary: Adverse events, patient satisfaction	Primary: The difference between the groups in the numeric rating score at rest was not significantly different at 0.5, 24, or 48 hours postoperatively, but at four and eight hours, it was significantly lower in the oxycodone group than in the fentanyl group (P<0.001). Secondary: The nausea level at four, eight, 24, and 48 hours, but not at 0.5 hour, was significantly higher in the oxycodone group than in the fentanyl group. The incidence of postoperative vomiting was significantly higher in the oxycodone group only at eight hours postoperatively, as was the administration of additional analgesics (P<0.05). In contrast, the administration of additional antiemetic drugs was significantly more frequent in the fentanyl group at eight hours postoperatively whereas, overall, dizziness and drowsiness occurred significantly more often in the oxycodone group. Respiratory depression was not observed in either of the groups, nor were there significant differences in their sedation scores. Postoperative patient satisfaction also did not significantly differ between the groups at eight hours postoperatively; however, at 48 hours, it was significantly higher in the fentanyl group than in the oxycodone group.
Shear et al.[52] (2010)	DB, RCT	N=60	Primary: Time required to	Primary: Treatment with fentanyl was associated with faster pain relief onset than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fentanyl 100 µg transbuccal vs oxycodone-APAP 5-325 mg	Adult patients who presented to the ED with a chief complain of extremity injury	1 hour	achieve a 2-point drop on a 10-point pain scale Secondary: Maximum pain scale reduction and vital signs	oxycodone-APAP (10 vs 35 minutes; P<0.0001). Secondary: Overall, rescue medication was required in 22 subjects; rescue analgesia was more frequently administered to those in the oxycodone-APAP group than in the fentanyl group (17 vs 57; P=0.003). Treatment with fentanyl was associated with faster time to maximum pain reduction than oxycodone-APAP (40 vs 55 minutes; P<0.01). The maximal pain score reduction was greater with fentanyl than oxycodone-APAP (6 vs 3; P=0.0004). Patients receiving fentanyl were more likely to be satisfied with the analgesia provided by the study drug. This was true regardless as to whether preference was measured as a median of the 1 to 5 rating scale (P=0.00001) or as a proportion of subjects indicating either 1 or 2 (meaning strong or probable preference to receive similar analgesia in the future; P<0.001). In the fentanyl group, 100% of patients achieved significant pain reduction compared to 83% of patients in the oxycodone-APAP group, which was not significant (P=0.52). The monitoring of vital signs identified no adverse effects in any subject in either group. No significant side effects occurred in the ED or during the next-day.
Coluzzi et al.[53] (2001) Fentanyl transmucosal lozenge 200 µg vs morphine IR 15 to	DB, DD, RCT, XO Adult patients with cancer-related pain who were regularly having one to four BTP episodes/day while using a stable fixed schedule oral opioid regimen	N=89 Up to 14 days or 10 BTP episodes	Primary: Pain intensity difference at 15, 30, 45 and 60 minutes post dose Secondary: Adverse events	Primary: Mean pain intensity differences across all time points significantly favored transmucosal fentanyl (P<0.008 for all). Transmucosal fentanyl produced a >33% change in 15 minute pain intensity difference values for 42.3% of the episodes treated compared to 31.8% for morphine IR (P<0.001). Secondary: Most adverse events reported during the study were considered unrelated or unlikely to be related to study medication. The most frequent drug-related adverse events included somnolence, nausea, constipation, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
60 mg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode. For any non-target BTP episodes, patients used their usual supply of morphine IR.	equivalent to 60 to1,000 mg/day of oral morphine or 50 to 300 µg/hour of transdermal fentanyl and who were using a successful dose of 15 to 60 mg of morphine IR to treat target BTP			dizziness. Due to the design of the study it is difficult to attribute an adverse event to either of the study medications.
Zeppetella et al.[54] (2006) Opioid analgesics vs placebo or opioid analgesics All RCTs were concerned with the use of transmucosal fentanyl in the management of BTP. Two trials examined the titration of	MA (4 RCTs) Patients of any age with cancer and BTP who were treated with opioids for cancer pain	N=393 Duration not reported	Primary: Reduction in pain intensity, adverse effects, attrition, patient satisfaction, and quality of life Secondary: Not reported	Primary: Results from four trials demonstrated that fentanyl transmucosal lozenge was more efficacious to placebo, morphine IR, and previous rescue medication with a WMD of -0.68 (95% CI, -1.03 to -0.34) for pain improvement at 15 minutes and -0.91 (95% CI, -1.23 to -0.59) for pain improvement at 30 minutes. Transmucosal fentanyl was more efficacious in providing pain relief at 15 minutes (WMD, 0.54; 95% CI, 0.40 to 0.69) and 30 minutes (WMD, 0.61; 95% CI, 0.47 to 0.75). Compared to previous rescue medication and placebo, transmucosal fentanyl was also more efficacious for global performance (WMD, 0.76; 95% CI, 0.58 to 0.95). *Fentanyl transmucosal lozenge dose titration:* Of the 62 patients on around-the-clock transdermal fentanyl, 47 (76%) were able to titrate transmucosal fentanyl to a safe and effective dose to treat their BTP. Three patients administering around-the-clock transdermal fentanyl withdrew during the titration phase because of treatment-emergent adverse effects and four patients titrated to the 1,600 µg dose without obtaining adequate relief. The mean±SD successful transmucosal fentanyl dose was 587±335 µg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
transmucosal fentanyl, one trial compared transmucosal fentanyl to morphine IR and one trial compared transmucosal fentanyl to placebo. Previous rescue medication included hydrocodone, hydromorphone, morphine, oxycodone, and propoxyphene.				Of the 67 patients on around-the-clock oral opioids, 48 (74%) were able to titrate to a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. Eight patients administering around-the-clock oral opioids withdrew during the titration phase because of treatment-emergent adverse effects and five participants titrated to the 1,600 µg dose without adequate obtaining relief. The mean±SD successful transmucosal fentanyl dose was 640±374 µg. It was determined that the optimal dose of transmucosal fentanyl cannot be predicted by the total daily dose of fixed scheduled opioids. The most common adverse events associated with transmucosal fentanyl were somnolence, nausea, dizziness, and vomiting. An OL comparison of transmucosal fentanyl and usual BTP medication demonstrated that transmucosal fentanyl produced significantly better pain relief at all time periods in patients administering around-the-clock transdermal fentanyl or oral opioids (P<0.0001 for both). Patient rated global satisfaction of transmucosal fentanyl was significantly higher compared to usual BTP medication (around-the-clock transdermal fentanyl, 2.6 vs 2.01; P=0.0001 and around-the-clock oral opioids, 2.74 vs 2.09; P=0.0002). Transmucosal fentanyl vs placebo: Of the 130 participants, 93 (72%) were able to titrate and find a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. The mean±SD successful transmucosal dose was 789±468 µg. Ninety-two patients agreed to enter a DB, randomized phase in which results from 86 patients demonstrated that transmucosal fentanyl produced significantly better pain relief than placebo as evidenced by better pain intensity and pain relief scores for all time points (P<0.0001). Patient rated global performance of transmucosal fentanyl was significantly better compared to placebo (1.98 vs 1.19; P<0.0001) and patients-treated with transmucosal fentanyl required significantly less additional BTP medication (15 vs 34%; P<0.0001). Of the original 92 patients, 74 (80%) chose to continue transmucosal fentanyl following the trial. The most frequent adverse effects included dizziness, nausea, somnolence,

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				constipation, asthenia, confusion, vomiting, and pruritus. *Transmucosal fentanyl vs normal release morphine:* Of the 134 patients, 93 (69%) were able to titrate to a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. Five patients titrated up to the 1,600 µg dose without obtaining adequate relief. Transmucosal fentanyl was significantly more efficacious to IR morphine in terms of pain intensity difference (P<0.008) and pain relief (P<0.009) at each time point, and global performance rating (P<0.001). Additionally, significantly more (P<0.001) more BTP episodes treated with transmucosal fentanyl had a >33% change in pain intensity at 15 minutes. Secondary: Not reported
Mercadante et al.[55] (2007) Fentanyl transmucosal lozenge, dose proportional to basal daily opioid dose vs IV morphine, dose proportional to basal daily opioid dose Patients were planned to receive fentanyl transmucosal lozenge and IV	RCT, XO Adult patients with cancer-related pain, receiving opioids regularly at doses >60 mg/day of oral morphine equivalents, had acceptable pain relief, and presented ≤2 pain flares/day	N=25 Duration not reported	Primary: Pain intensity at zero (T0), 15 (T1), and 30 (T2) minutes post dose; and opioid-related symptoms Secondary: Not reported	Primary: In BTP episodes treated with IV morphine, pain intensity decreased from 6.9 (95% CI, 6.6 to 7.2) to 3.3 (95% CI, 2.7 to 3.8) and 1.7 (95% CI, 1.2 to 2.3) at T1 and T2, respectively. This reduction was >33% in 39 (74%) and in 46 (87%) episodes at T1 and T2, respectively, and >50% in 29 (55%) and in 40 (75%) episodes at T1 and T2, respectively. In BTP episodes treated with transmucosal fentanyl, pain intensity decreased from 6.9 (95% CI, 6.6 to 7.2) to 4.1 (95% CI, 3.6 to 4.7) and 2.4 (95% CI, 1.8 to 2.9) at T1 and T2, respectively. This reduction was >33% in 30 (57%) and 45 (85%) episodes at T1 and T2, respectively, and >50% in 20 (38%) and in 40 (75%) episodes at T1 and T2, respectively. A statistical difference between the two treatments was found at T1 (P=0.013), whereas at T2 the difference did not attain a statistical significance (P=0.59). At T1, a decrease of 41.1 and 51.7% in pain intensity was observed after transmucosal fentanyl and IV morphine, respectively (P=0.026). At T2, a decrease of 65.9 and 73.8% in pain intensity was recorded after transmucosal fentanyl and IV morphine, respectively (P=0.136). No differences between the two groups were observed in the number of episodes with a reduction of >33 and >50% at T1 (P=0.66 and P=0.39) and T2 (P=0.23 and P=0.20), respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
morphine for each couple of BTP episodes between 0700 to 1900 hours. The order of administration was randomized.				Acute adverse effects occurring after IV morphine and transmucosal fentanyl were comparable and correspond to those commonly observed with opioid therapy. Moderate adverse effects in BTP episodes treated with transmucosal fentanyl and IV morphine were nausea, drowsiness and confusion. Secondary: Not reported
Mercadante et al.[56] (2009) Fentanyl nasal spray 50 to 200 µg vs fentanyl transmucosal lozenge 200 to 1,600 µg Enrolled patients entered a one week screening phase in which background pain intensity, BTP episodes, and use of rescue medication was assessed. Patients were then randomized to receive fentanyl nasal spray followed by	OL, XO Patients ≥18 years of age, with a life expectancy ≥3 months, who were experiencing ≥3 BTP episodes/week, but ≤4 BTP episodes/day and receiving stable opioid treatment for background pain (oral hydromorphone, morphine, oxycodone, or transdermal fentanyl) at a dose equivalent to 60 to 500 mg/day of oral morphine for ≥1 month prior to the study	N=139 8 to 11 weeks	Primary: Time to onset of 'meaningful' pain relief Secondary: Pain intensity, patient's general impression of drug efficacy and safety	Primary: The median time to onset of 'meaningful' pain relief was 11 minutes for intranasal fentanyl and 16 minutes for transmucosal fentanyl (P value not reported). Secondary: Statistically greater proportions of episodes treated with intranasal fentanyl compared to transmucosal fentanyl achieved ≥33 and ≥50% pain intensity reduction up to 30 minutes post dose. The proportion of BTP episodes treated with intranasal fentanyl and transmucosal fentanyl achieving a pain intensity reduction of ≥33% at five and ten minutes were 25.3 and 6.8% (P<0.001) and 51.0 vs 23.6% (P<0.001), respectively. The proportion of BTP episodes treated with intranasal fentanyl and transmucosal fentanyl achieving a ≥50% pain intensity reduction at 5 and 10 minutes were 12.8 vs 2.1% (P<0.001) and 36.9 vs 9.7% (P<0.001), respectively. The adjusted mean general impression score for treatment of the BTP episode as assessed by the patient at 60 minutes following the administration of intranasal fentanyl and start of transmucosal fentanyl use respectively was 2.1 (95% CI, 2.0 to 2.3) compared to 2.0 (95% CI, 0.1 to 0.2; P<0.001). Seventy-nine (56.8%) patients experienced ≥1 adverse event in the titration and efficacy phase. The only adverse event occurred in ≥5% of patients in either treatment group was nausea.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fentanyl transmucosal lozenge, or vice versa, and entered a five to eight week titration phase in which an effective dose of the study drug was determined. Patients then entered a <2 week efficacy phase during which six BTP episodes were treated with the identified effective dose of fentanyl nasal spray/ transmucosal lozenge.				
Vissers et al.[57] (2010) Fentanyl nasal spray vs fentanyl transmucosal lozenge vs fentanyl buccal	MA (six RCT) Adult cancer patients suffering from BTP, treated with opioid analgesics for management of background pain	N=Not available Duration unknown	Primary: Mean pain intensity difference Secondary: Not reported	Primary: Relative to placebo, fentanyl nasal spray provided a 1.7 (95% CI, 1.4 to 1.9) reduction in pain relief after 15 minutes, while the lozenge provided a 0.4 (95% CI, 0.0 to 0.8) reduction and the buccal tablet provided a 0.5 (95% CI, 0.3 to 0.7) reduction. Differences in pain intensity difference scores favoring fentanyl nasal spray were 1.2 (95% CI, 0.8 to 1.5) relative to the buccal tablet, 1.3 (95% CI, 0.9 to 1.6) relative to the transmucosal lozenge and 1.7 (95% CI, 1.1 to 2.3) relative to oral morphine. The significant difference in mean pain intensity difference scores favoring fentanyl nasal spray was maintained up to 45 minutes compared to the buccal tablet and up to 60 minutes compared to the transmucosal lozenge. According the author's analysis fentanyl nasal spray displayed >99% probability of providing the greatest pain reduction at 15 minutes out of all the interventions in the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tablet vs oral morphine vs placebo				Secondary: Not reported
Velázquez Rivera et al.[58] (2014) Fentanyl sublingual tablet vs oral morphine solution Doses were adjusted individually	DB, RCT Adults ≥18 years of age suffering from cancer pain whose background pain was treated with strong opioids and who had BTP	N=40 30 days	Primary: Pain intensity reduction the VAS, frequency of BTP, and onset of relief Secondary: Patient satisfaction, adverse events	Primary: The mean pain intensity level was consistently better for fentanyl than morphine at all recorded time points with a significance of P=0.001 at day three, and greater (P<0.001) at the other recorded time periods. Sublingual fentanyl provided faster onset of relief (P<0.001) in BTP and improved pain scores with a shorter dose titration period (mean 6.6 ± 3.3 vs 13.3 ± 4.9; P<0.001). Secondary: In the group treated with fentanyl no patient reported dissatisfaction with treatment for BTP, but 37.5% of the patients treated with morphine reported being dissatisfied (31.25%) or very dissatisfied (6.25%). Side effects were similar with both treatments and typical of opioid drugs.
Jandhyala et al.[59] (2013) Fentanyl buccal tablet, sublingual tablet or transmucosal lozenge vs morphine IR	MA (five studies) Patient population not specified	N=Not available Duration unknown	Primary: Likelihood of more efficacious pain relief (based on pain intensity difference) Secondary: Not reported	Primary: The probability of greater pain relief than placebo during first 60 minutes after dosing was 61% for morphine IR, 97% for fentanyl buccal tablet, 72% for fentanyl sublingual tablet and 66% for fentanyl transmucosal lozenge. The probability of greater pain relief than placebo during first 30 minutes after dosing was 56% for morphine IR, 83% for fentanyl buccal tablet, 66% for fentanyl sublingual tablet and 73% for fentanyl transmucosal lozenge (P values not reported). Mean pain intensity difference scores 60 minutes after dosing compared to placebo were 0.44 (95% CI, -2.07 to 2.95) for morphine, 1.16 (95% CI, 0.09 to 2.23) for the buccal tablet, 0.81 (95% CI, -1.40 to 3.04) for the sublingual tablet and 0.88 (95% CI, -0.76 to 2.55) for the transmucosal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				lozenge. The mean pain intensity difference scores compared to morphine IR were 0.75 (95% CI, -1.92 to 3.41) for the buccal tablet, 0.35 (95% CI, -3.00 to 3.63) for the sublingual tablet and 0.48 (95% CI, -1.34 to 2.34) for the transmucosal lozenge. Secondary: Not reported
Joshi et al.[60] (2007) Fentanyl 2 µg/kg IV vs sufentanil 0.2 µg/kg IV vs placebo All study meds administered 10 minutes before chest tube removal.	DB, PC, RCT Patients post-op cardiac surgery, scheduled for chest tube removal	N=141 Single dose	Primary: Pain intensity as assessed by 100 mm VAS pain score 10 minutes before removing chest tubes and five minutes after removing chest tubes Secondary: Level of sedation, heart rate, arterial pressure and respiratory rate	Primary: Mean pain intensity scores 10 minutes before removal of chest tubes in fentanyl, sufentanil and control groups were 23.88, 25.10 and 23.64, respectively. The pain scores five minutes after chest tube removal were reduced to 20.11 in the fentanyl group (P<0.05) vs 13.60 in the sufentanil group (P<0.05). There was an increase to 27.97 in placebo group (P<0.05). The pain scores in sufentanil group were significantly lower compared to fentanyl or the control group. Secondary: Sedation scores remained low in all groups, patients remained alert and none of the patients showed any adverse effects of opioids. Heart rate, arterial pressure and respiratory rate had least variations in sufentanil group vs fentanyl or placebo group.
Motamed et al.[61] (2006) Fentanyl 2 to 3 µg/kg IV bolus vs sufentanil 0.2 to 0.3 µg/kg IV bolus	RCT Adults scheduled for elective total thyroidectomy	N=75 24 hours post-op	Primary: Maximum post-op pain scores, Secondary: Necessity of morphine injection in both surgical ward and postoperative care unit; incidence of	Primary: Post-op pain scores in postoperative care unit were significantly lower in the sufentanil and fentanyl group compared to remifentanil group, (P<0.05). Secondary: Necessity and total amount of morphine titration in the postoperative care unit were significantly less in the sufentanil and fentanyl group compared to the remifentanil group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs remifentanil 0.4 to 5 µg/kg IV bolus All trial medications were administered intraoperatively.			opioid related side effects (nausea/ vomiting, sedation) Secondary: Not reported	In the surgical ward, maximum pain scores and the incidence and the amount of morphine requirements were not different between groups. No patient had heavy sedation in any of the groups. The incidence of nausea and vomiting was not different between groups. Secondary: Not reported
Chang et al.[62] (2006) Hydromorphone 0.015 mg/kg IV as a single dose vs morphine 0.1 mg/kg IV as a single dose	DB, RCT Patients 21 to 65 years of age who presented to an ED with acute pain (<7 days in duration) warranting use of IV opioids	N=191 Single dose	Primary: Difference between the two groups in pain reduction at 30 minutes Secondary: Adverse effects	Primary: The mean change in pain with hydromorphone was not significantly different from morphine (-5.5 numeric rating scale units' vs -4.1; 95% CI, -2.2 to -0.5). Secondary: Adverse effects were similar in both groups, with the exception of pruritus, which did not occur in the hydromorphone group (0 vs 6%; 95% CI, -11 to -1).
Barnaby et al.[63] (2018) Hydromorphone 1 mg IV vs acetaminophen 1 gram IV	DB, RCT Patients aged 21 to 64 years and presenting to the emergency department with acute pain (<7 days' duration) of sufficient severity in the judgment of the attending physician to warrant the use of IV opioids	N=220 Single dose	Primary: Between-group difference in change in numeric rating scale from baseline to 60 minutes post-administration of study medication Secondary: Difference in proportion of patients in each group who	Primary: At 60 minutes after study medication administration, the mean decrease in numeric rating scale pain score was 5.3 in the hydromorphone arm and 3.3 in the acetaminophen arm, representing a difference of 2.0 (95% CI, 1.2 to 2.7) favoring hydromorphone. Secondary: A greater proportion of patients in the hydromorphone arm declined additional analgesia at 60 minutes (65% vs 44%; difference 21%; 95% CI, 8% to 35%). There was no difference in the proportion of patients receiving rescue analgesia before 60 minutes. More subjects in the hydromorphone group developed nausea (19% vs 3%; difference 16%; 95% CI, 4% to 28%) and vomiting (14% vs 3%; difference 11%; 95% CI, 0% to 23%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			declined additional analgesia at 60 minutes, received additional medication before 60 minutes, and developed nausea, vomiting, or pruritus	
Lazaraki et al.[64] (2007) Midazolam 2 to 5 mg IV vs fentanyl 25 to 50 µg IV	RCT Adult patients scheduled for ambulatory colonoscopy	N=126 Single dose	Primary: Patient discomfort as measured on a 0 to 4 scale, and pain on a 0 to 10 scale Secondary: Adverse effects and recovery time	Primary: Mean discomfort scores were 0.4 in the fentanyl group and 1.0 in the midazolam group (P=0.002). Mean scores for pain and anus-to-cecum time were lower in the fentanyl group than in the midazolam group (2.59 vs 4.43; P=0.002 and 8.7 vs 12.9 minutes; P=0.012, respectively). Secondary: No adverse events were reported in the fentanyl group, while in the midazolam group, a decrease in oxygen saturation was noted in 35% patients. Mean recovery time was 5.6 minutes in the fentanyl group and 16 minutes in the midazolam group (P=0.014).
Plummer et al.[65] (1997) Morphine PCA 0.75, 1.0 or 1.5 mg bolus vs meperidine PCA 9, 12 or 18 mg bolus	DB, RCT Adult patients scheduled for major abdominal surgery	N=102 Variable duration	Primary: Pain at rest and on sitting Secondary: Incidence of nausea, unusual dreams, performance on standardized tests measuring mood and ability to concentrate	Primary: There was no significant difference in pain while at rest among the treatment groups (P=0.8). There was significantly higher pain relief in morphine group compared to the meperidine group in sitting position (P=0.037). Secondary: There were no differences in the incidence of nausea, unusual dreams, or mood measurements between groups. There was a lower ability to concentrate in the meperidine group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sudheer et al.[66] (2007) Morphine PCA (up to 50 mg/4 hours) vs tramadol PCA (up to 200 mg/4 hours) vs codeine 60 mg IM, then 60 mg after 1 hour if needed, then 60 mg every 4 hours as needed	RCT Postoperative pain control following elective craniotomy	N=60 Variable duration	Primary: P_aCO_2 four hours after eye opening, analgesia Secondary: Patient satisfaction, adverse effects	Primary: There were no differences between the groups in the change in P_aCO_2 and no change during the study period within each group. Neither the respiratory rate (range of eight to 28 breaths/minute) nor sedation showed differences between groups. Morphine produced significantly better analgesia than tramadol at all-time points (P<0.005) and better analgesia than codeine at four, 12 and 18 hours. Secondary: Patients were more satisfied with morphine than with codeine or tramadol (P<0.001). Vomiting and retching occurred in 50% of patients with tramadol, compared to 20% with morphine and 29% with codeine.
Poonai et al.[67] (2014) Morphine (0.5 mg/kg orally) every six hours as needed vs ibuprofen (10 mg/kg) every six hours as needed Participants were counselled to take acetaminophen at a	DD, PG, RCT Children 5 to 17 years of age who presented to the pediatric emergency department with a nonoperative, radiographically evident extremity fracture	N=134 24 hours	Primary: Change in pain using the Faces Pain Scale Secondary: Adverse events, APAP use	Primary: Both morphine and ibuprofen resulted in a decrease in pain scores at each dose administration. The between-group difference in pre–post changes in pain scores was not significant. Secondary: There were no significant differences in the percentage of participants requiring APAP for breakthrough pain in the morphine or ibuprofen groups (17 [25.7%] vs 10 [14.7%], P=0.1). Participants in the morphine group had significantly more adverse effects than those in the ibuprofen group (56.1 vs 30.9%, P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose of 15 mg/kg (max 975 mg) for breakthrough pain				
Kelly et al.[68] (2015) Morphine (0.2 to 0.5 mg/kg per dose every four hours as needed) vs ibuprofen (10 mg/kg per dose every six hours as needed) All patients were given APAP (10 to 15 mg/kg per dose every four hours as needed)	PRO, RCT Children 1 to 10 years of age who had sleep disordered breathing who were scheduled for tonsillectomy +/− adenoid removal	N=91 5 days	Primary: Changes in respiratory parameters after surgery Secondary: Pain, adverse drug reactions, tonsillar bleeding	Primary: On the first postoperative night, with respect to oxygen desaturations, 86% of children did not show improvement in the morphine group, whereas 68% of ibuprofen patients did show improvement. The number of desaturation events per hour (preoperative to postoperative) was reduced by a mean of 1.79 ± 7.57 in the ibuprofen group compared with an average increase of 11.17 ± 15.02 in the morphine group with an effect size of 0.96 (P<0.01). Secondary: The mean change in faces pain score from days one to five were 0.80 in the morphine group and 0.21 in the ibuprofen group (P=0.29). The mean change in objective pain scale score was similar between the groups (P=0.95). Tonsillar bleeding was reported in three children who received ibuprofen and two children who received morphine. Adverse drug events were reported at similar rates by parents in the two groups.
Poonai et al.[69] (2017) Morphine (0.5 mg/kg per dose every four hours as needed) vs ibuprofen (10 mg/kg per dose every six hours as needed)	DD, PG, RCT Children 5 to 17 years of age who had undergone minor outpatient orthopedic surgery	N=154 48 hours	Primary: Pain, according to the Faces Pain Scale – Revised, for the first dose Secondary: Additional analgesic requirements, adverse effects, unplanned health care visits and pain scores for doses	Primary: The median difference in pain score before and after the first dose of medication was 1 (interquartile range 0 to 1) for both morphine and ibuprofen (P=0.2). Secondary: For doses two to eight, the median differences in pain score before and after the dose were not significantly different between groups. Significantly more participants taking morphine reported adverse effects (45/65 [69%] vs 26/67 [39%], P<0.001), most commonly drowsiness (31/65 [48%] vs 15/67 [22%] in the morphine and ibuprofen groups, respectively; P=0.003). There was no significant difference in the number of participants who required APAP for breakthrough pain (P=0.2). Among participants who took APAP, there was no significant difference in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were given APAP (10 mg/kg per dose as needed)			two to eight	number of APAP doses taken per participant (P=0.09).
Karaman et al.[70] (2006) Morphine 0.2 mg vs sufentanil 5 µg	DB, RCT Female patients undergoing cesarean section who were receiving bupivacaine in spinal anesthesia	N=54 Single dose	Primary: Quality of anesthesia and postoperative analgesia Secondary: Adverse effects on mother and neonate	Primary: There were no differences between the morphine and sufentanil groups in onset time of sensory block, time to sensory block to T10, time to highest sensory block, highest sensory block level, time to regression of sensory block to T10 level and time to resolution of motor blockade. The time to first request for an analgesic was significantly longer (19.5 vs 6.3 hours) in morphine group (P<0.05). Secondary: Perioperative hemodynamic parameters, sedation scores, nausea/vomiting and pruritus incidences were similar in both groups. Neonatal Apgar scores, neurological and adaptive capacity scores and umbilical blood gas values were similar in both groups.
Friedman et al.[71] (2015) Oxycodone-APAP 5-325 mg vs cyclobenzaprine 5 mg vs placebo One or two of the randomized	DB, RCT Patients 21 to 64 years of age who presented with nontraumatic, nonradicular, acute low back pain of two weeks' duration or less were eligible for enrollment upon ED discharge if they had a score >5 on the RDQ	N=323 10 days of treatment; 3 months of follow-up	Primary: Improvement in RDQ seven days after ED discharge Secondary: Low back pain (severe, moderate, mild, or none), frequency of medication use, satisfaction with treatment	Primary: At 1-week follow-up, patients randomized to receive naproxen plus placebo improved by a mean of 9.8 (98.3% CI, 7.9 to 11.7) on the RDQ, those randomized to naproxen plus cyclobenzaprine improved by 10.1 (98.3% CI, 7.9 to 12.3), and those randomized to naproxen plus oxycodone-APAP improved by 11.1 (98.3% CI, 9.0 to 13.2). Between group differences in mean RDQ improvement were as follows: cyclobenzaprine vs placebo was 0.3 (98.3% CI, -2.6 to 3.2; P=0.77), oxycodone-APAP vs placebo was 1.3 (98.3% CI, -1.5 to 4.1; P=0.28), and oxycodone-APAP vs cyclobenzaprine was 0.9 (98.3% CI, -2.1 to 3.9; P=0.45). Secondary: At 1-week follow-up, regardless of study group, more than 50% of patients still required medication for low back pain. Many patients reported moderate or severe, and frequent pain. Despite these outcomes, more than two-thirds of patients reported that they would want to receive

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medication was taken every eight hours, as needed for low back pain All participants were given 20 tablets of naproxen, 500 mg, to be taken twice a day				the same medications during a subsequent ED visit for acute low back pain.
Chang et al.[72] (2015) Oxycodone-APAP 5-325 mg vs codeine-APAP 30-300 mg	DB, PRO, RCT Emergency department patients 21 to 64 years of age with acute musculoskeletal extremity pain who were discharged home	N=240 3 days	Primary: Between-group difference in improvement in mean Numerical Rating Scale pain score, measured at two hours following the most recent ingestion of the study drug Secondary: Between-group differences in proportion of patients with >50% pain reduction, frequency of prespecified side effects, and overall patient satisfaction	Primary: The mean Numerical Rating Scale pain score immediately prior to the most recent dose of study medication was 7.9 units in both groups, indicating a similar baseline level of pain. The mean change in pain scores two hours after the most recent dose of study medication was 4.5 Numerical Rating Scale units in the oxycodone-APAP arm vs 4.2 Numerical Rating Scale units in the codeine-APAP arm, for a difference of 0.2 units (95% CI, −0.4 to 0.9). Secondary: Approximately two-thirds of patients in each group achieved a 50% or greater decrease in pain. Patients in both groups were similarly satisfied with the analgesics they received. Consistent with this, there was no significant difference in the proportion of patients in each group wanting the same analgesic in the future. There were no clinically nor statistically significant between-group differences in any adverse event category.
Chang et al.[73] (2015) Oxycodone-APAP	DB, PRO, RCT Emergency department patients	N=220 3 days	Primary: Between-group difference in improvement in	Primary: The mean pain score prior to the most recent dose of pain medication was similar in both study groups. Mean change in pain scores two hours after the most recent dose of study medication was 4.4 units in the oxycodone-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5-325 mg vs hydrocodone-APAP 5-325 mg	21 to 64 years of age with acute musculoskeletal extremity pain who were discharged home		mean Numerical Rating Scale pain score, measured at 2 hours following the most recent ingestion of the study drug Secondary: Between-group differences in proportion of patients with >50% pain reduction, frequency of prespecified side effects, and overall patient satisfaction	APAP group versus 4.0 units in the hydrocodone-APAP group, for a difference of 0.4 NRS units (95% CI, −0.2 to 1.1). Secondary: Approximately 60% of patients in both groups achieved 50% or greater decreases in pain two hours after taking the study medication. Satisfaction with analgesics was clinically and statistically similar in both groups (86.9 vs 85.8%). Consistent with this, there were no significant differences in the percentages wanting the same analgesic in the future. Nausea and dizziness were both 10% more common in patients who received oxycodone-APAP than in those given hydrocodone-APAP. There were no clinical or statistically significant between-group differences in any of the other adverse events.
Kleinert et al.[74] (2008) Tapentadol 25 to 200 mg as a single dose vs morphine 60 mg as a single dose vs ibuprofen 400 mg as a single dose vs	DB, RCT Patients undergoing mandibular third molar extraction and experiencing moderate to severe pain postsurgery	N=400 8 hours	Primary: Mean TOTPAR over eight hours Secondary: Mean TOTPAR over eight hours and onset of analgesia	Primary: Compared to placebo, mean TOTPAR over eight hours was significantly greater for tapentadol 50 mg (P=0.041), 75 mg (P=0.001), 100 mg (P<0.001), and 200 mg (P<0.001); morphine 60 mg (P<0.001); and ibuprofen 400 mg (P<0.001). Secondary: Compared to placebo, mean TOTPAR over four hours was significantly higher for all tapentadol doses ≥50 mg, morphine 60 mg, and ibuprofen 400 mg (P≤0.05). All efficacy variables for tapentadol 100 and 200 mg showed greater analgesia compared to placebo (P≤0.05). The percentages of patients rating study medication treatment as good, very good, or excellent were as follows: tapentadol 25 mg (22%); tapentadol 50 mg (28%); tapentadol 75 mg (35%); tapentadol 100 mg (50%); tapentadol 200 mg (68%); morphine 60 mg (55%); and placebo (12%). Tapentadol 25 mg was not significantly different from placebo in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				patient global evaluation responses. The efficacy measures demonstrate an onset of analgesia for morphine 60 mg between that of tapentadol 100 and 200 mg doses. These data suggest that morphine 60 mg provides an analgesic dose comparable to a dose of tapentadol between 100 and 200 mg.
Gimbel et al.[75] (2004) Oxymorphone IR 10, 20, or 30 mg vs oxycodone IR 10 mg vs placebo	DB, DR, MC, PC, PG, RCT Men and nonpregnant, nonlactating women 18 to 75 years of age receiving total hip or knee replacement surgery and scoring I to III on the ASA physical status classification system	N=300 First phase: 8 hours Second phase: 48 hours	Primary: TOTPAR, SPID and SPRID at four, six, and eight hours, safety Secondary: Not reported	Primary: Mean TOTPAR scores at four, six, and eight hours for all doses of oxymorphone IR were statistically more efficacious compared to placebo (10 mg; P ≤0.034; 20 and 30 mg; P <0.001). Oxymorphone showed a statistically significant dose-response relationship in a regression model (TOTPAR8) by using the arithmetic dose as the regressor (slope estimate, 0.184; P<0.001; 95% CI, 0.089 to 0.279) and reached an analgesic plateau at the 20-mg dose. Oxymorphone IR at 10, 20, and 30 mg was statistically more efficacious compared to placebo for SPID (P≤0.001 for all doses) and SPRID at four, six, and eight hours (P≤0.007 for 10 mg and P<0.001 for 20 and 30 mg). Although oxycodone IR was generally numerically greater compared to placebo, the differences were not significant for any efficacy measures. The median time to meaningful pain relief was statistically significantly shorter in all of the oxymorphone IR groups (1 hour) than in the placebo group (1.5 hour; P<0.05). Fifty percent pain relief was achieved by 90.2% of patients in the oxymorphone IR 20 mg group (P<0.001), 82.4% of patients in the oxymorphone IR 10 mg group (P=0.022), 77.2% in the oxymorphone IR 30 mg group (P value not significant), and 69.2% in the oxycodone IR 10 mg group (P value not significant). The most frequent occurring adverse events in the oxymorphone IR groups were mild-to-moderate opioid side effects (i.e., nausea, vomiting, somnolence, and pruritus).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				During the single-dose phase, the incidence of adverse events was more frequent among the oxymorphone IR groups than in the oxycodone IR 10 mg group (39 to 50 vs 27%). In contrast, the incidence was somewhat more frequent in the oxycodone IR 10 mg group (82%) during the multiple-dose phase compared to the oxymorphone IR groups (61% to 71%). Secondary: Not reported
Özalevli et al.[76] (2005) Tramadol PCA 0.2 mg/kg bolus vs morphine PCA 0.02 mg/kg bolus	DB, RCT Children 6 to 12 years of age scheduled for tonsillectomy with general anesthesia	N=60 24 hours postoperative	Primary: Pain (as scored on a standardized 10-point scale), sedation (as assessed by a 5-point scale), nausea (as assessed on a 5-point scale) Secondary: Not reported	Primary: Pain scores decreased significantly with time in both groups (P<0.05), but were lower in morphine group vs tramadol group at one, two and four hours (P<0.05). Sedation scores increased with time in both groups (P<0.05), but there were no significant differences in sedation scores between the groups at any time point. Nausea scores were higher in morphine group at four, six and 24 hours (P<0.05). Secondary: Not reported
Silberstein et al.[77] (2005) Tramadol-APAP 75-650 mg vs placebo	DB, PC, PG, RCT Patients with history of migraine of moderate or severe intensity for ≥12 months, with a frequency of 1 to 6 migraine headaches per month in the previous year	N=305 Single dose	Primary: Severity of pain and migraine-related symptoms (photophobia, phonophobia, nausea) as recorded at baseline and at 0.5, one, two, three, four, six, and 24 hours post-dose Secondary:	Primary: Treatment response was higher for tramadol-APAP vs placebo at two hours post-dose (55.8 vs 33.8%; P<0.001) and at every other assessment from 30 minutes (12.3 vs 6.6%) through six hours (64.9 vs 37.7%; all P≤0.022). Subjects in tramadol-APAP group vs placebo group were more likely to be pain-free at two hours (22.1 vs 9.3%), six hours (42.9 vs 25.2%), and 24 hours (52.7 vs 37.9%; all P≤0.007). Two hours post-dose, moderate-to-severe symptoms that were less common for tramadol-APAP vs placebo included photophobia (34.6 vs 52.2%; P=0.003) and phonophobia (34.3 vs 44.9%; P=0.008), but not migraine-related nausea (38.5 vs 29.4%; P=0.681).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Incidence of adverse events	Secondary: Treatment-related adverse events included nausea (13.4%), dizziness (10.2%), vomiting (7.6%) and somnolence (6.4%). In the placebo group, no treatment-related adverse event was reported by more than 2% of subjects.
Helmerhorst et al.[78] (2017) Tramadol (50 mg every eight hours as needed) and APAP (maximum dose of 1000 mg every six hours) vs APAP (maximum dose of 1000 mg every six hours)	NI, RCT Patients ≥18 years of age who underwent surgical treatment for a single extremity fracture	N=52 2 weeks	Primary: Mean difference in self-reported satisfaction with pain relief score Secondary: Pain at this moment, worst pain, mean pain, acceptable pain	Primary: The mean satisfaction with pain management was 8.3 for APAP and 8.5 for tramadol and APAP. This mean difference of 0.2 point (95% CI, 20.78 to 1.30 points) did not exceed the noninferiority margin of 2.0 points, indicating that APAP was noninferior to tramadol and APAP. Secondary: The mean difference in secondary outcomes measures are as follows: pain at this moment: -0.7 (95% CI, -1.85 to 0.43), worst pain since surgery: -1.4 (95% CI, -2.74 to -0.19), mean pain since surgery: -0.9 (95% CI, -2.00 to 0.06), acceptable pain: 0.3 (95% CI, -0.72 to 1.34). Significantly more adverse events (p = 0.006) were reported in the tramadol and APAP group. Nausea was the most commonly reported adverse event in this group.
Palangio et al.[79] (2000) Hydrocodone-ibuprofen 7.5-200 mg 2 tablets vs oxycodone-APAP 5-325 mg 2 tablets vs placebo	DB, PC, PG, RCT Subjects >18 years of age with moderate to severe postoperative obstetric or gynecologic pain	N=180 8 hours	Primary: Pan relief, TOTPAR, SPID scores, time to onset, adverse events Secondary: Not reported	Primary: Mean pan relief scores were similar for hydrocodone-ibuprofen and oxycodone-APAP at 0.5, one, 1.5, two, 2.5, three, four, and seven hours and significantly greater for hydrocodone-ibuprofen than for oxycodone-APAP at five (P=0.003), six (P=0.043), and eight (P=0.044) hours. The mean TOTPAR was similar for hydrocodone-ibuprofen and oxycodone-APAP for the 0- to three- and 0- to four-hour intervals and significantly greater for hydrocodone-ibuprofen than for oxycodone-APAP at the 0- to six-hour (P=0.043) and 0- to eight-hour (P=0.029) intervals. The mean SPID was similar for hydrocodone-ibuprofen and oxycodone-APAP for each interval. The mean SPID was significantly greater for hydrocodone-ibuprofen or oxycodone-APAP than for placebo for each

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				interval (P <0.001). The median estimated time to onset of analgesia was similar for hydrocodone- ibuprofen (12.6 minutes) and oxycodone-APAP (15.4 minutes) and significantly shorter for either of these treatments than for placebo (29.5 minutes; P <0.001 and P=0.006, respectively). Eleven of 61 patients (18.0%) in the hydrocodone-ibuprofen group experienced adverse events, compared to seven of 59 patients (11.9%) in the oxycodone-APAP group and six of 60 (10.0%) in the placebo groups. These findings were not statistically significant. Secondary: Not reported
Palangio et al.[80] (2000) Hydrocodone-ibuprofen 7.5-200 mg (1 tablet) plus 1 tablet of placebo every 6 to 8 hours (HI1) vs hydrocodone-ibuprofen 15-400 mg (2 tablets) every 6 to 8 hours (HI2) vs codeine-APAP 60-600 mg (2 tablets) every 6 to 8 hours	DB, MC, PG, RCT Males and females >18 years of age with a chronic pain condition that required opioid or opioid-nonopioid combination analgesic therapy	N=469 4 weeks	Primary: Pain relief scores, number of daily doses of study medication, number of daily doses of supplemental analgesics, number of patients who discontinued therapy due to an unsatisfactory analgesic response, and global assessment scores Secondary: Not reported	Primary: The overall mean pain relief scores for the entire study period were significantly greater in the HI2 group than either the HI1 group (P=0.003) or the CA group (P<0.001). The weekly pain relief scores were significantly greater in the HI2 group than the HI1 group for weeks one (P<0.001), two (P<0.001), and three (P=0.008). The overall mean number of daily doses of supplemental analgesics was significantly less in the HI2 drop than either the HI1 group (P=0.21) or the CA group (P=0.01). There were no significant differences in the overall weekly mean number of daily doses of supplemental analgesics between the HI1 group and the CA group. The number of patients who discontinued treatment due to an unsatisfactory analgesic response was significantly less in the HI2 group (2/153; 1.3%) than in the CA group (12/160; 7.5%; P=0.08). There were no significant differences in the number of patients who discontinued treatment due to an unsatisfactory analgesic response between the HI1 group (8/156; 5.1%) and either the HI2 group or the CA group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(CA)				The weekly mean global assessment scores were significantly greater in the HI2 group than the HI1 group for weeks one (P=0.018), two (P=0.005), and four (P=0.013). The weekly mean global assessment scores were significantly greater in the HI2 group than the CA group for weeks one (P<0.001), two (P<0.001), three (P=0.009), and four (P=0.023), and end point (P=0.016). There were no significant differences in the weekly mean global assessment scores between the HI1 group and the CA group. Secondary: Not reported
Marco et al.[81] (2005) Oxycodone-APAP as a combination liquid formulation vs hydrocodone-APAP as a combination liquid formulation	DB, PRO, RCT ED patients over the age of 12 with fractures and severe pain, with pain scores >5 on a 0 to 10 scale	N=73 60 minutes	Primary: Pain score (verbal numeric rating scale) at 30 and 60 minutes Secondary: Presence and severity of side effects	Primary: Patients in both groups had pain relief from baseline to 30 minutes (oxycodone-APAP mean change 3.7; 95% CI, 2.9 to 4.6; hydrocodone-APAP mean change 2.5; 95% CI, 1.7 to 3.3) and from baseline to 60 minutes (oxycodone-APAP mean change 4.4; 95% CI, 3.2 to 5.6; hydrocodone-APAP mean change 3.0; 95% CI, 2.1 to 3.9). There was no difference in pain identified between the patients treated with oxycodone-APAP and hydrocodone-APAP at 30 minutes (mean difference between groups -0.6; 95% CI, -1.8 to 0.5) or at 60 minutes (mean difference -0.5; 95% CI, -2.0 to 1.0). Secondary: There was no difference between the groups in nausea, vomiting, itching, or drowsiness; however, the hydrocodone-APAP patients had a higher incidence of subsequent constipation (oxycodone-APAP 0%, hydrocodone-APAP 21%, difference in proportions 21%; 95% CI, 3 to 39%).
Litkowski et al.[82] (2005) Oxycodone-ibuprofen 5-400	AC, MC, PC, PG, RCT Men or women >12 years of age who	N=249 6 hours	Primary: TOTPAR through six hours after dosing (TOTPAR6), sum	Primary: The combination of oxycodone-ibuprofen provided higher pain relief values than any of the other combinations tested or placebo. TOTPAR6 scores were significantly better for each combination treatment compared to placebo (P<0.001). The combination of oxycodone-ibuprofen was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg vs oxycodone-APAP 5-325 mg vs hydrocodone-APAP 7.5-500 mg vs placebo	were scheduled to undergo complete removal of >2 ipsilateral, partially or completely impacted third molars		of pain intensity differences through six hours (SPID6), and adverse events Secondary: SPID3,TOTPAR3, peak pain relief, peak PID, time to onset of pain relief, time to use of rescue medication, proportion of patients reporting pain half gone, and the patient's global evaluation	associated with a significantly higher TOTPAR6 score compared to oxycodone-APAP, hydrocodone-APAP, and placebo (mean [SD], 14.98 [5.37], 9.53 [6.77], 8.36 [6.68], and 5.05 [6.90], respectively; all, P<0.001). The results for SPID6 were similar, with oxycodone-ibuprofen associated with significantly higher values compared to oxycodone-APAP, hydrocodone-APAP, and placebo (7.78 [4.11], 3.58 [4.64], 3.32 [4.73], and 0.69 [4.85]; all P<0.001). Both oxycodone-APAP and hydrocodone-APAP were associated with significantly higher SPID6 scores compared to placebo (P<0.001 and P=0.002, respectively). The combination of oxycodone-ibuprofen was well tolerated, as evidenced by an overall rate of patients experiencing >1 adverse event that was similar to that for placebo (11.3% [7/62] and 11.1% [7/63], respectively). Rates in the groups receiving oxycodone-APAP and hydrocodone-APAP (27.9% [17/61] and 25.4% [16/63], respectively) were >2-fold higher. Secondary: For TOTPAR3, SPID3, peak pain relief, pain half gone, and the patient's global assessment, oxycodone/ibuprofen was associated with significantly better scores compared to oxycodone-APAP, hydrocodone-APAP, and placebo (all, P<0.001). Peak SPID scores were also significantly higher for oxycodone-ibuprofen compared to oxycodone-APAP (P=0.006). Compared to placebo, oxycodone-APAP and hydrocodone-APAP also were significantly better in terms of TOTPAR3, SPID3, the patient's global assessment (all, P<0.001), and peak pain relief (P<0.001 and P=0.002, respectively). The median time to the onset of pain relief was significantly shorter for oxycodone-ibuprofen compared to hydrocodone-APAP (P=0.002) and placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both oxycodone-APAP and hydrocodone-APAP were associated with significantly shorter median times to the onset of pain relief compared to placebo (P<0.001 and P=0.002, respectively).
Smith et al.[83] (2004) Tramadol-APAP 75-650 mg vs codeine-APAP 30-300 mg vs placebo All study meds were administered as 2 tablets stat, then 1 to 2 tablets every 4 to 6 hours as needed.	DB, MC, PC, RCT Patients with moderate to severe abdominal or orthopedic postsurgical pain	N=305 6 days	Primary: TOTPAR, SPID, and sum of pain relief and pain intensity differences during the four hours after the first dose of study medication on day one Secondary: Average daily pain intensity scores and average daily pain relief scores reported on days one to six; overall rating of study medication by both patients and investigators using a five-point scale; incidence of adverse events	Primary: Tramadol-APAP was more effective than placebo for TOTPAR, SPID and sum of pain relief and pain intensity differences (P≤0.015); tramadol-APAP and codeine-APAP did not separate (P≥0.281). Secondary: For average daily pain relief, average daily pain intensity, and overall medication assessment, tramadol-APAP was more effective than placebo (P≤0.038). Codeine-APAP did not separate from placebo (P≥0.125). Discontinuation because of adverse events occurred in 8.2% of tramadol-APAP, 10.1% of codeine-APAP and 3.0% of placebo patients. Except for constipation (4.1% tramadol-APAP vs 10.1% codeine-APAP) and vomiting (9.2 vs 14.7%, respectively), adverse events were similar for active treatments.
Hewitt et al.[84] (2007) Tramadol-APAP 75-650 mg vs	RCT Patients 18 to 75 years of age with ankle sprain within previous 48 hours; clinical diagnosis of partial ligament	N=396 5 days	Primary: Pain relief as measured by patient response to two standardized pain relief/pain intensity scales	Primary: Tramadol-APAP and hydrocodone-APAP provided greater TOTPAR than placebo (P<0.001) during the first four hours, decreased pain intensity during the first four hours and increased average pain relief on days one to five. No efficacy measure was significantly different between the tramadol-APAP and hydrocodone-APAP groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hydrocodone-APAP 7.5-650 mg vs placebo	tear, pain on ambulation and ankle swelling.		Secondary: Adverse events	Secondary: Common adverse events included somnolence, nausea, dizziness, and vomiting.
Zenz et al.[85] (1992) Buprenorphine, dihydrocodeine sustained release, and morphine sustained release	OL Patients receiving chronic opioids for treatment of non-malignant pain	N=100 Variable duration	Primary: Pain reduction with visual analogue scales; patient function using the Karnofsky Performance Status Scale Secondary: Not reported	Primary: Good pain relief was obtained in 51 patients and partial pain relief was reported by 28 patients. Only 21 patients had no beneficial effect from opioid therapy. There was a close correlation between the sum and the peak visual analogue scale values (P<0.0001). Pain reduction was associated with an increase in performance (P<0.0001). Secondary: Not reported
Moyao-Garcia et al.[86] (2009) Nalbuphine 100 µg/kg bolus IV + 0.2 µg/kg/hour continuous infusion vs tramadol 1 mg/kg + 2.0 µg/kg/hour continuous infusion for 72 hours	DB, PRO, RCT Children 1 to 12 years of age undergoing scheduled surgery	N=24 72 hours	Primary: Number of patients requiring dose increments Secondary: Sedation, heart rate, blood pressure, and vomiting	Primary: Three patients who received nalbuphine required an extra bolus dose in the 12 hour post-surgery period, vs one child in the tramadol group. There were a similar number of patients in both treatment groups who required an increase in the infusion rate within the 72 hour post-surgery period. Secondary: Sedation was observed in two patients in the nalbuphine group and in one patient in the tramadol group. Vomiting occurred in four children receiving tramadol, and two receiving nalbuphine. No adverse cardiovascular events were detected in either group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Yeh et al.[87] (2009) Nalbuphine 10 µg/mL IV and morphine 1 mg/mL infusion via PCA vs morphine 1 mg/mL IV infusion via PCA	DB, PRO, RCT Female patients undergoing gynecological surgery	N=174 24 hours	Primary: Pain and medication dose Secondary: Nausea, vomiting, use of antiemetics, pruritus, use of antipruritics, opioid related adverse effects	Primary: Numerical pain rating scores and medication requirements were not significantly different between the treatment groups. Secondary: Nausea was lower in the nalbuphine group than the morphine-only group (45 vs 61%; P=0.03). Other secondary outcomes did not differ between the treatment groups.
Levine et al.[88] (1988) Pentazocine 60 mg IV vs naloxone 0.4 mg IV vs morphine 8 or 15 mg IV vs naloxone 0.4 mg + morphine 8 mg IV vs	DB, RCT Patients undergoing surgery for the removal of impacted third molars	N=105 Single dose	Primary: Pain intensity using a visual-analogue scale Secondary: Not reported	Primary: The mean pain intensity was increased in the group receiving placebo. Mean pain intensity was decreased in the groups that received either morphine (8 and 15 mg; P<0.05 and P<0.01, respectively) or pentazocine (60 mg; P<0.05) as a single agent. The combination of low-dose naloxone and pentazocine produced significantly greater analgesia than either low-dose naloxone (P<0.01), pentazocine (P<0.01), or even high-dose morphine administered alone (P<0.01). The combination of low-dose naloxone and 8 mg morphine produced less analgesia when compared to the same dose of morphine alone (P<0.05) or with high-dose morphine (P<0.01) but not when compared to low-dose naloxone administered alone. The mean pain intensity measured at three hours and 10 minutes after injection of single analgesic agents was not significantly decreased compared to placebo. The analgesia produced by the combination of low-dose naloxone and 8 mg morphine did not differ significantly from the analgesia produced by the same dose of morphine. The combination of low-dose naloxone and pentazocine produced significant analgesia when compared to either agent alone (both P<0.01). By three hours and 10 minutes after injection, only

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naloxone 0.4 mg + pentazocine 60 mg IV vs placebo				the group of patients receiving low-dose naloxone plus pentazocine still reported significant analgesia. Secondary: Not reported
Petti[89] (1985) Pentazocine 25 mg and APAP 650 mg vs codeine 30 mg and APAP 300 mg vs propoxyphene napsylate 100 mg and APAP 650 mg vs placebo	PC, PG, SB Patients with moderate postoperative pain	N=129 6 hours	Primary: Intensity of pain and degree of pain relief Secondary: Not reported	Primary: Pentazocine and APAP was significantly better than placebo and equivalent to codeine and APAP and propoxyphene and APAP in patients with moderate postoperative pain. No adverse events were reported with APAP and pentazocine, APAP and propoxyphene napsylate, or placebo. Secondary: Not reported
Graudins et al.[90] (2016) APAP 2 × 500 mg and ibuprofen 2 × 200 mg with thiamine 2 × 100 mg (non-opioid) vs	DB, NI, RCT Patients 18 to 75 years of age with acute limb injury, moderate pain on arrival, and oral analgesia deemed suitable	N=182 90 minutes	Primary: Difference in mean VAS change between groups at 30 minutes Secondary: Mean change in VAS rating from baseline to 30 min	Primary: At 30 minutes, the mean VAS reductions for the non-opioid, codeine, and oxycodone groups were −13.5, −16.1 and −16.2 mm, respectively. The difference in mean change was as follows: −2.6 (95% CI, −8.8 to 3.6) for non-opioid versus codeine; −2.7 (95% CI, −9.3 to 3.9) for non-opioid versus oxycodone; 0.1 (95% CI, −6.6 to 6.4) for codeine versus oxycodone. The non-opioid, codeine, and oxycodone groups were all non-inferior to each other at the primary outcome time of 30 minutes. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
APAP 2 × 500 mg and ibuprofen 2 × 200 mg with codeine 2 × 30 mg (codeine) vs APAP 2 × 500 mg and ibuprofen 2 × 200 mg with oxycodone 2 × 5 mg tablets (oxycodone)			for each group, patient satisfaction, need for additional analgesia and adverse events	Satisfaction with initial analgesia was reported by 58/61 (96%), 58/62 (94%), and 53/59 (90%) of the non-opioid, codeine, and oxycodone groups. Rescue analgesia was given to 11/61 (18.0%), 7/62 (11.3%), and 2/59 (3.4%), respectively. Adverse events were reported for 13/182 (7.1%).
Chang et al.[91] (2017) Ibuprofen 400 mg and APAP 1000 mg vs oxycodone 5 mg and APAP 325 mg vs hydrocodone 5 mg and APAP 300 mg vs codeine 30 mg and APAP 300 mg	DB, RCT Patients 21 to 64 years of age with moderate to severe acute extremity pain in the emergency department	N=411 2 hours	Primary: Between-group difference in decline in pain two hours after ingestion using an 11-point numerical rating scale Secondary: Between-group difference in decline in pain one hour after ingestion using an 11-point numerical rating scale	Primary: At two hours, the mean pain score decreased by 4.3 (95% CI, 3.6 to 4.9) in the ibuprofen and APAP group; by 4.4 (95% CI, 3.7 to 5.0) in the oxycodone and APAP group; by 3.5 (95% CI, 2.9 to 4.2) in the hydrocodone and APAP group; and by 3.9 (95% CI, 3.2 to 4.5) in the codeine and APAP group. The overall test of the null hypothesis that there is no difference in change in pain by treatment group from baseline to two hours (the primary outcome measure) was not statistically significant (P=0.053). Secondary: There was also no significant difference in pain score at one hour (P=0.13)
Bijur et al.[92] (2021)	DB, RCT	N=600	Primary: Change in pain	Primary: The mean decrease in pain scores from baseline to one hour postbaseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ibuprofen 400 mg plus APAP 1,000 mg vs ibuprofen 800 mg plus APAP 1,000 mg vs codeine 30 mg plus APAP 300 mg vs hydrocodone 5 mg plus APAP 300 mg vs oxycodone 5 mg plus APAP 325 mg	Emergency department (ED) patients 21 to 64 years of age with acute musculoskeletal pain	2 hours	before administration of medication (baseline) to one hour postbaseline Secondary: Receipt of rescue medication and adverse effects at one and two hours postbaseline	varied from 3.0 to 3.4 numeric rating scale (NRS) units in the five groups. The overall test of different change in pain by treatment was not statistically significant (P=0.69). The differences were substantially less than the criterion of 1.3-NRS-unit difference as being clinically meaningful. Secondary: Few patients received rescue medication in the first hour postbaseline (8/597; 1.3%). The proportion of patients who received rescue medication did not differ by treatment. Nausea and vomiting differed significantly across the five groups (P=0.048), although only 4.7% of all patients experienced these adverse effects. In a post hoc analysis, nausea and vomiting were found to be more common in patients who received opioid analgesics, 6.7%, than among those who did not, 1.7% (5.0% difference; 95% CI, 1.7 to 8.2%). The other adverse effects were similarly distributed in the five groups.
Chronic Pain				
Le Loët et al.[93] (2005) Fentanyl 25 µg/hour transdermal every 72 hours	MC, OL Patients ≥50 years of age with OA of knee or hip who were waiting for a knee or hip replacement; all patients required supplementary analgesia because of	N=159 28 days	Primary: Pain control Secondary: Pain assessment; pain intensity; treatment assessment; quality of life; functionality using the WOMAC;	Primary: At baseline, 25% of patients reported very poor pain control, 48% poor pain control and 25% moderate pain control. After the first week of treatment, 74% of patients reported adequate pain control, 37% reported moderate pain control, 29% reported good pain control and 8% reported excellent pain control. Adequate pain control was reported by 80 and 88% patients on days 14 and 28, respectively.

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	moderate/severe pain not adequately controlled with APAP, NSAIDs, COX-2 inhibitors or weak opioids.		adverse events	At endpoint, 83% of patients considered their pain controlled, with 37% reporting moderate pain control, 38% reporting good pain control, and 8% reporting excellent pain control. Secondary: The mean reduction in 'pain right now' was 2.6 points (from 6.1 to 3.5) from baseline to endpoint. A significant reduction in 'pain right now' was reported as early as 24 hours after baseline (1.3 points, from 6.0 to 4.7). The mean score for degree of pain was significantly decreased at each time point (P<0.001). While at baseline, 58% reported severe/extreme pain, 4% reported mild pain and only two patients were without pain. By study endpoint, 41% reported moderate pain, 30% reported mild pain and 7% reported no pain. In their assessment of treatment, 63% of patients rated fentanyl positively with respect to pain control and 84% would recommend fentanyl for their type of pain. A total of 93% of patients thought it easy/extremely easy to use; 85% were very/somewhat pleased by the way it's used, and 53% considered side effects were not an issue. In assessing how they had felt over the past week, the percentage of all patients who answered good or very good increased during the study from 7 to 32% at week 4, and their scores at all time points were significantly better than before treatment (P<0.001). By the end of the study, help with basic activities was required by only 28% of patients, with 49% relying less on their helper. For the 122 patients who completed the quality of life questionnaire, there were statistically significant improvements in all domains from baseline to endpoint, including overall physical health (P<0.001) and mental health (P<0.05). The mean score for all 24 questions from the three WOMAC summary parameters (pain, stiffness and physical functioning) improved significantly from baseline to endpoint for all groups (P<0.001). The percentage of patients who reported no pain, stiffness or physical

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				difficulties increased for all items. Mean overall WOMAC score improved significantly (P<0.001) from baseline to endpoint. Adverse events were reported by 65% of patients during the treatment period. The study medication was permanently stopped in 25% (39) of cases, particularly because of nausea (53%), vomiting (47%) and dizziness (18%). No falls or fractures were reported; no deaths occurred.
Weinstein et al.[94] (2009) Fentanyl transbuccal tablet	OL Opioid tolerant adults with cancer pain and a life expectancy of ≥2 months	N=232 ≥12 months	Primary: Adverse event monitoring, physical examination, and clinical laboratory tests Secondary: Patient-assessed comparison of fentanyl vs previous supplemental medication, Global Medication Performance questionnaire, dose changes over time	Primary: Ninety percent of patients reported at least one adverse event during the fentanyl titration and maintenance phases. The most common adverse events during the titration phase were dizziness, nausea, somnolence, and headache. The most common adverse events during the maintenance phase were nausea, vomiting, fatigue, constipation, peripheral edema, and anemia although study investigators did not consider peripheral edema and anemia to be related to the study drug. Abnormal hematology findings were consistent with the patient's medical history and no meaningful trends were observed in laboratory values. A successful fentanyl buccal tablet dose was identified by 71% of patients during the titration phase. Only three (1%) patients discontinued the study because of lack of fentanyl efficacy during the maintenance phase. Fentanyl buccal tablets were generally well tolerated by patients with chronic cancer pain. Secondary: Patients favored fentanyl compared to previous breakthrough medication (88 vs 12%). Patients rated fentanyl between "good" and "very good" on average for the Global Medication Performance questionnaire. The final fentanyl dose was the same as the initial successful dose for 69% of patients.
Mercadante et al.[95] (2010) Fentanyl transdermal patch	OL Opioid-naïve patients with advanced cancer	N=46 4 weeks	Primary: Pain intensity, time to dose stabilization, and quality of life	Primary: Pain control was achieved within a mean of 1.7 days after the start of transdermal fentanyl therapy. Pain intensity significantly decreased from baseline through the remaining weekly evaluations (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 µg/hour and titrated every 2 to 3 days as necessary Oral morphine at a dose of 5 mg was allowed for BTP.	and moderate pain		Secondary: Not reported	Significant differences in fentanyl doses were observed after week two and were almost doubled at week four. The mean calculated fentanyl escalation index were 4.04% and 0.012 mg. No differences in fentanyl escalation index were found when considering the pain mechanism and primary cancer. There were no significant changes in opioid, related symptoms and quality of life between weekly evaluations. The pain mechanism did not significantly affect the changes in pain intensity and doses of fentanyl. Transdermal fentanyl was well tolerated, with only five of 36 patients (13.8%) who discontinued fentanyl for alternative treatments or poor compliance. Secondary: Not reported
Agarwal et al.[96] (2007) Fentanyl transdermal system 25 to 150 µg/hour replaced every 72 hours	OL, PRO Patients >18 years of age with neuropathic pain persisting for >3 months	N=53 16 weeks	Primary: Change in pain intensity and daily activity Secondary: Pain relief, cognition, physical function and mood	Primary: The average pain reduction across the population using pain diary data was -2.94±0.27. Thirty patients (57%) reported >30% improvement in pain and 21 patients (40%) reported >50% change in pain intensity. Decreases in pain scores for the subgroups were; peripheral neuropathy, -3.40±0.44; CRPS-1, 2.40±0.40 and postamputation pain, -2.70±0.47. There was a trend toward a greater reduction in pain intensity in the peripheral neuropathy group compared to the CRPS-1 (P=0.06) and postamputation (P=0.07) groups among the ITT population. Among completers, fentanyl was more effective in reducing pain in the peripheral neuropathy subjects compared to the other two groups of patients (P<0.04). The average increase in daily activity from baseline was significant with fentanyl treatment (P<0.001). Overall, 32.5% of patients experienced both a >30.0% decrease in pain intensity and a >30.0% increase in activity. The effect of fentanyl on activity was that 62% of subjects experienced a >15% increase in activity levels compared to baseline, 20% showed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				minimal or no change (±15%) in activity, and 18% showed a >15% reduction in activity. The average increase in activity in the three subgroups was 42.6, 37.5 and 33.3%, respectively, in patients with peripheral neuropathy, CRPS, and postamputation pain. Secondary: The change in the grooved pegboard test for the entire population was -1.46±5.80 seconds and -5.9±12.2 seconds for the dominant and non-dominant hands (P value not significant). The change in MPI-Interference for the whole group was 0.20±0.94 (P value not significant), and the change in MPI-Activity was -0.03±0.80 (not significant). The difference in the BDI was 0.03±0.32 (P value not significant).
Finkel et al.[97] (2005) Fentanyl transdermal system 12.5 to 100 µg/hour applied every 3 days	MC, OL, SA Patients 2 to 16 years of age with moderate to severe chronic pain due to malignant or nonmalignant disease	N=199 15 days (with 3 month extension)	Primary: Global assessment of pain treatment; changes in pain level, PPS, and CHQ and safety Secondary: Not reported	Primary: The most common starting dose of fentanyl was 25 µg/hour, which was required by 90 patients (45.2%). The lowest starting dose, 12.5 µg/hour, was considered appropriate for 59 patients (29.6%). The average duration of treatment with fentanyl in the primary treatment period was 14.80±0.25 days in the ITT patient group. A total of 84.9% of patients received at least one rescue medication, with a mean oral morphine equivalent of 1.35±0.16 mg/kg during the primary treatment period. The average daily pain intensity levels reported by parents/guardians using the numeric pain scale for the ITT population decreased steadily throughout the study period from 3.50±0.23 at baseline to 2.60±0.21 by day 16. Parent/guardian-rated improvements in mean PPS scores were observed from baseline (41.22±1.68) to the data collection endpoint (53.80±1.91), resulting in a mean change of 11.5%. At the end of month one of the extension phase (n=36), parents reported improvement in 11/12 domains assessed by the CHQ with the largest improvement noted in bodily pain (29.52±4.52; baseline, 18.14). Other domains demonstrating an improvement of greater than five points from

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				baseline include mental health (8.28±2.76; baseline, 54.33), family activities (6.96±3.19; baseline, 43.04), role emotional behavior (12.36±6.08; baseline, 34.72), physical function (7.15±2.71; baseline, 23.65) and role physical (13.82±5.76; baseline, 17.07). At the end of month three, participating patients continued to demonstrate sustained improvements in 11/12 domains. One hundred eighty patients (90.5%) reported at least one adverse event during treatment. The most frequent adverse events were fever (n=71 patients), emesis (n=66 patients), nausea (n=42 patients), headache (n=37 patients) and abdominal pain (n=34 patients). Secondary: Not reported
Park et al.[98] (2011) Fentanyl transdermal patch 12.5 µg/hour, dose could be increased by 12.5 or 25 µg/hour	OL, PRO Patients ≥19 years of age, with overall good health, and complaining of chronic pain of the spine and limbs that scored >4 points on a numerical rating scale 72 hours prior to baseline data	N=65 12 weeks	Primary: Percentage of change in pain intensity from before the administration of the study drug to 12 weeks Secondary: Degree of satisfaction, patient's function/sleep interference, dose, safety	Primary: Changes in average pain intensity, evaluated by investigators, decreased from a level of 6.70 to 2.58 (61.5%) at trial end. The average individual pain intensity, evaluated by the patients, decreased from 7.02 to 2.86 (59.3%; P<0.001). The pain intensities evaluated by the patients, at rest and when moving, were decreased from 5.40 to 1.95 (63.9%; P<0.0001). Secondary: Within three visits, the sum of patients who answered "very satisfied" or "satisfied" was 76.8, 83.7, and 93.0%, respectively. Differences in the sums of the rates of 'very satisfied' and "satisfied" measured in week four and the rates on the last visit constituted a significant increase (P<0.05). The determinants of the patient's satisfaction with pain treatment were (in order of frequency): efficacy of pain treatment is good, satisfied overall, and convenient. Investigators' satisfaction with the pain treatment was also evaluated and the sum of the rates of "very satisfied" and "satisfied" on each visit was 83.7, 83.7, and 86.0%. Following treatment, each function of daily life, walking, and eating due to pain showed a decrease as follows: from 7.30 to 3.07, from 6.58 to 2.86, and from 3.33 to 0.35, respectively (P<0.001). Rate of patients whose sleep was not disturbed increased from 32.6% in the first evaluation to 86.1% in the fifth evaluation (P<0.0001).

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				The average dose administered was 13.95 µg/hour upon initial administration and 42.59 µg/hour at the termination of the trial (P<0.001). In 55 patients, more than one adverse event was observed during the trial. Nausea was observed in 32 patients, dizziness in 28 patients, drowsiness in 20 patients, constipation in 11 patients, and vomiting in 10 patients. In general all events were mild. There were 18 patients who discontinued the trial due to adverse events.
Langford et al.[99] (2006) Fentanyl transdermal system 25 to 100 µg/hour every 72 hours vs placebo	MC, PC, RCT Patients ≥40 years of age meeting the ACR diagnostic criteria for hip or knee OA and requiring joint replacement surgery, with moderate to severe pain that was not adequately controlled with weak opioids	N=399 6 weeks	Primary: Pain relief Secondary: Function and individual aspects of pain relief affecting mobility and quality of life	Primary: Fentanyl was associated with significantly better pain relief ($AUCMB_{avg}$ -20.0±1.4 vs -14.6±1.4; P=0.007). Secondary: WOMAC scores for pain, stiffness and physical function improved significantly from baseline to study end in both groups. The overall WOMAC score and the pain score were significantly better in the fentanyl group (P=0.009 and P=0.001), while stiffness and physical functioning scores showed non-significant trends in favor of fentanyl (P=0.051 and P=0.064). Significantly more patients who received fentanyl than those who received placebo reported that the transdermal systems definitely met their overall expectations (28 vs 17%; P=0.003). When asked to compare the study medication with previous treatments, significantly more patients who received fentanyl considered it to provide much better or somewhat better relief than other pain medication (fentanyl, 60% vs placebo, 35%; P<0.001). Not all of the individual domains of the SF-36 quality of life assessment showed significant improvements from baseline, although the physical functioning, pain index, and physical component scores improved significantly in both groups (all P<0.05 vs baseline). Scores on the SF-36 pain index were significantly better for patients receiving fentanyl (P=0.047), whereas changes in the mental component scores showed a small, but statistically significant, benefit in those receiving placebo (1.1±0.7; P=0.041).

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Morley et al.[100] (2003) Methadone 10 to 20 mg/day vs placebo In Phase 1 of the study patients were instructed to take methadone 5 mg BID or placebo on odd days and take no medication on even days (20 days total). In Phase 2 of the study, patients were instructed to take methadone 10 mg BID or placebo on odd days and to take no medication on even days (20 days total).	DB, RCT, XO Patients 18 to 80 years of age with a history of >3 months of nonmalignant neuropathic pain (defined as 'pain initiated or caused by a primary lesion or dysfunction of the nervous system') who had not been satisfactorily relieved by other interventions or by current or previous drug regimens	N=19 40 days	Primary: Analgesic effectiveness and adverse events Secondary: Not reported	Primary: When compared to placebo in Phase 2, methadone 20 mg/day significantly reduced VAS maximum pain intensity by 16.00 (P=0.013) and VAS average pain intensity by 11.85 (P=0.020) and increased VAS pain relief by 2.16 (P=0.015). Analgesic effects, by lowering VAS maximum pain intensity and increasing VAS pain relief, were also seen in Phase 1 on days in which methadone 10 mg/day was administered but failed to reach statistical significance (P=0.065 and P=0.67, respectively). Significant analgesic effects on rest days were only seen in Phase 2. Compared to placebo, there was lowering of VAS maximum pain intensity by 12.02 (P=0.010), a lowering of VAS average pain intensity by 10.46 (P=0.026), and an increase in VAS pain relief by 0.94 (P=0.025). During Phase 1, one patient withdrew because of severe nausea, dizziness, and sweating. Six patients withdrew from Phase 2 due to severe nausea, dizziness, vomiting, and sweating; and disorientation with severe headaches. Four patients in Phase 1 and 2 reported no adverse events and all adverse events were reported as mild to moderate in patients who completed the trial. Secondary: Not reported
Porta-Sales et al.[101] (2016) Methadone as a second-line opioid after rotation in routine clinical practice	OL, PRO Adult patients with advanced cancer	N=145 28 days	Primary: Change in the variable "worst pain" at day 28 Secondary: Reduction of worst pain at day 14 and	Primary: The median worst pain score decreased significantly from nine (interquartile range: 8 to 10) at baseline to six (interquartile range: 3 to 8) at day 28 (P<0.0001). Secondary: Secondary efficacy outcomes also improved from baseline to days 14 and 28. Decreases in pain from baseline were significant for both worst and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Indications for rotation to methadone were poor pain control in 77.9% patients, opioid side effects in 2.1%, and both indications in 20%			decrease in mean rescue-medication use, and reduction of pain interference and average pain scores at days 14 and 28 after rotation	average pain at day seven, declining from seven (interquartile range: 4 to 8; P<0.0001) and four (interquartile range: 2 to 5; P<0.0001), respectively. Similarly, the use of rescue medication also decreased significantly from baseline to day three, from four (interquartile range: 3 to 8) and two (interquartile range: 0 to 4; P<0.0001), respectively.
Bandieri et al.[102] (2016) Low-dose morphine vs weak-opioid (tramadol, tramadol-APAP, or codeine-APAP)	OL, RCT Adult patients with cancer who are opioid naïve, with moderate pain intensity (4 to 6 on the standard Numerical Rating Scale)	N=240 28 days	Primary: Number of responder patients, defined as patients with a 20% reduction in pain intensity on the numerical rating scale Secondary: Improvement in physical symptoms and overall well-being; number of patients with a clinically meaningful (≥30%) and highly meaningful (≥50%) reduction of pain intensity from baseline; mean increase of opioid dosage; adverse events	Primary: The primary end point was achieved in 88.2% of patients (97 of 110) in the morphine group and in 54.7% of patients (64 of 117) in the weak opioid group (odds ratio, 6.18; 95% CI, 3.12 to 12.24; P<0.001). Secondary: A clinically meaningful (≥30%) and highly meaningful (≥50%) pain reduction was found more frequently in patients treated with morphine than in those treated with a weak opioid (clinically meaningful: 82.7 vs 47.0%, respectively; P<0.001; highly meaningful: 75.5 vs 41.9%, respectively; P<0.001). The general condition of patients, which was based on the Edmonton Symptom Assessment System overall symptom score, was more improved in the morphine group (median score, 10) than in the weak-opioid group (median score, 19; P<0.001). The opioid escalation index was lower in the morphine than in the weak opioid group (4.76 ± 6.44 vs 8.76 ± 6.81; P=.002). Only five patients in each group discontinued their assigned treatment because of adverse effects or poor tolerability (three and two patients per group, respectively). No differences in the intensity and frequency of opioid-related symptoms were observed between the two groups.
Fleishmann et al.[103]	DB, MC, PC, PG, RCT	N=129	Primary: Efficacy (as	Primary: The mean final pain intensity score was not statistically different between

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(2001) Tramadol up to 400 mg/daily vs placebo	Patients aged 35 to 75 with symptomatic (painful) OA of the knee for ≥1 year and had used NSAIDs for ≥3 months	3 months	measured by pain intensity, relief, patient and investigator overall assessments, discontinuation, time to failure, and WOMAC OA index scores) Secondary: Tolerability and adverse events	groups (P=0.082). However, pain intensity scores improved progressively from baseline through day 91 for patients in both groups, and the mean final pain intensity score was 15% lower in the tramadol group (2.10) than in the placebo group (2.48; P=0.045). The mean final pain relief score for tramadol patients was significantly higher than that of the placebo patients (0.43 vs -0.57; P=0.004). The patient overall assessment score was significantly higher for tramadol than for placebo (P=0.038). The investigator overall assessment was also significantly more positive for tramadol than for placebo (P=0.001). A total of 26 tramadol-treated patients (41.3%) and 43 placebo patients (65.2%) discontinued the study because of drug ineffectiveness. Time to failure of effectiveness, as assessed by duration of therapy, was substantially shorter for the placebo group (median=19 days) compared with the tramadol group (median=57 days; P=0.042). Patients who received tramadol had significantly better scores for pain (P=0.012), stiffness (P=0.028), and physical function (P=0.033) (each category of the WOMAC score) than patients who received placebo. The mean final overall score was 17.5% lower in the tramadol group than in the placebo group (4.16 vs 5.04; P=0.015). Secondary: No clinically significant trends in vital signs were noted among tramadol patients. The most common side effects were nausea, constipation, dizziness, pruritus, and headache.
Ruoff et al.[104] (2003) Tramadol-APAP 37.5-325 mg up to 8 tablets daily vs	DB, MC, PC, PG, RCT Men and non-pregnant women 25 to 75 years of age, in general good health, ambulatory,	N=318 3 months	Primary: PVA score at final visit Secondary: Scores on the PRRS, SF-MPQ, RDQ, SF-36,	Primary: The tramadol-APAP group had a significantly lower final mean PVA score compared with the placebo group (P=0.015). The mean final PVA score was 44.4 mm in the tramadol-APAP group (down from baseline 71.1) and 52.3 mm in the placebo group (from baseline 68.8). Secondary: The tramadol-APAP group exhibited a significantly higher mean PRRS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	and with lower back pain such that daily medication was needed for ≥3 months		discontinuation due to insufficient pain relief, and overall assessments of medication by patients and investigators	score than the placebo group (1.8 vs 1.1; P<0.001). The tramadol-APAP group exhibited greater improvement from baseline on every category of the SF-MPQ compared with the placebo group. The mean change was statistically significant for the sensory component (P=0.011), present pain index (P=0.011), and total score (P=0.021). In the categorical responder analysis, 54.7% of the tramadol-APAP group had ≥30% reduction in PVA scores compared with 39.5% of the placebo group (P=0.011), and 44.1% of the tramadol-APAP group had ≥50% reduction in PVA scores compared with 32.5% of the placebo group (P=0.044). The tramadol-APAP group had a significantly greater improvement in bothersomeness score (RDQ; P=0.027) and total score (RDQ; P=0.023) compared with the placebo group. For every subcategory of the SF-36, mean improvements from baseline were greater in the tramadol-APAP group than in the placebo group. These changes were statistically significant for the subcategories of role-physical (P=0.005), bodily pain (P=0.046), role-emotional (P=0.001), mental health (P=0.026), reported health transition (P=0.038), mental component summary (P=0.008). The overall assessments of study medication by patients (P<0.001) and investigators (P=0.002) were significantly more positive for the tramadol-APAP group than for the placebo group. The incidence of efficacy failures was significantly lower in the tramadol-APAP group compared with the placebo group (19.3 vs 37.6%; P<0.001).
Beaulieu et al.[105] (2007) Tramadol ER 200-400 mg/ daily vs	DB, DD, RCT, XO Men and non-pregnant women aged 18 to 75 years with chronic (>1 month)	N=122 8 weeks	Primary: Pain intensity (measured by VAS and ordinal scales) Secondary: Tolerability	Primary: Mean pain intensity scores did not differ during the first two weeks of treatment in each phase, however, there was a significant difference between ER and IR tramadol during the second two weeks of treatment in each phase. In the completers' population, during the second two weeks of each phase,

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tramadol IR 50-100 mg every 4 to 6 hours vs placebo	noncancerous pain			the mean (SD) VAS scores were 29.9 (20.5) and 36.2 (20.4) mm for ER and IR tramadol, respectively (P<0.001). The mean (SD) ordinal scores were 1.41 (0.7) and 1.64 (0.6), respectively (P<0.001). In the ITT population, during the second two weeks of each phase the mean (SD) VAS scores were 32.5 (22.9) and 38.5 (21.2) mm for ER and IR tramadol, respectively (P<0.003). The mean (SD) ordinal scores were 1.50 (0.80) and 1.72 (0.70), respectively (P<0.002). In the completers' population, over the course of the entire study, the mean (SD) VAS pain intensity scores recorded in the daily diary were 34.1 (18.7) and 38.2 (20.0) mm (P=0.01) and the mean (SD) ordinal scores were 1.56 (0.50) and 1.72 (0.60) (P<0.003) during ER and IR tramadol treatment, respectively. Secondary: The most common adverse events and the numbers of patients reporting them during ER and IR tramadol treatment, respectively, were as follows: nausea (n=24, n=13), dizziness (n=20, n=9), constipation (n=18, n=10), somnolence (n=12, n=10), asthenia (n=11, n=9), headache (n=10, n=9), sweating (n=9, n=8), and vomiting (n=5, n=6). When the most common adverse events were analyzed individually, the only difference was for nausea, which occurred significantly more often in the ER tramadol group (P<0.021).
Allan et al.[106] (2001) Morphine (MS Contin®) 10 to 200 mg for 4 weeks vs fentanyl transdermal system 25 to 100 µg/hour	MC, OL, RCT, XO Patients >18 years of age with chronic non-cancer pain requiring continuous treatment with potent opioids for six weeks preceding the trial, who achieved moderate	N=256 8 weeks	Primary: Patient preference Secondary: Pain control and treatment assessment, rescue drug use, SF-36 quality of life, and safety	Primary: Preference could not be assessed in 39 of 251 patients, leaving a total of 212 patients for analysis. A higher proportion of patients preferred or very much preferred fentanyl to morphine (138 [65%] vs 59 [28%]; P<0.001). Preference for fentanyl was not significantly different in patients with nociceptive, neuropathic or mixed nociceptive and neuropathic pain. The predominant reason for preferring fentanyl was better pain relief. Secondary: Patients treated with fentanyl reported on average lower pain intensity scores than those treated with morphine (57.8 [range, 33.1 to 82.5] vs 62.9 [range, 41.2 to 84.6]; P<0.001), irrespective of the order of treatment.

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for 4 weeks	pain control with a stable dose of oral opioid for seven days before the trial			More patients receiving fentanyl considered their pain control to be good or very good vs those receiving morphine (35 vs 23%; P=0.002). Investigators' opinion of global efficacy for fentanyl was good or very good in 58% (131/225) of patients compared to 33% (75/224) of patients receiving morphine (P<0.001). The corresponding percentages from the patient assessments were 60% for fentanyl and 36% for morphine (P<0.001). Analysis of the consumption of rescue drug during the last three weeks of each treatment period showed that the mean (SD) consumption was significantly higher with fentanyl than with morphine (29.4 [33.0] mg vs 23.6 [32.0] mg; P<0.001). A significant period effect was also observed: the higher consumption during fentanyl treatment was more apparent in the second trial period (32.4 [38.5] mg) than the first (26.3 [26.0] mg), where the consumption of the rescue drug remained essentially the same over the two treatment periods in the morphine group (23.7 [35.3] mg vs 23.6 [27.3] mg). Patients receiving fentanyl had higher overall quality of life scores than patients receiving morphine in each of eight categories measured by the SF-36. Differences were significant in bodily pain (P<0.001), vitality (P<0.001), social functioning (P=0.002), and mental health (P=0.020). The overall incidence of treatment related adverse events was similar in both groups as was the proportion of patients with adverse events. Fentanyl was associated with a higher incidence of nausea (26 vs 18%) but less constipation (16 vs 22%).
van Seventer et al.[107] (2003) Fentanyl 25 µg/hour transdermal every 3 days	MC, RCT Patients with moderate-to-severe cancer-related pain	N=131 4 weeks	Primary: Analgesia Secondary: Constipation; tolerability; safety	Primary: There was similar pain control and improved sleep quality between two treatment groups. Secondary: Fewer patients in the fentanyl group reported constipation during the trial. This finding was statistically significant after one week of treatment (27 vs 57%; P=0.003).

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vs morphine ER 30 mg every 12 hours				Transdermal fentanyl was better tolerated than oral morphine. A higher number of patients taking morphine dropped out due to adverse events (36% morphine vs 4% fentanyl). Patient assessment favored fentanyl treatment in terms of a significantly lower rate of troublesome side-effects ('quite a bit' to 'very much' troublesome side-effects in 14 vs 36% of patients; P=0.003) and less interruption of daily activities (absence of any interruption of daily activities in 88 vs 63% of patients; P=0.012).
Bruera et al.[108] (2004) Methadone 7.5 mg every 12 hours, in addition to methadone 5 mg every 4 hours as needed for BTP vs slow-release morphine 15 mg every 12 hours, in addition to IR morphine 5 mg every 4 hours as needed for BTP	DB, MC, PG, RCT Patients with poor control of pain caused by advanced cancer necessitating initiation of strong opioids; normal renal function; life expectancy of ≥4 weeks; normal cognition and written informed consent	N=103 4 weeks	Primary: Difference in pain intensity Secondary: Change in toxicity and patient-reported global benefit	Primary: Evaluation of trends by day eight revealed that the proportion of patients with a ≥20% improvement in pain expression was similar for both groups, with 75.5% (95% CI, 62.0 to 89.0) and 75.9% (95% CI, 63.0 to 89.0). By Day 29, there was no significant difference between methadone and morphine for the proportion of treatment responders (49%; 95% CI, 31 to 64 vs 56%; 95% CI, 41 to 70; P=0.50). Secondary: The proportion of patients in the methadone and morphine groups who reported a ≥20% worsening of composite toxicity was similar (67%; 95% CI, 53 to 82 vs 67%; 95% CI, 53 to 80; P=0.94). There was also no significant difference between the methadone and morphine groups for patient-reported global benefit scores (53%; 95% CI, 38 to 68 vs 61%; 95% CI, 47 to 75; P=0.41).
De Conno et al.[109] (2008) Morphine 5 mg IR every 4 hours, if taking Step 1 analgesics	OL Cancer patients ≥18 years of age, never treated with strong opioids, and with pain score of >5 points on a 0 to 11	N=159 5 days	Primary: Proportion of time with pain control (reduction of ≥50% with respect to the baseline pain score) during the titration phase	Primary: Pain control was observed for 75% (95% CI, 70 to 80) of the follow-up period in the intent-to-treat population. Overall, 50 and 75% of patients achieved pain control eight to 24 hours after starting 5 and 10 mg morphine therapy respectively. Mean pain score was 7.63 points at baseline, and decreased to 2.43 and 1.67 points (both P<0.001) at days three and five respectively.

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or morphine 10 mg IR every 4 hours, if taking Step 2 analgesics Patients currently receiving treatment with WHO Step I or Step II analgesics.	point standard scale for ≥24 hours		Secondary: Adverse events	Secondary: The most commonly reported adverse events were somnolence (24% of patients), constipation (22%), vomiting (13%), nausea (10%) and confusion (7%).
Reid et al.[110] (2006) Oxycodone vs morphine vs hydromorphone	MA Patients with moderate to severe cancer pain	N=1,013 Variable duration	Primary: Pain relief, as assessed on two standardized verbal/visual pain scoring methods Secondary: Patient acceptance, quality of life and adverse events	Primary: Mean pain scores did not differ between oxycodone and control drugs (P=0.8). Pain scores were higher for oxycodone compared to morphine (0.20; 95% CI, -0.04 to 0.44) and lower compared to hydromorphone (-0.36; 95% CI, -0.71 to 0.00), although these effect sizes were small. The investigators estimated that for oxycodone compared to morphine or hydromorphone, the pooled standardized differences represented only 2 to 3 mm on a 100-mm VAS, and suggested such standardized differences are unlikely to be clinically important or meaningful to patients. Secondary: No differences in patient preference or quality of life were demonstrated, although one study suggested that nighttime acceptability of morphine was better than that of oxycodone. The point estimates for the pooled data comparing oxycodone with control groups were 0.75 (95% CI, 0.51 to1.10) for nausea and 0.2 (95% CI, 0.49 to1.06) for vomiting. Estimates of the association of oxycodone with dry mouth and drowsiness varied widely across trials. When the MA was repeated using only data from the trials with morphine as the control treatment, the pooled OR favored oxycodone for dry mouth and drowsiness. As many as 90% of patients experienced opioid-related adverse effects in each trial.
Schwartz et al.[111]	DB, PC, PG, RCT	N=395	Primary:	Primary:

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(2011) Tapentadol ER 100 to 250 mg BID (fixed, optimal dose identified for patients during OL phase of trial) vs placebo Initial treatment with tapentadol ER 50 mg BID for 3 days; then titrated to tapentadol ER 100 mg BID for 3 days (minimum study dose for maintenance); subsequent titration in 50 mg increments every 3 days (within dose range of 100 to 250 mg BID). APAP ≤2,000 mg/day was permitted during the OL phase, except during the last 4 days.	Adults ≥18 years with Type 1 or 2 diabetes and painful diabetic peripheral neuropathy for ≥6 months with a history of analgesic use for diabetic peripheral neuropathy and dissatisfaction with current treatment (opioid daily doses equivalent to < 160 mg of oral morphine), an average pain intensity score ≥5 on an 11-point rating scale, and effective method of birth control (if applicable)	(A total of 588 received study drug through OL titration phase; a total of 395 were randomized to DB phase of the study) 12 weeks (maintenance phase after a 3-week titration phase)	The change from baseline in average pain intensity over the last week (week-12) of the maintenance phase Secondary: Proportion of patients with improvements in pain intensity of at least 30 and 50% at week 12 (i.e., responder rate), PGIC at weeks two, six, and 12, and safety measures	The least square mean change in average pain intensity from the start of DB treatment to week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol ER group, indicating no change in pain intensity. The least square mean difference between tapentadol ER and placebo was -1.3 (95% CI, -1.70 to -0.92; P<0.001). Secondary: The mean changes in average pain intensity scores (on 11-point rating scale) from baseline to week-12 were similar between males and females who received tapentadol ER, for those <65 years of age and those >65 years who received tapentadol ER, as well as those who were opioid-naïve and opioid-experienced. From pre-titration to week 12 of maintenance treatment, at least a 30% improvement in pain intensity was observed in 53.6% of tapentadol ER-treated patients and 42.2% of placebo-treated patients (P=0.017). At least a 50% improvement in pain intensity from pre-titration to week-12 was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients. There was a statistically significant difference in the distribution of responder rates for patients with any degree of improvement (pre-titration to week-12) between the tapentadol ER and placebo groups (P=0.032). Of the patients who achieved ≥ 30% improvement in pain intensity (titration phase) and were randomized to tapentadol ER treatment, 60.8% maintained ≥30% improvement through week 12 (maintenance phase); whereas 34.0% of patients who had not achieved at least a 30% improvement in pain intensity (titration phase) and were randomized to tapentadol ER reached ≥30% improvement from pre-titration by week 12 of the maintenance period. Of those patients who were randomized to placebo after achieving ≥30%improvement in pain intensity (titration phase), 48.7% of patients maintained ≥30% improvement through the maintenance phase, while only 17.5% of patients who were randomized to placebo and had not

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				reached ≥30% improvement (titration phase) achieved ≥30% improvement in pain intensity during the maintenance phase. Among patients who achieved ≥50% improvement in pain intensity (titration phase) and were randomized to treatment with tapentadol ER, 59.1% of patients maintained ≥50% improvement through week 12 (maintenance phase); whereas 18.0% of patients who had not achieved ≥50% improvement (titration phase) and were randomized to tapentadol ER reached ≥50% improvement from pre-titration by week 12 of the maintenance period. Among patients who were randomized to placebo after achieving ≥50% improvement in pain intensity (titration phase), 36.4% of patients maintained ≥50% improvement through the maintenance phase, while only 16.5% of those randomized to placebo and had not reached ≥50% improvement during titration reached ≥50% improvement during the maintenance phase. A total of 64.4% of tapentadol ER-treated patients and 38.4% of placebo-treated patients reported on the PGIC scale that their overall status was "very much improved" or "much improved" (P<0.001). The overall incidence of adverse events (maintenance phase) was 70.9% among the tapentadol ER group and 51.8% among the placebo group. The most commonly reported events among the active treatment group were nausea, anxiety, diarrhea, and dizziness. During the maintenance phase, the overall incidence of adverse events was similar between males and females, those ages <65 years and >65 years, and among opioid-naïve and opioid-experienced individuals who received tapentadol ER. Treatment-emergent serious adverse events occurred in 1.4% of tapentadol ER-treated patients in the titration phase; and among 5.1% of the tapentadol ER-treated patients and 1.6% of placebo-treated patients in the maintenance phase.
Hartrick et al.[112]	DB, RCT	N=674	Primary:	Primary:

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(2009) Tapentadol 50 to 75 mg every 4 to 6 hours vs oxycodone 10 mg every 4 to 6 hours vs placebo	Patients 18 to 80 years of age who were candidates for primary joint replacement surgery as a result of end-stage degenerative joint disease	10 days	SPID over five days Secondary: Two- and 10-day SPID: two-,five-, and 10-day TOTPAR, and the sum of TOTPAR and pain intensity difference (SPRID)	After five days, both tapentadol treatment groups had a significant reduction in pain intensity compared to placebo (P<0.001). A significant difference was also seen between oxycodone and placebo (P<0.001). Secondary: Both tapentadol treatment groups had significant reductions in pain intensity compared to placebo, with increasing two- and 10-day SPID values (all, P<0.001). Significant reductions in pain intensity were also seen in the oxycodone group compared to placebo (all, P<0.001). The proportion of patients with a decrease in pain intensity of ≥30% at day five were 43% in the tapentadol 50 mg group (P=0.018 vs placebo), 41% in the tapentadol 75 mg group (P=0.033 vs placebo), 40% in the oxycodone group (P value not significant), and 30% in the placebo group. The corresponding responder rates of patients with a decrease in pain intensity of at least 50% at day five were 27% (APAP=0.003 vs placebo), 26% (P=0.002 vs placebo), 25% (P=0.007 vs placebo), and 13%. At the end of the study, overall status was rated as very much improved or much improved by 49 and 42% of patients in the tapentadol 50 and 75 mg groups, respectively (both, P<0.001 vs placebo), 41% of those in the oxycodone group (P=0.005 vs placebo), and 21% of those in the placebo group. Adverse effects were reported by 52% of patients in the tapentadol 50 mg group, 71% of patients in the tapentadol 75 mg group, 84% of patients in the oxycodone group, and 32% of patients in the placebo group. The most frequently reported adverse effects were dizziness, nausea, vomiting, somnolence, constipation, pruritus, and fatigue. No serious adverse events were reported in the tapentadol groups.
Afilalo et al.[113] (2010) Tapentadol ER 100 mg BID vs	AC, DB, MC, PC, RCT Patients ≥40 years of age with a diagnosis of OA of the knee (per ACR	N=1,030 12 weeks (maintenance phase after a 3-week titration phase)	Primary: Change in average pain intensity at week-12 of the maintenance period compared to baseline	Primary: Significant pain relief was achieved with tapentadol ER vs placebo at study endpoint. The least square mean difference was - 0.7 (95% CI, -1.04, -0.33) at week 12 of the maintenance period compared to placebo. Secondary: The least square mean difference was -0.7 (95% CI, -1.00 to -0.33) for the

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placebo vs oxycodone CR 20 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). APAP ≤1,000 mg/day (max of 3 consecutive days) was permitted.	criteria) functional capacity class I-III, and pain at reference joint requiring analgesics (both non-opioid and opioid doses ≤ 160 mg oral morphine daily) for ≥3 months, who were dissatisfied with their current analgesic regimen, and had a baseline pain intensity score ≥5 during the 3 days prior to randomization		Secondary: Change in average pain intensity over the entire 12-week maintenance period compared to baseline	overall maintenance period for tapentadol compared to placebo (P-values not reported). The average pain intensity rating with oxycodone CR was reduced significantly compared to placebo from baseline for the overall maintenance period (least square mean difference vs placebo, -0.3; 95% CI, -0.67 to 0.00), but was not statistically significantly lower at week-12 of the maintenance period (-0.3; 95% CI, -0.68 to 0.02); P-values not reported. The percentage of patients who achieved ≥30% reduction from baseline in average pain intensity at week-12 of the maintenance period was not significantly different between tapentadol ER and placebo (43.0 vs 35.9%; P=0.058), but was significantly lower for oxycodone CR compared to placebo (24.9 vs 35.9%; P=0.002). Treatment with tapentadol ER resulted in a significantly higher percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week-12 of the maintenance period vs treatment with placebo (32.0 vs 24.3%; P=0.027). Conversely, treatment with oxycodone CR resulted in a significantly lower percentage of patients achieving at least a 50% reduction in average pain intensity from baseline at week-12 of the maintenance period vs treatment with placebo (17.3 vs 24.3%; P=0.023). Tapentadol ER was significantly better than placebo at week-12 on the WOMAC global scale with a least square mean difference of -0.21 (95% CI, -0.357 to -0.065; P=0.0047) compared to the least square mean difference between oxycodone CR and placebo -0.18 (95% CI, -0.343 to -0.010; P=0.0381). The pain subscale for tapentadol ER compared to placebo was a least square mean difference of -0.27 (95% CI, -0.422 to -0.126; P<0.001) compared to the least square mean difference between oxycodone CR and placebo of -0.17 (95% CI, -0.338 to -0.000; P=0.051). The physical function subscale at week-12 was significantly improved with tapentadol ER and placebo (least square mean difference of -0.21;

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				95% CI, -0.357 to -0.060; P=0.006), whereas the least square mean difference between oxycodone CR and placebo was -0.20 (95% CI, -0.373 to -0.034; P=0.019). The stiffness subscale assessment was improved with tapentadol ER compared to placebo with a least square mean difference of -0.17 (95% CI, -0.377 to -0.002; P=0.053); however the difference was not statistically significant. Conversely, the least square mean difference between oxycodone ER and placebo was -0.10 (95% CI, -0.292 to 0.096; P=0.321), which also was not statistically significant. The incidence of adverse events was 61.1% with placebo, 75.9% with tapentadol ER, and 87.4% with oxycodone CR. The most common events (≥10% in any group) in the active treatment groups were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus. The majority of reported events were mild to moderate in severity. Events leading to discontinuation occurred in 6.5% of patients treated with placebo, 19.2% of patients treated with tapentadol ER, and 42.7% of patients treated with oxycodone ER. Gastrointestinal-related events were the most common events in both active treatment groups.
Buynak et al.[114] (2010) Tapentadol ER 100 mg BID vs oxycodone CR 20 mg BID vs placebo Initial treatment with tapentadol ER	AC, DB, MC, PC, PRO, RCT Patients ≥18 years with a history of non-malignant low back pain for ≥3 months who were dissatisfied with their current treatment, had a baseline pain intensity ≥5 on an 11-point rating scale after washout, and whose previous opioid daily doses,	N=981 12 weeks (maintenance phase after a 3-week titration phase)	Primary: Change from baseline in mean pain intensity at week-12 of the maintenance period Secondary: Change from baseline in mean pain intensity over the entire 12-week maintenance period, proportion of patients with ≥30 and ≥50%	Primary: Throughout the 12-week maintenance period, average pain intensity scores improved in both the tapentadol ER and oxycodone CR groups relative to placebo. The mean (SD) change in pain intensity from baseline to week 12 was -2.9 (2.66) for tapentadol ER and -2.1 (2.33) for placebo resulting in a least square mean difference vs placebo of -0.8 (95% CI, -1.22 to -0.47; P<0.001). The mean change in pain intensity from baseline over the entire maintenance period was -2.8 (2.50) for tapentadol ER and -2.1 (2.20) for placebo, corresponding to a least square mean difference vs placebo of -0.7 (95% CI, -1.06 to -0.35; P<0.001). Secondary: The mean pain intensity was also reduced for the oxycodone CR group.

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50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). APAP ≤1,000 mg/day (max of 3 consecutive days) was permitted.	if applicable, were equivalent to ≤160 mg of oral morphine		reduction in pain intensity at week-12 of maintenance, PGIC score, BPI survey, SF-36 health survey	Compared to the placebo group at week 12 the least square mean difference was -0.9 (95% CI, -1.24 to -0.49; P<0.001); and over the entire maintenance period the least square mean difference was -0.8 (95% CI, -1.16 to -0.46; P<0.001). Reductions in mean pain intensity were significantly greater with tapentadol ER than with placebo at week-12 of the maintenance period both for patients with moderate and severe baseline pain intensity. Significantly greater reductions in mean pain intensity with tapentadol ER compared to placebo were also observed for the overall maintenance period in patients with both moderate baseline pain intensity and severe baseline pain intensity. Reductions in mean pain intensity were also significantly greater with oxycodone CR than with placebo for patients with moderate and severe baseline pain intensity at both week 12 of the maintenance period and for the overall maintenance period. The overall distribution of responders at week 12 of the maintenance period was significantly different between the tapentadol ER group and the placebo group (P=0.004), with a higher percentage of patients showing improvements in pain scores in the tapentadol ER group than in the placebo group. The overall distribution of responders at week 12 in the oxycodone CR group, however, was not significantly different from the placebo group (P=0.090). A total of 39.7% of patients treated with tapentadol ER compared to 27.1% of patients treated with placebo responded with ≥30% improvement in pain intensity at week-12 compared to baseline (P<0.001). A total of 27.0% of patients treated with tapentadol ER compared to 18.9% of patients treated with placebo responded with 50% improvement in pain intensity at week-12 compared to baseline (P<0.016). The percentage of patients in the oxycodone CR group with ≥30% improvement in pain intensity at week-12 compared to baseline was 30.4% (P=0.365) and did not differ significantly from placebo (percent

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				among placebo group not reported). Conversely, the percentage of patients in the oxycodone CR group with ≥50% improvement in pain intensity at week-12 compared to baseline was 23.3% (P=0.174) and did not differ significantly from placebo (percent among placebo group not reported). At endpoint, there was a significant difference in PGIC ratings for both tapentadol ER (P< 0.001) and oxycodone CR (P<0.001) compared to placebo. Compared to placebo, both tapentadol ER and oxycodone CR showed significant reductions from baseline to week-12 in the BPI total score, the pain interference subscale score, and the pain subscale score. The percentage of patients with "any pain today other than everyday kinds of pain" on the BPI survey at baseline was 88.6, 85.6, and 86.1% for the placebo group, tapentadol ER group, and oxycodone CR group, respectively. At week 12, the percentage scores decreased to 80.7% for the placebo group, 69.8% for the tapentadol ER group, and 67.3% for the oxycodone CR group. The percentage of patients who reported "at least 50% pain relief during the past week" was similar for all three treatment groups at baseline for the placebo, tapentadol ER, and oxycodone ER groups (23.4, 24.7, and 20.9%, respectively). These results increased to 59.7, 75.4, and 80.0% among the placebo, tapentadol ER, and placebo groups, respectively at week 12. Treatment with both tapentadol ER and oxycodone CR significantly improved physical health status compared to placebo, as reflected by the physical component summary score. The mean changes at week-12 from baseline on the SF-36 survey for four of eight measures (physical functioning, role-physical, bodily pain, and vitality) were significantly improved in the tapentadol ER group compared to the placebo group.

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				The mean changes from baseline were significantly improved for role-physical and bodily pain scores among the oxycodone CR group compared to the placebo group. No clinically important changes in laboratory values, vital signs, or electrocardiogram findings were attributed to treatment. Overall, at least one adverse event was reported by 59.6, 75.5, and 84.8% of patients in the placebo, tapentadol ER, and oxycodone CR groups, respectively. The most commonly reported events (reported by >10% in any treatment group) were nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence, the majority of which were categorized as mild to moderate in intensity across all treatment groups. In the oxycodone CR group, the incidence of vomiting, constipation, and pruritus was nearly double incidence in the tapentadol ER group.
Wild et al.[115] (2010) Tapentadol 100 to 250 mg BID vs oxycodone CR 20 to 50 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20	AC, MC, OL, PG, RCT Men and (non-pregnant) women ≥18 years of age with a diagnosis of moderate to severe knee or hip OA pain or low back pain (non-malignant) with a ≥ 3 month history of pain, who were dissatisfied with current analgesic therapy, and had a pain intensity score ≥4 on an 11-point rating scale after therapy washout	N=1,121 51 weeks (maintenance phase)	Primary: Safety and tolerability Secondary: Change in mean pain intensity score	Primary: The proportion of patients who completed treatment in the tapentadol ER and oxycodone CR groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1% for tapentadol ER vs 36.8% for oxycodone ER). Overall, 85.7% of patients in the tapentadol ER group and 90.6% of patients in the oxycodone CR group experienced at least one adverse event. The most commonly reported events (reported by >10% in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), and vomiting (7.0 vs 13.5%) were lower in the tapentadol ER group than in the oxycodone CR group, respectively. The incidence of pruritus was 5.4% among the tapentadol ER-treated patients and 10.3% among oxycodone-treated patients. No clinically relevant treatment-related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for 4 days (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg BID or oxycodone CR 10 mg BID (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Occasional pain relief with NSAIDs, aspirin doses ≤325 mg/day for cardiac prophylaxis, and APAP ≤1,000 mg/day (up to a max of 7 consecutive days and no more that 14 out of 30 days) were permitted.				tapentadol ER group and 36.8% of patients in the oxycodone CR group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol ER group than in the oxycodone CR group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol ER and oxycodone CR groups (5.5 vs 4.0%, respectively). Among those who reported constipation, the mean change from baseline to endpoint was lower for patients in the tapentadol ER group than for those in the oxycodone CR group as well as for the overall rectal and overall stool subscale scores. Secondary: Baseline mean pain intensity scores at endpoint among the tapentadol ER and oxycodone CR groups decreased to 4.4 and 4.5 from the baseline scores of 7.6 and 7.6, respectively. Ratings on the global assessment of study medication of "excellent," "very good," or "good" among the tapentadol ER and oxycodone CR groups were reported by the majority of patients (75.1 and 72.3%, respectively) and investigators (77.3 and 72.3%, respectively). The most commonly reported rating on the PGIC at endpoint was "much improved" for both the tapentadol ER and oxycodone CR groups (35.7 and 32.8%, respectively). A rating of "very much improved" or "much improved" was reported by 48.1 and 41.2%, respectively.
Fricke et al.[116] (2004) Tramadol 50 mg vs. tramadol-APAP	DB, PC, RCT Men and women aged 18 to 75 who underwent elective outpatient surgery for extraction of at least two upper or	N=456 1 dose	Primary: Efficacy (measured by hourly PAR and pain intensity scores) Secondary: PID and PAR at	Primary: Tramadol-APAP was more efficacious to tramadol (P<0.001) or placebo (P<0.001) for all the primary efficacy endpoints, regardless of the time interval examined. Tramadol was numerically more efficacious to placebo but was not statistically different from placebo for any of the endpoints. Mean PAR scores were greater at all time points after a dose of tramadol-APAP compared with tramadol (P<0.001) or placebo (P<0.001). Tramadol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
37.5-325 mg vs placebo	lower impacted third molars		each time point, time to onset of perceptible/ meaningful PAR, time to rescue analgesia, and adverse events	was significantly more effective than placebo for mean PAR scores at hour two (P=0.022), but not at other times. Mean PID scores also demonstrated greater improvement throughout the study in the tramadol-APAP group compared with the tramadol (P<0.001) or placebo (P<0.001) group. Secondary: Tramadol-APAP-treated patients reported meaningful PAR more rapidly than tramadol-treated (P<0.001) or placebo-treated (P<0.001) patients. Tramadol-treated patients reported meaningful PAR more rapidly than placebo-treated patients (P=0.035). Tramadol-APAP also had significantly faster onset of action than tramadol (P<0.001) or placebo (P<0.001) with respect to perceptible PAR, but tramadol did not demonstrate significantly faster onset of perceptible PAR than placebo (P=0.805). The overall incidences of adverse events were 54% in the tramadol-APAP group, 64% in the tramadol group, and 39% in the placebo group. Nausea was significantly less common in the tramadol/APAP group (33%) than the tramadol group (46%; P=0.019).
Rodriguez et al.[117] (2007) Codeine-APAP vs hydrocodone-APAP vs tramadol	DB, RCT Patients with persistent moderate or severe cancer-associated pain	N=177 3 weeks	Primary: Analgesic efficacy Secondary: Adverse effects	Primary: There was no significant difference in the analgesic efficacy of the three opioids (P=0.69). Secondary: Tramadol produced higher rates of adverse events than codeine and hydrocodone, including vomiting, dizziness, loss of appetite, and weakness (P<0.05).
Mullican et al.[118] (2001)	AC, DB, DD, PG, RCT	N=462	Primary: Efficacy (measured	Primary: Mean TOTPAR scores were comparable between the two groups at each

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tramadol-APAP 37.5-325 mg once to twice every 4 to 6 hours vs codeine-APAP 30-300 mg once to twice every 4 to 6 hours	Men and non-pregnant women >18 years of age with chronic nonmalignant low back pain, OA pain, or both	4 weeks	by patient reported pain relief and pain intensity using Likert scales, and overall efficacy as reported by investigators) Secondary: Safety	weekly observation. Mean SPID scores were similar for tramadol-APAP and codeine-APAP at each visit. The maximum number of doses required in a single day for pain relief was a mean of 5.5 tablets of tramadol-APAP and 5.7 capsules of codeine-APAP. The percentage of patients requiring supplemental ibuprofen at any point was comparable between the two groups and ranged from 21 to 30% for each week of the study. The mean duration of therapy was 25.5 days for tramadol-APAP and 25.0 days for codeine-APAP. Secondary: The overall rates of treatment-emergent adverse events were comparable for the two groups. 71% of the tramadol-APAP and 76% of the codeine-APAP treated patients reported adverse events. Somnolence (24% [37/153] and constipation (21% [32/153]) were significantly more common in the codeine-APAP group than in the tramadol group (17% [54/309] and 11% [35/309]; P=0.05 and P<0.01, respectively).
Fricke et al.[119] (2002) Tramadol-APAP 37.5-325 mg vs tramadol-APAP 75-650 mg vs	AC, DB, PC, PG, SC Men and women 16 to 75 years of age who experiencing moderate or severe pain within 5 hours after surgical removal of > 2 impacted third molars and	N=200 8 hours	Primary: Efficacy based on TOTPAR, SPID, and SPRID measures Secondary: Efficacy measured by PAR, PID, and PRID scores; onset and duration of pain relief, time to	Primary: For TOTPAR, SPID, and SPRID, tramadol-APAP 75-650 mg and hydrocodone-APAP provided statistically superior pain relief during all three intervals (0 to four, four to eight, and 0 to eight hours) compared to placebo (P<0.024), but were not significantly different from each other. There was a statistically significant dose response for tramadol-APAP compared to placebo (two tramadol-APAP tablets >1 tablet >placebo) on all three primary efficacy variables during all three time periods (P<0.001, 0 to four and 0 to eight hours; P<0.018, four to eight hours) Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hydrocodone-APAP 10-650 mg vs placebo	associated bone		re-medication with a supplemental analgesic agent; and patients' overall assessment of medication	The median times to onset of pain relief were 34.0 and 33.3 minutes in the tramadol-APAP 75-650 mg and tramadol-APAP 37.5-325 mg groups, respectively, and 25.4 minutes in the hydrocodone-APAP group (P<0.001, active treatments vs placebo). There was no significant difference between tramadol-APAP 75-650 mg and hydrocodone-APAP in terms of duration of pain relief as measured by the areas under the curve for PAR, PID, and PRID over the second half of the study (four to eight hours). Both treatments had significantly longer duration of activity than placebo (TOTPAR; P<0.018; SPID; P<0.024; SPRID; P<0.019). Fewer patients required supplemental analgesic medication during the eight-hour observation period in the tramadol-APAP 75-650 mg (78.0%) and hydrocodone-APAP (84.0%) groups compared to the tramadol-APAP 37.5-325 mg (94.0%) and placebo (94.0%) groups. The median time to re-medication with a supplemental analgesic was shortest in the placebo group (78.5 minutes), followed by tramadol-APAP 37.5-325 mg (113.0 minutes), tramadol-APAP 75-650 mg (169.0 minutes), and hydrocodone-APAP (204.0) minutes. The time to remedication was significantly longer for all active treatments compared to placebo (tramadol-APAP 75-650 mg and hydrocodone-APAP; P<0.001; tramadol-APAP 37.5-325 mg; P=0.036). Patients' mean overall assessment of study medication was statistically superior in all active-treatment groups compared to placebo (P<0.001).
Furlan et al.[120] (2006) Weak opioids: Tramadol, propoxyphene, codeine Strong opioids: morphine,	MA Patients with nociceptive pain (OA, rheumatoid arthritis or back pain), neuropathic pain (postherpetic neuralgia, diabetic neuropathy or	N=6,019 1 to 16 weeks	Primary: Pain relief; improvement in functional outcome, based upon standardized indices and scoring methods Secondary:	Primary: Opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive pain, neuropathic pain or fibromyalgia. Strong opioids were significantly more effective than naproxen and nortriptyline for pain relief, but not for functional outcomes. Weak opioids did not significantly outperform NSAIDs or tricyclic antidepressants for either pain relief or functional outcomes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oxycodone	phantom limb pain), fibromyalgia, and mixed pain		Adverse events	Tramadol reduced pain and improved functional outcomes in patients with fibromyalgia. Secondary: Among the side effects of opioids, only constipation and nausea were clinically and statistically significant.
Steiner et al.[121] (2011) Buprenorphine transdermal system 5 or 20 µg/hour every 7 days vs oxycodone immediate-release 10 mg every 6 hours	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age with clinical diagnosis of low back pain for ≥3 months, taking between 30 to 80 mg of oral morphine sulfate or opioid equivalent daily, at least 4 days a week, for ≥30 days prior to visit 1	N=1,160 12 weeks	Primary: Average pain score over the last 24 hours on an 11-point numerical pain scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine) at weeks four, eight and 12 Secondary: Treatment differences with respect to less sleep disturbances and the daily number of tablets of supplemental analgesic medication during DB period, and the Oswestry Disability Index at weeks four, eight, and 12	Primary: The protocol-specified analysis of the primary efficacy variable, in which missing values were not imputed, resulted in a statistically significant treatment difference of -0.67 between buprenorphine 20 and 5 µg/hour in favor of buprenorphine 20 µg/hour (P<0.001). The treatment difference of -0.75 between oxycodone IR and buprenorphine 5 µg/hour in favor of oxycodone IR was also statistically significant (P<0.001). The four sensitivity analyses of the primary efficacy variable resulted in statistically significant treatment differences in favor of buprenorphine 20 µg/hour and oxycodone IR compared to buprenorphine 5 µg/hour. Secondary: Treatment with buprenorphine 20 µg/hour led to statistically significant treatment differences with respect to less sleep disturbance (P<0.001) and decreased use of supplemental analgesic medication (P=0.006) compared to buprenorphine 5 µg/hour. The difference between buprenorphine 20 µg/hour and 5 µg/hour with respect to the Oswestry Disability Index was not statistically significant (P value not reported).
Karlsson et al.[122] (2009)	AC, MC, OL, PG, RCT	N=135 12 weeks	Primary: Mean weekly Box Scale-11 pain score	Primary: In the ITT analysis, the least squares mean change from baseline in Box Scale-11 pain score at week 12 was -2.26 for buprenorphine and -2.09 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine transdermal system 5, 10, 15 or 20 µg/hour every 7 days vs tramadol prolonged-release 150 to 400 mg/day orally divided in two doses	Patients ≥18 years of age with a clinical diagnosis of OA of the hip and/or knee with suboptimal analgesia in the primary osteoarthritic joint in the week before visit 1		ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, sleep disturbance and quality of sleep assessment, patient-investigator-rated and global assessment of pain relief, patient preference and safety	tramadol prolonged-release. The difference between the two treatment groups was -0.17 (95% CI, -0.89 to 0.54; P value not reported), which was within the non-inferiority margin, showing that buprenorphine was non-inferior to tramadol prolonged-release. Secondary: The mean number of supplemental analgesic medication used during the study was 206.4 tablets for buprenorphine and 203.7 tablets for tramadol prolonged-release. The difference between the two treatment groups did not reach statistical significance (P value not reported). There were no statistically significant differences in sleep disturbance and quality of sleep between the buprenorphine and tramadol prolonged-release groups (P value not reported). There were statistically significant differences in favor of buprenorphine compared to tramadol prolonged-release with regard to patient- and investigator-rated global assessment of pain relief (P=0.039 and P=0.020, respectively). Ninety of 128 patients (70.3%; 95% CI, 62 to 78) preferred a once-weekly patch as a basic analgesic treatment for OA pain in the future. There were no differences between the two treatment groups in the total number of reported adverse events (P value not reported). The most commonly observed adverse events in the buprenorphine group were nausea (30.4%), constipation (18.8%) and dizziness (15.9%).
Felden et al.[123] (2011) Hydromorphone vs morphine	MA (11 RCTs) Patients with acute or chronic pain	N=1,215 Duration not specified	Primary: Pain relief and adverse events Secondary: Not reported	Primary: Hydromorphone was associated with greater acute pain relief compared to morphine (pooled standard mean difference, -0.226; P=0.006). No differences were observed for the treatment of chronic pain relief (P=0.889). The overall incidences of nausea, vomiting and pruritus were comparable between the two opioids. When the four studies on chronic pain were analyzed separately, hydromorphone was associated with less nausea (P=0.005) and vomiting (P=0.001).

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary:
Not reported</td></tr>
<tr><td>Corli et al.[124] (2016)

Oral controlled-release morphine (active comparator)

vs

oral controlled-release oxycodone

vs

transdermal fentanyl

vs

transdermal buprenorphine

All treatments taken around the clock for pain relief</td><td>AC, MC, OL, RCT

Patients >18 years of age with diagnostic evidence of locally advanced or metastatic tumor; persistent moderate to severe cancer pain [average pain intensity experienced in the last 24 h ≥4 points on a 0 to 10 Numerical Rating Scale]; need for WHO step III strong opioids never previously given</td><td>N=520

28 days</td><td>Primary:
Proportion of nonresponders, meaning patients with worse or unchanged average pain intensity between the first and last visit, measured on a 0 to 10 numerical rating scale

Secondary:
Nonresponders based on the Worst Pain Intensity difference; patients requiring a mean increase in the opioid daily dose >5%; requiring a switch to another opioid; needing supplementary doses of opioids; needing adjuvant analgesic drugs; and discontinuing the opioid</td><td>Primary:
There were no significant differences from morphine in the proportions of nonresponders (morphine vs oxycodone, P=0.494; morphine vs buprenorphine, P=0.910; morphine vs fentanyl, P=0.499).

Secondary:
<table>
<tr><th></th><th>Morphine (N=122)</th><th>Oxycodone (N=125)</th><th>Morphine vs oxycodone</th></tr>
<tr><td>Worst pain intensity–nonresponders</td><td>13.9%</td><td>17.6%</td><td>P=0.430</td></tr>
<tr><td>Average pain intensity–responders</td><td>75.4%</td><td>73.6%</td><td>P=0.744</td></tr>
<tr><td>Mean dose increase</td><td>32.7%</td><td>70.9%</td><td></td></tr>
<tr><td>Opioid escalation index >5%</td><td>10.7%</td><td>19.2%</td><td>P=0.060</td></tr>
<tr><td>Patients requiring additional opioids</td><td>29.5%</td><td>26.4%</td><td>P=0.586</td></tr>
<tr><td>Patients requiring adjuvant drugs</td><td>68.9%</td><td>81.6%</td><td>P=0.020</td></tr>
<tr><td>Switches</td><td>22.1%</td><td>12%</td><td>P=0.034</td></tr>
<tr><td>Premature discontinuations for pain treatment-related reasons</td><td>27%</td><td>15.2%</td><td>P=0.051</td></tr>
</table>
<table>
<tr><th></th><th>Buprenorphine (N=127)</th><th>Morphine vs buprenorphine</th><th>Fentanyl (N=124)</th><th>Morphine vs fentanyl</th></tr>
<tr><td>Worst pain intensity–nonresponders</td><td>9.4%</td><td>P=0.270</td><td>13.7%</td><td>P=0.959</td></tr>
<tr><td>Average pain intensity–responders</td><td>78%</td><td>P=0.635</td><td>75.8%</td><td>P=0.942</td></tr>
<tr><td>Mean dose increase</td><td>56.4%</td><td></td><td>121.2%</td><td></td></tr>
<tr><td>Opioid escalation index >5%</td><td>14.2%</td><td>P=0.401</td><td>36.3%</td><td>P<0.001</td></tr>
<tr><td>Patients requiring additional opioids</td><td>37.8%</td><td>P=0.167</td><td>37.1%</td><td>P=0.207</td></tr>
<tr><td>Patients requiring adjuvant drugs</td><td>78.7%</td><td>P=0.076</td><td>80.6%</td><td>P=0.033</td></tr>
<tr><td>Switches</td><td>16.5%</td><td>P=0.263</td><td>12.9%</td><td>P=0.057</td></tr>
<tr><td>Premature discontinuations for pain treatment-related reasons</td><td>20.5%</td><td>P=0.222</td><td>14.5%</td><td>P=0.015</td></tr>
</table></td></tr>
<tr><td colspan="5">Opioid Dependence</td></tr>
<tr><td>Johnson et al.[125]</td><td>DB, PG, RCT</td><td>N=162</td><td>Primary:</td><td>Primary:</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1992) Buprenorphine 8 mg daily vs methadone 60 mg daily vs methadone 20 mg daily	Adults seeking treatment for opioid dependence	17-week maintenance phase, followed by a 8-week detoxification phase	Retention time in treatment, urine samples negative for opioids, and failure to maintain abstinence Secondary: Not reported	During the maintenance phase, the retention rates were significantly greater for buprenorphine (42%) than for methadone 20 mg/day (20%; P<0.04). During the maintenance phase, the percentage of urine samples negative for opioids was significantly greater for buprenorphine (53%; P<0.001) and methadone 60 mg/day (44%; P<0.04), than for methadone 20 mg/day (29%). Failure to maintain abstinence during the maintenance phase was significantly greater for methadone 20 mg/day, than for buprenorphine (P<0.03). During the detoxification phase, there were no differences between the treatment groups with regards to urine samples negative for opioids. During the 25 week study period, retention rates for buprenorphine (30%; P<0.01) and methadone 60 mg/day (20%; P<0.05) were significantly greater than for methadone 20 mg/day (6%). All treatments were well tolerated, with similar profiles of self-reported adverse effects. The percentages of patients who received counseling did not differ between groups. Secondary: Not reported
Petitjean et al.[126] (1992) Buprenorphine sublingual tablets (flexible dosing schedule) vs	DB, RCT Patients seeking treatment for opioid dependence	N=58 6 weeks	Primary: Treatment retention rate, urine samples positive for opiates, substance use Secondary:	Primary: The retention rate was significantly better in the methadone group than in the buprenorphine group (90 vs 56%, respectively; P<0.001). There were similar proportions of opioid positive urine samples in both treatment groups (buprenorphine, 62%; methadone, 59%) and positive urine specimens, as well as mean heroin craving scores decreased significantly over time (P=0.035 and P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
methadone (flexible dosing schedule)			Not reported	The proportion of cocaine-positive toxicology results did not differ between groups. At week six, the mean stabilization doses were 10.5 mg/day for buprenorphine and 69.8 mg/day for methadone. Secondary: Not reported
Strain et al.[127] (1994) Buprenorphine sublingual tablets (flexible dosing schedule) vs methadone (flexible dosing schedule)	DB, DD, RCT Patients seeking treatment for opioid dependence	N=164 26 weeks	Primary: Treatment retention rate, medication and counseling compliance, urine samples positive for opiates Secondary: Not reported	Primary: Buprenorphine (mean dose ~9 mg/day) and methadone (mean dose 54 mg/day) were equally effective in sustaining retention in treatment, compliance with medication, and counseling regimens. In both groups, 56% of patients remained in the treatment program through the 16-week flexible dosing period. Opioid-positive urine sample rates were 55 and 47% for buprenorphine and methadone groups, respectively. Cocaine-positive urine sample rates were 70 and 58%, respectively. Secondary: Not reported
Ling et al.[128] (1996) Buprenorphine 8 mg daily vs methadone 30 mg daily vs methadone 80 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=225 1 year	Primary: Urine toxicology, retention, craving, and withdrawal symptoms Secondary: Not reported	Primary: Patients receiving high-dose methadone maintenance therapy performed significantly better on measures of retention, opioid use, and opioid craving than either the low-dose methadone group or the buprenorphine group. Performance on measures of retention, opioid use, and opioid craving were not significantly different between the low-dose methadone group or the buprenorphine group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Schottenfeld et al.[129] (1997) Buprenorphine 4 mg daily vs buprenorphine 12 mg daily vs methadone 20 mg daily vs methadone 65 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=116 24 weeks	Primary: Retention in treatment and illicit opioid and cocaine use Secondary: Not reported	Primary: There were significant effects of maintenance treatment on rates of illicit opioid use, but no significant differences in treatment retention or the rates of cocaine use. The rates of opioid-positive toxicology tests were lowest for treatment with 65 mg of methadone (45%), followed by 12 mg of buprenorphine (58%), 20 mg of methadone (72%), and 4 mg of buprenorphine (77%), with significant contrasts found between 65 mg of methadone and both lower-dose treatments and between 12 mg of buprenorphine and both lower-dose treatments. Secondary: Not reported
Soyka et al.[130] (2008) Buprenorphine (mean daily dose 9 to 12 mg) vs methadone (mean daily dose 44 to 50 mg)	RCT Opioid-dependent patients who had been without opioid substitution therapy	N=140 6 months	Primary: Retention rate; substance use; predictors of outcome Secondary: Not reported	Primary: There was an overall retention rate of 52.1%. There was no significant difference between buprenorphine-treated patients and methadone-treated patients (55.3 vs 48.4%). Substance use decreased significantly over time in both groups and was non-significantly lower in the buprenorphine group. Predictors of outcome were length of continuous opioid use and age at onset of opioid use (significant in the buprenorphine group only). Mean dosage and other parameters were not significant predictors of outcome. The intensity of withdrawal symptoms showed the strongest correlation with drop-out. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gibson et al.[131] (2008) Buprenorphine vs methadone	RCT Heroin-dependent patients ≥18 years of age	N=405 10 years	Primary: Mortality Secondary: Not reported	Primary: There was an overall mortality rate of 8.84 deaths per 1,000 person-years of follow-up. Increased exposure to episodes of opioid treatment longer than seven days reduced the risk of mortality. There was no difference in mortality among methadone vs buprenorphine participants. More dependent, heavier users of heroin at baseline had a lower risk of death, and also higher exposure to opioid treatment. Older patients on buprenorphine had significantly improved survival. Secondary: Not reported
Maremmani et al.[132] (2007) Buprenorphine vs methadone	OL Patients involved in a long-term treatment program with buprenorphine or methadone	N=213 12 months	Primary: Opioid use, psychiatric status, quality of life Secondary: Not reported	Primary: There were significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for buprenorphine-treated and methadone-treated patients. Secondary: Not reported
Jones et al.[133] (2010) Buprenorphine 2 to 32 mg per day vs methadone 20 to 140 mg per day	DB, DD, MC, RCT Opioid-dependent women 18 to 41 years of age with a singleton pregnancy between 6 and 30 weeks	N=175 ≥10 days	Primary: Neonates requiring neonate abstinence syndrome therapy, total morphine needed, length of hospital stay, and head circumference Secondary:	Primary: Percentage neonates requiring neonate abstinence syndrome treatment, peak neonate abstinence syndrome scores, or head circumference did not differ significantly between groups. Neonates exposed to buprenorphine required an average 89% less morphine (1.1 and 10.4 mg; P<0.0091) than did neonates exposed to morphine. Neonates exposed to buprenorphine required an average 43% less time in hospital (10.0 vs 17.5 days; P<0.0091).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	The methadone group had higher rates of nonserious maternal events overall (P=0.003) and of nonserious cardiac events in particular (P=0.01). No differences in serious adverse events were detected in mothers or nonserious adverse events in neonates. Secondary: Not reported
Cornish et al.[134] (2010) Buprenorphine vs methadone	MC, OS, PRO Opioid dependent patients <60 years of age	N=5,577 585 days	Primary: All cause mortality Secondary: Duration of therapy effect on mortality	Primary: Three percent of patients died while receiving treatment, or within a year of receiving the last prescription. Of these, 35% died while on treatment. Overall, the risk of death during opiate substitution treatment was lower than the risk of death while off treatment. Crude mortality rates off therapy nearly doubled (1.3 vs 0.7 per 100-person years). Standardized mortality rates were 5.3 (95% CI, 4.0 to 6.8) on treatment vs 10.9 (95% CI, 9.0 to13.1). After adjustment for age, sex, calendar period, and comorbidity, the mortality rate ratio was 2.3 (95% CI, 1.7 to 3.1). The risk of death increased eight to nine-fold in the month immediately after the end of opiate substitution therapy, which did not vary according to medication, dosing within standard thresholds, or planned cessation. There was no difference in the overall mortality rate between patients who received methadone and those who received buprenorphine. Secondary: Substitution therapy has a greater than 85% chance of reducing overall mortality when average duration of treatment is at least 12 months.
Pinto et al.[135] (2010) Buprenorphine vs methadone	OS, PRO Cohort of opioid-dependent patients new to substitution therapy	N=361 6 months	Primary: Retention in treatment at six months or successful detoxification based on patient selected	Primary: A total of 63% of patients chose methadone and 37% chose buprenorphine. At six months, 50% of buprenorphine patients compared to 70% of methadone patients had favorable outcomes (OR, 0.43; 95% CI, 0.20 to 0.59; P<0.001). Methadone patients were more likely to remain on therapy than those on buprenorphine (HR, 2.08; 95% CI, 1.49 to 2.94). Retention was the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			substitution therapy Secondary: Not reported	primary factor in favorable outcomes at six months. Buprenorphine patients were more likely to not use illicit opiates (OR, 2.13; 95% CI, 1.509 to 3.027; P<0.001) and to achieve detoxification. A total of 28% of patients selecting buprenorphine reported they would not have accessed treatment with methadone therapy. Secondary: Not reported
Farré et al.[136] (2002) Buprenorphine ≥8 mg daily (high dose vs buprenorphine <8 mg daily (low dose) vs methadone ≥50 mg daily (high dose) vs methadone <50 mg daily (low dose) vs levo-acetylmethadol	MA Patients seeking treatment for opioid dependence	N=1,944 (13 trials) Variable duration	Primary: Retention rate and reduction of opioid use Secondary: Not reported	Primary: High doses of methadone were more effective than low doses of methadone in the reduction of illicit opioid use (OR, 1.72; 95% CI, 1.26 to 2.36). High doses of methadone were significantly more effective than low doses of buprenorphine (<8 mg/day) for retention rates and illicit opioid use, but similar to high doses of buprenorphine (≥8 mg/day). Patients treated with levo-acetylmethadol had more risk of failure of retention than those receiving high doses of methadone (OR, 1.92; 95% CI 1.32 to 2.78). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mattick et al.[137] (2008) Buprenorphine vs methadone vs placebo	MA Patients dependent on heroin or other opioids	N=4,497 (24 trials) Variable duration	Primary: Treatment retention, suppression of opioid use, use of other substances Secondary: Not reported	Primary: <u>Flexible Dose Buprenorphine vs Flexible Dose Methadone</u> Methadone was more likely to retain patients than buprenorphine (RR, 0.85; 95% CI, 0.73 to 0.98). There was no significant difference between the treatment groups with regards to heroin use (95% CI, -0.26 to 0.02), cocaine use (95% CI, -0.03 to 0.25), or benzodiazepine use (95% CI, -0.04 to 0.26). <u>Low Dose Buprenorphine vs Low Dose Methadone</u> Low dose methadone was more likely to retain patients than low dose buprenorphine (RR, 0.67; 95% CI, 0.52 to 0.87). There was no significant difference between the treatment groups with regards to morphine use (95% CI, -0.87 to 0.16), heroin use (95% CI, -0.38 to 0.96), cocaine use (95% CI, -0.43 to 0.59), or benzodiazepine use (95% CI, -0.33 to 0.38). <u>Low Dose Buprenorphine vs Medium Dose Methadone</u> There was a statistical difference in retention in treatment RR, 0.67; (95% CI, 0.55 to 0.81) favoring medium dose methadone. Medium dose methadone was more effective than low dose buprenorphine in suppressing heroin use as indexed by the extent of morphine positive urine, one study (95% CI, 0.33 to 1.42). There was no significant difference among the treatment groups in heroin use (95% CI, -0.48 to 0.68) or cocaine use (95% CI, -0.60 to 0.44). <u>Medium Dose Buprenorphine vs Low Dose Methadone</u> There was one study which favored low dose methadone in terms of retention, and the remaining three studies showed no statistically significant difference. There was no significant difference among the treatment groups in cocaine use (95% CI, -0.14 to 0.89).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Medium Dose Buprenorphine vs Medium Dose Methadone Two of the six studies suggest that medium doses of buprenorphine are less likely to retain patients than medium dose methadone and the remainder showed no statistical significant difference. Medium dose buprenorphine was significantly less able to suppress heroin use, three studies (95% CI, 0.05 to 0.50). There was no significant difference among the treatment groups in cocaine use (95% CI, -0.30 to 0.74). Low Dose Buprenorphine Maintenance vs Placebo There was a benefit for low dose buprenorphine above placebo in terms of retaining patients in treatment (RR, 1.50; 95% CI, 1.19 to 1.88). Low dose buprenorphine patients had no less heroin use as indexed by morphine positive urines (95% CI, -0.80 to 1.01). There was no significant difference among the treatment groups in cocaine use (95% CI, -0.10 to 0.62) or benzodiazepine use (95% CI, -0.33 to 0.38). Medium Dose Buprenorphine Maintenance vs Placebo There was a benefit for buprenorphine above placebo in terms of retaining patients in treatment (RR, 1.74; 95% CI, 1.06 to 2.87). Patients in the buprenorphine group had less heroin use as indexed by morphine positive urines (95% CI, -0.47 to 0.10). For cocaine use, there was an advantage for placebo in one study (95% CI, 0.05 to 0.94). For benzodiazepine use, buprenorphine was more effective than placebo in one study (95% CI, -1.27 to -0.36). High Dose Buprenorphine Maintenance vs Placebo There was a benefit for buprenorphine above placebo in terms of retaining patients in treatment (RR, 1.74; 95% CI, 1.02 to 2.96). Patients in the buprenorphine group had less heroin use when receiving 16mg of buprenorphine than placebo patients (95% CI, -0.95 to -0.51). There was no significant difference among the treatment groups in cocaine use (95% CI, -0.20 to 0.36) or benzodiazepine use (95% CI, -0.52 to 0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Kakko et al.[138] (2007) Buprenorphine-naloxone (stepped treatment) vs methadone (maintenance treatment)	RCT Patients >20 years of age with heroin dependence for >1 year	N=96 24-day induction phase, followed by a 6 month follow-up phase	Primary: Retention in treatment Secondary: Completer analyses of problem severity (Addiction Severity Index); proportion of urine samples free of illicit drugs	Primary: The six-month retention was 78% with buprenorphine-naloxone stepped treatment and methadone maintenance therapy being virtually identical (adjusted OR, 1.02; 95% CI, 0.65 to 1.60). The proportion of urine samples free of illicit opiates over time increased and ultimately reached approximately 80% in both arms at the end of the study (P=0.00003). No difference between the two groups was found (P=0.87). Secondary: Problem severity as measured by the Addiction Severity Index decreased over time (P<0.000001). No difference between the treatment arms was found (P=0.90).
Kamien et al.[139] (2008) Buprenorphine-naloxone 8-2 mg daily vs buprenorphine-naloxone 16-4 mg daily vs methadone 45 to 90 mg daily	DB, DD, RCT Patients ≥18 years of age who met criteria for opioid dependence and who were using heroin or prescription opioids or receiving methadone maintenance treatment	N=268 17 weeks	Primary: Amount of opioid abstinence achieved over time Secondary: Proportion of patients who achieved 12 consecutive opioid-negative samples, proportion of patients with successful inductions, medication compliance, non-opioid illicit drug use, and treatment	Primary: The percentage of opioid-free urine samples over time did not differ significantly among drug groups (P=0.81) or among drug doses (P=0.46). Secondary: The proportion of patients who had at least 12 consecutive opioid-negative urine samples were as follows: 10% (buprenorphine-naloxone 8-2 mg) 17% (buprenorphine-naloxone 16-4 mg), 12% (methadone 45 mg), and 16% (methadone 90 mg). The percentage of patients with at least 12 consecutive opioid-negative urine samples differed by dose (8 vs 16 mg buprenorphine-naloxone; P<0.001, 45 vs 90 mg methadone; P=0.02), but not by drug (8 mg buprenorphine-naloxone vs 45 mg methadone; P=0.18, 16 mg buprenorphine-naloxone vs 90 mg methadone; P=0.22). Those receiving higher doses of methadone or buprenorphine-naloxone were more likely to have at least 12 consecutive opioid-negative urine samples than those receiving lower doses. Successful inductions occurred in 80.5, 81.0, 82.7 and 82.9% of the patients receiving buprenorphine-naloxone 8-2 mg, buprenorphine-naloxone 16-4 mg, methadone 45 and 90 mg, respectively. There were no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			retention	significant differences among the treatment groups (P=0.22 to P=0.98). Medication compliance did not differ significantly among the treatment groups (P=0.41). Non-opioid drug use did not change significantly over time, nor did it differ significantly across groups (P=0.32 to P=0.83). Treatment retention did not differ significantly in the low dose groups (P=0.09) or in the high dose groups (P=0.28).
Hser et al.[140] (2016) Buprenorphine-naloxone vs methadone	MC, OL Opioid-dependent participants entering opioid treatment programs in the USA between 2006 and 2009	N=1,080 (mortality) N=795 (other outcomes) Mean of 4.5 years	Primary: Mortality, opioid use Secondary: Not reported	Primary: There were 23 deaths in the buprenorphine-naloxone group (n=630, or 3.6%) and 26 deaths in the methadone group (n=450, or 5.8%); the difference was not statistically different (P=0.10). Opioid use was higher among participants randomized to buprenorphine-naloxone relative to methadone at the follow-up interview (42.8 vs 31.7% positive opioid urine specimens, P<0.01; 5.8 vs 4.4 days of past 30-day heroin use, P<0.05). Overall, 46.8% participants were currently using opioids as indicated by a positive urine test or self-reported past-30-day opioid use with significantly more opioid use among buprenorphine-naloxone than methadone participants (50.9 vs 41.1%). For both groups, opioid use drops immediately after entering the trial, increases somewhat thereafter (approximately six months after randomization for both groups), reaches a high point approximately 10 to 12 months post-randomization, and then gradually tapers off; relative to those in buprenorphine-naloxone, opioid use by individuals in the methadone condition dropped more and had lower relapse rates immediately after the trial, although the groups converged in approximately two years post-randomization. Participation in methadone or buprenorphine-naloxone treatment, relative to no methadone or buprenorphine-naloxone treatment, was associated with reduced opioid use. The estimated reduction on days of opioid use was 8.5 days for methadone and 7.8 days for buprenorphine-naloxone treatment, respectively, with no statistically significant difference between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the two types of treatments (P=0.06). Secondary: Not reported
Strain et al.[141] (2000) Buprenorphine 4 mg to 16 mg per day vs buprenorphine-naloxone sublingual tablets 1-0.25, 2-0.5, 4-1, 8-2, 16-4 mg per day vs hydromorphone 2 and 4 mg IM vs placebo	DB, DD, PC Adults with active opioid abuse, but not physically dependent	N=7	Primary: Peak drug effect; physiologic and psychomotor measures Secondary: Not reported	Primary: Dose-related increases in ratings of Drug Effects, High, Good Effects, and Liking were seen for hydromorphone, for buprenorphine, and for the combination of buprenorphine-naloxone. The predominant effects were seen with the highest doses tested (hydromorphone 4 mg, buprenorphine-naloxone 8-2 and 16-4 mg, and buprenorphine 8 and 16 mg). None of the treatments produced significant changes in ratings of Bad Effects or Sick. For ratings of Drug Effects, only the two higher doses of buprenorphine alone (8 and 16 mg) produced significantly increased ratings compared to placebo (P<0.05 and P<0.01, respectively). The combination dose of 8-2 mg and 16-4 produced ratings of drug effects that were lower than those produced by the buprenorphine dose of 8 mg. The differences between buprenorphine alone and buprenorphine-naloxone doses were not statistically significant for these or any other measures. None of the treatments produced significant changes on measures of blood pressure, heart rate, or respiratory rate. There were no significant differences in psychomotor effects among the treatments. Secondary: Not reported

Drug abbreviations: BID=twice daily, CR=controlled release, ER=extended-release, IM=intramuscular, IR=immediate release, IV=intravenous, SR=sustained-release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, DR=dose ranging, ES=extension study, HR=hazard ratio, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, MD=multi-dose, NI=non-inferiority, OL=open label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SA=single-arm, SC=single center, SD=standard deviation, SE=standard error, SEM=standard error of mean, WMD=weighted mean difference, XO=crossover
Miscellaneous abbreviations: APAP=acetaminophen, ASA=American Society of Anesthesiologists, AUCMBavg=average area under the curve of VAS scores overtime between baseline and end of study, BPI=Brief Pain Inventory, BTP=breakthrough pain, CGI=Clinical Global Impression, CHQ=Child Health Questionnaire, COX-2=cyclooxygenase 2, CRPS=Complex Regional Pain Syndrome, ED=emergency department, MPI=multidimensional pain inventory, NSAIDs=non-steroidal anti-inflammatory drugs, OA=osteoarthritis, PAR=hourly pain relief, PaCO2=partial pressure of arterial carbon dioxide, PCA=patient-controlled analgesia, PDI=Pain Disability Index, PGIC=Patient's Global Impression of Change, PID=Pain Intensity Differences, PPS=Play Performance Scale, PRRS=pain relief rating scale, PVA=pain visual analog scale, RDQ=Roland disability questionnaire, SF-36=Short-Form health survey 36 questions, SPID=Summed Pain Intensity Differences, TOTPAR=Total Pain Relief, VAS=visual analog scale, WHO=World Health Organization, WOMAC index=Western Ontario and McMaster Universities Index

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 28. Relative Cost of the Opiate Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Alfentanil	injection^	N/A	N/A	$-$$
Codeine	tablet	N/A	N/A	$
Fentanyl	buccal lozenge, buccal tablet, injection, transdermal patch	Actiq®*, Fentora®*	$$$$$	$$$
Hydromorphone	injection, liquid, rectal suppository, tablet	Dilaudid®*	$$$$$	$
Levorphanol	tablet	N/A	N/A	$$$$$
Meperidine	injection, solution, tablet	Demerol®*	$$$$$	$$$$$
Methadone	injection, oral concentrate, solution, tablet	Methadose®*	$$$$$	$
Morphine	epidural, injection, rectal suppository, solution, tablet	Duramorph®, Infumorph®	$$$$$	$$
Oxycodone	capsule, oral	Oxaydo®, Roxicodone®*	$$$$$	$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
	concentrate, solution, tablet			
Oxymorphone	injection, tablet	N/A	N/A	$$$$$
Remifentanil	injection^	Ultiva®*	$$$$$	$$$$$
Sufentanil	injection^, sublingual tablet applicator^	Dsuvia®	$$$$$	$$$
Tapentadol	extended-release tablet, tablet	Nucynta®, Nucynta ER®	$$$$$	N/A
Tramadol	extended-release capsule, extended-release tablet, tablet	Conzip ER®*, Ultram®*	$$$$-$$$$$	$
Combination Products				
Benzhydrocodone and acetaminophen	tablet	Apadaz®*	$-$$	$-$$
Codeine and acetaminophen	solution, tablet	N/A	N/A	$
Codeine, butalbital, acetaminophen, and caffeine	capsule	N/A	N/A	$$$
Codeine, butalbital, aspirin, and caffeine	capsule	Fiorinal With Codeine®*	$$$$$	$
Dihydrocodeine, acetaminophen, and caffeine	capsule	N/A	N/A	$$$$
Hydrocodone and acetaminophen	solution, tablet	Lortab®*, Verdrocet®*	$$$$$	$
Hydrocodone and ibuprofen	tablet	Xylon®*	N/A	$$
Opium and belladonna	rectal suppository	N/A	N/A	$$$$$
Oxycodone and acetaminophen	tablet	Percocet®*	$$$$$	$
Tramadol and acetaminophen	tablet	Ultracet®*	$$	$
Tramadol and celecoxib	tablet	Seglentis®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
N/A=Not available

X. Conclusions

Currently, there is no standard treatment regimen that will satisfy the needs of all patients with pain. The opiate agonists are considered to be the most potent analgesics available and are frequently prescribed for the treatment of acute pain, chronic pain, and palliative care. They are available in a variety of dosage forms as single entity agents, as well as in combination with acetaminophen, aspirin, butalbital, caffeine, celecoxib, and ibuprofen. All of the products are available in a generic formulation, with the exception of tapentadol and tramadol-celecoxib.

Support for efficacy of Apadaz® (benzhydrocodone/acetaminophen) was based upon the efficacy of its reference drug, hydrocodone/acetaminophen, and in an open-label, single dose, randomized, crossover study where Apadaz® (benzhydrocodone/acetaminophen) showed relative comparable bioavailability.[6] In an oral, single-center, randomized, double-blind, crossover, human abuse potential study, there were no statistically significant differences nor any clinically meaningful differences between Apadaz® and the hydrocodone/acetaminophen control for the pre-specified primary endpoint of maximal score (E_{max}) for Drug Liking visual analog scale (VAS) or secondary endpoints of E_{max} for High VAS and Take Drug Again VAS. Overall, the in vitro studies that

evaluated physical manipulation and extraction for the purpose of preparing Apadaz® for abuse by the intravenous route or by smoking did not find an advantage for Apadaz® over the hydrocodone/acetaminophen control. The results of the oral and intranasal human abuse potential studies do not support a finding that Apadaz® can be expected to deter abuse by the oral or nasal routes of administration.[6]

Patients with cancer often suffer from pain due to tumor infiltration, which significantly affects their quality of life. For the treatment of cancer pain, guidelines recommend the use of an opiate agonist in patients with moderate to severe pain. For patients with continuous pain, it is appropriate to prescribe opioids around-the-clock and provide supplemental doses for breakthrough pain. Long-acting formulations are recommended in patients whose pain is controlled on stable doses of short-acting opioids, or for patients who require >4 breakthrough doses per day. Guidelines do not give preference to one opiate agonist over another for the treatment of cancer pain.[20,22]

For the treatment of chronic noncancer pain, guidelines recommend nonpharmacologic therapy and non-opioid therapy as initial treatments. Opioid therapy should be considered only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. When opioids are initiated, the lowest effective dosage should be prescribed.[10,23,24] Opioid doses over 90 mg morphine equivalent daily dose are not recommended for treating chronic pain according to the Veterans Affairs and Centers for Disease Control guidelines.[10,24] Opiate agonists may be an appropriate therapeutic option in patients with moderate to severe pain.[10,21,23,24] In general, no single opioid or opioid formulation is preferred over the others.[10,21,23,24] Implementing risk mitigation strategies upon initiation of long-term opioid therapy is recommended, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. Risk mitigation strategies may include urine drug testing, checking prescription drug monitoring programs, monitoring for overdose potential, and/or providing naloxone.[10,23,24]

Interventions for opioid-related conditions (dependence, abuse, intoxication, and withdrawal) include psychosocial therapy and pharmacotherapy. The selection of therapy should be based on patient preference, past response to therapy, probability of achieving and maintaining abstinence, and the effects of continued use of opioids.[9] For the maintenance treatment of opioid dependence, guidelines recommend the use of methadone or the combination product buprenorphine and naloxone as first-line therapy.[9,25-26] Maintenance treatment with methadone has been shown to decrease illicit opioid use, decrease morbidity and mortality, decrease criminal activity, improve health status and social functioning, and reduce the spread of Human Immunodeficiency Virus infection among intravenous drug users. Studies directly comparing methadone to buprenorphine (with or without naloxone) have shown mixed results, which is thought to be due to differences in the dosing regimens used.[9,124-140] Serious adverse events have occurred in patients receiving methadone, including death, respiratory depression and cardiac arrhythmias.[4-6] These adverse events may have been caused by unintentional overdoses, drug interactions, and/or cardiac toxicities (QT prolongation and Torsades de Pointes).[142] Methadone's pharmacokinetic properties, as well as high inter-patient variability in its absorption, metabolism, and analgesic potency, require an individualized approach to prescribing.[4-6]

In May 2010, the FDA notified healthcare providers about an increased risk of suicide with tramadol. Deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other central nervous system-active drugs.[15] An additional safety communication regarding the risks of using tramadol in children aged 17 years and younger was released in September 2015.[16] In 2017, the FDA announced labeling changes to products containing tramadol, which include a contraindication to treating pain in children under 12 years of age, a contraindication to use in children under 18 years of age to treat pain after surgery to remove the tonsils and/or adenoids, a warning against use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, and a warning to restrict use in mothers who are breastfeeding.[17] In January 2018, the FDA announced that they are requiring safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18. They are also requiring the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the Boxed Warning of the drug labels for prescription cough and cold medicines containing codeine or hydrocodone.[18] An FDA Drug Safety Communication was also released on April 2019 regarding harm reported from sudden discontinuation of opioid pain medicines and requiring label changes to guide prescribers on gradual, individualized tapering.[19]

In January 2016, CMS released an informational bulletin addressing prescription opioid overdoses, misuse, and addiction. The purpose of the bulletin was to highlight strategies for preventing opioid-related harms.[9] CMS emphasizes that methadone accounts for a disproportionate share of opioid-related overdoses and deaths, and encourages states to consider additional steps to reduce the use of methadone prescribed for pain relief. The pharmacokinetic and pharmacodynamic parameters of methadone make it a complex medication to prescribe for pain relief.[9] Of note, its elimination half-life is longer than its duration of analgesic action, there is high interpatient variability in absorption, metabolism, and relative analgesic potency, it is retained in the liver with repeat dosing, and it has a narrow therapeutic index.[6,7] CMS recommends removing methadone from preferred drug lists and limiting its use only to patients for whom treatment with other pain medications is ineffective.[9]

On March 18, 2016 the CDC published guidelines for prescribing opioids for chronic pain. This guideline provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and/or end-of-life care.[10] This guideline states that nonpharmacologic and nonopioid pharmacologic therapies are preferred for chronic pain. When opioid therapy is initiated for chronic pain, IR opioids should be used before ER/LA agents. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received IR opioids daily for at least a one-week duration. The guideline states that methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for chronic pain. Methadone should not be the first choice for an ER/LA opioid.[10]

There is insufficient evidence to support that one brand opiate agonist is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process. Methadone should be managed through the medical justification portion of the prior authorization process due to the potential risk of abuse and overdose, the known complexities with appropriately prescribing this medication, and the guideline recommendations for not using this medication as a first-line agent.

Therefore, all brand opiate agonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand opiate agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Methadone should not be placed in preferred status regardless of cost.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Opiate Partial Agonists
AHFS Class 280812
November 9, 2022

I. Overview

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of damage." Chronic pain is further defined as "pain which persists past the normal time of healing," generally lasting ≥3 months.[1] Pain is a subjective experience that is unique to the individual.[2] There are numerous etiologies of pain and successful pain management can be difficult to achieve.

Opioids exert their effect by binding to opioid receptors widely distributed within the brain, spinal cord, and gastrointestinal tract. Mu receptors are responsible for analgesia, respiratory depression, euphoria, sedation, decreased gastrointestinal motility, and physical dependence.[3] Partial opiate agonists bind to and activate mu receptors, but not to the same degree as full agonists. They have a ceiling to their effect and are less likely than full agonists to cause physical dependence. Kappa receptors are responsible for analgesia, sedation, dyspnea, dysphoria, and respiratory depression.[3-5] Butorphanol, nalbuphine, and pentazocine act as mu receptor antagonists and partial kappa receptor agonists.[3-7] Buprenorphine is a partial mu receptor agonist and kappa receptor antagonist. It has a high affinity for, low intrinsic activity at, and a slow disassociation rate from the mu receptor. This activity at the mu receptor, combined with its kappa receptor antagonist activity, allows buprenorphine to be effective as an analgesic, but also in opioid abuse deterrence, detoxification, and maintenance therapies.[8-15] Naloxone is a competitive antagonist at the mu receptor and displaces full agonists from receptor sites. When taken orally, naloxone exerts no clinically significant effect leaving the opioid agonist effects of buprenorphine to predominate. However, when administered intravenously, it rapidly reverses the effects of an opiate agonist.[6-13]

Opioid dependence is a significant health problem in the United States. Interventions for opioid-related conditions (dependence, abuse, intoxication, and withdrawal) include both psychosocial and pharmacological treatments.[16] Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence.[6-13] The use of methadone is restricted to federally approved Opioid Treatment Programs (OTPs). Qualified office-based physicians may prescribe buprenorphine-containing products for the treatment of opioid dependence, which has significantly expanded access to treatment. Since methadone is a full agonist at the mu receptor, the potential for abuse, misuse, and diversion exists.[16,17] Patients may also experience withdrawal symptoms when a dose is missed. Since there is no ceiling to its effect, an overdose can be fatal. Compared to full agonists, buprenorphine has a lower potential for abuse and is safer in an overdose situation. However, it can still produce euphoria and physical dependence. Naloxone has been combined with buprenorphine to reduce the risk of abuse.[17]

Butrans® (buprenorphine transdermal system) is an FDA-approved partial agonist for the management of moderate to severe chronic pain.[11] Belbuca® is a buccal film indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Belbuca® uses a dissolving film that is absorbed through the inner lining of the cheek.[8] Sublocade® is an extended-release, monthly, subcutaneous injection which is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of seven days. Sublocade® is a drug-device combination product that utilizes buprenorphine and the Atrigel Delivery System in a pre-filled syringe and should only be prepared and administered by healthcare providers.[9]

The opiate partial agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in August 2020.

Table 1. Opiate Partial Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)†

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)†
Single Entity Agents			
Buprenorphine	buccal film, extended release solution, injection, sublingual tablet, transdermal patch	Belbuca®, Buprenex®*, Butrans®*, Sublocade®	Sublocade®CC
Butorphanol	injection, nasal spray	N/A	butorphanol
Nalbuphine	injection	N/A	nalbuphine
Combination Products			
Buprenorphine and naloxone	sublingual film*, sublingual tablet*	Suboxone®*, Zubsolv®	buprenorphine and naloxone tabletsCC, Suboxone*CC, Zubsolv®CC
Pentazocine and naloxone	tablet	N/A	pentazocine and naloxone

*Generic is available in at least one dosage form or strength.
†Generic buprenorphine products were placed on prior authorization due to abuse potential through P&T and Drug Utilization Review.
CCDenotes agent is preferred with clinical criteria in place.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the opiate partial agonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Opiate Partial Agonists

Clinical Guideline	Recommendation(s)
National Comprehensive Cancer Network: **Adult Cancer Pain (2022)**[18]	• The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization (WHO) which suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a "weak opioid," such as codeine, and then to a "strong opioid," such as morphine. • The pain management algorithm distinguishes three levels of pain intensity, based on a 0 to 10 numerical rating scale: severe pain (8 to 10), moderate pain (4 to 7) and mild pain (1 to 3). • Pain associated with oncology emergency should be addressed while concurrently treating the underlying condition. <u>General principles of opioid treatment</u> • Periodically review prescription drug monitoring program databases. • Consider documentation of opioid and controlled substance agreement. • Dose and titrate with caution in patients with risk factors such as decreased renal/hepatic function, chronic lung disease, upper airway compromise, sleep apnea, and poor performance status. • The appropriate opioid dose is the lowest dose that relieves the patient's pain and maximizes function throughout the dosing interval without causing unmanageable adverse effects. • Generally, oral route is most common; however, other routes can be considered as indicated to maximize patient comfort. • Calculate dosage increase based upon total opioid dose (around the clock/scheduled and as needed) taken in the previous 24 hours and increase both around-the-clock and as-needed dose as required. The rapidity of dose escalation should be related to the severity of the symptoms, expected analgesic onset and duration, and ability to monitor during dose titration. • According to Food and Drug Administration (FDA) guidelines, when higher doses of analgesic are needed, switch from preparations of opioid combined with other medications (such as aspirin and acetaminophen) to a pure opioid preparation to

Clinical Guideline	Recommendation(s)
	allow optimized titration of both agents. • Steady state drug levels will be achieved when a stable drug dose has been routinely administered for a period equal to five times the drug elimination half life. • Consider opioid rotation if pain is inadequately controlled and further dose titration is limited by adverse effects. Other indications for switching to a different opioid include: out-of-pocket costs, limitations based on formularies, or change in a patient's condition (e.g., dysphagia, nothing by mouth status, initiation of tube feeding, renal/hepatic function). • Patient evaluations should include the routine assessment of risk factors for aberrant use of pain medications. • Educate the patients and caregivers about safe use, storage, and disposal of opioids. • Use caution when combining opioid medications with other medications that have a sedating effect (e.g., benzodiazepines). • Consider pain or palliative care consult. <u>Principles of maintenance opioid therapy</u> • For continuous pain, it is appropriate to give pain medication on a regular schedule with supplemental doses for breakthrough pain. • Add extended-release or long-acting formulation to provide background analgesia for control of chronic persistent pain controlled on stable doses of short-acting opioids. Initial range for converting to long-acting opioid would be 50 to 100% of the daily requirement, depending on expected pain natural history. • When using methadone as a long-acting opioid, a short-acting opioid should also be provided for breakthrough pain. • Increase the dose of regularly scheduled opioid if patient persistently needs doses of as-needed opioids or when dose of around-the-clock opioid fails to relieve pain at peak effect or at end of dose. • Breakthrough pain may require additional doses of opioid for pain not relieved by regular schedule of long-acting opioid. • Allow rescue use of short-acting opioids at doses of 10 to 20% of the 24-hour total of long-acting or regularly scheduled oral opioid dose up to every three to four hours as needed. Titrate rescue dose as needed. • Consider rapidly acting transmucosal fentanyl in opioid-tolerant patients for brief episodes of incident pain not relieved by traditional immediate-release opioids and not attributed to inadequate dosing of around-the-clock opioids. • Continue to monitor patients for opioid adverse effects and patients/family for abnormal patterns of opioid use that may suggest aberrant drug use and/or diversion. • Consider potential drug interactions. <u>Principles of opioid dose reduction</u> • Consider opioid dose reduction by 10 to 20% when possible; situations that may warrant dose reduction include: o Patient never or rarely needs breakthrough analgesic. o Completion of acute pain event or response to cancer-directed therapies. o Improvement of pain control through use of non-opioid pain management therapies. • If patient is experiencing unmanageable adverse effects and pain is ≤3 (mild), consider downward dose titration by approximately 10 to 25% and re-evaluate. Close follow-up is required to make sure that the pain does not escalate, and that the patient does not develop symptoms of withdrawal. If patient has rapid clinical deterioration (e.g., marked sedation due to sepsis), temporary opioid dose reduction by 50 to 75% may be necessary. • If pain is worsened with increasing dose, consider opioid-induced hyperalgesia; opioid dose reduction or rotation with attention to other pain therapies may be

Clinical Guideline	Recommendation(s)
	indicated. Opioids and Risk Evaluation and Mitigation Strategy (REMS) • Opioids are the principal analgesics for moderate to severe pain, yet opioids pose risks to patients and society. • Responding to the "public health crisis of addiction, misuse, abuse, overdose, and death," the FDA established REMS programs for all potent opioid products. Provider and patient education are the principal recommendations of proposed opioid REMS programs. • REMS programs are currently in place for all opioid analgesics. • It is important for prescribers to be aware of the range of opioid use patterns to detect any potential aberrant behaviors. • Patients receiving treatment for addiction should be encouraged to continue with therapy and pain management should be carried out in coordination with an addiction specialist. Strategies to maintain patient safety and minimize the risk of opioid misuse and abuse during chronic opioid use • Use caution when combining opioid medications with other medications that have a sedating effect (e.g., benzodiazepines). • Risk assessment prior to treatment is recommended, although current assessment tools have not been validated in the setting of cancer care and clinical judgment should be exercised. • Education regarding the potential risks and benefits of opioid therapy; educate regarding not sharing opioids with family members or friends. • Educate regarding safe manipulation, storage, and disposal of controlled substances. • Risk mitigation for all patients receiving opioid analgesics o Consider prescribing naloxone for administration by caregivers as needed for patients taking opioids who are at high risk for respiratory depression and sedation. o Pain medication diaries are recommended for patients to document the dose and/or number of tablets and the date and time taken. o Pill counts may be used at outpatient visits or by home health/hospice to assist in correct use of medication. o Urine drug testing at baseline and during treatment should be considered to help document opioid analgesic adherence, detect illegal drug use, and identify opioid diversion. • High-risk patients who exhibit one or more opioid misuse and abuse risk factors may benefit from additional education and support services. Behavioral and cognitive-behavioral interventions may increase a patient's ability to implement problem-solving strategies and reduce the impact of modifiable risk factors. o Increase frequency of outpatient visits to weekly, if possible, and/or reduce quantity of drug prescribed per prescription. o Consider earlier referral to interventional pain specialists to maximize non-opioid options for pain control. o Consider referral to interdisciplinary team including an addiction specialist. o Counsel high-risk patients that continuation of opioid therapy is contingent upon appropriate, safe use of prescribed analgesics. o Consider utilizing programmable electronic medication dispensers. Management of pain in opioid-naïve patients • Opioid-naïve patients (those not chronically receiving opioid therapy on a daily basis) should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support, as well as patient and family

Clinical Guideline	Recommendation(s)
	education. • Opioid-naïve patients experiencing mild pain should first consider non-opioids and adjuvant therapies, unless these are contraindicated due to adverse effects or potential drug interactions. • For opioid-naïve patients whose pain intensity is moderate/severe at presentation, non-opioids and adjuvant therapies should be initiated as appropriate with short-acting opioids as needed. If four or more doses are needed per day consistently, consider addition of long-acting opioid. For persistent pain, initiate regular schedule of opioid with rescue dose as needed. • Opioid-naïve patients experiencing acute, severe pain or pain crisis, consider hospital or inpatient hospice admission to achieve patient-specific goals for comfort and function. <u>Management of pain in opioid-tolerant patients</u> • Opioid-tolerant patients are those chronically taking opioids on a daily basis. According to the FDA, opioid-tolerant patients "are those who are taking at least 60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, or an equianalgesic dose of another opioid for one week or longer." • Patients should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support, as well as patient and family education. • Opioid-tolerant patients experiencing mild pain should first consider non-opioids and adjuvant therapies, unless these are contraindicated due to adverse effects or potential drug interactions. Re-evaluate need for opioids and reduce if appropriate. • Opioid-tolerant patients experiencing moderate pain should receive non-opioids and adjuvant therapies as appropriate with short-acting opioids as needed. Titrate short-acting opioid, with the goal of increasing daily dose by 30 to 50%. If four or more doses are needed per day consistently, consider addition of long-acting opioid. For persistent pain, initiate regular schedule of opioid with rescue dose as needed. • For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission to achieve patient-specific goals for comfort and function. <u>Opioid prescription, titration, and maintenance</u> • Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). An individual approach should be used to determine opioid starting dose, frequency, and titration in order to achieve a balance between pain relief and medication adverse effects. • Pure agonists (such as morphine, oxycodone, oxymorphone, and fentanyl) are the most commonly used medications in the management of cancer pain. • The short half-life opioid agonists (morphine, hydromorphone, fentanyl, and oxycodone) are preferred because they can be more easily titrated than the long half-life opioids (methadone and levorphanol). • In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice. Oral administration is preferred. • Morphine, hydromorphone, hydrocodone, oxymorphone, and codeine should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. • Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid-tolerant patients. It is usually the drug of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance. • Individual variations in methadone pharmacokinetics make using this agent in cancer pain difficult. Methadone should be started at lower-than-anticipated doses

Clinical Guideline	Recommendation(s)
	and slowly titrated upwards with provision of adequate short acting breakthrough pain medications during the titration period. • Meperidine, mixed agonist-antagonists (e.g., butorphanol, pentazocine), and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain, especially in patients with impaired renal function or dehydration. • The least invasive, easiest and safest route of administration should be provided to ensure adequate analgesia. Oral administration is preferred for chronic opioid therapy. The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences adverse events associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect in comparison with oral dosing.
American Society of Interventional Pain Physicians: **Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain (2012)**[19]	• Once medical necessity is established, opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid side effects. • Up to 40 mg of morphine equivalent is considered as a low dose, 41 to 90 mg of morphine equivalent as a moderate dose, and greater than 91 mg of morphine equivalent as a high dose. • In reference to long-acting opioids, titration must be carried out with caution, and overdose and misuse must be avoided. • The long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amendable to short-acting or moderate doses of long-acting opioids, as there is no significant difference between long-acting and short-acting opioids for their effectiveness or adverse effects. • Methadone and buprenorphine are recommended for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. • It is essential to monitor for side effects and manage them appropriately, including discontinuation of opioids if indicated. • A trial of opioid rotation may be considered for patients experiencing intolerable adverse events or inadequate benefit despite dose increases. • Chronic opioid therapy may be continued, with continuous adherence monitoring, in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects.
European Society for Medical Oncology: **Management of Cancer Pain in Adult Patients (2018)**[20]	• The intensity of pain and the treatment outcomes should be assessed regularly and consistently using the visual analog scale or numerical rating school using the question: 'What has been your worst pain in the last 24 hours? • Observation of pain-related behaviors and discomfort is indicated in patients with cognitive impairment to assess the presence of pain. • The assessment of all components of suffering, such as psychosocial distress, should be considered and evaluated. • Patients should be informed about pain and pain management and should be encouraged to take an active role in their pain management. • The onset of pain should be prevented by means of around-the-clock administration, taking into account the half-life, bioavailability and duration of action of different drugs. • Analgesics for chronic pain should be prescribed on a regular basis and not on an 'as required' schedule. • The oral route of administration of analgesic drugs should be advocated as the first choice. • Treatment of mild pain (WHO Step 1 analgesics):

Clinical Guideline	Recommendation(s)
	○ Analgesic treatment should start with drugs indicated by the WHO analgesic ladder appropriate for the severity of pain (Acetaminophen or NSAIDs). ○ There is no significant evidence to support or refute the use of paracetamol alone or in combination with opioids for mild to moderate pain. ○ There is no significant evidence to support or refute the use of NSAIDs alone or in combination with opioids for mild to moderate pain. • Treatment of mild to moderate pain (WHO Step 2 analgesics): ○ For mild to moderate pain, weak opioids such as tramadol, dihydrocodeine and codeine can be given in combination with non-opioid analgesics. ○ As an alternative to weak opioids, low doses of strong opioids could be an option, although this recommendation is not currently part of WHO guidance. ○ There is no evidence of increase in adverse effects from the use of low-dose strong opioids instead of the standard step 2 approach with weak opioids. • Treatment of moderate to severe pain (WHO Step III analgesics): ○ The opioid of first choice for moderate to severe cancer pain is oral morphine. ○ The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3. ○ The average relative potency ratio of oral to subcutaneous morphine is between 1:2 and 1:3. ○ Morphine is most commonly used in severe pain and oral administration is the preferred route. ○ Hydromorphone and oxycodone are an alternative to oral morphine. ○ Transdermal fentanyl and transdermal buprenorphine should be reserved for patients whose opioid requirements are stable. They are usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance to morphine and patients with poor compliance. ○ Fentanyl and buprenorphine (via the transdermal or intravenous route) are the safest opioids in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate < 30 mL/min). ○ A different opioid should be considered in the absence of adequate analgesia (despite opioid dose escalation) or in the presence of unacceptable opioid side effects. ○ The subcutaneous route is simple and effective for the administration of morphine, diamorphine and hydromorphone and it should be the first-choice alternative route for patients unable to receive opioids by oral or transdermal routes. ○ Intravenous infusion should be considered when subcutaneous administration is contraindicated (peripheral edema, coagulation disorders, poor peripheral circulation and need for high volumes and doses). ○ Intravenous administration is an option for opioid titration when rapid pain control is needed. • Management of opioid side effects ○ Laxatives must be routinely prescribed for both the prophylaxis and the management of opioid-induced constipation. ○ The use of naloxone in association with oxycodone or methylnaltrexone to control opioid-induced constipation may be considered. ○ Naloxegol has been shown to be highly effective in opioid-induced constipation, but, to date, there is no specific reported experience in the cancer population. ○ Metoclopramide and antidopaminergic drugs should be recommended for treatment of opioid-related nausea/vomiting.

Clinical Guideline	Recommendation(s)
	○ Psychostimulants (e.g. methylphenidate) to treat opioid-induced sedation are only advised when other methods to treat this have been tried (e.g. rationalize all medication with a sedative side effect). ○ Mu receptor antagonists (e.g. naloxone) must be used promptly in the treatment of opioid-induced respiratory depression. • Break-through cancer pain ○ Immediate-release opioids should be used to treat break-through cancer pain that is opioid-responsive and for which background cancer pain management has been optimized. ○ Transmucosal fentanyl formulations (oral, buccal, sublingual and intranasal) have a role in unpredictable and rapid-onset break-through cancer pain. ○ There are indications for standard normal-release oral opioids (e.g. morphine) that include a slow-onset break-through cancer pain or a pre-emptive administration of oral opioids 30 minutes before a predictable break-through cancer pain triggered by known events.
National Opioid Use Guideline Group: **Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain (2017)**[21]	<u>Initiation and dosing of opioids in patients with chronic noncancer pain</u> • When considering therapy for patients with chronic non-cancer pain, optimize non-opioid pharmacotherapy and non-pharmacological therapy rather than initiate a trial of opioids. • For patients with chronic noncancer pain, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized nonopioid therapy, add a trial of opioids rather than continue therapy without opioids. • For patients with chronic noncancer pain with an active substance use disorder, the use of opioids is not recommended. • For patients with chronic noncancer pain with an active psychiatric disorder whose nonopioid therapy has been optimized, and who have persistent problematic pain, stabilize the psychiatric disorder before a trial of opioids is considered. • For patients with chronic noncancer pain with a history of substance use disorder, whose nonopioid therapy has been optimized, and who have persistent problematic pain, continue nonopioid therapy rather than a trial of opioids. • For patients with chronic noncancer pain who are beginning long term opioid therapy, restrict the prescribed dose to <90 mg morphine equivalents daily. <u>Rotation and tapering of opioids, for patients with chronic noncancer pain</u> • For patients with chronic noncancer pain who are currently using opioids, and have persistent problematic pain and/or problematic adverse effects, rotate to other opioids. • For patients with chronic noncancer pain who are currently using ≥90 mg morphine equivalents of opioids per day, taper opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy. • For patients with chronic noncancer pain who are using opioids and experiencing serious challenges in tapering, utilize a formal multidisciplinary program. <u>Best practice statements</u> • Acquire informed consent prior to initiating opioid use for chronic non-cancer pain. A discussion about potential benefits, adverse effects, and complications will facilitate shared-care decision making regarding whether to proceed with opioid therapy. • Monitor chronic non-cancer pain patients using opioid therapy for their response to treatment, and adjust treatment accordingly. • Clinicians with chronic non-cancer pain patients prescribed opioids should address any potential contraindications and exchange relevant information with the

Clinical Guideline	Recommendation(s)
	patient's general practitioner (if they are not the general practitioner) and/or pharmacists. Expert guidance statements • Dangers of overdose and diversion both mandate not prescribing large doses of opioids at one time. • In patients with continuous pain including pain at rest, clinicians can prescribe controlled release opioids both for comfort and simplicity of treatment. Activity related pain may not require sustained release treatment and opioid therapy may be initiated with immediate release alone. • Available studies yield conflicting results regarding the consequences of the concomitant use of opioids and sedatives such as benzodiazepines. The pharmacology suggests that sedatives and opioids would enhance the depressant effect of the other, worsening the balance of harms vs. benefits and increasing the risk of cognitive effects, falls, motor vehicle accidents and drug-related death, though the supporting evidence is unavailable. The expert perspective is that opioids and benzodiazepines should very rarely be prescribed together. • Patients with opioid-induced sleep apnea should be advised of the associated health risks, and particularly the risks of operating a motor vehicle. Clinicians may have a statutory duty to report to governmental licensing authorities. There are three main treatment approaches available to clinicians managing patients with opioid-induced sleep disordered breathing: o Reduce opioid dose without specific treatment for sleep apnea. o Provide specific treatment for sleep apnea without reducing opioid dose. o Reduce opioid dose and provide specific treatment for apnea. • As there is a high prevalence of secondary hypogonadism in this patient population, clinicians treating men using chronic opioid therapy should consider an evaluation for hypogonadism. Clinicians should advise patients who are diagnosed with opioid-induced hypogonadism regarding the potential short-term adverse effects, including reduced sexual function, amenorrhea, fatigue, mood changes and the long-term risk of osteoporosis. Patients should be offered opioid tapering as the initial strategy to correct hypogonadism. If opioid tapering is unsuccessful or declined, clinicians may offer testosterone supplementation therapy. • Risk mitigation o Systematic reviews found only low or very low quality evidence regarding strategies intended to reduce the adverse impact of opioid prescribing. o A baseline urine drug screen may be useful for patients currently receiving or being considered for a trial of opioids. Clinicians may repeat urine drug screening on an annual basis and more frequently if the patient is at elevated risk or in the presence of any aberrant drug-related behaviors. o Approximately 30% of urine drug screening will demonstrate aberrant results, largely because of prescribed opioid non-detection and tetrahydrocannabinol. o A written treatment agreement may be useful in structuring a process of informed consent around opioid use, clarifying expectations for both patient and physician, and providing clarity regarding the nature of an opioid trial with endpoints, goals, and strategies in event of a failed trial. o When available and affordable, tamper-resistant formulations may be used to reduce the risks of altering the intended delivery system (i.e., from oral to nasal or intravenous injection). They do not reduce the most common mode of misuse (oral ingestion), but are less favored by people who misuse opioids by any route. o When prescribing fentanyl or other drugs dispensed in a transdermal patch preparation, it may be advisable to ask patients to return used patches to the pharmacy when presenting for the next dispensing. o Clinicians may provide naloxone to patients receiving opioids for chronic pain who are identified as at risk due to high dose, medical history, or

Clinical Guideline	Recommendation(s)
	comorbidities.
Veterans Affairs/ Department of Defense: **Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (2017)**[22]	Initiation and Continuation of Opioids • Initiation of long-term opioid therapy for chronic pain is not recommended. • Alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments are recommended. • When pharmacologic therapies are used, nonopioids are recommended over opioids. • If prescribing opioid therapy for patients with chronic pain, a short duration is recommended. • Note: Consideration of opioid therapy beyond 90 days requires reevaluation and discussion with patient of risks and benefits. • For patients currently on long-term opioid therapy, ongoing risk mitigation strategies, assessment for opioid use disorder, and consideration for tapering when risks exceed benefits are recommended. • Long-term opioid therapy for pain in patients with untreated substance use disorder is not recommended. • For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering are recommended. • The concurrent use of benzodiazepines and opioids is not recommended. • Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate. • Long-term opioid therapy for patients <30 years of age secondary to higher risk of opioid use disorder and overdose is not recommended. • For patients <30 years of age currently on long-term opioid therapy, close monitoring and consideration for tapering when risks exceed benefits are recommended. • In general, no single opioid or opioid formulation is preferred over the others. Risk Mitigation • Implementing risk mitigation strategies upon initiation of long-term opioid therapy is recommended, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include: o Ongoing, random urine drug testing (including appropriate confirmatory testing). o Checking state prescription drug monitoring programs. o Monitoring for overdose potential and suicidality. o Providing overdose education. o Prescribing of naloxone rescue and accompanying education. • Assess suicide risk when considering initiating or continuing long-term opioid therapy and intervene when necessary. • Evaluate benefits of continued opioid therapy and risk for opioid-related adverse events at least every three months. Type, Dose, Follow-up, and Taper of Opioids • If prescribing opioids, prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits is recommended. Note: There is no absolutely safe dose of opioids. • As opioid dosage and risk increase, more frequent monitoring for adverse events including opioid use disorder and overdose is recommended. Note: o Risks for opioid use disorder start at any dose and increase in a dose dependent manner.

Clinical Guideline	Recommendation(s)
	○ Risks for overdose and death significantly increase at a range of 20 to 50 mg morphine equivalent daily dose. • Opioid doses over 90 mg morphine equivalent daily dose is not recommended for treating chronic pain. • Note: For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate for tapering to reduced dose or to discontinuation. • Prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy is not recommended. • Tapering to reduced dose or to discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits is recommended. • Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns. • Individualize opioid tapering based on risk assessment and patient needs and characteristics. • Note: There is insufficient evidence to recommend for or against specific tapering strategies and schedules. • Interdisciplinary care that addresses pain, substance use disorders, and/or mental health problems for patients presenting with high risk and/or aberrant behavior is recommended. • Offer medication assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder. Note: See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. <u>Opioid Therapy for Acute Pain</u> • Alternatives to opioids are recommended for mild-to-moderate acute pain. • Use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain is suggested. • If take-home opioids are prescribed, immediate-release opioids are recommended at the lowest effective dose with opioid therapy reassessment no later than three to five days to determine if adjustments or continuing opioid therapy is indicated. • Note: Patient education about opioid risks and alternatives to opioid therapy should be offered.
Veterans Affairs/ Department of Defense: **Clinical Practice Guideline for Management of Substance Use Disorders (2021)**[23]	<u>Opioid use disorder- pharmacotherapy</u> • For patients with opioid use disorder, offering one of the following medications considering patient preferences is recommended: ○ Buprenorphine/naloxone ○ Methadone in an Opioid Treatment Program • For patients with opioid use disorder, we suggest offering extended-release naltrexone. • There is insufficient evidence to recommend any one of the different FDA-approved formulations or routes of delivery of buprenorphine over another. • There is insufficient evidence to recommend for or against oral naltrexone for the treatment of opioid use disorder. <u>Opioid use disorder- psychosocial interventions</u> • For patients receiving medication treatment for opioid use disorder, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused Medical Management. • For patients with opioid use disorder for whom opioid use disorder pharmacotherapy is contraindicated, unacceptable, or unavailable, there is insufficient evidence to recommend for or against any specific psychosocial interventions. <u>Opioid use disorder- stabilization and withdrawal</u> • For patients with opioid use disorder, we recommend against withdrawal

Clinical Guideline	Recommendation(s)
	management, without planned ongoing pharmacotherapy treatment, due to high risk of relapse and overdose. • For patients with opioid use disorder for whom opioid withdrawal management is indicated, buprenorphine/naloxone (in any setting) or methadone or buprenorphine/naloxone (in inpatient or accredited opioid treatment programs) are suggested. • For patients with opioid use disorder for whom withdrawal management is indicated and for whom methadone and buprenorphine are contraindicated, unacceptable, or unavailable, we suggest offering clonidine or lofexidine as a second-line agent for opioid withdrawal management.
Center for Substance Abuse Treatment: **Medications for Opioid Use Disorder (TIP 63) (2021)**[17]	Introduction to Medications for Opioid Use Disorder (OUD) Treatment • Increasing opioid overdose deaths, illicit opioid use, and prescription opioid misuse constitute a public health crisis. • OUD medications reduce illicit opioid use, retain people in treatment, and reduce risk of opioid overdose death better than treatment with placebo or no medication. • Only physicians; nurse practitioners; physician assistants; and, until October 1, 2023, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives can prescribe buprenorphine for OUD. They must get a federal waiver to do so. • Only federally certified, accredited opioid treatment programs (OTPs) can dispense methadone to treat OUD. OTPs can administer and dispense buprenorphine without a federal waiver. • Any prescriber can offer naltrexone. • OUD medication can be taken on a short- or long-term basis, including as part of medically supervised withdrawal and as maintenance treatment. • Patients taking medication for OUD are considered to be in recovery. • Several barriers contribute to the underuse of medication for OUD. Addressing Opioid Use Disorder in General Medical Settings • All healthcare practices should screen for alcohol, tobacco, and other substance misuse (including opioid misuse). • Validated screening tools, symptom surveys, and other resources are readily available. • When patients screen positive for risk of harm from substance use, practitioners should assess them using tools that determine whether substance use meets diagnostic criteria for a substance use disorder (SUD). • Thorough assessment should address patients' medical, social, SUD, and family histories. • Laboratory tests can inform treatment planning. • Practitioners should develop treatment plans or referral strategies (if onsite SUD treatment is unavailable) for patients who need SUD treatment. Medications for Opioid Use Disorder • OUD medications are safe and effective when used appropriately. • OUD medications can help patients reduce or stop illicit opioid use and improve their health and functioning. • Pharmacotherapy should be considered for all patients with OUD. Opioid pharmacotherapies should be reserved for those with moderate-to-severe OUD with physical dependence. • Patients with OUD should be informed of the risks and benefits of pharmacotherapy, treatment without medication, and no treatment. • Patients should be advised on where and how to get treatment with OUD medication. • Doses and schedules of pharmacotherapy must be individualized.

Clinical Guideline	Recommendation(s)
	• There are three FDA-approved medications used to treat OUD, including the mu-opioid receptor partial agonist buprenorphine, the mu-opioid receptor full agonist methadone, and the mu-opioid receptor antagonist naltrexone. Extended-release naltrexone (XR-NTX) is FDA approved to prevent relapse in patients who have remained opioid abstinent for sufficient time. o Methadone retains patients in treatment and reduces illicit opioid use more effectively than placebo, medically supervised withdrawal, or no treatment. o XR-NTX has demonstrated efficacy in reducing return to illicit opioid use, increasing treatment retention, and reducing opioid craving compared with placebo or no medication. o XR-NTX initiated prior to release from controlled environments (e.g., jails, prisons, residential rehabilitation programs) may be useful in preventing return to opioid use after release. o The oral formulation of naltrexone is not widely used to treat OUD because of low rates of patient acceptance and high rates of nonadherence leading to a lack of efficacy. o Buprenorphine is effective in retaining patients in treatment and reducing illicit opioid use. o Buprenorphine is a partial agonist with a ceiling effect on opioid activity. Hence, it is less likely than methadone and other full agonists to cause respiratory depression in an accidental overdose. o Currently, no empirical data indicate which patients will respond better to which OUD medications. All patients considering treatment should be educated about the effectiveness, risks, and benefits of each of the three OUD medications, treatment without medication, and no treatment. <u>Partnering Addiction Treatment Counselors with Clients and Healthcare Professionals</u> • Many patients taking OUD medication benefit from counseling as part of treatment. • Counselors play the same role for clients with OUD who take medication as for clients with any other SUD. • Counselors help clients recover by addressing the challenges and consequences of addiction. • OUD is often a chronic illness requiring ongoing communication among patients and providers to ensure that patients fully benefit from both pharmacotherapy and psychosocial treatment and support. • OUD medications are safe and effective when prescribed and taken appropriately. • Medication is integral to recovery for many people with OUD. Medication usually produces better treatment outcomes than outpatient treatment without medication. • Supportive counseling environments for clients who take OUD medication can promote treatment and help build recovery capital.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the opiate partial agonists are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Opiate Partial Agonists[6-13]

Indication	Single Entity Agents			Combination Products	
	Buprenorphine*	Butorphanol	Nalbuphine	Buprenorphine and Naloxone*	Pentazocine and Naloxone
Analgesia					
Management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate	✔ †	✔	✔		✔
Relief of pain during labor		✔ †	✔		
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate	✔ ‡^				
Anesthesia					
Preoperative or preanesthetic medication		✔ †	✔		
Supplement to surgical anesthesia		✔ †	✔		
Opioid Dependence					
Treatment of opioid use disorder	✔ §¶			✔ §‖	

*Buprenorphine and naloxone sublingual film should be used in patients who have been initially inducted using buprenorphine sublingual tablets. Zubsolv® sublingual tablet has been approved for the induction and maintenance treatment of opioid dependence. Buprenorphine contains no naloxone and is preferred for use during induction. Following induction, buprenorphine and naloxone due to the presence of naloxone, is preferred when clinical use includes unsupervised administration. The use of buprenorphine for unsupervised administration should be limited to those patients who cannot tolerate buprenorphine and naloxone (e.g., those patients who have been shown to be hypersensitive to naloxone).
†Injection formulation.
‡Transdermal patch.
§Sublingual tablet.
‖ Sublingual film.
^Buccal film.
¶ Extended-release subcutaneous solution.

IV. Pharmacokinetics

The pharmacokinetic parameters of the opiate partial agonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Opiate Partial Agonists[6-13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Buprenorphine	Buccal: 46 to 65 Injection: 90 to 100 SL: 31	96	Liver	Renal (27 to 30) Feces (69 to 70)	Buccal: 24 to 48 Injection:

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
	TD: 15				1.2 to 7.2 SL: 31 to 35 SubQ: 43 to 60 days TD: 26
Butorphanol	Oral: 17 Intranasal: 69	80 to 83	Liver	Renal (70 to 80) Feces (15)	4 to 7
Nalbuphine	Not reported	Not reported	Liver	Renal (7) Feces (not reported)	5
Combination Products					
Buprenorphine and naloxone	B: 15 N: 3	B: 96 N: 45	Liver	B: Renal (30) B: Feces (69) N: Not reported	B: 33 to 37 N: 1 to 6
Pentazocine and naloxone	N: 3 P: Not reported	N: 45 P: 60	Liver	N: Not reported P: Renal (60 to 70) P: Feces (<2)	N: 1 to 6 P: 2 to 10

A=acetaminophen, B=buprenorphine, N=naloxone, P=pentazocine, SL=sublingual, TD=transdermal

V. Drug Interactions

Major drug interactions with the opiate partial agonists are listed in Table 5.

Table 5. Major Drug Interactions with the Opiate Partial Agonists[7]

Generic Name(s)	Interaction	Mechanism
Buprenorphine	Azole antifungals	The pharmacologic effects and adverse reactions of certain opioids may be increased due to possible inhibition of certain opioid analgesic metabolism (CYP3A4) by azole antifungal agents.
Opiate partial agonists (buprenorphine, butorphanol, nalbuphine, pentazocine)	Benzodiazepines	Synergistic effects of opioids and benzodiazepines increase the risk of sedation and life-threatening respiratory depression, especially with overdosage.
Buprenorphine	Cyclobenzaprine	Concurrent use of buprenorphine and cyclobenzaprine may result in increased risk of serotonin syndrome, respiratory depression, and QT prolongation.
Buprenorphine	Macrolide and related antibiotics	Opioid plasma concentrations may be elevated due to inhibition of opioid analgesic metabolism (CYP3A4) by macrolide and related antibiotics, increasing the pharmacologic effects and toxicity.
Opiate partial agonists (buprenorphine, butorphanol, nalbuphine, pentazocine)	Monoamine oxidase inhibitors	Concurrent use of opiate partial agonists and monoamine oxidase inhibitors may result in increased risk of serotonin syndrome or opioid toxicity.
Buprenorphine	Protease inhibitors	Opioid plasma concentrations may be increased and the half-life prolonged, increasing the risk of adverse reactions (e.g., respiratory depression) due to possible inhibition of opioid metabolism (CYP3A4) in the gut wall and liver.
Opiate partial agonists (buprenorphine, butorphanol, nalbuphine, pentazocine)	Serotonergic agents	Concurrent use of opiate partial agonists and serotonergic agents may result in increased risk of serotonin syndrome.
Buprenorphine	Ziprasidone,	Concurrent use of buprenorphine and selected antipsychotics

Generic Name(s)	Interaction	Mechanism
	lurasidone	may result in increased risk of QT-interval prolongation and respiratory and CNS depression.
Opiate partial agonists (buprenorphine, butorphanol, nalbuphine, pentazocine)	Barbiturate anesthetics	The combination of barbiturate anesthetics and opiate partial agonists may result in increased respiratory and central nervous system depressive effects.
Opiate partial agonists (buprenorphine, butorphanol, nalbuphine)	Opioid Agonists	Narcotic antagonists and agonist-antagonists may decrease or attenuate the pharmacologic effects of opioid agonists. Precipitation of withdrawal symptoms in those dependent on opioid drugs may occur.

VI. Adverse Drug Events

The most common adverse drug events reported with the opiate partial agonists are listed in Table 6. The boxed warnings for the opiate partial agonists are listed in Tables 7 through 11.

Table 6. Adverse Drug Events (%) Reported with the Opiate Partial Agonists[6-13]

Adverse Events	Single Entity Agents			Combination Products	
	Buprenorphine	Butorphanol	Nalbuphine	Buprenorphine and Naloxone	Pentazocine and Naloxone
Cardiovascular					
Bradycardia	-	-	≤1	-	-
Circulatory depression/collapse	-	-	-	-	✔
Flushing	-	-	-	-	✔
Hypertension	<1 to 5	-	≤1	<1	✔
Hypotension	1 to 5	<1	≤1	✔	✔
Palpitation	-	>1	-	-	-
Syncope	-	<1	-	-	✔
Systemic vascular resistance	-	-	-	-	-
Tachycardia	<1	-	≤1	<1	✔
Vasodilation	4 to 10	>1	-	9	-
Central Nervous System					
Abnormal dreams	-	<1	≤1	-	✔
Agitation	<1	<1	<1	-	-
Anxiety	<5 to 12	>1	<1	✔	-
Asthenia	5 to 7	>1	-	✔	-
Chills	2	-	-	-	✔
Coma	<1	-	-	<1	-
Confusion	<1	>1	≤1	<1	✔
Depersonalization	<1	-	-	<1	-
Depression	<5 to 11	-	≤1	<1	✔
Disorientation	-	-	-	-	✔
Dizziness	4 to 10	19	5	✔	✔
Drowsiness	3	43	-	✔	✔
Dysphoria	-	<1	≤1	-	-
Euphoria	<1	>1	≤1	>1	✔
Fatigue	<1 to 5	-	-	-	-
Foot drop	-	<1	-	<1	-
Hallucinations	<1	-	≤1	-	✔
Headache	13 to 36	>1	3	>1	✔
Hostility/irritability	-	<1	≤1	<1	✔

Adverse Events	Single Entity Agents			Combination Products	
	Buprenorphine	Butorphanol	Nalbuphine	Buprenorphine and Naloxone	Pentazocine and Naloxone
Impairment of performance	-	-	-	-	✔
Insomnia	<5 to 22	11	-	✔	✔
Nervousness	6	>1	≤1	<1	-
Nightmares	-	-	-	-	✔
Paresthesia	<1	>1	-	<1	✔
Psychosis	<1	-	-	<1	-
Restlessness	-	-	≤1	✔	-
Sedation	✔	-	✔	-	✔
Seizures	<1	-	-	<1	✔
Tremor	<1	>1	-	<1	✔
Weakness	<1	-	-	<1	✔
Withdrawal syndrome	<5 to 27	<1	-	✔	-
Dermatological					
Edema at implant site	5*	-	-	-	-
Erythema multiforme	10*	-	-	-	✔
Pruritus	<1 to 12	>1	≤1	<1	✔
Rash	<1 to 2	-	-	<1	✔
Skin discoloration	-	>1	-	-	-
Stevens-Johnson syndrome	-	-	-	-	✔
Toxic epidermal necrolysis	-	-	-	-	✔
Urticaria	<1	<1	≤1	<1	✔
Wheal/flare	-	-	-	-	✔
Gastrointestinal					
Abdominal pain	-	-	<1	11	✔
Abnormal liver function tests	12	>1	-	✔	-
Anorexia	-	-	-	-	✔
Appetite decreased	<1	-	-	<1	-
Appetite increased	-	>1	-	-	-
Biliary spasm	-	-	-	-	✔
Constipation	6	-	-	12	✔
Cramps	8 to 13	>1	-	✔	✔
Dry mouth	<1	-	4	<1	✔
Diarrhea	<1	-	4	✔	✔
Dyspepsia	4 to 5	-	-	✔	-
Dysphagia	-	-	≤1	-	-
Flatulence	<1	-	-	<1	-

Adverse Events	Single Entity Agents			Combination Products	
	Buprenorphine	Butorphanol	Nalbuphine	Buprenorphine and Naloxone	Pentazocine and Naloxone
Hepatitis	-	-	-	✔	-
Nausea	6	13	6	15	✔
Oral moniliasis	14 to 16		6	-	✔
Vomiting	1 to 6	-	6	7	✔
Weight loss	8	-	6	-	✔
Genitourinary					
Urinary retention	<1	-	-	<1	✔
Urinary urgency	-	<1	-	-	✔
Urinary tract infection	-	-	≤1	-	-
Respiratory					
Apnea	<1	-	-	<1	-
Bronchitis	-	-	≤1	-	-
Bronchospasm	-	-	-	✔	-
Cough	3	>1	-	-	-
Dyspnea	1	-	-	<1	✔
Epistaxis	-	>1	-	-	-
Hemoptysis	<1	>1	≤1	<1	✔
Hiccoughs	-	>1	-	-	-
Pharyngitis	-	-	-	✔	-
Pulmonary edema	-	-	-	✔	-
Respiratory insufficiency	-	-	≤1	-	✔
Respiratory depression	✔	-	-	-	✔
Rhinitis	-	-	-	✔	-
Sputum increased	5 to 10	>1	-	-	-
Stertorous breathing	-	>1	-	-	-
Other					
Agranulocytosis	-	-	-	-	✔
Allergic laryngeal edema	1 to 2	-	-	-	-
Allergic laryngospasm	3	-	-	-	-
Allergic reaction	<1	-	<1	✔	-
Anaphylaxis	-	-	<1	✔	✔
Back pain	6	-	✔	✔	✔
Bone pain	4 to 8	-	-	-	-
Blurred vision	<1	-	-	<1	-
Carcinoma	>1	>1	≤1	-	✔
Chills	-	-	-	✔	-

Adverse Events	Single Entity Agents			Combination Products	
	Buprenorphine	Butorphanol	Nalbuphine	Buprenorphine and Naloxone	Pentazocine and Naloxone
Cyanosis	<1	-	-	<1	-
Dehydration	8	-	-	-	-
Diaphoresis	13 to 15	-	9	14	✔
Diplopia	<1	-	-	<1	-
Dysgeusia	<1	-	-	<1	-
Ear pain	-	>1	-	-	-
Edema	-	>1	-	-	-
Eosinophilia	-	-	-	-	✔
Facial edema	-	-	-	-	✔
Fever	3	-	-	✔	-
Flu syndrome	-	-	-	✔	-
Flushing	<1	-	-	<1	-
Hemorrhage at implant site	7*	-	-	-	-
Hyperacusis	6	-	-	-	-
Infection	-	-	-	✔	-
Intraoperative muscle movement	6 to 12	-	-	-	-
Lacrimation disorder	<1	-	-	✔	✔
Leukopenia	-	-	-	-	✔
Malaise	<1	-	-	<1	✔
Miosis	5	-	-	-	✔
Neck pain	1 to 5	-	-	-	-
Pain	-	-	-	22	-
Pallor	<1	-	-	<1	-
Pelvic pain	19 to 24	-	-	-	-
Slurred speech	<1	-	-	<1	-
Tinnitus	<1	-	-	<1	✔
Visual disturbances	-	>1	-	-	✔
Weakness	<1	-	-	<1	-

✔ Percent not specified.
- Event not reported.
• Subdermal implant formulation.

Table 7. Boxed Warning for buprenorphine buccal, injection, transdermal[6]

WARNING
Addiction, Abuse, and Misuse Buprenorphine exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing buprenorphine, and monitor all patients regularly for the development of these behaviors or conditions. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of buprenorphine. Monitor for respiratory depression, especially during initiation of buprenorphine or following a dose increase. Misuse or abuse of buprenorphine by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal/buccal system will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death. Accidental Exposure Accidental exposure to even one dose of buprenorphine, especially by children, can result in a fatal overdose of buprenorphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of buprenorphine during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. • Reserve concomitant prescribing of buprenorphine and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. • Limit dosages and durations to the minimum required. • Follow patients for signs and symptoms of respiratory depression and sedation.

Table 8. Boxed Warning for buprenorphine extended-release injection (Sublocade®)[9]

WARNING
WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously. Because of the risk of serious harm or death that could result from intravenous self-administration, SUBLOCADE is only available through a restricted program called the SUBLOCADE REMS Program. Healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified in this program and comply with the REMS requirements.

Table 9. Boxed Warning for Butorphanol[6]

WARNING
Addiction, Abuse, and Misuse Butorphanol Tartrate Nasal Spray exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Butorphanol Tartrate Nasal Spray, and monitor all patients regularly for the development of these behaviors and conditions. Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Butorphanol Tartrate Nasal Spray. Monitor for respiratory depression, especially during initiation of Butorphanol Tartrate Nasal Spray or following a dose increase.

Accidental Exposure
Accidental Exposure of butorphanol, especially by children, can result in a fatal overdose of butorphanol.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Butorphanol Tartrate Nasal Spray during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Butorphanol Tartrate Nasal Spray with all cytochrome P450 3A4 inhibitors may result in an increase in butorphanol plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in butorphanol plasma concentration. Monitor patients receiving Butorphanol Tartrate Nasal Spray and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Butorphanol Tartrate Injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Table 10. Boxed Warning for Nalbuphine[6]

WARNING
Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Nalbuphine Hydrochloride Injection, particularly when used concomitantly with other opioids or central nervous system depressants. Monitor for respiratory depression, especially during initiation of Nalbuphine Hydrochloride Injection or following a dose increase. Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. • Reserve concomitant prescribing of nalbuphine hydrochloride and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. • Limit dosages and durations to the minimum required. • Follow patients for signs and symptoms of respiratory depression and sedation.

Table 11. Boxed Warning for Pentazocine and Naloxone[6]

WARNING
Addiction, abuse, and misuse Pentazocine/naloxone exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing pentazocine/naloxone, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening respiratory depression Serious, life-threatening, or fatal respiratory depression may occur with use of pentazocine/naloxone. Monitor for respiratory depression, especially during initiation of pentazocine and naloxone tablets or following a dose

increase.

Accidental ingestion
Accidental ingestion of even one dose of pentazocine/naloxone, especially by children, can result in a fatal overdose of pentazocine.

Neonatal opioid withdrawal syndrome
Prolonged use of pentazocine/naloxone during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 interaction
The concomitant use of pentazocine/naloxone with all cytochrome P450 3A4 inhibitors may result in an increase in pentazocine plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in pentazocine plasma concentration. Monitor patients receiving pentazocine/naloxone and any CYP3A4 inhibitor or inducer.

Risks from concomitant use with benzodiazepines or other CNS depressants
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of pentazocine/naloxone and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

VII. Dosing and Administration

The usual dosing regimens for the opiate partial agonists are listed in Table 12.

Table 12. Usual Dosing Regimens for the Opiate Partial Agonists[6-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Buprenorphine	Opioid dependence: Extended-release injection*: the recommended dose following induction and dose adjustment with transmucosal buprenorphine is 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly; only healthcare providers should prepare and administer the injection; administer monthly with a minimum of 26 days between doses Sublingual tablet: induction, buprenorphine sublingual tablets contain no naloxone and are preferred for use during induction; following induction, buprenorphine and naloxone is preferred when clinical use	Opioid dependence ≥16 years of age: Sublingual tablet: induction, buprenorphine sublingual tablets contain no naloxone and are preferred for use during induction; following induction, buprenorphine and naloxone is preferred when clinical use includes unsupervised administration because of the presence of naloxone; initial, 8 mg on day one and 16 mg on day two; from day three onward, patients received buprenorphine and naloxone at the same buprenorphine dose as day two; maintenance, 12 to 16 mg as a single dose	Buccal film: 75 µg 150 µg 300 µg 450 µg 600 µg 750 µg 900 µg Extended-release injection: 100 mg/ 0.5 mL 300 mg/ 1.5 mL Injection: 0.3 mg/mL Sublingual tablet: 2 mg 8 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	includes unsupervised administration because of the presence of naloxone; initial: 8 mg on day one and 16 mg on day two; from day three onward, patients received buprenorphine and naloxone at the same buprenorphine dose as day two; maintenance, 12 to 16 mg as a single dose Moderate to severe pain: Buccal film: Initiate treatment in opioid-naïve and opioid-non-tolerant patients with a 75 µg film once daily or, if tolerated, every 12 hours for at least 4 days, then increase dose to 150 µg every 12 hours; individualize dose by titrating in increments of 150 µg every 12 hours, no more frequently than every 4 days; maximum, 900 µg every 12 hours Injection: 0.3 mg administered IM or slow IV (over 2 minutes) every six hours as needed; an additional dose of up to 0.3 mg may be given 30 to 60 minutes following initial dose, if needed; dosage may be increased to 0.6 mg (IM only) Transdermal patch: intended to be worn for seven days; in patients with prior daily dose of opioids <30 mg of oral morphine equivalents per day: initial, 5 µg/hr transdermally; titrate based on analgesic requirement and tolerance at a minimum interval of every 72 hours; maximum, 20 µg/hr transdermally; in patients with prior daily dose of opioids between 30 and 80 mg of oral morphine equivalents per day: initial, 10 µg/hr transdermally; titrate based on analgesic requirement and tolerance at a minimum interval of every 72 hours; maximum, 20 µg/hr transdermally	Moderate to severe pain: Injection: two to 12 years of age, 2 to 6 µg/kg administered IM or slow IV (over 2 minutes) every four to six hours as needed; >13 years of age, 0.3 mg administer IM or slow IV (over 2 minutes) every six hours as needed; an additional dose of up to 0.3 mg may be given 30 to 60 minutes following initial dose, if needed; dosage may be increased to 0.6 mg (IM only)	Transdermal patch: 5 µg/hr 7.5 µg/hr 10 µg/hr 15 µg/hr 20 µg/hr
Butorphanol	Analgesia: Injection: IV, 1 mg IV every three to four hours as needed; IM, 2 mg IM every three to four hours as needed; pre-op, 2 mg IM given 60	Safety and efficacy in children have not been established.	Injection: 1 mg/mL 2 mg/mL Nasal spray:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	to 90 minutes before surgery Nasal spray: one spray (1 mg) in one nostril, an additional dose within 60 to 90 minutes may be given if adequate pain relief is not achieved, the two-dose sequence can be given every three to four hours as needed.		10 mg/mL
Nalbuphine	Analgesia: Injection: 10 mg administered SC, IM, or IV every three to six hours as needed Anesthesia supplement: Injection: 0.3 mg/kg IV given over a 10 to 15 minute period initially, then 0.25 mg to 0.5 mg/kg as a single IV administration for maintenance	Safety and efficacy in children have not been established.	Injection: 10 mg/mL 20 mg/mL
Combination Products			
Buprenorphine and naloxone	Opioid dependence: Sublingual film: the film should be used in patients who have been initially inducted using buprenorphine sublingual tablets, for maintenance treatment, the recommended dose is 16-4 mg buprenorphine and naloxone per day administered as a single dose; the dose should be adjusted in increments of 2-0.5 mg or 4-1 mg buprenorphine and naloxone; the usual dose range is 4-1 mg to 24-6 mg buprenorphine and naloxone per day Sublingual tablet (Suboxone®): Buprenorphine and naloxone sublingual tablets should be used in patients who have been initially inducted using buprenorphine sublingual tablets; for maintenance treatment, the recommended target dose is 16-4 mg daily as a single dose; the dose should be adjusted in increments of 2-0.5 mg or 4-1 mg; the usual dose range is 4-1 mg to 24-6 mg per day Sublingual tablet (Zubsolv®): Induction, to avoid precipitating an opioid withdrawal syndrome, the first dose of buprenorphine-naloxone should be administered	Opioid dependence: Patients ≥16 years of age: dosing same as adult use	Sublingual film: 2-0.5 mg 4-1 mg 8-2 mg 12-3 mg Sublingual tablet (Suboxone®, generic): 2-0.5 mg 8-2 mg Sublingual tablet (Zubsolv®): 0.7-0.18 mg 1.4-0.36 mg 2.9-0.71 mg 5.7-1.4 mg 8.6-2.1 mg 11.4-2.9 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	only when objective and clear signs of moderate withdrawal are evident, and divided doses should be used, on day one an induction dosage of 5.7-1.4 mg is recommended given in divided doses under supervision beginning with a 1.4-0.36 mg sublingual tablet, on day 2 a single daily dose of up to 11.4-2.9 mg is recommended; for maintenance treatment, the recommended target dose is 11.4-2.9 mg daily as a single dose; the dose should be adjusted in increments of 1.4-0.36 mg or 2.9-0.71 mg; the usual dose range is 2.9-0.71 mg to 17.2-4.2 mg per day		
Pentazocine and naloxone	Analgesia: Tablet: 50-0.5 mg (one tablet) every three to four hours; may increase to two tablets if necessary; maximum, 12 tablets/day	Analgesia ≥12 years of age: Tablet: 50-0.5 mg (one tablet) every three to four hours; may increase to two tablets if necessary; maximum, 12 tablets/day	Tablet: 50-0.5 mg

IM=Intramuscular, IV=Intravenous, SC=Subcutaneous
*Extended-release injection is appropriate for patients who have initiated treatment on a transmucosal buprenorphine-containing product delivering the equivalent of 8 to 24 mg of buprenorphine daily. The patient may only be transitioned to Sublocade after a minimum of 7 days.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the opiate partial agonists are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Opiate Partial Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Analgesia				
Rauck et al.[24] (2016) Buprenorphine buccal film (Belbuca®) 150 to 450 µg every 12 hours vs placebo	DB, MC, PC, RCT Opioid-naïve patients ≥18 years of age with moderate to severe chronic low back pain requiring around-the-clock analgesia	N=749 8 week titration phase; 12 week DB treatment phase	Primary: Change from baseline to week 12 of treatment in the mean of daily average pain intensity scores (numeric rating scale from 0 [no pain] to 10 [worst pain imaginable]) Secondary: Proportion of patients with ≥30% reduction or a ≥50% reduction in numeric rating scale score (responder analyses), the use of non-opioid and opioid rescue medication, safety	Primary: The mean ± SD increase at week 12 from baseline in numeric rating scale pain intensity scores was greater in patients treated with placebo (1.59 ± 2.04) compared with those continuing with buprenorphine (0.94 ± 1.85; P=0.0012); the mean treatment difference was −0.67 (95% CI, −1.07 to −0.26). Secondary: A significantly greater (P=0.0012) proportion of patients treated with buprenorphine compared with patients treated with placebo were considered responders at the ≥30% level of pain reduction. The proportion of those with ≥50% pain reduction was not significantly different for buprenorphine (41%) versus placebo (33%; P=0.0754). Patients in the placebo group used rescue medications more frequently (ranging from 77% at week one to 40% at week 12) than those in the buprenorphine group (ranging from 68% at week one to 31% at week 12) during the double-blind treatment phase. Significantly (P<0.05) fewer patients receiving buprenorphine used rescue medications at weeks two, three, six, eight, and 10. The most frequently reported treatment-related adverse events with buprenorphine during titration were nausea (47.3%), constipation (12.4%), somnolence (6.8%), vomiting (6.1%), dizziness (5.7%) and headache (5.2%). During the double-blind treatment phase, the percent of patients reporting any adverse event was similar between patients treated with buprenorphine (41.0%) or placebo (43.5%).
Gimbel et al.[25] (2016) Buprenorphine buccal film	DB, MC, PC, RCT Opioid-experienced (30 to ≤160 mg/day morphine sulfate	N=511 8 week titration phase; 12 week DB	Primary: Change from baseline to week 12 of treatment in the mean of daily	Primary: From baseline to week 12, mean (SD) numeric rating scale pain scores increased significantly more in the placebo group (1.92 [1.87]) than in the buprenorphine group (0.88 [1.79]), with a between-group difference (favoring buprenorphine) of −0.98 (95% CI, −1.32 to −0.64; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Belbuca®) 150 to 900 µg every 12 hours vs placebo	equivalent) patients ≥18 years of age with moderate to severe chronic low back pain requiring around-the-clock analgesia	treatment phase	average pain intensity scores (numeric rating scale from 0 [no pain] to 10 [worst pain imaginable]) Secondary: Proportion of patients with ≥30% reduction or a ≥50% reduction in numeric rating scale score (responder analyses), rescue medication use, safety	Compared with patients in the placebo group, patients in the buprenorphine group had significantly lower pain scores at week one and at all subsequent weekly time points through week 12. Secondary: A significantly greater proportion of patients in the buprenorphine group compared with the placebo group were classified as responders based on achieving ≥30% pain reduction (buprenorphine group, 64.2%; placebo group, 30.6%; P<0.001) or ≥50% pain reduction (buprenorphine group, 39.5%; placebo group, 16.9%; P<0.001). Consistent with this, the percentage of patients using rescue medication at week 12 was significantly lower in the buprenorphine group than in the placebo group (P<0.001). Significant differences between groups were also observed for patient-reported outcomes. Patient-reported impression of treatment benefit was significantly greater with buprenorphine: the mean (SD) Patient Global Impression of Change score at week 12 was 4.5 (1.86) in the buprenorphine group vs 3.2 (1.98) in the placebo group (treatment difference, 1.3; 95% CI, 0.9 to 1.6; P<0.001). Ninety-six (39.7%) patients in the buprenorphine group vs 49 (20.6%) in the placebo group showed a clinically meaningful improvement as indicated by a response of 6 or 7 on the Patient Global Impression of Change. During the double-blind period, adverse events were reported by 48% of patients, and 5.1% discontinued because of adverse events: 5 (2.0%) randomized to buprenorphine and 21 (8.2%) randomized to placebo. Serious adverse events were reported by 1.6% of patients, and there were no deaths. Discontinuation rates were 18.9% in the buprenorphine group and 42.8% in the placebo group. Discontinuations due to lack of efficacy were 7.5% in the buprenorphine group and 23.7% in the placebo group.
Zenz et al.[26] (1992) Buprenorphine, dihydrocodeine sustained release, and morphine sustained release	OL Patients receiving chronic opioids for treatment of non-malignant pain	N=100 Variable duration	Primary: Pain reduction with visual analogue scales; patient function using the Karnofsky Performance Status Scale	Primary: Good pain relief was obtained in 51 patients and partial pain relief was reported by 28 patients. Only 21 patients had no beneficial effect from opioid therapy. There was a close correlation between the sum and the peak visual analogue scale values (P<0.0001) Pain reduction was associated with an increase in performance

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	(P<0.0001). Secondary: Not reported
Steiner et al.[27] (2011) Buprenorphine transdermal system 5 or 20 µg/hour every 7 days vs oxycodone immediate-release 10 mg every 6 hours	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age with clinical diagnosis of low back pain for ≥3 months, taking between 30 to 80 mg of oral morphine sulfate or opioid equivalent daily, at least 4 days a week, for ≥30 days prior to visit 1	N=1,160 12 weeks	Primary: Average pain score over the last 24 hours on an 11-point numerical pain scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine) at weeks four, eight and 12 Secondary: Treatment differences with respect to less sleep disturbances and the daily number of tablets of supplemental analgesic medication during DB period, and the Oswestry Disability Index at weeks four, eight, and 12	Primary: The protocol-specified analysis of the primary efficacy variable, in which missing values were not imputed, resulted in a statistically significant treatment difference of -0.67 between buprenorphine 20 and 5 µg/hour in favor of buprenorphine 20 µg/hour (P<0.001). The treatment difference of -0.75 between oxycodone immediate-release and buprenorphine 5 µg/hour in favor of oxycodone immediate release was also statistically significant (P<0.001). The four sensitivity analyses of the primary efficacy variable resulted in statistically significant treatment differences in favor of buprenorphine 20 µg/hour and oxycodone immediate-release compared to buprenorphine 5 µg/hour. Secondary: Treatment with buprenorphine 20 µg/hour led to statistically significant treatment differences with respect to less sleep disturbance (P<0.001) and decreased use of supplemental analgesic medication (P=0.006) compared to buprenorphine 5 µg/hour. The difference between buprenorphine 20 µg/hour and 5 µg/hour with respect to the Oswestry Disability Index was not statistically significant (P value not reported).
Gordon et al.[28] (2010) Buprenorphine transdermal system 5, 10, or 20 µg/hr	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years	N=79 DB: 8 weeks (XO at the end of week 4)	Primary: Average pain score over the last week on a five-point pain intensity scale ranging from 0 (no	Primary: In the intent-to-treat analysis, the average pain score reported by patients using the five-point scale at the last week of each treatment phase was 1.8±0.6 for buprenorphine and 2.0±0.7 for placebo (P=0.0226). When the pain score was reported using the visual analogue scale, the score was 40.2±20.2 for buprenorphine and 44.4±20.2 for placebo (P=0.0919).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
every 7 days vs placebo	of age with low back pain of at least moderate severity, not adequately controlled with non-opioid analgesic medications for ≥6 weeks	ES: 6 weeks	pain) to 4 (excruciating pain) and a visual analogue scale ranging from 0 mm (no pain) to 100 mm (excruciating pain) Secondary: PDI, Pain and Sleep Questionnaire, level of activity, Short Form-36, treatment effectiveness on a four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	Secondary: In the per-protocol analysis, when buprenorphine was compared to placebo at the last week of each treatment phase, there were no treatment differences with regard to improvement in any of the subscales or the total score of the PDI (results not reported; P=0.4860), the Pain and Sleep Questionnaire (172.4±122.8 vs 178.2±112.6; P value not reported), the level of activity (43.8±23.0 vs 43.9±23.7; P=0.9355) or the Short Form-36 (results not reported; P value not reported). There was no difference between the two treatment groups in patient- and investigator-rated treatment effectiveness at the end of each treatment phase. The patient-rated scores were 1.3±1.1 and 0.9±1.0 for buprenorphine and placebo, respectively (P=0.1782), while the investigator-rated scores were 1.2±1.0 and 0.9±1.0, respectively (P=0.1221). Forty-three percent of patients preferred the buprenorphine treatment phase, 38% of patients preferred the placebo phase and 19% of patients had no preference (P=0.6473). Similarly, 43% of investigators preferred buprenorphine for their patients, 36% of investigators preferred placebo and 21% of investigators had no preference (P=0.5371). More patients reported drowsiness with buprenorphine compared to placebo (P=0.0066). More patients reported at least one adverse event during treatment with buprenorphine compared to placebo (P=0.0143). The most commonly reported adverse events include nausea, somnolence and application site reactions. ES Phase: Forty-two of 51 patients (82%) who completed the DB phase continued to receive OL buprenorphine treatment. The average pain intensity score over the past 24 hours measured by visual analogue scale were significantly lower at the end of the ES phase compared to the DB phase (13.2±20.2 vs 39.5±19.1; P=0.0001). There were no differences between the ES and DB phases in the average pain score over the last week and all other study endpoints, with the exception of the standardized physical

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				component of the Short Form-36, which was significantly lower in the ES phase compared to the DB phase (P=0.0226).
Gordon et al.[29] (2010) Buprenorphine transdermal system 10 to 40 µg/hour every 7 days vs placebo	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with moderate to severe chronic low back pain for >3 months, requiring one or more tablet of opioid analgesics daily	N=78 DB: 8 weeks (XO at the end of week 4) ES: 6 months	Primary: Average pain score over the last 24 hours on a five-point pain intensity scale ranging from 0 (no pain) to 4 (excruciating pain) and a visual analogue scale ranging from 0 (no pain) to 100 mm (excruciating pain) Secondary: Pain and Sleep Questionnaire, PDI, Short Form-36, treatment effectiveness on a four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	Primary: In the intent-to-treat analysis, buprenorphine was associated with a lower average pain score over the last 24 hours compared to placebo. When reported using visual analogue scale, the pain score was 44.6±21.4 for buprenorphine and 52.4±24.0 for placebo (P=0.005). The score reported using the five-point scale was 2.0±0.7 and 2.2±0.8 for buprenorphine and placebo, respectively (P=0.016). Secondary: The overall score of the Pain and Sleep Questionnaire was significantly lower for buprenorphine compared to placebo (117.6±125.5 vs 232.9±131.9; P=0.027). No significant differences were noted between the two treatment groups with regard to the PDI and Short Form-36 (P value not reported for all endpoints). The treatment effectiveness of buprenorphine was rated significantly higher than placebo by patients (1.8±1.1 vs 1.0±1.1; P=0.016) and investigators (1.8±1.1 vs 1.0±1.1; P=0.013). Sixty-six percent of patients preferred the buprenorphine treatment phase, 24% of patients preferred the placebo phase and 10% of patients had no preference (P=0.001). Similarly, 60% of investigators preferred the buprenorphine treatment phase for their patients, 28% of investigators preferred the placebo phase and 12% of investigators had no preference (P=0.008). Significantly more patients in the buprenorphine group reported adverse events compared to patients in the placebo group (65.0 vs 64.7%; P=0.003). The most commonly reported adverse events with buprenorphine were nausea, dizziness, pruritus, vomiting, and somnolence. ES Phase:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Forty of 49 patients (81.6%) who completed the ES phase continued to receive OL buprenorphine treatment. The improvements in daily pain intensity, PDI and Short Form-36 were maintained throughout the ES phase.
Karlsson et al.[30] (2009) Buprenorphine transdermal system 5, 10, 15 or 20 µg/hour every 7 days vs tramadol prolonged-release 150 to 400 mg/day orally divided in two doses	AC, MC, OL, PG, RCT Patients ≥18 years of age with a clinical diagnosis of osteoarthritis of the hip and/or knee with suboptimal analgesia in the primary osteoarthritic joint in the week before visit 1	N=135 12 weeks	Primary: Mean weekly Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, sleep disturbance and quality of sleep assessment, patient-investigator-rated and global assessment of pain relief, patient preference and safety	Primary: In the intent-to-treat analysis, the least squares mean change from baseline in Box Scale-11 pain score at week 12 was -2.26 for buprenorphine and -2.09 for tramadol prolonged-release. The difference between the two treatment groups was -0.17 (95% CI, -0.89 to 0.54; P value not reported), which was within the non-inferiority margin, showing that buprenorphine was non-inferior to tramadol prolonged-release. Secondary: The mean number of supplemental analgesic medication used during the study was 206.4 tablets for buprenorphine and 203.7 tablets for tramadol prolonged-release. The difference between the two treatment groups did not reach statistical significance (P value not reported). There were no statistically significant differences in sleep disturbance and quality of sleep between the buprenorphine and tramadol prolonged-release groups (P value not reported). There were statistically significant differences in favor of buprenorphine compared to tramadol prolonged-release with regard to patient- and investigator-rated global assessment of pain relief (P=0.039 and P=0.020, respectively). Ninety of 128 patients (70.3%; 95% CI, 62 to 78) preferred a once-weekly patch as a basic analgesic treatment for osteoarthritis pain in the future. There were no differences between the two treatment groups in the total number of reported adverse events (P value not reported). The most commonly observed adverse events in the buprenorphine group were nausea (30.4%), constipation (18.8%) and dizziness (15.9%).
Conaghan et al.[31] (2011)	AC, MC, OL, PG, RCT	N=220 10 weeks of	Primary: Average pain score over the last 24	Primary: In the intent-to-treat analysis, the treatment difference between buprenorphine plus paracetamol and codeine-paracetamol with regard to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine transdermal system 5 to 25 µg/hour every 7 days plus paracetamol* 1,000 mg orally four times daily vs codeine-paracetamol* 8-500 mg or 30-500 mg orally one or two tablets four times daily	Patients ≥60 years of age with a clinical diagnosis of osteoarthritis of the hip and/or knee with severe pain and taking the maximum tolerated dose of paracetamol (four or more 500 mg tablets each day)	titration period followed by 12 weeks of assessment period	hours on Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, laxative use, sleep parameters on the Medical Outcome Study-Sleep Scale, time to achieve stable pain control, length of time on anti-emetics, discontinuation rate during the titration period and safety	the average daily pain score was -0.07 (95% CI, -0.67 to 0.54; P value not reported), demonstrating that buprenorphine plus paracetamol was non-inferior to codeine-paracetamol. Secondary: In the per-protocol analysis, patients receiving buprenorphine plus paracetamol required 33% fewer supplemental analgesic medications compared to those receiving codeine-paracetamol. The treatment difference was -0.98 (95% CI, -1.55 to -0.40; P=0.002). Fifty percent of patients in each treatment group required laxatives during the study (P value not reported). In the per-protocol analysis, the mean sleep disturbance score on the Medical Outcome Study-Sleep Scale decreased from 33.90±22.09 at baseline to 24.30±25.32 at the end of the study in the buprenorphine plus paracetamol group, while the score decreased from 41.8±28.6 to 32.9±26.1 in the codeine-paracetamol group (P value not reported). Patients receiving buprenorphine plus paracetamol reported improvement in sleep adequacy, with an increase in score from 50.80±25.35 at baseline to 62.50±28.26 at the end of the study, whereas the score increased from 56.10±25.84 to 59.10±26.41 in patients receiving codeine-paracetamol (P value not reported). There was no difference in the number of hours slept between the two groups. The number of patients with optimal sleep slightly increased in the buprenorphine plus paracetamol group and slightly decreased in the codeine-paracetamol group. The snoring score did not change with buprenorphine plus paracetamol and slightly improved with codeine-paracetamol. Neither treatment had any effect on shortness of breath, headache or somnolence (P values not reported for all parameters). The mean time to achieve stable pain control during the titration period was 19.5±11.5 days for buprenorphine plus paracetamol and 21.80±13.76 days for codeine-paracetamol (P value not reported).

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>The median percentage of days on which anti-emetics were used during the titration period was 18.5% (interquartile range, 0 to 70.6) for buprenorphine plus paracetamol and 0% (interquartile range, 0 to 26.8) for codeine-paracetamol (P value not reported).

Forty-three of 110 patients in the buprenorphine plus paracetamol group withdrew from the study during the titration period; 34 patients withdrew due to adverse events and five patients withdrew due to lack of therapeutic effect. In the codeine-paracetamol group, 63 of 110 patients withdrew during the titration period; 23 patients withdrew were due to adverse events and 12 patients withdrew due to lack of therapeutic effect.

Eighty-six percent and 82% of patients in the buprenorphine plus paracetamol and codeine-paracetamol groups, respectively, reported treatment emergent adverse events. The most commonly reported adverse events in the buprenorphine plus paracetamol group were nausea, application site reaction and constipation.</td></tr>
<tr><td>Corli et al.[32] (2016)

Oral controlled-release morphine (active comparator)

vs

oral controlled-release oxycodone

vs

transdermal fentanyl

vs</td><td>AC, MC, OL, RCT

Patients >18 years of age with diagnostic evidence of locally advanced or metastatic tumor; persistent moderate to severe cancer pain [average pain intensity experienced in the last 24 h ≥4 points on a 0 to 10 Numerical Rating Scale]; need for WHO step III strong opioids never previously given</td><td>N=520

28 days</td><td>Primary:
Proportion of nonresponders, meaning patients with worse or unchanged average pain intensity between the first and last visit, measured on a 0 to 10 numerical rating scale

Secondary:
Nonresponders based on the Worst Pain Intensity difference; patients requiring a mean increase in the</td><td>Primary:
There were no significant differences from morphine in the proportions of nonresponders (morphine vs oxycodone, P=0.494; morphine vs buprenorphine, P=0.910; morphine vs fentanyl, P=0.499).

Secondary:
<table>
<tr><th></th><th>Morphine (N=122)</th><th>Oxycodone (N=125)</th><th>Morphine vs oxycodone</th></tr>
<tr><td>Worst pain intensity–nonresponders</td><td>13.9%</td><td>17.6%</td><td>P=0.430</td></tr>
<tr><td>Average pain intensity–responders</td><td>75.4%</td><td>73.6%</td><td>P=0.744</td></tr>
<tr><td>Mean dose increase</td><td>32.7%</td><td>70.9%</td><td></td></tr>
<tr><td>Opioid escalation index >5%</td><td>10.7%</td><td>19.2%</td><td>P=0.060</td></tr>
<tr><td>Patients requiring additional opioids</td><td>29.5%</td><td>26.4%</td><td>P=0.586</td></tr>
<tr><td>Patients requiring adjuvant drugs</td><td>68.9%</td><td>81.6%</td><td>P=0.020</td></tr>
<tr><td>Switches</td><td>22.1%</td><td>12%</td><td>P=0.034</td></tr>
<tr><td>Premature discontinuations for pain treatment-related reasons</td><td>27%</td><td>15.2%</td><td>P=0.051</td></tr>
</table>
<table>
<tr><th></th><th>Buprenorphine (N=127)</th><th>Morphine vs buprenorphine</th><th>Fentanyl (N=124)</th><th>Morphine vs fentanyl</th></tr>
<tr><td>Worst pain intensity–nonresponders</td><td>9.4%</td><td>P=0.270</td><td>13.7%</td><td>P=0.959</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>transdermal buprenorphine

All treatments taken around the clock for pain relief</td><td></td><td></td><td>opioid daily dose >5%; requiring a switch to another opioid; needing supplementary doses of opioids; needing adjuvant analgesic drugs; and discontinuing the opioid</td><td>
<table>
<tr><td>Average pain intensity–responders</td><td>78%</td><td>P=0.635</td><td>75.8%</td><td>P=0.942</td></tr>
<tr><td>Mean dose increase</td><td>56.4%</td><td></td><td>121.2%</td><td></td></tr>
<tr><td>Opioid escalation index >5%</td><td>14.2%</td><td>P=0.401</td><td>36.3%</td><td>P<0.001</td></tr>
<tr><td>Patients requiring additional opioids</td><td>37.8%</td><td>P=0.167</td><td>37.1%</td><td>P=0.207</td></tr>
<tr><td>Patients requiring adjuvant drugs</td><td>78.7%</td><td>P=0.076</td><td>80.6%</td><td>P=0.033</td></tr>
<tr><td>Switches</td><td>16.5%</td><td>P=0.263</td><td>12.9%</td><td>P=0.057</td></tr>
<tr><td>Premature discontinuations for pain treatment-related reasons</td><td>20.5%</td><td>P=0.222</td><td>14.5%</td><td>P=0.015</td></tr>
</table>
</td></tr>
<tr><td>Desjardins et al.[33] (2000)

Butorphanol 0.25 mg

vs

butorphanol 0.5 mg

vs

butorphanol 1 mg

vs

butorphanol 2 mg

vs

placebo</td><td>DB, MC, PG, RCT

Patients with pain after the removal of impacted third molars</td><td>N=151

Single dose intranasal formulation</td><td>Primary:
Patient-rated pain intensity, pain relief, pain half gone, adverse events at 0.25, 0.5, one, two, three, four, five, and six hours after treatment; global evaluation

Secondary:
Not reported</td><td>Primary:
A linear dose-response regression (P<0.05) was observed for the means of pain intensity difference, pain relief, and pain half gone at 0.25, 0.5, and one hour, and for sum of pain intensity differences, sum of pain relief, peak PDI and pain relief, and global evaluation.

The 1.0 and 2.0 mg groups experienced greater pain relief compared to placebo (P=0.05) during the first hour after drug administration.

The 1.0 and 2.0 mg groups had significantly better global evaluations than the placebo group, but were not significantly different from placebo.

Incidence and severity of the most common adverse events were dose-related. Two severe adverse events (drowsiness and dizziness) occurred after the 2.0 mg dose.

Secondary:
Not reported</td></tr>
<tr><td>Wermeling et al.[34] (2005)</td><td>DB, PC, PG, RCT

Patients receiving</td><td>N=30

Single dose</td><td>Primary:
Summed pain intensity difference</td><td>Primary:
A dose response was observed in summed pain intensity differences scores, with the 2 mg dose of butorphanol providing the greatest response</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Butorphanol 1 mg vs butorphanol 2 mg vs placebo	standard anesthesia with moderate to severe pain after dental impaction surgery	intranasal formulation	at two, four, and six hours after administration of study medication and total pain relief at six hours Secondary: Not reported	compared to placebo (P<0.05). Overall, 86.7% patients requested rescue medication: 91.7% in the 1 mg group, 79.2% in the 2 mg group, and 91.7% in the placebo group. The time to use of rescue medication occurred at a median of 75 to 110 minutes after nasal spray dosing. Pain relief was recorded in most patients within 15 minutes of receiving active treatment. The analysis of total pain relief at six hours showed no significant differences overall or in pairwise comparisons. On the global assessment, 58.3% of patients in each of the active-treatment groups and 83.3% of patients in the placebo group evaluated the study drug as "poor." Patients receiving butorphanol nasal spray reported central nervous system adverse effects compared to placebo (P=0.029). Dizziness occurred in 45.8% patients who received butorphanol 1 mg, 58.3% who received butorphanol 2 mg, and 33.3% of patients who received placebo. Headache occurred in 45.8, 29.2, and 16.7% of patients, respectively. Secondary: Not reported
Scott et al.[35] (1994) Butorphanol 1 mg	OL, PRO Patients with strains, fractures, contusions, and stab wounds	N=28 Single dose intranasal formulation	Primary: Pain relief Secondary: Not reported	Primary: All patients received pain relief from transnasal butorphanol, and only one requested alternative analgesic medication. Fifty-seven percent of patients noticed at least a little relief of pain within five minutes of administration and 93% received at least a little relief within 15 minutes. Seventy-one percent of the patients received a 50% reduction of pain within 60 minutes. No serious side effects were noted. Drowsiness occurred in 82% and dizziness occurred in 54% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Olsen et al.[36] (2008) Butorphanol 1 mg intravenous vs ketorolac 30 mg intravenous	DB, RCT Patients presenting to the emergency department with abdominal pain suspected to be biliary colic	N=46 Single dose	Primary: Pain level using visual analog pain scale; adverse events; need for rescue analgesia Secondary: Not reported	Primary: The mean pain score in the butorphanol group decreased from 7.1 to 2.1 after 30 minutes. The mean pain score in the ketorolac group decreased from 7.4 to 3.1 after 30 minutes. Both butorphanol-treated patients and ketorolac-treated patients had similar needs for rescue analgesia. Adverse events included dizziness and sedation with butorphanol and nausea with ketorolac. Secondary: Not reported
Moyao-Garcia et al.[37] (2009) Nalbuphine 100 µg/kg bolus intravenous + 0.2 µg/kg/hour continuous infusion vs tramadol 1 mg/kg + 2.0 µg/kg/hour continuous infusion for 72 hours	DB, PRO, RCT Children 1 to 12 years of age undergoing scheduled surgery	N=24 72 hours	Primary: Number of patients requiring dose increments Secondary: Sedation, heart rate, blood pressure, and vomiting	Primary: Three patients who received nalbuphine required an extra bolus dose in the 12 hour post-surgery period, vs one child in the tramadol group. There were a similar number of patients in both treatment groups who required an increase in the infusion rate within the 72 hour post-surgery period. Secondary: Sedation was observed in two patients in the nalbuphine group and in one patient in the tramadol group. Vomiting occurred in four children receiving tramadol, and two receiving nalbuphine. No adverse cardiovascular events were detected in either group.
Yeh et al.[38] (2009)	DB, PRO, RCT Female patients	N=174 24 hours	Primary: Pain and medication dose	Primary: Numerical pain rating scores and medication requirements were not significantly different between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nalbuphine 10 µg/mL intravenous and morphine 1 mg/mL infusion via patient-controlled analgesia vs morphine 1 mg/mL intravenous infusion via patient-controlled analgesia	undergoing gynecological surgery		Secondary: Nausea, vomiting, use of antiemetics, pruritus, use of antipruritics, opioid related adverse effects	Secondary: Nausea was lower in the nalbuphine group than the morphine-only group (45 vs 61%; P=0.03). Other secondary outcomes did not differ between the treatment groups.
Levine et al.[39] (1988) Pentazocine 60 mg intravenous vs naloxone 0.4 mg intravenous vs morphine 8 or 15 mg intravenous vs naloxone 0.4 mg + morphine 8 mg intravenous	DB, RCT Patients undergoing surgery for the removal of impacted third molars	N=105 Single dose	Primary: Pain intensity using a visual-analogue scale Secondary: Not reported	Primary: The mean pain intensity was increased in the group receiving placebo. Mean pain intensity was decreased in the groups that received either morphine (8 and 15 mg; P<0.05 and P<0.01, respectively) or pentazocine (60 mg; P<0.05) as a single agent. The combination of low-dose naloxone and pentazocine produced significantly greater analgesia than either low-dose naloxone (P<0.01), pentazocine (P<0.01), or even high-dose morphine administered alone (P<0.01). The combination of low-dose naloxone and 8 mg morphine produced less analgesia when compared to the same dose of morphine alone (P<0.05) or with high-dose morphine (P<0.01) but not when compared to low-dose naloxone administered alone. The mean pain intensity measured at three hours and 10 minutes after injection of single analgesic agents was not significantly decreased compared to placebo. The analgesia produced by the combination of low-dose naloxone and 8 mg morphine did not differ significantly from the analgesia produced by the same dose of morphine. The combination of low-dose naloxone and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs naloxone 0.4 mg + pentazocine 60 mg intravenous vs placebo				pentazocine produced significant analgesia when compared to either agent alone (both P<0.01). By three hours and 10 minutes after injection, only the group of patients receiving low-dose naloxone plus pentazocine still reported significant analgesia.
Petti[40] (1985) Pentazocine 25 mg and acetaminophen 650 mg vs codeine 30 mg and acetaminophen 300 mg vs propoxyphene napsylate 100 mg and acetaminophen 650 mg vs placebo	PC, PG, SB Patients with moderate postoperative pain	N=129 6 hours	Primary: Intensity of pain and degree of pain relief Secondary: Not reported	Primary: Pentazocine and acetaminophen was significantly better than placebo and equivalent to codeine and acetaminophen and propoxyphene and acetaminophen in patients with moderate postoperative pain. No adverse events were reported with acetaminophen and pentazocine, acetaminophen and propoxyphene napsylate, or placebo. Secondary: Not reported
Opioid Use Disorder				
Kornor et al.[41] (2007)	OL Patients ≥22 years	N=75 9 months	Primary: Self reported opioid abstinence	Primary: More program completers compared to non-completers reported abstinence from opioids during the 30 days prior to the follow-up, a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine flexible daily dosing to a maximum dose of 16 mg daily	of age with opioid dependence who were willing to enroll in a nine-month buprenorphine program		in program completers and non-completers Secondary: Difference in number of days within 30 days prior to follow up interview in which the following occurred: heavy drinking, street opioid use, sedative, amphetamine, cannabis, polysubstance and intravenous use, employment, illegal activities, psychiatric problems and medical problems	difference that was not significant (7 vs 2; P=0.16). Secondary: Completers were employed for a higher number of days than non-completers at follow up (9 vs 2 days, respectively; P=0.012). There were no statistically significant differences between the two groups with regard to other psychosocial variables and substance use (P values not reported). At follow-up, 37 patients received agonist replacement therapy in the past 30 days while 31 patients did not. There was a higher rate of abstinence from street opioids in the patients who received agonist therapy (24 of 37) compared to those who did not (9 of 31; P=0.003). Patients who received agonist therapy within 30 days prior to follow-up had spent fewer days using street opioids (P<0.001), using two or more substances (P<0.038), injecting substances (P<0.007) and engaging in illegal activities (P<0.001) compared to those who did not. Patients who received agonist therapy had also been employed for a higher number of days (P=0.046). There was no difference between the two groups in health problems, heavy drinking and use of sedatives, amphetamine and cannabis (P values not reported).
Andorn et al.[42] (2020) Buprenorphine extended-release subcutaneous injection; initial 300 mg then subsequent monthly 300 mg or 100 mg flexible doses	MC, OL Adults 18 to 65 years of age with moderate or severe opioid use disorder	N=669 257 participants from a previously conducted placebo-controlled, double-blind phase III study (rollover group) and	Primary: Treatment-emergent adverse events Secondary: Opioid abstinence, medication satisfaction	Primary: Overall, 66.8% of participants reported more than one treatment-emergent adverse event. Injection-site treatment-emergent adverse events (13.2% of participants) were mostly mild or moderate in severity. There were no clinically meaningful changes in safety assessments. Secondary: After 12 months of treatment, 61.5% of the rollover participants and 75.8% of the de novo participants were abstinent. Retention rates after 12 months were 50.6% for the participants who initiated BUP-XR in the double-blind study and 50.5% for de novo participants. Participant satisfaction with medication measured in the open-label study

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
		412 not previously treated with BUP-XR (de novo group) Up to 12 months		was high at all time points, with 85.0% to 89.7% of de novo participants and 85.0% to 85.2% of rollover participants satisfied, very satisfied, or extremely satisfied with BUP-XR treatment across time points.
Fareed et al.[43] (2012) Buprenorphine ≥16 mg/day vs buprenorphine <16 mg/day	MA (21 RCTs) Patients with opioid dependence who were receiving buprenorphine maintenance treatment	N=2,703 3 to 48 weeks	Primary: Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine Secondary: Not reported	Primary: Patients receiving the higher doses of buprenorphine had a higher treatment retention rate compared to those receiving the lower doses (69±12 vs 51±14%; P=0.006). The incidence of positive urine drug screen for opioids and cocaine was similar between the higher and lower dose groups (41±16 vs 47±13%; P=0.35, 44±13 vs 49±20%; P=0.64, respectively). Secondary: Not reported
Fareed et al.[44] (2012) Buprenorphine >16 mg/day (mean dose, 27.5±4.8 mg) vs buprenorphine ≤16 mg/day (mean dose, 11.5±4.8 mg)	OS Patients with opioid dependence who were receiving buprenorphine maintenance treatment	N=77 ≥1 month	Primary: Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine Secondary: Not reported	Primary: Treatment drop-out rate was similar between the high- and moderate-dose groups (37.5 vs 43.0%; P=0.67). The percentage of the first four urine drug screens that were positive for opioids was higher in the high-dose group compared to the moderate-dose group (45, 14, 9 and 5 vs 29, 5, 10 and 5%, respectively; P<0.00001). No significant differences were seen between the two groups in the percentage of the first four urine drug screens positive for cocaine (P=0.74) or the last four urine drug screens positive for opioids or cocaine (P=0.21 and P=0.47, respectively). Secondary: Not reported
Bickel et al.[45] (1999) Buprenorphine	DB, PC Patients ≥18 years of age who were in	N=16 80 days	Primary: Self-report measures (i.e., VAS and adjective	Primary: Overall, there were no statistically significant differences among the different dosing schedules in any of the outcome measures, including opioid agonist and withdrawal effects observed during the study (P values

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
maintenance dose (range from 4 to 8 mg/70 kg) SL every 24 hours vs double maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours Maintenance dose was administered to patients for 13 consecutive days prior to the initiation of the above dosing schedules.	good health and met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment		rating scales) and observer measures Secondary: Not reported	not reported). Significant differences were observed in some of the measures (i.e., percent identifications as placebo, percent identification as greater than maintenance dose, ARCI subscales) when comparing the daily maintenance dosing to those measures obtained 24, 48 and 72 hours following dosing schedules. Secondary: Not reported
Petry et al.[46] (1999) Buprenorphine maintenance dose (ranged from 4 to 8 mg/70 kg) SL every 24 hours vs double	DB, PC, XO Patients ≥18 years of age who were in good health and met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment	N=14 43 days	Primary: Subjective opioid agonist and withdrawal effects Secondary: Not reported	Primary: There were no statistically significant differences among the different dosing schedules in any of the outcome measures, including subjective opioid agonist and withdrawal effects (P values not reported). When patients received quadrupled doses, there were no significant increases observed in opioid agonist effects compared to their usual maintenance dose (P values not reported). Subjects did report some differences in withdrawal effects (i.e., VAS, ARCI subscales) as the time between buprenorphine doses increased, but the clinical significance of these differences may be limited.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours vs quadruple maintenance dose SL every 96 hours Patients were administered 10 days of their daily SL maintenance dose to ensure stabilization.				Secondary: Not reported
Schottenfeld et al.[47] (2000) Buprenorphine 16 mg/70 kg SL daily vs buprenorphine 34 mg/70 kg SL on Fridays and Sundays and 44 mg/70 kg SL on Tuesdays	DB, RCT Patients who met FDA criteria for methadone maintenance, had a urine toxicology test positive for opioids and met the DMS-IV criteria for opioid dependence	N=92 12 weeks	Primary: Retention, three times per week urine toxicology tests and weekly self-reported illicit drug use Secondary: Not reported	Primary: There was no difference in percentage of patients who completed the 12 weeks of treatment between the daily and thrice-weekly groups (76.6 vs 71.1%; P value not reported). There was also no statistical difference observed between the two treatment groups in the average number of weeks in treatment (11.0±4.0 and 11.2±3.7 weeks, respectively; P=0.64). A significant decline in the proportion of opioid-positive urine tests was observed during the study (P<0.001), but there was no statistical difference between the two treatment groups (57% in the daily group vs 58% in the thrice-weekly group; P=0.84). A significant decline in the number of self-reported days per week of heroin use was observed during the study (P<0.001), but there was no statistical difference between the two treatment groups (1.30±0.23 in the daily group vs 1.70±0.22 in the thrice-weekly group; P=0.27).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
There was a three-day buprenorphine induction phase prior to randomization.				Secondary: Not reported
Rosenthal et al.[48] (2016) Buprenorphine implants (buprenorphine hydrochloride, 80 mg each) vs daily sublingual buprenorphine	AC, DB, DD, NI, RCT Clinically stable outpatients 18 to 65 years of age receiving 8 mg/d or less of sublingual buprenorphine	N=177 6 months	Primary: Between-group difference in proportion of responders (≥4 of 6 months without opioid-positive urine test result [monthly and 4 times randomly] and self-report) Secondary: Cumulative percentage of negative opioid urine results, abstinence, time to first illicit opioid use	Primary: In the buprenorphine implant and sublingual buprenorphine groups, 81 of 84 participants (96.4%) and 78 of 89 participants (87.6%), respectively, were responders. The difference was 8.8% (1-sided 97.5% CI, 0.009 to ∞; P<0.001 for noninferiority; P=0.03 for superiority) on the primary outcome measure, with a calculated number needed to treat of 11.36 vs sublingual buprenorphine. Secondary: At six months, cumulative abstinence was 72 of 84 (85.7%) for buprenorphine implants vs 64 of 89 (71.9%) for sublingual buprenorphine (HR, 13.8; 95% CI, 0.018 to 0.258; P=0.03), with a number needed to treat of 7.25. Time to first evidence of illicit opioid use was significantly longer for buprenorphine implants relative to sublingual buprenorphine (HR, 0.49; 95% CI, 0.25 to 0.97; P=0.04). Non-implant-related and implant-related adverse events occurred in 48.3% and 23% of the buprenorphine implant group and in 52.8% and 13.5% of participants in the sublingual buprenorphine group, respectively.
Nasser et al.[49] (2016) Buprenorphine monthly injection (RBP-6000, brand name Sublocade®) as a 300 mg subcutaneous injection on days 1 and 29	Phase 2 multiple-dose study Men and nonpregnant women aged 18 to 55 years with moderate or severe opioid use disorder	N=38 12 weeks	Primary: Visual analogue scale of subjective drug effects Secondary: Hydromorphone breakpoint values for the drug-money choice task	Primary: At baseline, the least squares (LS) mean difference from placebo for drug liking visual analogue scale scores was 45 mm (95% CI, 37.2 to 53.6) for 6 mg of hydromorphone and 61 mm (95% CI, 52.3 to 68.9) for 18 mg of hydromorphone. After stabilization on sublingual buprenorphine-naloxone, the LS mean difference from placebo for drug liking scores decreased to 8 mm (95% CI, 1.5 to 14.9) for 6 mg of hydromorphone and 17 mm (95% CI, 10.4 to 23.9) for 18 mg of hydromorphone. The visual analogue scale scores generally decreased until the end of the study, where the LS mean difference from placebo for drug liking scores was −0.03 mm (95% CI, −2.19 to 2.12) for 6 mg of hydromorphone and 2.78 (95% CI, 0.61 to 4.96) for 18 mg of hydromorphone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Inducted subjects received 8 to 24 mg per day of sublingual buprenorphine-naloxone (Suboxone sublingual film) until a stable dose was established				Secondary: The difference from placebo in log-transformed breakpoint decreased from 2.1 at baseline to 1.9 (95% CI, 1.1 to 2.8) for 6 mg hydromorphone and 1.3 (95% CI, 0.5 to 2.2) for 18 mg hydromorphone during stabilization. During the treatment period (weeks one to 12), breakpoint values decreased after each injection of buprenorphine, and by the end of the treatment period, the difference from placebo in log-transformed breakpoint values was 0.6 (95% CI, −0.573 to 1.8) for 6 mg of hydromorphone and 1.6 (95% CI, 0.50 to 2.7) for 18 mg of hydromorphone. The most common related treatment-emergent adverse events (occurring in ≥10% of subjects) in this study were sedation (10.3%), nausea (12.8%), constipation (30.8%), and injection site reactions (79.5%).
Haight et al.[50] (2019) Buprenorphine extended-release (BUP-XR) 300 mg/300 mg (six injections of 300 mg; one every 28 days) vs BUP-XR 300 mg/100 mg (two injections of 300 mg plus four injections of 100 mg; given every 28 days) vs	DB, MC, PC, RCT Treatment-seeking adults 18 to 65 years of age who had moderate or severe opioid use disorder	N=504 24 weeks	Primary: Participants' percentage abstinence from opioid use, defined as the percentage of each participant's negative urine samples and self-reports of illicit opioid use from week five to week 24, analyzed in the full analysis set Secondary: Treatment success, defined as at least 80% opioid abstinence during weeks five to 24;	Primary: Participants' percentage abstinence was, on average, 41.3% (SD 39.7) in the BUP-XR 300 mg/300 mg group, 42.7% SD (38.5) in the BUP-XR 300 mg/100 mg group, and 5.0% (SD 17.0) in the placebo group. There was a significant difference in participants' percentage abstinence in both BUP-XR groups, compared with placebo (P<0.0001). Secondary: Treatment success (≥80% abstinence) was higher in both the BUP-XR 300 mg/300 mg group (29% of participants; P<0.0001) and the BUP-XR 300 mg/100 mg group (28% of participants; P<0.0001) than in the placebo group (2% of participants). More than 60% of participants in both BUP-XR groups completed the study (64% of participants in the 300 mg/300 mg group, 62% of participants in the 300 mg/100 mg group) versus 34 (34%) of participants in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
volume-matched placebo every 28 days All patients received weekly individual drug counselling			treatment retention	
Gibson et al.[51] (2008) Buprenorphine (dosing not specified) vs methadone (dosing not specified)	DB, MC, RCT Patients ≥18 years of age who were heroin-dependent and lived within commuting distance of the clinic	N=405 91 day treatment period followed by a 10 year longitudinal follow-up	Primary: Effects of opioid maintenance treatment on mortality rate Secondary: Difference between two treatment groups in exposure to opioid maintenance treatment episodes greater than seven and 14 days, causes of death and effects of race, level of heroin dependence and age on mortality rate	Primary: There were 30 deaths in the follow-up period (16 in the buprenorphine group vs 14 in the methadone group). Each additional treatment episode of methadone or buprenorphine treatment lasting longer than seven days reduced the risk of death on average by 28% (95% CI, 7 to 44). Secondary: There was no significant difference over the follow-up period in percentage time exposure to opioid maintenance treatment episodes greater than seven days between the buprenorphine and methadone groups (P=0.52). The methadone group was significantly more likely to spend greater percentage follow-up time in methadone treatment episodes longer than 14 days (P<0.0001).The buprenorphine group was also significantly more likely to spend longer time in buprenorphine treatment episodes longer than 14 days (P<0.0001). Drug overdose or related complications were the most common causes of death in the 30 deceased participants (40% of the deaths). Aboriginal or Torres Strait Islander patients had 5.32 times the risk of death of non-Aboriginal or Torres Strait Islander participants (95% CI, 1.89 to 14.95). The risk of death among participants using more heroin at baseline during follow-up was 12% lower (95% CI, 5 to 18; P value not reported) than less frequent heroin users at baseline. The risk of death during the follow-up period was 11% lower for older

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients (95% CI, 2 to 19) than younger participants who were randomized to methadone.
Johnson et al.[52] (1992) Buprenorphine 8 mg daily vs methadone 60 mg daily vs methadone 20 mg daily	DB, PG, RCT Adults seeking treatment for opioid dependence	N=162 17-week maintenance phase, followed by a 8-week detoxification phase	Primary: Retention time in treatment, urine samples negative for opioids, and failure to maintain abstinence Secondary: Not reported	Primary: During the maintenance phase, the retention rates were significantly greater for buprenorphine (42%) than for methadone 20 mg/day (20%; P<0.04). During the maintenance phase, the percentage of urine samples negative for opioids was significantly greater for buprenorphine (53%; P<0.001) and methadone 60 mg/day (44%; P<0.04), than for methadone 20 mg/day (29%). Failure to maintain abstinence during the maintenance phase was significantly greater for methadone 20 mg/day, than for buprenorphine (P<0.03). During the detoxification phase, there were no differences between the treatment groups with regards to urine samples negative for opioids. During the 25 week study period, retention rates for buprenorphine (30%; P<0.01) and methadone 60 mg/day (20%; P<0.05) were significantly greater than for methadone 20 mg/day (6%). All treatments were well tolerated, with similar profiles of self-reported adverse effects. The percentages of patients who received counseling did not differ between groups. Secondary: Not reported
Petitjean et al.[53] (1992) Buprenorphine SL tablets (flexible dosing schedule)	DB, RCT Patients seeking treatment for opioid dependence	N=58 6 weeks	Primary: Treatment retention rate, urine samples positive for opiates, substance	Primary: The retention rate was significantly better in the methadone group than in the buprenorphine group (90 vs 56%, respectively; P<0.001). There were similar proportions of opioid positive urine samples in both treatment groups (buprenorphine, 62%; methadone, 59%) and positive

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs methadone (flexible dosing schedule)			use Secondary: Not reported	urine specimens, as well as mean heroin craving scores decreased significantly over time (P=0.035 and P<0.001). The proportion of cocaine-positive toxicology results did not differ between groups. At week six, the mean stabilization doses were 10.5 mg/day for buprenorphine and 69.8 mg/day for methadone. Secondary: Not reported
Strain et al.[54] (1994) Buprenorphine SL tablets (flexible dosing schedule) vs methadone (flexible dosing schedule)	DB, DD, RCT Patients seeking treatment for opioid dependence	N=164 26 weeks	Primary: Treatment retention rate, medication and counseling compliance, urine samples positive for opiates Secondary: Not reported	Primary: Buprenorphine (mean dose ~9 mg/day) and methadone (mean dose 54 mg/day) were equally effective in sustaining retention in treatment, compliance with medication, and counseling regimens. In both groups, 56% of patients remained in the treatment program through the 16-week flexible dosing period. Opioid-positive urine sample rates were 55 and 47% for buprenorphine and methadone groups, respectively. Cocaine-positive urine sample rates were 70 and 58%, respectively. Secondary: Not reported
Ling et al.[55] (1996) Buprenorphine 8 mg daily vs methadone 30 mg daily vs	DB, RCT Patients seeking treatment for opioid dependence	N=225 1 year	Primary: Urine toxicology, retention, craving, and withdrawal symptoms Secondary: Not reported	Primary: Patients receiving high-dose methadone maintenance therapy performed significantly better on measures of retention, opioid use, and opioid craving than either the low-dose methadone group or the buprenorphine group. Performance on measures of retention, opioid use, and opioid craving were not significantly different between the low-dose methadone group or the buprenorphine group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
methadone 80 mg daily				
Schottenfeld et al.[56] (1997) Buprenorphine 4 mg daily vs buprenorphine 12 mg daily vs methadone 20 mg daily vs methadone 65 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=116 24 weeks	Primary: Retention in treatment and illicit opioid and cocaine use Secondary: Not reported	Primary: There were significant effects of maintenance treatment on rates of illicit opioid use, but no significant differences in treatment retention or the rates of cocaine use. The rates of opioid-positive toxicology tests were lowest for treatment with 65 mg of methadone (45%), followed by 12 mg of buprenorphine (58%), 20 mg of methadone (72%), and 4 mg of buprenorphine (77%), with significant contrasts found between 65 mg of methadone and both lower-dose treatments and between 12 mg of buprenorphine and both lower-dose treatments. Secondary: Not reported
Soyka et al.[57] (2008) Buprenorphine (mean daily dose 9 to 12 mg) vs methadone (mean daily dose 44 to 50 mg)	RCT Opioid-dependent patients who had been without opioid substitution therapy	N=140 6 months	Primary: Retention rate; substance use; predictors of outcome Secondary: Not reported	Primary: There was an overall retention rate of 52.1%. There was no significant difference between buprenorphine-treated patients and methadone-treated patients (55.3 vs 48.4%). Substance use decreased significantly over time in both groups and was non-significantly lower in the buprenorphine group. Predictors of outcome were length of continuous opioid use and age at onset of opioid use (significant in the buprenorphine group only). Mean dosage and other parameters were not significant predictors of outcome. The intensity of withdrawal symptoms showed the strongest correlation with drop-out.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Maremmani et al.[58] (2007) Buprenorphine vs methadone	OL Patients involved in a long-term treatment program with buprenorphine or methadone	N=213 12 months	Primary: Opioid use, psychiatric status, quality of life Secondary: Not reported	Primary: There were significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for buprenorphine-treated and methadone-treated patients. Secondary: Not reported
Jones et al.[59] (2010) Buprenorphine 2 to 32 mg per day vs methadone 20 to 140 mg per day	DB, DD, MC, RCT Opioid-dependent women 18 to 41 years of age with a singleton pregnancy between 6 and 30 weeks	N=175 ≥10 days	Primary: Neonates requiring neonate abstinence syndrome therapy, total morphine needed, length of hospital stay, and head circumference Secondary: Not reported	Primary: Percentage neonates requiring neonate abstinence syndrome treatment, peak neonate abstinence syndrome scores, or head circumference did not differ significantly between groups. Neonates exposed to buprenorphine required an average 89% less morphine (1.1 and 10.4 mg; P<0.0091) than did neonates exposed to morphine. Neonates exposed to buprenorphine required an average 43% less time in hospital (10.0 vs 17.5 days; P<0.0091). The methadone group had higher rates of nonserious maternal events overall (P=0.003) and of nonserious cardiac events in particular (P=0.01). No differences in serious adverse events were detected in mothers or nonserious adverse events in neonates. Secondary: Not reported
Gibson et al.[60] (2008) Buprenorphine vs methadone	RCT Heroin-dependent patients ≥18 years of age	N=405 10 years	Primary: Mortality Secondary: Not reported	Primary: There was an overall mortality rate of 8.84 deaths per 1,000 person-years of follow-up. Increased exposure to episodes of opioid treatment longer than seven days reduced the risk of mortality. There was no difference in mortality among methadone vs buprenorphine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				participants. More dependent, heavier users of heroin at baseline had a lower risk of death, and also higher exposure to opioid treatment. Older patients on buprenorphine had significantly improved survival. Secondary: Not reported
Cornish et al.[61] (2010) Buprenorphine vs methadone	MC, OS, PRO Opioid dependent patients <60 years of age	N=5,577 585 days	Primary: All cause mortality Secondary: Duration of therapy effect on mortality	Primary: Three percent of patients died while receiving treatment, or within a year of receiving the last prescription. Of these, 35% died while on treatment. Overall, the risk of death during opiate substitution treatment was lower than the risk of death while off treatment. Crude mortality rates off therapy nearly doubled (1.3 vs 0.7 per 100-person years). Standardized mortality rates were 5.3 (95% CI, 4.0 to 6.8) on treatment vs 10.9 (95% CI, 9.0 to13.1). After adjustment for age, sex, calendar period, and comorbidity, the mortality rate ratio was 2.3 (95% CI, 1.7 to 3.1). The risk of death increased 8 to 9-fold in the month immediately after the end of opiate substitution therapy, which did not vary according to medication, dosing within standard thresholds, or planned cessation. There was no difference in the overall mortality rate between patients who received methadone and those who received buprenorphine. Secondary: Substitution therapy has a greater than 85% chance of reducing overall mortality when average duration of treatment is at least 12 months.
Pinto et al.[62] (2010) Buprenorphine vs	OS, PRO Cohort of opioid-dependent patients new to substitution therapy	N=361 6 months	Primary: Retention in treatment at six months or successful detoxification based on patient	Primary: A total of 63% of patients chose methadone and 37% chose buprenorphine. At six months, 50% of buprenorphine patients compared to 70% of methadone patients had favorable outcomes (OR, 0.43; 95% CI, 0.20 to 0.59; P<0.001). Methadone patients were more likely to remain on therapy than those on

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
methadone			selected substitution therapy Secondary: Not reported	buprenorphine (HR, 2.08; 95% CI, 1.49 to 2.94). Retention was the primary factor in favorable outcomes at six months. Buprenorphine patients were more likely to not use illicit opiates (OR, 2.13; 95% CI, 1.509 to 3.027; P<0.001) and to achieve detoxification. A total of 28% of patients selecting buprenorphine reported they would not have accessed treatment with methadone therapy. Secondary: Not reported
Farré et al.[63] (2002) Buprenorphine ≥8 mg daily (high dose vs buprenorphine <8 mg daily (low dose) vs methadone ≥50 mg daily (high dose) vs methadone <50 mg daily (low dose) vs levo-	MA Patients seeking treatment for opioid dependence	N=1,944 (13 trials) Variable duration	Primary: Retention rate and reduction of opioid use Secondary: Not reported	Primary: High doses of methadone were more effective than low doses of methadone in the reduction of illicit opioid use (OR, 1.72; 95% CI, 1.26 to 2.36). High doses of methadone were significantly more effective than low doses of buprenorphine (<8 mg/day) for retention rates and illicit opioid use, but similar to high doses of buprenorphine (≥8 mg/day). Patients treated with levo-acetylmethadol had more risk of failure of retention than those receiving high doses of methadone (OR, 1.92; 95% CI, 1.32 to 2.78). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acetylmethadol				
Mattick et al.[64] (2008) Buprenorphine vs methadone vs placebo	MA Patients dependent on heroin or other opioids	N=4,497 (24 trials) Variable duration	Primary: Treatment retention, suppression of opioid use, use of other substances Secondary: Not reported	Primary: <u>Flexible Dose Buprenorphine vs Flexible Dose Methadone</u> Methadone was more likely to retain patients than buprenorphine (RR, 0.85; 95% CI, 0.73 to 0.98). There was no significant difference between the treatment groups with regards to heroin use (95% CI, -0.26 to 0.02), cocaine use (95% CI, -0.03 to 0.25), or benzodiazepine use (95% CI, -0.04 to 0.26). <u>Low Dose Buprenorphine vs Low Dose Methadone</u> Low dose methadone was more likely to retain patients than low dose buprenorphine (RR, 0.67; 95% CI, 0.52 to 0.87). There was no significant difference between the treatment groups with regards to morphine use (95% CI, -0.87 to 0.16), heroin use (95% CI, -0.38 to 0.96), cocaine use (95% CI, -0.43 to 0.59), or benzodiazepine use (95% CI, -0.33 to 0.38). <u>Low Dose Buprenorphine vs Medium Dose Methadone</u> There was a statistical difference in retention in treatment RR, 0.67; (95% CI, 0.55 to 0.81) favoring medium dose methadone. Medium dose methadone was more effective than low dose buprenorphine in suppressing heroin use as indexed by the extent of morphine positive urine, one study (95% CI, 0.33 to 1.42). There was no significant difference among the treatment groups in heroin use (95% CI, -0.48 to 0.68) or cocaine use (95% CI, -0.60 to 0.44). <u>Medium Dose Buprenorphine vs Low Dose Methadone</u> There was one study which favored low dose methadone in terms of retention, and the remaining three studies showed no statistically significant difference. There was no significant difference among the treatment groups in cocaine use (95% CI, -0.14 to 0.89).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Medium Dose Buprenorphine vs Medium Dose Methadone Two of the six studies suggest that medium doses of buprenorphine are less likely to retain patients than medium dose methadone and the remainder showed no statistical significant difference. Medium dose buprenorphine was significantly less able to suppress heroin use, three studies (95% CI, 0.05 to 0.50). There was no significant difference among the treatment groups in cocaine use (95% CI, -0.30 to 0.74). Low Dose Buprenorphine Maintenance vs Placebo There was a benefit for low dose buprenorphine above placebo in terms of retaining patients in treatment (RR, 1.50; 95% CI, 1.19 to 1.88). Low dose buprenorphine patients had no less heroin use as indexed by morphine positive urines (95% CI, -0.80 to 1.01). There was no significant difference among the treatment groups in cocaine use (95% CI, -0.10 to 0.62) or benzodiazepine use (95% CI, -0.33 to 0.38). Medium Dose Buprenorphine Maintenance vs Placebo There was a benefit for buprenorphine above placebo in terms of retaining patients in treatment (RR, 1.74; 95% CI, 1.06 to 2.87). Patients in the buprenorphine group had less heroin use as indexed by morphine positive urines (95% CI, -0.47 to 0.10). For cocaine use, there was an advantage for placebo in one study (95% CI, 0.05 to 0.94). For benzodiazepine use, buprenorphine was more effective than placebo in one study (95% CI, -1.27 to -0.36). High Dose Buprenorphine Maintenance vs Placebo There was a benefit for buprenorphine above placebo in terms of retaining patients in treatment (RR, 1.74; 95% CI, 1.02 to 2.96). Patients in the buprenorphine group had less heroin use when receiving 16mg of buprenorphine than placebo patients (95% CI, -0.95 to -0.51). There was no significant difference among the treatment groups in cocaine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				use (95% CI, -0.20 to 0.36) or benzodiazepine use (95% CI, -0.52 to 0.02). Secondary: Not reported
Daulouede et al.[65] (2010) Buprenorphine at patient's current dosage SL vs buprenorphine-naloxone at the same buprenorphine dose SL	MC, OL, PRO, XO Patients ≥18 years of age who were receiving stable, maintenance treatment with buprenorphine 2 to 16 mg/day for at least six months	N=53 5 days	Primary: Patient-rated global satisfaction with study medication Secondary: Well-being in the past 24 hours, tablet taste, tablet size, SL dissolution time, patient preference and adverse events	Primary: Daily mean VAS score for global satisfaction was similar between buprenorphine (6.83 to 7.04) and buprenorphine-naloxone (6.89 to 7.38; P=0.781). Secondary: Daily mean VAS score for well-being in the past 24 hours were similar between buprenorphine (7.17) and buprenorphine-naloxone (6.33 to 7.04; P=0.824). Patients preferred buprenorphine-naloxone over buprenorphine with regard to tablet size (6.83 to 7.02 vs 5.29 to 5.76; P=0.151), tablet taste (6.83 to 6.98 vs 2.45 to 2.74; P=0.57) and SL dissolution time (6.62 to 6.84 vs 3.73 to 3.92; P=0.751), though no statistical significance was reached. On day five, 54 and 31% of patients indicated preference to buprenorphine-naloxone and buprenorphine, respectively. Fifteen percent of patients indicated that they had no preference (P value not reported). Seventy-one percent of patients also indicated that they would like to continue treatment with buprenorphine/naloxone. Patients were more likely to want to continue treatment with buprenorphine/naloxone if they had a history of injecting buprenorphine. Twenty-three adverse events were reported during study period. The most commonly reported adverse events were fatigue, hyperhidrosis, diarrhea and headache.
Strain et al.[66] (2011) Buprenorphine soluble film 16 mg SL daily	RCT Patients 25 to 56 years of age with opioid dependence	N=34 5 days	Primary: Change in COWS scores Secondary: Pupillometry, VAS	Primary: No significant differences were observed between buprenorphine and buprenorphine-naloxone with respect to baseline COWS scores (9.1 and 10.1, respectively) and peak post-administration COWS scores (4.2 and 5.7, respectively). COWS scores improved significantly at one hour after dose administration in both treatment groups compared to baseline (P

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs buprenorphine-naloxone soluble film 16 mg SL daily			and subjective adjective rating scales and adverse events	values not reported). Secondary: In both treatment groups, pupil diameter decreased, rating on good effects were elevated, and ratings on bad effects and high feeling remained relatively low after dose administration (data not reported). The most common adverse events were those consistent with opioid withdrawal. Four patients reported mild non-ulcerous irritation of oral mucosa, and one patient with a history of hepatitis C had clinically significant elevation of liver function tests.
Minozzi et al.[67] (2009) Buprenorphine vs buprenorphine-based treatment (one study) or clonidine (one study)	SR (2 RCTs) Patients 13 to 18 years of age with opioid dependence	N=190 2 to 12 weeks	Primary: Drop-out rate, opioid-positive urine test results or self-reported drug use, tolerability and rate of relapse Secondary: Enrollment in other treatment, use of other substances of abuse, overdose, criminal activity and social functioning	Primary: The authors stated that more clinical trials, especially ones involving methadone, were needed to draw a conclusion in the detoxification treatment for opioid dependent adolescents. *Buprenorphine vs clonidine* There were no significant differences between buprenorphine and clonidine in drop-out rate (RR, 0.45; 95% CI, 0.20 to 1.04) or duration and severity of withdrawal symptoms (WMD, 3.97; 95% CI, -1.38 to 9.32). *Buprenorphine-naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)* Drop-out rate and relapse rate were significantly higher with detoxification compared to maintenance treatment (RR, 2.67; 95% CI, 1.85 to 3.86; RR, 1.36; 95% CI, 1.05 to 1.76, respectively). No significant differences were seen in opioid positive urine test results (RR, 1.03; 95% CI, 0.82 to 1.28). Self-reported drug use was higher with detoxification compared to maintenance treatment (RR, 1.36; 95% CI, 1.05 to 1.76). Secondary: *Buprenorphine vs clonidine* Patients receiving buprenorphine were more likely to receive psychosocial or naltrexone treatment (RR, 11.00; 95% CI, 1.58 to 76.55). *Buprenorphine-naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)*

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Self-reported alcohol and marijuana use were similar between the two groups (RR, 1.13; 95% CI, 0.63 to 2.02; RR, 1.58; 95% CI, 0.83 to 3.00, respectively). More patients in the detoxification group reported use of cocaine (RR, 8.54; 95% CI, 1.11 to 65.75).
Strain et al.[68] (2000) Buprenorphine 4 mg to 16 mg per day vs buprenorphine-naloxone SL tablets 1-0.25, 2-0.5, 4-1, 8-2, 16-4 mg per day vs hydromorphone 2 and 4 mg intramuscular vs placebo	DB, DD, PC Adults with active opioid abuse, but not physically dependent	N=7	Primary: Peak drug effect; physiologic and psychomotor measures Secondary: Not reported	Primary: Dose-related increases in ratings of Drug Effects, High, Good Effects, and Liking were seen for hydromorphone, for buprenorphine, and for the combination of buprenorphine-naloxone. The predominant effects were seen with the highest doses tested (hydromorphone 4 mg, buprenorphine-naloxone 8-2 and 16-4 mg, and buprenorphine 8 and 16 mg). None of the treatments produced significant changes in ratings of Bad Effects or Sick. For ratings of Drug Effects, only the two higher doses of buprenorphine alone (8 and 16 mg) produced significantly increased ratings compared to placebo ($P<0.05$ and $P<0.01$, respectively). The combination dose of 8-2 mg and 16-4 produced ratings of drug effects that were lower than those produced by the buprenorphine dose of 8 mg. The differences between buprenorphine alone and buprenorphine-naloxone doses were not statistically significant for these or any other measures. None of the treatments produced significant changes on measures of blood pressure, heart rate, or respiratory rate. There were no significant differences in psychomotor effects among the treatments. Secondary: Not reported
Fudala et al.[69] (2003) <u>RCT</u> Buprenorphine-naloxone SL tablets 16-4 mg	DB, MC, PC, RCT, followed by OL phase Patients 18 to 59 years of age who met the diagnostic	N=326 (RCT) N=461 (OL) RCT: 4 weeks OL: 48 to 52 weeks	Primary: Percentage of urine samples negative for opiates and the subjects' self-reported craving for opiates	Primary: <u>RCT</u> The DB trial was terminated early because buprenorphine-naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. The percentages of urine tests that were opiate-negative were 17.8% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs buprenorphine SL tablets 16 mg daily vs placebo <u>OL Phase</u> Buprenorphine-naloxone up to 24-6 mg daily	criteria for opiate dependence and were seeking opiate-substitution pharmacotherapy		Secondary: Impressions of overall status since enrollment in the study and since the previous visit, percentages of urine samples that were negative for other drugs of abuse, subject retention, and rates of adverse medical events	buprenorphine-naloxone group, 20.7% in the buprenorphine group and 5.8% in the placebo group (P<0.001 for both comparisons). The mean craving scores in the buprenorphine-naloxone group and the buprenorphine group were significantly lower than those in the placebo group (P<0.001 for both comparisons). Secondary: The overall health and well-being of the subjects in the buprenorphine-naloxone group and buprenorphine group improved to a significantly greater extent than they did in the placebo group, as measured by a global-impression rating scale (P<0.001 for both groups vs placebo). Subjects' self-assessments of their overall status relative to the previous assessment also showed improvements in all treatment groups (P=NS). The clinicians' ratings of their impressions of the subjects' status relative to the start of the study were generally lower than the subjects' own ratings but showed similar improvements. The frequency of cocaine-positive samples did not differ significantly among the groups (45% in the buprenorphine-naloxone group, 44% in the group that received buprenorphine alone, and 40% in the placebo group). Benzodiazepines were detected in 10% of patients. Amphetamines, barbiturates, and methadone were each detected in <5% of the samples. The rate of adverse events did not differ significantly among the groups (78% in the buprenorphine-naloxone group, 85% in the buprenorphine group, and 80% in the placebo group). <u>OL Phase</u> The percentage of opiate-negative urine samples ranged from 35.2% to 67.4% in multiple assessments. The overall rate of opiate use was lower than that in the DB trial, whereas the use of cocaine or benzodiazepines remained relatively constant.
Lofwall et al.[70]	DB, MC, RCT	N=428	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2018) Buprenorphine subcutaneously weekly (first 12 weeks; phase 1) and monthly (last 12 weeks; phase 2) (SC-BPN group) vs buprenorphine sublingual with naloxone (24 weeks) (SL-BPN/NX group)	Patients 18 to 65 years of age diagnosed with and seeking treatment for moderate-to-severe opioid use disorder, considered to be good candidates for buprenorphine treatment based on medical and psychosocial history, and willing to use reliable contraception	6 months	Response rate (10% margin for NI) and the mean proportion of opioid-negative urine samples for 24 weeks (11% margin for NI) Secondary: Mean percentage of opioid-negative samples examined by a cumulative distribution function for weeks four to 24 and study retention	Both primary outcomes met prespecified criteria for noninferiority. The response rates were 14.4% for the SL-BPN/NX group and 17.4% for the SC-BPN group, a 3.0% difference (95% CI, -4.0% to 9.9%; P<0.001). The proportion of opioid-negative urine samples was 28.4% for the SL-BPN/NX group and 35.1% for the SC-BPN group, a 6.7% difference (95% CI, -0.1% to 13.6%; P<0.001). Secondary: The cumulative distribution function for the SC-BPN group (26.7%) was statistically superior to the cumulative distribution function for the SL-BPN/NX group (0; P=0.004). Injection site adverse events (none severe) occurred in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group.
Woody et al.[71] (2008) Buprenorphine-naloxone 24 mg/day for 9 weeks, then tapered to week 12 (extended) vs buprenorphine-naloxone up to 14 mg/day, then tapered to day 14 (detox)	RCT Opioid-addicted youth 15 to 21 years of age	N=152 12 weeks (extended) 14 day (detox)	Primary: Opioid-positive urine test result at weeks four, eight, and 12 Secondary: Proportion of patients remaining in treatment; reported opioid use, injection use, non-study addiction treatments	Primary: Patients in the detox group (61%) had higher proportions of opioid-positive urine test results at week four compared to the extended treatment group (26%; P=0.09). Patients in the detox group (54%) had higher proportions of opioid-positive urine test results at week eight compared to the extended treatment group (23%; P=0.09). Patients in the detox group (51%) had higher proportions of opioid-positive urine test results at week eight compared to the extended treatment group (43%; P=NS). Secondary: By week 12, 20.5% of detox patients remained in treatment vs 70% of extended treatment patients (P<0.001). During weeks one through 12, patients in the extended treatment group reported less opioid use (P<0.001), injecting (P=0.01), and non-study

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				addiction treatment (P<0.001) compared to the detox group.
Weiss et al.[72] POATS (2011) Phase 1 Buprenorphine-naloxone induction and two-week stabilization at 8 to 32 mg/day of buprenorphine, followed by two-week taper and eight-week post medication follow-up Phase 2 Buprenorphine-naloxone at 8 to 32 mg/day of buprenorphine for 12 weeks followed by four-week taper and eight-week follow-up (Phase 2) Patients who did not have successful outcome at week 12 proceeded to Phase 2. All patients were	MC, RCT Patients ≥18 years of age who met DSM-IV criteria for opioid dependence and who were seeking treatment	Phase 1 N=653 12 weeks Phase 2 N=360 24 weeks	Primary: Percentage of patients achieving successful outcome Secondary: Adverse events	Primary: In Phase 1, successful outcome was defined by self-reported opioid use on no more than four days in a month, absence of two consecutive opioid-positive urine test results, no additional substance use disorder treatment and no more than one missing urine sample during the past 12 weeks. Overall, 43 of 653 patients (6.6%) had successful outcome with brief buprenorphine-naloxone treatment. In Phase 2, successful outcome was defined by abstinence from opioids during week 12 and at least two of the previous three weeks (during weeks nine to 11). One hundred and seventy-seven of 360 patients (49.2%) achieved successful outcome in the extended buprenorphine-naloxone treatment. However, the success rate at week 24 dropped to 8.6% (P<0.001 compared to week 12). No differences were seen between patients who received standard medical management and those who received additional opioid dependence counseling. Secondary: The most common adverse events were headache, constipation, insomnia, nasopharyngitis, and nausea. Twelve and 24 serious adverse events were reported in Phase 1 and 2, respectively. Psychiatric symptoms, particularly depression leading to hospitalization (N=5), were the most common serious adverse events, all of which occurred soon after completion of treatment taper.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
randomized to receive standard medical management or standard medical management plus opioid dependence counseling prior to entering each study phase.				
Bell et al.[73] (2007) Buprenorphine-naloxone	RCT Heroin users seeking maintenance treatment	N=119 3 months	Primary: Retention in treatment and heroin use at three months Secondary: Not reported	Primary: At three months, 57% randomized to unobserved treatment, and 61% randomized to observed treatment were retained in the heroin treatment program (P=0.84). On an intention-to-treat analysis, reductions in days of heroin use in the preceding month, from baseline to three months, did not differ significantly; 18.5 days (95% CI, 21.8 to 15.3) and 22 days (95% CI, 24.3 to 19.7), respectively (P=0.13). Secondary: Not reported
Fiellin et al.[74] (2008) Buprenorphine-naloxone	OS Patients meeting criteria for opioid dependence	N=166 2 to 5 years	Primary: Retention in treatment; percentage of opioid-negative urine specimens Secondary: Percentage of cocaine-negative urine specimens; buprenorphine dose; patient satisfaction; serum transaminases;	Primary: During the follow-up period, 40 patients left treatment. A total of 91% of urine specimens had no evidence of illicit opioids. Secondary: Overall, 96% had no evidence of cocaine; 98% of tested urines had no evidence of benzodiazepines; 99% of tested urines had no evidence of methadone. The mean dose of buprenorphine-naloxone was 17 mg. The mean score on the patient satisfaction instruments was 86 out of a possible 95.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			adverse events	No patients developed elevations in their aspartate aminotransferase or alanine aminotransferase values that required changes in buprenorphine-naloxone dose or discontinuation. No serious adverse events directly related to buprenorphine-naloxone treatment occurred over the two to five-year follow-up period.
Hoffman et al.[75] (2017) Buprenorphine-naloxone rapidly dissolving sublingual tablet (Zubsolv®)	MC, OL, ES Adults aged 18 to 65 years and in generally good health, who met DSM-IV criteria for opioid dependence in the past 12 months and who had completed a study of induction/ stabilization treatment using buprenorphine-naloxone rapidly dissolving sublingual tablet	N=665 24 weeks	Primary: Safety (including adverse events, vital signs, and lab values) Secondary: Efficacy (including cravings, severity of dependence, quality of life, urine drug screens)	Primary: In all, 258 patients (38.8%) experienced 557 treatment-emergent adverse events, of which headache (21 patients; 3.2%) and constipation (20 patients; 3.0%) were the most frequently reported. A total of 71 patients (10.7%) had 100 treatment-emergent adverse events considered related to treatment with buprenorphine- naloxone; constipation was the most common (19 patients, 2.9%). In all, 29 patients had laboratory abnormalities that were considered treatment-emergent; three patients discontinued the study due to increased levels of aspartate and alanine aminotransferase (n=2), and gamma glutamyl transferase (n=1), which were primarily related to hepatitis C and liver function, but also considered possibly related to treatment. Seven patients experienced vital sign abnormalities that were considered treatment-emergent; one patient had an increase in blood pressure of moderate intensity that was determined to be possibly related to treatment. Secondary: Craving scores showed continued improvement on 100-mm visual analog scale (mean change from primary trial baseline, −52.8 at screening; mean change from extension trial baseline, −60.5 at week 24). Reductions in addiction severity from baseline of both the primary and extension trial were maintained through week 24 on multiple assessments, as were improvements in quality of life on Short Form 36. Employment increased by 15% and mean (SD) hours worked per week increased by 4.6 (20.1) from baseline to study end. Urinalysis results were positive for buprenorphine in more than 90% of participants through the week 20 assessment, and were positive in 88.8% at week 24. Positive screens for non-buprenorphine opiates were observed in 24.4% of participants on day one, 29.6% at week four, 24.7% at week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				eight, 22.0% at week 12, 24.6% at week 16, 21.0% at week 20, and 24.1% at week 24.
Gunderson et al.[76] (2016) Buprenorphine-naloxone rapidly dissolving sublingual tablet (Zubsolv®) vs buprenorphine-naloxone film (Suboxone®)	XO Adults aged 18 to 65 years and in generally good health, who met DSM-IV criteria for opioid dependence in the past 12 months, agreed to abstain from opioid use and other addictive drugs, and demonstrated at least mild withdrawal predose on day 1	N=701 Days 1 to 2: induction Days 3 to 22: OL stabilization Day 15: treatments were switched	Primary: Retention in treatment at each visit, opioid withdrawal Secondary: Adverse events	Primary: Of the 287 patients who switched from sublingual tablet to film and 279 patients who switched from film to sublingual tablet at day 15, 8.7% and 6.1% withdrew, respectively. Reductions in opioid withdrawal and cravings were similar with both formulations through day 15; after switching treatment, reductions were maintained through day 22 in both groups. Preference ratings at day 22 (patients had received both formulations) favored sublingual tablet for taste, mouthfeel, ease of administration, and overall preference (all P<0.0001). Secondary: During the entire OL phase, the incidence of treatment-related adverse events was 8.3% (53/635) with sublingual tablet and 7.5% (47/630) with film. Of treatment-related adverse events, constipation occurred in 1.9% (12/635) of patients receiving sublingual tablet and 2.2% (14/630) of patients receiving film. During the open-label stabilization phase from days three to 15, the incidences of treatment-related adverse events in the sublingual tablet and film groups were 11.8% (42/357) and 10.8% (37/344), respectively (P=0.67). The most common adverse events were constipation (2.8 vs 3.5%) and headache (1.4 vs 2.0%).
Kakko et al.[77] (2007) Buprenorphine-naloxone (stepped treatment) vs methadone (maintenance treatment)	RCT Patients >20 years of age with heroin dependence for >1 year	N=96 24-day induction phase, followed by a 6 month follow-up phase	Primary: Retention in treatment Secondary: Completer analyses of problem severity (Addiction Severity Index); proportion of urine samples free of illicit drugs	Primary: The 6-month retention was 78% with buprenorphine-naloxone stepped treatment and methadone maintenance therapy being virtually identical (adjusted OR, 1.02; 95% CI, 0.65 to 1.60). The proportion of urine samples free of illicit opiates over time increased and ultimately reached approximately 80% in both arms at the end of the study (P=0.00003). No difference between the two groups was found (P=0.87). Secondary: Problem severity as measured by the Addiction Severity Index decreased over time (P<0.000001). No difference between the treatment arms was found (P=0.90).
Hser et al.[78]	OL, RCT	N=1267	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2014) Buprenorphine-naloxone vs methadone Doses were titrated as determined by the local study physician	Opioid-dependent individuals	24 weeks	Treatment completion (the participant continuing in the assigned medication group for 24 weeks without being withdrawn), treatment retention (days in treatment since randomization until the last day of medication during the 24 weeks of treatment) Secondary: Not reported	Fewer buprenorphine-naloxone participants (46%) than methadone participants (74%) completed treatment (P<0.01) at 24 weeks. Doses of methadone > 60 mg demonstrated 80% or better retention, with 120 mg or higher showing a 91% completion rate. In contrast, buprenorphine-naloxone doses and retention rates showed a linear relationship, with increasing dose yielding improved retention, with the highest dose category of 30–32 mg buprenorphine-naloxone resulting in a completion rate of about 60%. Secondary: Not reported
Kamien et al.[79] (2008) Buprenorphine-naloxone 8-2 mg daily vs buprenorphine-naloxone 16-4 mg daily vs methadone 45 to 90 mg daily	DB, DD, RCT Patients ≥18 years of age who met criteria for opioid dependence and who were using heroin or prescription opioids or receiving methadone maintenance treatment	N=268 17 weeks	Primary: Amount of opioid abstinence achieved over time Secondary: Proportion of patients who achieved 12 consecutive opioid-negative samples, proportion of patients with successful inductions, medication	Primary: The percentage of opioid-free urine samples over time did not differ significantly among drug groups (P=0.81) or among drug doses (P=0.46). Secondary: The proportion of patients who had at least 12 consecutive opioid-negative urine samples were as follows: 10% (buprenorphine-naloxone 8-2 mg) 17% (buprenorphine-naloxone 16-4 mg), 12% (methadone 45 mg), and 16% (methadone 90 mg). The percentage of patients with at least 12 consecutive opioid-negative urine samples differed by dose (8 vs 16 mg buprenorphine-naloxone; P<0.001, 45 vs 90 mg methadone; P=0.02), but not by drug (8 mg buprenorphine-naloxone vs 45 mg methadone; P=0.18, 16 mg buprenorphine-naloxone vs 90 mg methadone; P=0.22). Those receiving higher doses of methadone or buprenorphine-naloxone were more likely to have at least 12 consecutive opioid-negative urine samples than those receiving lower doses.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			compliance, non-opioid illicit drug use, and treatment retention	Successful inductions occurred in 80.5, 81.0, 82.7 and 82.9% of the patients receiving buprenorphine-naloxone 8-2 mg, buprenorphine-naloxone 16-4 mg, methadone 45 and 90 mg, respectively. There were no significant differences among the treatment groups (P=0.22 to P=0.98). Medication compliance did not differ significantly among the treatment groups (P=0.41). Non-opioid drug use did not change significantly over time, nor did it differ significantly across groups (P=0.32 to P=0.83). Treatment retention did not differ significantly in the low dose groups (P=0.09) or in the high dose groups (P=0.28).
Hser et al.[80] (2016) Buprenorphine-naloxone vs methadone	MC, OL Opioid-dependent participants entering opioid treatment programs in the USA between 2006 and 2009	N=1,080 (mortality) N=795 (other outcomes) Mean of 4.5 years	Primary: Mortality, opioid use Secondary: Not reported	Primary: There were 23 deaths in the buprenorphine-naloxone group (n=630, or 3.6%) and 26 deaths in the methadone group (n=450, or 5.8%); the difference was not statistically different (P=0.10). Opioid use was higher among participants randomized to buprenorphine-naloxone relative to methadone at the follow-up interview (42.8 vs 31.7% positive opioid urine specimens, P<0.01; 5.8 vs 4.4 days of past 30-day heroin use, P<0.05). Overall, 46.8% participants were currently using opioids as indicated by a positive urine test or self-reported past-30-day opioid use with significantly more opioid use among buprenorphine-naloxone than methadone participants (50.9 vs 41.1%). For both groups, opioid use drops immediately after entering the trial, increases somewhat thereafter (approximately six months after randomization for both groups), reaches a high point approximately 10 to 12 months post-randomization, and then gradually tapers off; relative to those in buprenorphine-naloxone, opioid use by individuals in the methadone condition dropped more and had lower relapse rates immediately after the trial, although the groups converged in approximately two years post-randomization. Participation in methadone or buprenorphine-naloxone treatment, relative to no methadone or buprenorphine-naloxone treatment, was associated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with reduced opioid use. The estimated reduction on days of opioid use was 8.5 days for methadone and 7.8 days for buprenorphine-naloxone treatment, respectively, with no statistically significant difference between the two types of treatments (P=0.06). Secondary: Not reported

*Synonym for acetaminophen.
Study abbreviations: AC=active controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative reduction, SB=single-blind, SR=systematic review, XO=crossover
Miscellaneous abbreviations: ARCI=addiction research center inventory, COWS=clinical opiate withdrawal scale, DSM=Diagnostic and Statistical Manual, FDA=Food and Drug Administration, PDI=pain disability index, SL=sublingual, VAS=visual analog scale, WMD=weighted mean difference

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
Simojoki et al. conducted a retrospective analysis to evaluate the effects of switching patients from buprenorphine to buprenorphine and naloxone.[81] During the first four weeks, 50% of the patients reported adverse events compared to 26.6% of patients after four months of therapy. During the follow-up period, buprenorphine and naloxone was misused by five patients. The patients reported that injecting buprenorphine and naloxone was like injecting "nothing" with regards to euphoria, or that it was a bad experience. The authors concluded that buprenorphine and naloxone appears to have less potential for abuse compared to buprenorphine alone.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 14. Relative Cost of the Opiate Partial Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Buprenorphine†	buccal film, extended release solution, injection, sublingual tablet, transdermal patch	Belbuca®*, Buprenex®*, Butrans®*, Sublocade®	$$$$$	$$$
Butorphanol	injection, nasal spray	N/A	N/A	$$
Nalbuphine	injection	N/A	N/A	$
Combination Products				
Buprenorphine and naloxone†	sublingual film*, sublingual tablet*	Suboxone®*, Zubsolv®	$$$$$	$$$$
Pentazocine and naloxone	tablet	N/A	N/A	$$$$

*Generic is available in at least one dosage form or strength.
†Generic buprenorphine products were placed on prior authorization due to abuse potential through P&T and Drug Utilization Review.
N/A=Not available

X. Conclusions

Currently, there is no standard opiate regimen that will satisfy the pain needs of all patients. The role of the partial opiate agonists in pain management must be weighed against the severity of pain and appropriateness of use. Opiate selection should take into account pain etiology, pain quality and severity, anticipated duration of therapy, routes of administration, and comorbid conditions. Partial opiate agonists have a ceiling to their effect and are less likely than full agonists to cause physical dependence; however, none of the agents are entirely free of dependence liability.[3-5]

In January 2022 the FDA released a Drug Safety Communication warning that dental problems have been reported with medicines containing buprenorphine that are dissolved in the mouth. The dental problems, including tooth decay, cavities, oral infections, and loss of teeth, can be serious and have been reported even in patients with no history of dental issues. Despite these risks, buprenorphine is an important treatment option for opioid use disorder (OUD) and pain, and the benefits of these medicines outweigh the risks.[82]

Patients with cancer often suffer from pain due to tumor infiltration, which significantly affects their quality of life. For the treatment of cancer pain, guidelines recommend the use of an opiate agonist in patients with moderate to severe pain.[18,20] According to the National Comprehensive Cancer Network guidelines, mixed agonists-antagonists have limited usefulness in the treatment of cancer pain.[18] For the treatment of chronic noncancer pain, guidelines recommend the use of an opiate agonist in patients with moderate to severe pain.[19,21-22] The selection of therapy should be based on patient preference, ease of administration, prior treatment trials, tolerance, adverse events, and risk for misuse or abuse.[22] According to the Veterans Affairs, Department of Defense guidelines, the use of mixed agonist-antagonists should be avoided for the treatment of chronic pain as they may precipitate withdrawal in patients who have physical dependence.[22] There are limited studies directly comparing the efficacy and safety of the partial opiate agonists. Efficacy has been demonstrated in short-term trials for the acute treatment of noncancer pain.[24-40]

Interventions for opioid-related conditions (dependence, abuse, intoxication, and withdrawal) include psychosocial therapy and pharmacotherapy with long-acting opioids.[16] The selection of therapy should be based on patient preference, past response to therapy, probability of achieving and maintaining abstinence, and the effects of continued use of opioids.[16] For the maintenance treatment of opioid dependence, guidelines recommend the use of methadone or buprenorphine and naloxone as first-line therapy.[16,17,23] Patients who are transferred from long-acting opioids to buprenorphine should begin therapy with buprenorphine monotherapy, followed by conversion to buprenorphine and naloxone shortly thereafter.[16] Buprenorphine monotherapy is preferred during pregnancy. Clinical trials have demonstrated that buprenorphine (with or without naloxone) reduces opioid use, retains patients in treatment, and is associated with minimal adverse events when used for the detoxification and maintenance treatment of opioid dependence.[41-80] Studies directly comparing buprenorphine (with or without naloxone) to methadone have shown mixed results, which is thought to be due to differences in the dosing regimens used.[52-58,61-63,74-80] Compared to methadone, buprenorphine has a lower potential for abuse and is safer in an overdose situation. However, it can still produce euphoria and physical dependence. The fixed-dose combination of buprenorphine and naloxone has less potential for abuse and diversion than buprenorphine monotherapy. Currently available guidelines for the treatment of opioid use disorder generally support that buprenorphine/naloxone should be used for the induction, stabilization and maintenance phases of treatment for most patients. Preference for any formulation over another is not established. These guidelines do not discuss the use of the long-acting buprenorphine products.[16,17,23]

There is insufficient evidence to support that one brand opiate partial agonist is safer or more efficacious than another. Due to the potential risk of abuse, buprenorphine and buprenorphine-naloxone should be managed through the medical justification portion of the prior authorization process. Approval should only be granted for patients with a diagnosis of opioid use disorder. Treatment should only be prescribed by a licensed physician who qualifies for a waiver under the Drug Addiction Treatment Act (DATA) and has notified the Center for Substance Abuse Treatment of the intention to treat addiction patients and has been assigned a DEA (X) number.

Therefore, all brand opiate partial agonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand opiate partial agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

No brand or generic buprenorphine containing product should be placed in preferred status. Alabama Medicaid may accept cost proposals from manufacturers to designate one or more preferred agents. Preferred agents may be managed through the "preferred with clinical criteria" program.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Selective Serotonin Agonists
AHFS Class 283228
November 9, 2022

I. Overview

Migraine is an idiopathic headache disorder, which is characterized by moderate to severe pulsating pain that can last up to 72 hours. It is often accompanied by nausea, photophobia, lightheadedness, and vomiting. The successful treatment of a migraine headache is often defined as one or more of the following endpoints in clinical trials: 1) pain free after two hours; 2) improvement of headache from moderate or severe to mild or none after two hours; 3) consistent efficacy in two of three attacks; 4) no headache recurrence and no further drug intake within 24 hours after successful treatment (sustained pain relief or pain free). Cluster headache is a unilateral headache attack of short duration (15 to 180 minutes), which is characterized by severe orbital, supraorbital, or temporal pain. The headache is frequently accompanied by at least one of the following autonomic symptoms: ptosis, miosis, lacrimation, conjunctival injection, rhinorrhea, and nasal congestion. During a cluster period, the attacks may occur up to eight times per day. Cluster headaches are relatively uncommon compared to migraine headaches and primarily affect men.[1-6]

The selective serotonin agonists (triptans and lasmiditan) are approved for the treatment of acute migraines, with or without aura. The subcutaneous formulation of sumatriptan is also approved for the treatment of cluster headaches. The triptans are chemically and structurally related to the neurotransmitter 5-hydroxytryptamine (5-HT), which is present in the blood, as well as in the peripheral and central nervous systems. Triptans and lasmiditan are potent, highly selective 5-HT_1 receptor agonists, with no significant affinity for other 5-HT subgroups. They stimulate receptors located on cerebral vessels to redistribute blood flow and relieve pain.[7-20]

The selective serotonin agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, and sumatriptan-naproxen are available in a generic formulation. This class was last reviewed in August 2020.

Table 1. Selective Serotonin Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Almotriptan	tablet	N/A	almotriptan
Eletriptan	tablet	Relpax®*	eletriptan
Frovatriptan	tablet	Frova®*	frovatriptan
Lasmiditan	tablet	Reyvow®	none
Naratriptan	tablet	Amerge®*	naratriptan
Rizatriptan	orally disintegrating tablet, tablet	Maxalt®*, Maxalt MLT®*	rizatriptan
Sumatriptan	nasal powder, nasal spray, subcutaneous injection, tablet	Imitrex®*, Onzetra Xsail®, Tosymra®, Zembrace®	sumatriptan
Zolmitriptan	nasal spray, orally disintegrating tablet, tablet	Zomig®*, Zomig ZMT®*	zolmitriptan
Combination Products			
Sumatriptan and naproxen	tablet	Treximet®*	sumatriptan and naproxen

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the selective serotonin agonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Selective Serotonin Agonists

Clinical Guideline	Recommendation(s)
American Academy of Neurology and the American Headache Society: **Evidence-based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults (2012)**[1] (Reaffirmed July 2015)	• The following medications are established as effective and should be offered for migraine prevention: o Antiepileptic drugs: divalproex sodium, sodium valproate, topiramate. o β-blockers: metoprolol, propranolol, timolol o Triptans: frovatriptan for short-term menstrually associated migraine prevention. • The following medications are probably effective and should be considered for migraine prevention: o Antidepressants: amitriptyline, venlafaxine. o β-blockers: atenolol, nadolol. o Triptans: naratriptan, zolmitriptan for short-term menstrually associated migraine prevention. • The following medications are possibly effective and may be considered for migraine prevention: o Angiotensin converting enzyme inhibitors: lisinopril. o Angiotensin receptor blockers: candesartan. o α 1 agonists: clonidine, guanfacine. o Antiepileptic drugs: carbamazepine. o β-blockers: nebivolol, pindolol. • Evidence is conflicting or inadequate to support or refute the use of the following medications for migraine prevention: o Antiepileptic drugs: gabapentin. o Antidepressants: ▪ Selective serotonin reuptake inhibitor/selective/serotonin-norepinephrine reuptake inhibitors: fluoxetine, fluvoxamine. ▪ Tricyclics: protriptyline. o Antithrombotics: acenocoumarol, Coumadin, picotamide. o β-blockers: bisoprolol. o Calcium-channel blockers: nicardipine, nifedipine, nimodipine, verapamil. o Acetazolamide. o Cyclandelate. • The following medication is established as ineffective and should not be offered for migraine prevention: o Lamotrigine. • The following medication is probably ineffective and should not be considered for migraine prevention: o Clomipramine. • The following medications are possibly ineffective and may not be considered for migraine prevention: o Acebutolol. o Clonazepam. o Nabumetone. o Oxcarbazepine. o Telmisartan.
American Academy of Neurology and the American Headache Society: **Pharmacological**	<u>Pediatric migraine prevention</u> • Clinicians should inform patients and caregivers that in clinical trials of preventive treatments for pediatric migraine, many children and adolescents who received placebo improved and most preventive medications were not superior to

Clinical Guideline	Recommendation(s)
Treatment for Pediatric Migraine Prevention (2019) and **Acute Treatment of Migraine in Children and Adolescents (2018)**[2,3]	placebo. • Clinicians should engage in shared decision-making regarding the use of short-term treatment trials (a minimum of two months) for those who could benefit from preventive treatment. • Clinicians should discuss the evidence for amitriptyline combined with cognitive behavioral treatment (CBT) for migraine prevention, inform patients of the potential side effects of amitriptyline including risk of suicide, and work with families to identify providers who can offer this type of treatment. • Clinicians should discuss the evidence for topiramate and propranolol for migraine prevention in children and adolescents and their side effects in this population. • There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents. • Clinicians must consider the teratogenic effects of topiramate and valproate in their choice of migraine prevention therapy recommendations to patients of childbearing potential. • Clinicians must recommend daily folic acid supplementation to patients of childbearing potential who take topiramate or valproate. <u>Pediatric migraine treatment</u> • Clinicians should prescribe ibuprofen oral solution (10 mg/kg) as an initial treatment option to reduce pain in children and adolescents with migraine. • For adolescents with migraine, clinicians should prescribe sumatriptan/naproxen tablet, zolmitriptan nasal spray (NS), sumatriptan NS, rizatriptan orally disintegrating tablet, or almotriptan tablet to reduce headache pain. • Clinicians should counsel patients and families that a series of medications may need to be used to find treatments that most benefit the patient. • Clinicians should offer an alternate triptan, if one triptan fails to provide pain relief, to find the most effective agent to reduce migraine symptoms. • Clinicians may prescribe a nonoral route when headache peaks in severity quickly, is accompanied by nausea or vomiting, or oral formulations fail to provide relief. • Clinicians should counsel patients and families that if their headache is successfully treated by their acute migraine medication, but headache recurs within 24 hours of their initial treatment, taking a second dose of acute migraine medication can treat the recurrent headache. • In adolescents whose migraine is incompletely responsive to a triptan, clinicians should offer ibuprofen or naproxen in addition to a triptan to improve migraine relief. • Clinicians must not prescribe triptans to those with a history of ischemic vascular disease or accessory conduction pathway disorders to avoid the morbidity and mortality associated with aggravating these conditions. • Clinicians may consider referral of children and adolescents with hemiplegic migraine or migraine with brainstem aura who do not respond to other treatments to a headache specialist to find effective treatment.
American Academy of Family Physicians: **Migraine Headache Prophylaxis (2019)** and **Acute Migraine Headache: Treatment Strategies (2019)**[4,5]	<u>Migraine headache prophylaxis</u> • First-line agents for prophylactic treatment include: divalproex, metoprolol, propranolol, timolol, and topiramate. • Second-line agent for prophylactic treatment include: amitriptyline, atenolol, nadolol, and venlafaxine. • Frovatriptan is a first-line treatment for the prevention of menstrual-associated migraines. Naratriptan and zolmitriptan are second-line treatments for the same indication. • Amitriptyline is considered an option for patients with depression or insomnia

Clinical Guideline	Recommendation(s)
	and is the only tricyclic antidepressant that has substantial data that supports its effectiveness. <u>Acute treatment</u> • First-line treatment options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan), and combined regimens (e.g., acetaminophen/aspirin/caffeine and sumatriptan/naproxen). ▪ Eletriptan has the least cardiovascular risk. ▪ Frovatriptan is recommended for menstrual migraine. • Second-line treatment options include antiemetics, intranasal dihydroergotamine, and ketorolac. • Options for refractory migraine include intravenous dexamethasone, parenteral dihydroergotamine, intravenous magnesium sulfate, opioids, and intravenous valproate.
American Academy of Neurology: **Acute and Preventative Pharmacologic Treatment of Cluster Headache (2010)[6]**	<u>Acute treatment</u> • Subcutaneous sumatriptan, zolmitriptan nasal spray and oxygen should be offered. • Sumatriptan nasal spray and zolmitriptan should be considered. • Cocaine/lidocaine and octreotide may be considered. • There is insufficient evidence to advise on the use of dihydroergotamine nasal spray, somatostatin and prednisone.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the selective serotonin agonists are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Selective Serotonin Agonists[7-20]

Indication	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Acute treatment of cluster headache episodes							✔ *		
Acute treatment of migraine attacks with or without aura in adults	✔	✔	✔	✔	✔		✔	✔	
Acute treatment of migraine attacks with or without aura in adults and pediatric patients 12 years of age and older								✔ †	✔
Acute treatment of migraine headache pain in adolescents 12 to 17 years of age with a history of migraine attacks with or without aura, and who have migraine attacks usually lasting four hours or more	✔								
Acute treatment of migraine with or without aura in adults and pediatric patients six to 17 years of age						✔			

*Subcutaneous injection only.
†Nasal spray only.

IV. Pharmacokinetics

The pharmacokinetic parameters of the selective serotonin agonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Selective Serotonin Agonists[7-20]

Generic Name(s)	Bioavailability (%)	Elimination (%)	Active Metabolites	Serum Half-Life (hours)	Onset (hours)	Duration (hours)
Single-Entity Agents						
Almotriptan	70	Feces (13) Renal (75)	None	3 to 4	1 to 2	Not reported
Eletriptan	50	Renal (9) Non-renal (90)	N-demethylation	4 to 5	1	18
Frovatriptan	24 to 30	Feces (62) Renal (10 to 32)	Desmethyl frovatriptan	25	2	Not reported
Lasmiditan	Not reported	Renal (3)	None	5.7	Not reported	Not reported
Naratriptan	70	Renal (50)	None	5 to 6	1	24
Rizatriptan	40 to 50	Feces (12) Renal (82)	N-monodes-methyl-rizatriptan	2 to 3	0.5	14 to 16
Sumatriptan	14 to 19 (IN)	Feces (40) Renal (57)	None	2 to 3	Not reported (IN)	Not reported (IN)
	15 (PO)				0.5 (PO)	Not reported (PO)
	97 (SC)				0.1 (SC)	Not reported (SC)
Zolmitriptan	102 (IN)* 39 to 48 (PO)	Feces (20 to 30) Renal (60)	N-desmethyl zolmitriptan	2.5 to 3.0	1	24
Combination Products						
Sumatriptan and naproxen	15/95	Feces (40/not reported) Renal (60/95)	None	2/19	Not reported	Not reported

IN=intranasal, PO=oral, SC=subcutaneous
*Relative to oral formulation.

V. Drug Interactions

Major drug interactions with the selective serotonin agonists are listed in Table 5.

Table 5. Major Drug Interactions with the Selective Serotonin Agonists[8]

Generic Name(s)	Interaction	Mechanism
Selective serotonin agonist (almotriptan, eletriptan, frovatriptan, lasmiditan, naratriptan, rizatriptan, zolmitriptan)	Selective serotonin agonists	The concurrent use of selective serotonin agonists with another selective serotonin agonist may increase the risk for vasospastic reactions.
Selective serotonin agonists	Ergot alkaloids	The risk of vasospastic reactions may be increased. Possibly additive vasospastic effects. Use of 5-HT_1 agonists within 24

Generic Name(s)	Interaction	Mechanism
(almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)		hours of treatment with an ergot-containing medication is contraindicated.
Selective serotonin agonists (rizatriptan, sumatriptan, zolmitriptan)	Monoamine oxidase inhibitors	Inhibition of metabolism via monoamine oxidase, subtype-A. Use of certain 5-HT_1 agonists concomitantly with or within two weeks following the discontinuation of monoamine oxidase inhibitors is contraindicated. If it is necessary to use such agents together, naratriptan appears to be less likely to interact with monoamine oxidase inhibitors.
Selective serotonin agonists (almotriptan, eletriptan, frovatriptan, lasmiditan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)	Serotonergic agents (e.g., linezolid, lithium, serotonin reuptake inhibitors, and serotonin/ norepinephrine reuptake inhibitors)	Serotonin syndrome, including agitation, altered consciousness, ataxia, myoclonus, overactive, reflexes, and shivering may occur. The serotonergic effects of these agents may be additive.
Selective serotonin agonists (almotriptan, eletriptan)	Azole antifungals and other potent CYP 3A4 inhibitors	Plasma concentrations of certain 5-HT_1 receptor agonists may be elevated, increasing the pharmacologic and adverse effects. Inhibition of certain 5-HT_1 receptor agonists and first-pass metabolism (CYP3A4) or decreased renal clearance by certain azole antifungal agents is suspected. Eletriptan should not be taken within 72 hours of itraconazole or ketoconazole, and almotriptan should not be taken within seven days of itraconazole or ketoconazole.
Selective serotonin agonists (almotriptan)	Opioids (e.g., hydrocodone, hydromorphone)	Concomitant use of opioids with serotonergic drugs has resulted in serotonin syndrome. If concomitant use is needed, carefully observe the patient, particularly during treatment initiation and dose adjustments. Discontinue opioids if serotonin syndrome is suspected.
Lasmiditan	Breast Cancer Resistant Protein (BCRP) substrates (e.g., methotrexate, sulfasalazine, irinotecan, rosuvastatin)	Concurrent use of lasmiditan and BCRP substrates may result in increased exposure of BCRP substrate.
Lasmiditan	P-glycoprotein (P-gp) substrates (e.g., digoxin, colchicine, sirolimus, apixaban)	Concurrent use of lasmiditan and P-gp substrates may result in Increased exposure of P-gp substrate.
Naproxen	Nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates (e.g., ibuprofen, aspirin)	Coadministration of two NSAIDs or an NSAID and a salicylate may increase the risk of gastrointestinal toxicity including serious bleeding, with little or no increase in efficacy. Such concomitant use should be avoided.
Naproxen	Digoxin	Coadministration of digoxin and NSAIDs may increase digoxin plasma concentrations and prolong the half-life of

Generic Name(s)	Interaction	Mechanism
		digoxin. If concurrent use is required, monitoring of serum digoxin levels is recommended.
Naproxen	Corticosteroids	Concurrent administration of NSAIDs with oral corticosteroids may increase the risk of gastrointestinal ulcer or bleeding. If coadministration is necessary, monitor for signs of bleeding.
Naproxen	Heparin and factor Xa inhibitors	The risk of heparin and factor Xa inhibitor-induced bleeding may be increased by naproxen, including the development of procedure-related epidural or spinal hematomas.
Naproxen	Methotrexate	Naproxen may contribute to reduced renal clearance and increased methotrexate toxicity. Co- administration of some nonsteroidal antiinflammatory drugs with high-dose methotrexate therapy has resulted in death from severe hematologic and gastrointestinal toxicity. Use combination with caution.
Naproxen	Warfarin	Risk of hemorrhagic adverse reactions may be increased and gastric erosion. Monitor warfarin levels.
Rizatriptan	Propranolol	Rizatriptan concentrations may be elevated, increasing the pharmacologic effects and adverse reaction. Inhibition of rizatriptan metabolism by propranolol is suspected.
Naproxen	Angiotensin-converting-enzyme inhibitors	Naproxen may reduce the antihypertensive effect of angiotensin-converting-enzyme inhibitors and may potentiate renal disease states.
Naproxen	Bisphosphonates	Gastrointestinal adverse effects may be increased with concurrent administration of bisphosphonates and naproxen. The mechanism is unknown.
Naproxen	Cyclosporine	The nephrotoxicity of cyclosporine and naproxen may both be increased. Monitor renal function frequently.
Naproxen	Diuretics	Naproxen may reduce the natriuretic effect of furosemide and thiazides. Monitor blood pressure, weight, and signs of renal failure if co administer.
Naproxen	Lithium	Naproxen may reduce renal lithium clearance and cause increase in plasma lithium plasma levels by up to 20%. Monitor for lithium toxicity.
Naproxen	Probenecid	The pharmacologic toxic effects may be increased by probenecid; however, the clinical significance is unknown.
Naproxen	Quinolones	The risk of central nervous system stimulation and seizures from quinolones may be increased by the addition of naproxen. Naproxen may reduce the renal elimination of quinolones.
Naproxen	Serotonin reuptake inhibitors	The risk of upper gastrointestinal bleeding may be increased. Unknown mechanism though prolonged use of serotonin reuptake inhibitors may lead to depletion of serotonin in platelets.
Naproxen	Thienopyridines	May increase the risk of bleeding. Oral naproxen-induced alteration in gastric mucosal function coupled with inhibition of platelet aggregation by thienopyridines may further increase the risk of gastrointestinal bleeding.

VI. Adverse Drug Events

The most common adverse drug events reported with the selective serotonin agonists are listed in Table 6. The boxed warning for the combination product sumatriptan and naproxen is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Selective Serotonin Agonists[7-20]

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Cardiovascular									
Acute coronary syndrome	-	-	-	-	-	-	-	-	≤1
Angina	-	<1	-	-	-	-	-	<1	-
Arrhythmia	-	✔	-	-	-	-	<1	<1	-
Atrial fibrillation	-	<1	-	-	<1	-	<1	<1‖	-
Atrial flutter	-	-	-	-	<1	-	-	-	≤1
Atrial-ventricular block	-	<1	-	-	-	-	-	-	-
Bradycardia	-	<1	<1	-	<1	<1	-	-	-
Chest discomfort	-	-	-	<2	-	-	5	-	3
Chest tightness/pain	<1	1 to 4	2	-	-	<2 to 3	1 to 2‡/3§	2 to 4‡	3
Congestive heart failure	-	-	-	-	-	-	-	-	≤1
Coronary artery vasospasm	-	-	-	-	<1	-	-	<1	-
Cyanosis	-	<1	-	-	-	-	-	<1	-
Electrocardiogram changes	-	-	<1	-	<1	-	<1	-	-
Flushing	-	-	4	-	-	✔	-	-	≤1
Gastrointestinal ischemia	-	✔	-	-	-	-	-	-	-
Heart block	-	-	-	-	-	-	<1	-	-
Heart murmur	-	-	-	-	<1	-	-	-	-
Hypertension	<1	<1	-	-	<1	-	1‡§	<1	≤1
Hypertensive crisis	-	-	-	-	-	-	-	<1	-
Hypotension	-	<1	-	-	<1	-	<1	-	-
Myocardial infarction	-	<1	<1	-	<1	-	-	<1	-
Myocardial ischemia	-	-	-	-	-	-	<1	<1	-
Myocarditis, viral	-	-	-	-	-	-	-	-	≤1
Ischemic heart disease	-	-	-	-	<1	-	-	-	-
Palpitation	<1	✔	1	<2	<1	1	<1	1 to 2‖	>1
Peripheral vascular disease	-	<1	-	-	-	-	-	-	-
PR prolongation	-	-	-	-	<1	-	-	-	-
Premature ventricle contractions	-	-	-	-	<1	-	-	-	-
Prinzmetal angina	-	-	-	-	-	-	<1	-	-
Pulmonary embolism	-	-	-	-	-	-	<1	-	-
QTc prolongation	-	-	-	-	<1	-	-	<1	-

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Significant cardiovascular event	-	-	<1	-	-	-	<1	-	-
Tachycardia	<1	<1	<1	-	-	<1	-	-	≤1
Thrombophlebitis	-	-	-	-	-	-	<1	-	-
Thrombosis	-	-	-	-	-	-	<1	-	-
Transient ischemic attacks	-	-	-	-	<1	-	-	-	-
Vasodilation	<1	-	-	-	-	-	-	-	-
Vasospasm	-	<1	-	-	-	-	-	-	-
Ventricular arrhythmia	-	<1	-	-	-	-	-	-	-
Ventricular extrasystoles	-	-	-	-	-	-	-	-	≤1
Ventricular failure, right	-	-	-	-	-	-	-	-	≤1
Ventricular fibrillation	-	-	-	-	<1	-	-	-	-
Ventricular tachycardia	-	-	-	-	<1	-	-	-	-
Central Nervous System									
Abnormal dreams	-	<1	<1	<2	-	-	-	-	-
Abnormal thinking	-	<1	-	-	-	-	-	-	-
Agitation	-	<1	<1	-	-	<1	<1	-	-
Amnesia	-	<1	<1	-	-	-	1§	-	-
Anxiety	<1	<1	1	<2	-	-	1§	-	≤1
Apathy	-	<1	-	-	-	-	-	-	-
Aphasia	-	<1	-	-	-	-	-	-	≤1
Ataxia	-	<1	<1	-	-	-	-	<1	-
Attention disturbances	-	-	-	-	-	<1†	-	-	≤1
Atypical sensation	-	-	-	-	2 to 4	-	-	-	-
Back pain	<1	✔	<1	-	-	-	-	-	-
Burning	-	-	-	-	-	-	1‖/1‡/7§	-	≤1
Catatonic reaction	-	<1	-	-	-	-	-	-	-
Central nervous system	<1	-	-	-	-	-	-	-	-
Cerebral infarction	-	-	-	-	<1	-	-	-	-
Cerebral ischemia	-	-	-	-	-	-	<1	<1	-
Cerebrovascular accident	-	-	-	-	-	-	<1	-	-
Cerebrovascular disorder	-	<1	-	-	-	-	-	-	-
Change in dreams	<1	-	-	-	-	-	-	-	-
Cognitive changes	-	-	-	<2	-	-	-	-	-
Cold extremities	-	-	-	-	-	<1	-	-	-
Cold sensation	-	-	-	-	-	-	1§	-	≤1
Confusion	-	<1	<1	<2	-	<1	-	-	-
Convulsions	-	-	-	-	-	-	<1	-	-
Dementia	-	<1	-	-	-	-	-	-	-
Depersonalization	-	<1	<1	-	-	-	-	1 to 2‖	-

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Depression	<1	<1	<1	-	<1	-	-	<1	≤1
Disorientation	-	-	-	-	-	-	-	-	≤1
Dizziness	3 to 4*	3 to 7	8	9 to 17	1 to 2	4 to 9	≤2‖/>1‡/≤12§	3 to 6‖/6 to 10‡	4
Drowsiness	-	-	-	-	1 to 2	-	>1‡/3§	-	-
Dysesthesia	-	-	1	-	-	-	-	-	-
Emotional lability	-	<1	<1	-	-	-	-	-	-
Euphoria	<1	<1	<1	<2	-	1	-	-	-
Fatigue	<1	-	5	4 to 6	1 to 2	4 to 7, 1†	≤3‡/1§	-	≥1
Feeling strange	-	-	-	<2	-	-	2 §	-	-
Hallucination	-	<1	-	<2	<1	<1†	<1	<1	-
Headache	✔,1 to 2*	3 to 4	4	-	-	<2 to 2	<1‖/>1‡/2§	<1	-
Hearing loss	-	-	-	-	-	-	1§	-	-
Heaviness	-	-	-	-	-	-	7§	-	-
Hemiplegia	-	<1	-	-	-	-	-	-	-
Hot/cold sensation	-	-	3	-	-	-	-	-	-
Hyperacusis	<1	-	<1	-	-	-	-	-	-
Hyperalgesia	-	<1	-	-	-	-	-	-	-
Hyperesthesia	-	<1	<1	-	-	-	-	1 to 5‖	-
Hyperkinesia	-	<1	-	-	-	-	-	-	-
Hyperreflexia	<1	-	-	-	-	-	-	-	-
Hypertonia	<1	✔	<1	-	-	-	-	-	-
Hypoesthesia	<1	✔	1	-	-	1	-	1 to 2	-
Hypokinesia	-	<1	-	-	-	-	-	-	-
Hypotonia	-	-	<1	-	-	-	-	-	-
Hysteria	-	<1	-	-	-	-	-	-	-
Impaired concentration	<1	-	<1	-	-	-	-	-	-
Incoordination	<1	<1	-	<2	-	<1†	-	-	-
Insomnia	<1	<1	1	-	-	<1	-	<1	≤1
Intracranial pressure increased	-	-	-	-	-	-	<1	-	-
Manic reaction	-	<1	-	-	-	-	-	-	-
Memory impairment	-	-	-	-	-	<1	-	-	-
Mental impairment	-	-	-	-	-	-	-	-	≤1
Migraine	-	<1	-	-	-	-	-	-	-
Nervousness	<1	<1	<1	-	-	-	-	-	≤1
Neurological	-	-	-	-	4 to 7	-	-	-	-
Neuropathy	<1	<1	-	-	-	-	-	-	-
Neurosis	-	<1	-	-	-	-	-	-	-
Nightmares	<1	-	-	-	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Nystagmus	<1	-	-	-	-	-	-	-	-
Oculogyric crisis	-	<1	-	-	-	-	-	-	-
Optic neuropathy	-	-	-	-	-	-	<1	-	-
Pain	-	✔	1	-	2 to 4	-	≤8‡/1 to 2§	2 to 4‖/12 to 18‡	-
Panic	-	-	-	-	<1	-	-	-	-
Paralysis	-	<1	-	-	-	-	-	-	-
Paresthesia	1, <1 to 1	3 to 4	4	3 to 9	1 to 2	3 to 4	<5‖/5‡/3 to 14§	5 to 10‖	2
Personality disorder	-	-	<1	-	-	-	-	-	-
Psychomotor disorders	-	-	-	-	-	-	<1	-	≤1
Psychotic depression	-	<1	-	<2	-	-	-	-	-
Restlessness	<1	-	-	-	-	-	-	-	-
Shakiness	<1	-	-	-	-	-	-	-	-
Sleep disorder	-	<1	-	-	-	-	-	-	-
Sleep disturbance	-	-	-	<2	-	-	-	-	-
Somnolence	<1 to 5*	3 to 7	-	-	-	4 to 8	-	1 to 4‖/5 to 8‡	3
Stupor	-	<1	-	-	-	-	-	-	-
Subarachnoid hemorrhage	-	-	-	-	<1	-	<1	-	-
Tingling sensation	-	-	-	-	-	-	14§		
Twitching	-	<1	-	-	-	-	-	-	-
Vertigo	<1	✔	<1	<2	-	<1	≤2‖/2‡/≤12§	2‡	≤1
Warm/cold sensation	-	-	-	-	-	-	2 to 3‡	4‖/5 to 7‡	-
Warm/hot sensation	-	-	-	-	-	1	≤11§	-	>1
Weakness	-	<1	-	-	-	-	5§	3 to 9	≥1
Dermatological									
Alopecia	-	<1	-	-	-	-	-	-	-
Angioedema	-	-	-	<1	-	-	<1	-	-
Bullous eruption	-	-	<1	-	-	-	-	-	-
Cheilitis	-	-	<1	-	-	-	-	-	-
Dermatitis	<1	<1	-	-	-	-	-	-	-
Diaphoresis	-	-	-	-	-	-	2§	-	-
Dry skin	-	<1	-	-	-	-	-	-	-
Eczema	-	<1	-	-	-	-	-	-	-
Erythema	<1	-	-	-	-	<1	-	-	-
Flushing	-	2	-	-	-	1	<1‡‖/7§	-	-
Hypersensitivity	-	-	<1	<1	<1	-	<1	-	-
Itching	-	-	<1	-	-	-	<1	-	-
Photosensitivity	<1	-	-	<1	-	-	<1	<1	-

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Pruritus	<1	<1	-	-	-	<1	-	-	≤1
Psoriasis	-	<1	-	-	-	-	-	-	-
Rash	<1	<1	-	<1	<1	<1	<1	<1	≤1
Skin discoloration	-	<1	-	-	-	-	-	-	-
Skin hypertrophy	-	<1	-	-	-	-	-	-	-
Sweating	<1	✔	1	-	-	<1	2§	2 to 3‡	-
Urticaria	-	<1	-	-	-	<1	-	<1	≤1
Vasculitis	-	-	-	-	-	-	<1	-	-
Endocrine and Metabolic									
Alkaline phosphatase increased	-	<1	-	-	-	-	-	-	-
Bilirubin	-	<1	-	-	<1	-	-	-	-
Colonic ischemia	-	-	-	-	<1	-	-	-	-
Diabetes mellitus	-	-	-	-	-	-	-	-	≤1
Edema	-	<1	-	-	-	<1	<1	-	-
Glycosuria	-	-	-	-	<1	-	-	-	-
Goiter	-	<1	-	-	-	-	-	-	≤1
Growth hormone increase (mild)	-	-	-	-	-	1 to 10	-	-	-
Hot flashes	-	-	<1	-	-	<1	3‡	-	<1 to 2*
Hypercholesterolemia	<1	-	-	-	<1	-	-	-	-
Hyperglycemia	<1	<1	-	-	<1	-	-	-	-
Hyperlipidemia	-	-	-	-	<1	-	-	-	-
Hypocalcemia	-	-	<1	-	-	-	-	-	-
Hypoglycemia	-	-	<1	-	-	-	-	-	≤1
Hypothyroidism	-	-	-	-	<1	-	-	-	≤1
Increased gamma glutamyl transpeptidase	<1	-	-	-	-	-	-	-	-
Ketonuria	-	-	-	-	<1	-	-	-	-
Liver function tests abnormal or elevated	-	<1	-	-	<1	-	<1	-	-
Menstrual irregularity	<1	<1	-	-	-	-	<1	-	-
Thyroid adenoma	-	<1	-	-	-	-	-	-	-
Thyroiditis	-	<1	-	-	-	-	-	-	-
Thyrotropin stimulating hormone levels increased	-	-	-	-	-	-	<1	-	-
Weight gain	-	<1	-	-	-	-	-	-	-
Weight loss	-	<1	-	-	-	-	-	-	-
Gastrointestinal									
Abdominal aortic aneurysm	-	-	-	-	-	-	<1	-	-
Abdominal distension	-	<1	-	-	-	<1, ✔ †	-	-	≤1
Abdominal cramp or pain	<1	1 to 2	1	-	-	-	<1‡‖/1§	1 to 2‖	≥1
Anorexia	-	<1	<1	-	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Bad taste	-	-	-	-	-	-	13 to 24‖	-	-
Biliary colic	-	-	-	-	-	-	-	-	≤1
Changes in bowel habits	-	-	<1	-	-	-	-	-	-
Colitis	<1	-	-	-	-	-	<1	<1	≤1
Constipation	-	<1	<1	-	-	-	-	-	≤1
Diarrhea	<1	<1	1	-	-	<1	<1§‖/1‡	-	≤1
Diverticulitis	-	-	-	-	-	-	≤25‖	-	≤1
Dysgeusia	-	-	<1	-	-	-	-	-	≤1
Dyspepsia	<1	1 to 2	2	-	-	<1	<1	1 to 3‡	2
Dysphagia	-	1 to 2	<1	-	-	-	<1‡‖/1§	1 to 2	≤1
Eructation	-	<1	<1	-	-	-	-	-	-
Esophageal spasm	-	-	<1	-	-	-	-	-	-
Esophagitis	-	<1	-	-	-	-	-	-	-
Flatulence	-	<1	<1	-	-	-	-	-	≤1
Gastric ulcer	-	-	-	-	-	-	-	-	≤1
Gastritis	<1	<1	-	-	-	-	-	-	≤1
Gastroenteritis	<1	-	-	-	-	-	-	-	-
Gastroesophageal reflux	<1	-	<1	-	-	-	-	-	≤1
Gastrointestinal disorder	-	<1	-	-	-	-	-	-	-
Gastrointestinal pain	-	-	-	-	6 to 7	-	<1	-	-
Glossitis	-	<1	-	-	-	-	-	-	-
Hematemesis	-	<1	-	-	-	-	-	<1	-
Hiccup	-	-	<1	-	-	-	-	-	-
Hypersalivation	<1	<1	<1	-	-	-	-	-	-
Hyposalivation	-	-	3	-	-	-	>1‡	-	-
Intestinal obstruction	-	-	-	-	-	-	<1	-	-
Irritable bowel syndrome	-	-	-	-	-	-	-	-	≤1
Melena	-	-	-	-	-	-	-	<1	-
Nausea	1 to 2, 1 to 3*	4 to 8	-	3 to 4	4 to 5	4 to 6	4§/≤14‖/>1‡	1 to 4‖/4 to 9‡	3
Pancreatitis	-	-	-	-	-	-	-	<1	-
Peptic ulcer disease	-	-	<1	-	-	-	-	<1	-
Rectal disorder	-	<1	-	-	-	-	-	-	-
Salivary gland pain	-	-	<1	-	-	-	-	-	-
Splenic infarction	-	-	-	-	-	-	✔	<1	-
Swallowing disorders	-	-	-	-	-	-	<1	-	-
Taste alteration	<1	<1	<1	-	-	-	≤25‖	17 to 21‖	-
Vomiting	<1, 2*	<1	1	3 to 4	1 to 10	<1	4§/≤14‖/>1‡	-	≤1
Genitourinary									
Acute renal failure	-	-	-	-	-	-	<1	-	-

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Dysuria	-	-	<1	-	-	-	-	-	-
Hematuria	-	-	-	-	-	-	<1[§‖]/1[‡]	-	-
Impotence	-	<1	-	-	-	-	-	-	-
Kidney pain	-	<1	-	-	-	-	-	-	-
Leukorrhea	-	<1	-	-	-	-	-	-	-
Menorrhagia	-	<1	-	-	-	-	-	-	-
Micturition	-	-	<1	-	-	-	-	-	-
Nephrolithiasis	-	-	-	-	-	-	-	-	≤1
Nocturia	-	-	<1	-	-	-	-	-	-
Polyuria	-	<1	<1	-	-	-	-	-	-
Renal insufficiency	-	-	-	-	-	-	-	-	≤1
Renal pain	-	-	<1	-	-	-	-	-	-
Urinary tract disorder	-	<1	-	-	-	-	-	-	-
Urine abnormality	-	-	<1	-	-	-	-	-	-
Vaginitis	-	<1	-	-	-	-	-	-	-
Hematologic									
Anemia	-	<1	-	-	<1	-	-	-	≤1
Eosinophilia	-	-	-	-	-	-	-	<1	-
Hemolytic anemia	-	-	-	-	-	-	<1[§‖]/1[‡]	-	-
Monocytosis	-	<1	-	-	-	-	-	-	-
Pancytopenia	-	-	-	-	-	-	<1	-	-
Purpura	-	<1	<1	-	-	-	-	-	-
Thrombocytopenia	-	-	-	-	<1	-	<1	<1	-
Musculoskeletal									
Abnormal gait	-	<1	<1	-	-	<1	-	-	≤1
Abnormal reflexes	-	-	<1	-	-	-	-	-	-
Arthralgia	<1	<1	<1	-	-	-	-	1 to 2[‖]	≤1
Arthritis	<1	<1	-	-	-	-	-	-	-
Arthrosis	-	<1	<1	-	-	-	-	-	-
Asthenia	<1	4 to 10	<1	-	-	-	5[§]	3[‖]/3 to 9[‡]	-
Ataxia	-	-	<1	-	-	-	-	-	-
Back pain	-	-	<1	-	-	-	-	-	≤1
Bone neoplasm	-	<1	-	-	-	-	-	-	-
Bone pain	-	<1	-	-	-	-	-	-	-
Creatinine phosphokinase increase	<1	<1	<1	-	-	-	-	-	-
Dystonias	-	<1	-	-	-	-	<1	-	-
Facial palsy	-	-	-	-	-	-	-	-	≤1
Involuntary muscle contractions	-	-	<1	-	-	-	-	-	-
Joint ache	-	-	-	-	-	-	<1	-	-

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Joint disorder	-	<1	-	-	-	-	-	-	-
Limb discomfort	-	-	-	<2	-	-	-	-	-
Muscle cramps	-	-	<1	-	-	<1	1§	-	-
Muscle tightness	-	-	-	-	-	-	-	-	2*
Muscle spasm	-	-	-	<2	-	-	-	-	-
Muscle stiffness	-	-	-	-	-	<1	<1	-	-
Muscle weakness	<1	-	<1	1 to 2	-	<1	1§	-	≥1
Myalgia	<1	<1	<1	-	-	<1	1‡/2§	1 to 2‖	≤1
Myasthenia	-	<1	<1	-	-	-	-	<2	-
Myopathy	<1	<1	-	-	-	-	-	-	-
Numbness	-	-	-	-	-	-	≤5‖/1‡/5§	-	-
Osteoarthritis	-	-	<1	-	-	-	-	-	-
Rigid neck	<1	-	-	-	-	-	-	-	-
Rigors	-	-	<1	-	-	-	-	-	-
Skeletal pain	-	-	3	-	-	3	-	-	-
Tenosynovitis	-	<1	-	-	-	-	-	-	-
Tetany	-	-	-	-	-	-	-	<1	-
Tremor	<1	<1	<1	<2	-	1	<1	-	≤1
Respiratory									
Asthma	-	<1	-	-	-	-	-	-	≤1
Bronchitis	<1	<1	-	-	-	-	-	-	-
Bronchospasm	-	-	-	-	-	-	<1	<1	-
Choking sensation	-	<1	-	-	-	-	-	-	-
Dyspnea	<1	<1	<1	<2	<1	1	1§	-	≤1
Esophagitis	-	<1	-	-	-	-	-	<1	-
Hyperventilation	<1	<1	<1	-	-	-	-	-	-
Laryngitis	<1	<1	<1	-	-	-	-	-	-
Nasal disorder/discomfort	-	-	-	-	-	-	≤11‖/≤2§	1 to 3‖	-
Nose/throat hemorrhage	-	-	-	-	-	-	<1§‖/1‡	-	-
Pharyngeal edema	-	-	-	-	-	<1	-	-	-
Pharyngitis	<1	✔	<1	-	-	-	-	-	-
Pleurisy	-	-	-	-	-	-	-	-	≤1
Respiratory disorder	-	<1	-	-	-	-	-	-	-
Respiratory tract infection	-	<1	-	-	-	-	-	-	-
Rhinorrhea	-	-	-	-	-	-	≤5‖	-	-
Rhinitis	<1	<1	1	-	-	-	1‡	-	-
Sinusitis	<1	<1	1	-	-	-	1‡	-	-
Sneezing	<1	-	-	-	-	-	-	-	-
Sputum	-	<1	-	-	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Throat discomfort	-	-	-	-	-	-	≤3‡/1 to 2‖/2 to 3§	-	-
Throat or neck pain/pressure	<1	-	-	-	1 to 2	2	≤5‡	<1 to 4‖	-
Upper respiratory inflammation	-	-	-	-	-	-	1‡	-	-
Voice alteration	-	<1	-	-	-	-	-	-	-
Other									
Abscess	-	<1	-	-	-	-	-	-	-
Accidental injury	-	<1	-	-	-	-	-	-	-
Accommodation disorders	-	-	-	-	-	-	<1	-	-
Allergic reaction	-	<1	-	-	<1	-	<1§‖, 1‡	<1	-
Anaphylactoid reaction	-	-	<1	-	-	-	<1	<1	-
Anaphylaxis	-	-	<1	-	<1	-	<1	<1	-
Angioneurotic edema	-	-	-	-	-	-	<1	-	-
Breast pain	-	<1	-	-	-	-	-	-	-
Bruising	-	-	-	-	-	-	-	-	≤1
Cataract	-	-	-	-	-	-	-	-	≤1
Chills	<1	✔	-	-	-	-	-	1 to 2‖	-
Conjunctival hemorrhage	-	-	-	-	-	-	-	-	≤1
Conjunctivitis	<1	<1	<1	-	-	-	-	-	≤1
Cough	-	<1	-	-	-	-	-	-	≤1
Deafness	-	-	-	-	-	-	<1	-	-
Death	-	-	-	-	-	-	<1	-	-
Decreased appetite	-	-	-	-	-	-	<1	-	-
Dental pain	-	-	-	-	-	-	<1	-	-
Dry eyes	<1	<1	-	-	-	-	-	-	-
Diplopia	<1	<1	-	-	-	-	-	-	-
Dry mouth	1	2 to 4	-	-	-	3	-	2 to 3‖/3 to 5‡	2
Earache	<1	<1	<1	-	-	-	-	-	≤1
Ear hemorrhage	-	<1	-	-	-	-	-	-	-
Epistaxis	<1	<1	<1	-	-	-	<1	-	≤1
Eye irritation	<1	-	-	-	-	-	-	-	-
Eye pain	<1	<1	<1	-	-	-	-	-	-
Eye swelling	-	-	-	-	-	<1	-	-	-
Facial edema	-	-	-	-	-	<1	-	1 to 2‖	≤1
Fever	<1	<1	<1	-	-	-	-	-	≤1
Flu syndrome	-	<1	-	-	-	-	-	-	-
Gingivitis	-	<1	-	-	-	-	-	-	-
Halitosis	-	<1	-	-	-	-	-	-	-
Heaviness sensation	-	-	-	-	-	-	≤3‡/7§	-	≤1

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Hernia	-	<1	-	-	-	-	-	-	-
Hiccups	-	<1	-	-	-	-	<1	-	-
Hyperhidrosis	-	-	-	-	-	-	-	-	≤1
Hypoacusis	-	-	-	-	-	<1†	-	-	-
Hypothermia	-	<1	-	-	-	-	-	-	-
Increased appetite	-	<1	-	-	-	-	-	-	-
Infection (various)	-	-	-	-	-	-	-	-	≤1
Irritability	-	-	-	-	-	-	-	-	≤1
Jittery	-	-	-	-	-	-	-	-	≤1
Lab test abnormal	-	<1	-	-	-	-	-	-	-
Lacrimation disorder	-	<1	<1	-	-	-	-	-	-
Lethargy	-	-	-	<2	-	-	-	-	≤1
Leukopenia	-	<1	-	-	-	-	-	-	≤1
Lymphadenopathy	-	<1	-	-	-	-	-	-	≤1
Malaise	-	<1	<1	-	-	-	≤3‡	-	≤1
Miscarriage	-	-	-	-	-	-	-	<1	-
Moniliasis	-	<1	-	-	-	-	-	-	-
Motion sickness	-	-	-	-	-	-	-	-	≤1
Mouth/tongue discomfort	-	-	-	-	-	-	5§	-	-
Neck/throat/jaw pain/ tightness/Pressure	-	✔	<1	-	-	<2 to 2	2 to 5§/≤3‡	4 to 10‡	3
Numbness of tongue	-	-	-	-	-	-	<1	-	-
Optic neuropathy (ischemic)	-	-	-	-	-	-	<1	-	-
Oral mucosal blistering	-	-	-	-	-	-	-	-	≤1
Oropharyngeal edema	-	-	<1	-	-	-	-	-	≤1
Otitis media	<1	<1	-	-	-	-	-	-	-
Pain at injection site	-	-	-	-	-	-	30 to 59§	-	-
Parosmia	<1	<1	-	-	-	-	-	-	-
Peripheral edema	-	<1	-	-	-	-	-	-	≤1
Photophobia	-	<1	-	-	-	-	-	-	-
Pressure sensation	-	-	-	-	-	-	7§/≤8‡	-	-
Presyncope	-	-	-	-	-	<1†	-	-	-
Ptosis	-	<1	-	-	-	-	-	-	-
Raynaud's syndrome	-	-	-	-	-	-	<1	-	-
Rheumatoid arthritis	-	<1	-	-	-	-	-	-	-
Scotoma	<1	-	-	-	-	-	-	-	-
Sedation	-	-	-	6 to 7	-	-	-	-	≤1
Seizure	-	-	<1	-	<1	-	<1	-	-
Shock	-	<1	-	-	-	-	-	-	-
Speech disorder	-	<1	<1	<2	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents								Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Lasmiditan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Stomatitis	-	<1	<1	-	-	-	-	-	-
Stroke	-	-	-	-	-	-	-	-	-
Syncope	<1	<1	<1	-	<1	<1	<1§‖/1‡	<1	-
Systemic lupus erythematosus	-	-	-	-	-	-	-	-	≤1
Temperature intolerance	-	-	-	-	-	-	-	-	≤1
Thirst	<1	<1	<1	-	-	-	-	-	≤1
Thrombophlebitis	-	<1	-	-	-	-	-	-	-
Tightness feeling	-	✔	-	-	-	-	5§	-	-
Tinnitus	<1	<1	1	-	-	<1	1‡	≤3‡	≤1
Toothache	-	-	<1	-	-	-	-	-	-
Tooth disorder	-	<1	-	-	-	-	-	-	-
Tongue edema	-	<1	-	-	-	<1	-	-	≤1
Tongue paralysis	-	-	<1	-	-	-	-	-	-
Vision abnormalities	-	<1	1	-	-	-	1§	-	≤1
Vision impairment	-	-	-	<2	-	-	-	-	-
Vision loss	-	-	-	-	-	<1	<1	-	-
Warm sensation at injection site	-	-	-	-	-	-	≤11§		
Xerostomia	-	2 to 4	3	-	-	3	<1	3 to 5	2

* Rate of adverse event in adolescents 12 to 17 years of age.
† Rate of adverse event in pediatric and adolescent patients six to 17 years of age.
‡By mouth.
§Subcutaneous.
‖Intranasal.
-Event not reported.
✔ Percent not specified.

Table 7. Boxed Warning for Sumatriptan and Naproxen[8]

WARNING
Cardiovascular Thrombotic Events: Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. Sumatriptan/naproxen is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. Gastrointestinal Bleeding, Ulceration, and Perforation: NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events, including bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

VII. Dosing and Administration

The usual dosing regimens for the selective serotonin agonists are listed in Table 8.

Table 8. Usual Dosing Regimens for the Selective Serotonin Agonists[7-20]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Almotriptan	Acute treatment of migraine attacks in adults with a history of migraine with or without aura: Tablet: initial, 6.25 or 12.5 dose, may repeat after two hours if headache returns; maximum, 25 mg/day	Acute treatment of migraine headache pain in children 12 to 17 years of age with a history of migraine attacks with or without aura, and who have migraine attacks usually lasting four hours or more: Tablet: initial, 6.25 or 12.5 mg, may repeat after two hours if headache returns; maximum, 25 mg/day	Tablet: 6.25 mg 12.5 mg
Eletriptan	Acute treatment of migraine attacks with or without aura: Tablet: initial, 20 or 40 mg, may repeat after two hours if headache returns; maximum, 80 mg/day	Safety and efficacy in children have not been established.	Tablet: 20 mg 40 mg
Frovatriptan	Acute treatment of migraine attacks with or without aura: Tablet: initial, 2.5 mg, may repeat after two hours if headache returns; maximum, 7.5 mg/day	Safety and efficacy in children have not been established.	Tablet: 2.5 mg
Lasmiditan	Acute treatment of migraine attacks with or without aura: Tablet: 50 mg, 100 mg, or 200 mg; maximum, one dose/day	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg
Naratriptan	Acute treatment of migraine attacks with or without aura: Tablet: initial, 1 or 2.5 mg, may repeat after four hours if headache returns; maximum, 5 mg/day	Safety and efficacy in children <18 years of age have not been established.	Tablet: 1 mg 2.5 mg
Rizatriptan	Acute treatment of migraine attacks with or without aura: Orally disintegrating tablet, tablet: 5 or 10 mg, may repeat after two hours if headache	Acute treatment of migraine with or without aura in pediatric patients six to 17 years of age:	Orally disintegrating tablet: 5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	returns; maximum, 30 mg/day	Orally disintegrating tablet, tablet: 5 mg for patients <40 kg, 10 mg for patients ≥40 kg	10 mg Tablet: 5 mg 10 mg
Sumatriptan	Acute treatment of migraine attacks with or without aura: Nasal powder: initial, 22 mg, may repeat after two hours if headache returns; maximum, 44 mg/day Nasal spray: initial, 5, 10, or 20 mg, may repeat after two hours if headache returns; maximum, 40 mg/day for Imitrex®; maximum, 30 mg/day for Tosymra® Subcutaneous injection: initial, 1 to 6 mg, may repeat after one hour if headache returns; maximum, 12 mg/day Tablet: initial, 25, 50, or 100 mg, may repeat after two hours if headache returns; maximum, 200 mg/day Acute treatment of cluster headache episodes: Subcutaneous injection: initial, 6 mg, may repeat after one hour if headache returns; maximum, 12 mg/day	Safety and efficacy in children <18 years of age have not been established.	Nasal powder: 11 mg Nasal spray: 5 mg 10 mg 20 mg Subcutaneous injection: 3 mg/ 0.5 mL 4 mg/0.5 mL 6 mg/0.5 mL Tablet: 25 mg 50 mg 100 mg
Zolmitriptan	Acute treatment of migraine attacks with or without aura: Orally disintegrating tablet, tablet: initial, 1.25 or 2.5 mg, may repeat after two hours if headache returns; maximum, 10 mg/day Nasal spray: initial, 2.5 mg, may repeat after two hours if headache returns; maximum, 10 mg/day	Acute treatment of migraine attacks with or without aura in children 12 years of age and older: Nasal spray: initial, 2.5 mg, may repeat after two hours if headache returns; maximum, 10 mg/day	Nasal spray: 2.5 mg 5 mg Orally disintegrating tablet: 2.5 mg 5 mg Tablet: 2.5 mg 5 mg
Combination Products			
Sumatriptan and naproxen	Acute treatment of migraine attacks with or without aura: Tablet: initial, 85-500 mg, may repeat after two hours if headache returns; maximum, 170-1,000 mg/day	Acute treatment of migraine attacks with or without aura in children 12 to 17 years of age: Tablet: initial, 10-60 mg; maximum, 85-500 mg/day	Tablet: 10-60 mg 85-500 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the selective serotonin agonists are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Selective Serotonin Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cluster Headache				
Siow et al.[21] (2004) Frovatriptan 2.5 to 5 mg daily	OL Patients with a history of cluster headache	N=17 3 weeks	Primary: Headache occurrence in patients with episodic and chronic cluster headaches for preventative and transitional therapy Secondary: Not reported	Primary: A total of 8/9 patients with episodic cluster headache reported at least 75% improvement, with 100% relief within 48 hours of treatment. A total of 3/8 patients with chronic cluster headaches had complete relief. Secondary: Not reported
Gobel et al.[22] (1998) Sumatriptan 6 mg SC	MC, OL Patients 18 to 65 years of age with a diagnosis of cluster headache or episodic cluster headache	N=52 1 year	Primary: Freedom from pain within 15 minutes in >90% of attacks Secondary: Tolerability	Primary: Freedom from pain within 15 minutes in >90% of attacks was reported by 42% of patients (P value not reported). Secondary: Adverse events were reported by 62% of patients (P value not reported).
Ekbom et al.[23] (1993) Sumatriptan 6 to 12 mg SC vs placebo	DB, MC, PC, RCT, XO Patients 18 to 65 years of age with a diagnosis of cluster headache or episodic cluster headache	N=134 Single migraine attack	Primary: Headache improvement to mild or no pain at 10 and 15 minutes Secondary: Not reported	Primary: At 10 minutes, headache relief was reported by 25, 49 and 63% of patients receiving placebo, sumatriptan 6 mg and sumatriptan 12 mg (P values not reported). At 15 minutes, headache relief was reported by 35, 75 and 80% of patients receiving placebo, sumatriptan 6 mg and sumatriptan 12 mg, respectively (P<0.001 for all compared to placebo). There were no differences between sumatriptan 6 and 12 mg (P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Rapoport et al.[24] (2007) Zolmitriptan 5 to 10 mg administered IN vs placebo	DB, MC, RCT, XO Patients aged 18 to 65 years, with a diagnosis of episodic or chronic cluster headache, with a minimum duration of at least 45 minutes untreated	N=52 3 attacks	Primary: Headache response at 30 minutes post-dose, with intensity rated by 5-point scale ranging from 'none' to 'severe' Secondary: Use of rescue medication and tolerability	Primary: 63.3% of zolmitriptan 10 mg patients and 50% of zolmitriptan 5 mg patients reported headache relief at 30 minutes vs 30% in placebo group (P<0.01 and P<0.05 respectively). Secondary: Frequency of use of rescue medication did not vary significantly among the different groups: 38% in the placebo group, 30% in the zolmitriptan 5 mg group and 28% in the zolmitriptan 10 mg group. Fewer patients receiving placebo (16%) reported adverse events compared to those receiving zolmitriptan 5 mg (25%; P<0.05) and zolmitriptan 10 mg (33%; P<0.05). Adverse events were mild and nonspecific; no serious adverse events were reported.
Migraine With or Without Aura				
Cabarrocas et al.[25] (2001) Almotriptan 12.5 mg	OL Patients 18 to 65 years of age with migraine with or without aura	N=747 1 year	Primary: Headache response rates at one and two hours Secondary: Safety	Primary: Headache response rates at one and two hours were 43 and 73%, respectively (P value not reported). Secondary: The most common adverse events were back pain, bronchitis and flu-like symptoms (P value not reported).
Berenson et al.[26] (2010) Almotriptan 12.5 mg	OL Patients 12 to 17 years of age with at least a one year history of migraine with or without aura, an average of one to 14 migraines per month with <15 total headache days per month for at	N=447 1 year	Primary: Safety Secondary: Patient-rated intensity of the migraine-associated symptoms of phonophobia, photophobia and nausea; use of	Primary: Overall, 282 patients (67.1%) reported one or more adverse events for one or more headaches during the trial. Thirty two patients (7.6%) had an adverse event that was judged to be related to almotriptan and 44% of patients had at least one adverse event that was considered to be moderate or marked in intensity. Eight patients (1.9%) had a serious adverse event and 10 patients (2.4%) discontinued treatment because of an adverse event. No deaths were reported during the trial and all serious adverse events resolved. The most commonly reported adverse events (≥5% incidence) were: nasopharyngitis, sinusitis, upper respiratory tract infection, pharyngitis

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	least six months prior to trial enrollment, receiving one or fewer prophylactic medication and had ≥24 hours of freedom from headache between migraine attacks		rescue medication or a second dose of study medication	streptococcal, nausea, vomiting, pharyngolaryngeal pain and nasal congestion. Secondary: Photophobia was common at baseline (76.6%) and after treatment photophobia was present in 39.1 and 11.6% of all migraines at two and 24 hours after treatment. Phonophobia was common at baseline (71.8%) and after treatment it was present in 35.4 and 10.0% of all migraines two and 24 hours after treatment. Nausea was common at baseline (40.5%) and after treatment it was present in 22.2 and 6.7% of all migraines two and 24 hours after treatment. Overall, rescue medication was taken by 334 patients (79.5%) for one or more migraines during the trial. Rescue medication was used for 681 migraines (8.5%) within two hours of first dose of almotriptan and for 1,999 migraines (24.8%) within 24 hours of the first dose of almotriptan. A second dose of almotriptan was taken by 306 patients (72.9%) for one or more migraines during the trial, with 441 (5.5%) and 1,676 patients (20.8%) treated with a second dose within two and 24 hours of the first dose.
Lanteri-Minet et al.[27] (2001) START Almotriptan 12.5 mg Patients administered almotriptan either within one hour of pain onset when pain was still mild (early intervention) or beyond one hour and/or until	OL, OS, PRO Patients 18 to 65 years of age with a diagnosis of migraine with or without aura, at least a one year history of migraine which progressed from mild to at least moderate intensity with a frequency of two to six attacks per month during the previous three months	N=501 3 migraine attacks	Primary: Proportion of patients who were pain-free at two hours Secondary: Proportion of patients pain-free at two hours across all attacks, proportion of patients achieving sustained pain-free status with or without adverse events, relapse at	Primary: Early intervention resulted in a significantly greater proportion of patients achieving freedom of pain at two hours for the first migraine attack (61.90 vs 35.37%; P<0.001). Secondary: Early intervention resulted in a significantly greater proportion of patients achieving freedom of pain at two hours for all three migraine attacks (65.22 vs 37.64%; P<0.001). Across all attacks, early intervention resulted in a significantly greater proportion of patients achieving sustained pain-free status (59 vs 33%; P<0.001). Similar results were observed for sustained pain-free status with no adverse events (55 vs 31; P<0.001). A significantly smaller proportion of patients who received early treatment required rescue medication (15 vs 27%; P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pain progressed to moderate/severe (delayed intervention).			24 hours, use of rescue medication, evolution of migraine symptoms, duration of pain, functional disability and tolerability	Early intervention was associated with a significantly shorter period of migraine and functional disability (P<0.001 for both). There was no difference between early or delayed intervention with regard to relapse in 24 hours was observed (P value not reported). Early intervention was associated with significantly fewer migraine-associated symptoms after two hours (nausea, 7.5 vs 19.2%; P<0.001, vomiting, 1.5 vs 3.9%; P=0.218, photophobia, 10.5 vs 24.7%; P<0.001, phonophobia, 10.5 vs 23.5%; P<0.001). A total of 65 treatment-emergent adverse events were reported during the trial, none of which were serious or lead to treatment discontinuation. Only two were considered possibly related to study medication (dizziness and tremor). There was no difference in the incidence of adverse events between early and delayed intervention (P=0.202).
Diener et al.[28] (2005) Almotriptan 12.5 mg vs placebo All patients were poor responders to sumatriptan 50 mg.	DB, MC, PC, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for at least one year and had experienced unsatisfactory responses to sumatriptan on at least two occasions	N=328 Single migraine attack	Primary: Relief from headache at two hours Secondary: Pain-free efficacy at two hours, use of rescue medication within 24 hours	Primary: A significantly greater proportion of patients receiving almotriptan achieved pain relief at two hours compared to patients receiving placebo (47.5 vs 23.2%; P<0.01). Secondary: A significantly greater proportion of patients receiving almotriptan achieved pain-free status at two hours compared to patients receiving placebo (33.3 vs 14.1%; P<0.005). Rescue medications were required by significantly fewer patients receiving almotriptan compared to patients receiving placebo (26.6 vs 46.9%; P<0.005).
Pascual et al.[29] (2001) Almotriptan 6.25 mg vs	DB, OL Patients 18 to 65 years of age with at least a one year history of migraine, with or without	N=762 1 year	Primary: Incidence of treatment-emergent adverse events Secondary:	Primary: During the trial, 391 patients (51.3%) experienced at least one adverse event. Patients reported at least one adverse event in 11.0% of attacks treated. The incidence of adverse events decreased during the trial; 30.7% of patients had at least one adverse event during the first three months of the trial compared to only 21.5% of patients during the last three months.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
almotriptan 12.5 mg	aura; all patients experienced one to six migraine attacks per month with ≥24 hours of freedom between attacks		Percent of attacks resolved (to mild or no pain) by two hours after dose (attacks of moderate/ severe baseline intensity only)	The majority (88.6%) of adverse events were of mild to moderate intensity. Only 28.8% of adverse events were considered to be possibly, probably or definitely related to the study drug. Of these drug-related events, those which occurred in at least one percent of patients were vomiting (2.1%), somnolence (1.7%), dizziness (1.6%), fatigue (1.4%) and nausea (1.4%; P values not reported). Secondary: Pain relief at two hours after the initial dose was achieved in 84.2% of moderate/severe attacks. Patients were pain-free at two hours after dose in 58.2% of all attacks (P values not reported).
Dowson et al.[30] (2002) Almotriptan 12.5 mg x 1 dose vs almotriptan 25 mg x 1 dose vs sumatriptan 100 mg x 1 dose vs placebo A second dose was allowed if headache relapsed in 2 to 24 hours after first dose.	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for more than one year	N=668 Single migraine attack	Primary: Pain relief at two hours Secondary: Pain relief at one hour, pain-free status at one and two hours, migraine recurrence within 24 hours and rescue medication use	Primary: The proportion of patients achieving pain relief at two hours was higher with almotriptan (12.5 mg, 56.8%; 25 mg, 56.5%) and sumatriptan (63.7%) compared to placebo (42.2%; P values not reported). Both doses of almotriptan were equivalent to sumatriptan with the 90% CI inside the range of the equivalence region (P value not reported). Secondary: Pain relief at one hour was not different between the three treatments (P values not reported). Recurrence within 24 hours for patients with moderate pain at baseline was reported as follows: almotriptan 12.5 mg, 22.7%; almotriptan 25 mg, 14.9%; sumatriptan 100 mg, 22.4% and placebo, 16.7% (P values not reported). Corresponding rates at 24 hours for patients with severe pain at baseline were: 8.8, 16.2, 28.9 and 27.3% (P values not reported). The use of escape medication was reported as follows: almotriptan 12.5 mg, 38.6%; almotriptan 25 mg, 38.2%; sumatriptan 100 mg, 32.4% and placebo, 55.5% (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Escape medication was allowed if pain persisted beyond 2 hours.				
Dahlof et al.[31] (2001) Almotriptan 2 to 25 mg vs placebo Another dose of study drug was allowed if pain severity increased within 2 to 24 hours. Escape medication was allowed if pain did not decrease after 2 hours.	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for more than one year and migraines occurring up to six times per month	N=742 Single migraine attack	Primary: Change in headache pain intensity at two hours without rescue medication Secondary: Freedom from pain, relief from migraine-associated symptoms	Primary: Almotriptan demonstrated a dose-dependent increase in the proportion of patients with improvement in headache pain intensity (58.5 and 66.5% improvement for the 12.5 and 25 mg doses, respectively, compared to 32.5% for placebo; P<0.001). Almotriptan 2 mg was equivalent to placebo (P value not reported). Secondary: With regard to freedom from pain, almotriptan produced a significant dose-dependent increase over placebo at one, one and a half and two hours (P<0.0001 for all). Almotriptan 12.5 mg produced significant improvement compared to placebo at half an hour (P<0.0485). Almotriptan demonstrated a significant dose-dependent improvement in pain-free state at two hours both with 12.5 and 25 mg compared to placebo (P<0.001). A significantly better response was observed for patients with baseline moderate headache than patients with severe headache (P value not reported). A dose-dependent decrease in the incidence of migraine-associated symptoms was noted for almotriptan. The incidence of migraine recurrence was not different among the treatment groups, ranging from 25.2 to 28.7% (P value not reported).
Dahlof et al.[32] (2006) Almotriptan 2 to 150 mg vs	MA (4 DB, PC, RCT) Patients 18 to 65 years of age who had at least a six month history of	N=2,294 Single migraine attack	Primary: Efficacy, speed of onset and tolerability of almotriptan in the acute treatment of migraine;	Primary: As early as 30 minutes after dosing, almotriptan 12.5 mg was significantly more effective than placebo for pain relief (14.9 vs 8.2%; P<0.05) and freedom from pain (2.5 vs 0.7%; P<0.05). At two hours, pain relief rates were 56.0, 63.7 and 66.0% for almotriptan 6.25, 12.5 and 25 mg, respectively, compared to 35.0% for placebo; two

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	migraine and experienced one to six migraine attacks per month		proportion of patients achieving sustained pain-free with no adverse events Secondary: Not reported	hour pain-free rates were 26.7, 36.4 and 43.4% compared to 13.9% for placebo (P values not reported). All almotriptan dosages were significantly more effective compared to placebo in eliminating migraine-associated symptoms (P<0.05) and in achieving sustained pain relief up to 24 hours (P<0.05). The incidences of adverse events for almotriptan 6.25 and 12.5 mg were not different from that of placebo. Secondary: Not reported
Mathew et al.[33] (2007) Almotriptan 12.5 mg vs placebo	DB, MC, PC, PG Patients 18 to 65 years of age with history of migraine of at least moderate pain intensity with/without aura for at least 1 year and an average migraine frequency of 2 to 6 each month for the past 3 months	N=378 Treatment of 3 migraines	Primary: Pain free with no supplemental pain and/or anti-emetic meds at two hours post-dose for the first headache Secondary: Pain free at 0.5, one, four, and 24 hours with no supplemental pain and/or antiemetic medications	Primary: Almotriptan group showed significantly greater number of patients achieving two-hour pain free (37.0 vs 23.9%; P=0.010), two-hour pain relief (72.3 vs 48.4%; P<0.001) and sustained pain free (24.7 vs 16.1%; P=0.040). Significant differences in pain free (P=0.026) and pain relief (P=0.019) between almotriptan and placebo groups also were observed at one hour. At two to four hours and four to 24 hours after treatment, the mean intensity of phonophobia and photophobia were significantly lower in the almotriptan group vs placebo group. A greater proportion of patients in almotriptan group reported normal functionality within two hours post-dose (54.4 vs 38.1%; P=0.007) and four hours post-dose (74.5 vs 54.3%; P<0.001). The percentage of patients experiencing one or more treatment-emergent adverse events was 9.8% for almotriptan and 6.4% for placebo.
Colman et al.[34] (2001) Almotriptan 12.5 mg	DB, RCT Patients 18 to 71 years of age who had not been treated previously with a	N=1,173 48 hours	Primary: Change in treatment satisfaction measure, functional status	Primary: There were no significant differences between the two treatments in terms of satisfaction with pain relief (mean score, 50.85 vs 52.10; P=0.67). Patients receiving either treatment improved by about 44 points on the 100-point functional status scale after 24 hours. Patients receiving both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sumatriptan 50 mg	triptan, with a history of migraine with or without aura for at least six months		measure, MqoLQ values from baseline to 48 hours Secondary: Not reported	treatments reported improvement in functional status after treatment, from marginally functional at onset of migraine (mean scores, 42.54 vs 42.50, respectively) to about 90% of normal (mean scores, 86.49 vs 86.99, respectively) at 24 hours. No difference was found between the two treatments in a comparison of MqoLQ at 24 hours after treatment (P value not reported). Patients receiving almotriptan were significantly more satisfied and experienced fewer adverse events compared to patients receiving sumatriptan (P=0.016). Secondary: Not reported
Spierings et al.[35] (2001) Almotriptan 12.5 mg vs sumatriptan 50 mg	DB, MC, PG, RCT Patients 18 to 65 years of age with migraine with or without aura	N=1,255 24 hours	Primary: Headache relief and pain-free status at two hours Secondary: Migraine relief, improvement of migraine-associated symptoms, incidence of migraine recurrence at 24 hours after dosing and use of rescue medication	Primary: Headache relief at two hours was observed in 58.0 and 57.3% of patients receiving almotriptan and sumatriptan, with no difference between the two treatments (P value not reported). Pain-free response rates at two hours were observed in 17.9 and 24.6% of patients, respectively (P=0.005). Secondary: There was no difference between the treatments with regard to relief from migraine-associated symptoms of nausea, vomiting, photophobia and phonophobia (P values not reported). Rescue medications were taken by 36.7 and 33.2% of patients receiving almotriptan and sumatriptan, respectively (P value not reported). Of the 343 responders receiving almotriptan, 27.4% experienced a migraine recurrence within 24 hours, compared to 24.0% of the 333 responders receiving sumatriptan. The difference was not significant (P value not reported).
Goadsby et al.[36] (2007) Almotriptan 12.5 mg	DB, MC, PG, RCT Patients 18 to 65 years of age with at least a 12-month	N=1062 Single dose	Primary: Sustained pain free plus no adverse events	Primary: No significant difference was seen in sustained pain free plus no adverse events (almotriptan, 29.2% vs zolmitriptan, 31.8%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs zolmitriptan 2.5 mg	history of migraine with onset before age 50, and 2 to 6 migraine attacks per month in the 2 months preceding the trial		Secondary: Pain relief and pain free at various time points, sustained pain free, headache recurrence and use of rescue medication, functional impairment, time lost due to migraine, treatment acceptability and overall satisfaction	Incidence of triptan-associated adverse events and triptan-associated central nervous system adverse events was significantly lower for patients receiving almotriptan compared to zolmitriptan (P=0.03). No significant differences indicated among other efficacy endpoints measured.
Ferrari et al.[37] (2002) Almotriptan 12.5 mg vs eletriptan 20 to 80 mg vs frovatriptan 2.5 mg vs naratriptan 2.5 mg vs rizatriptan 5 to 10 mg	MA (53 DB, RCTs) Patients 18 to 65 years of age receiving treatment with an oral triptan at a recommended clinical dose for moderate or severe migraine attacks within eight hours of onset	N=24,089 Duration varied	Primary: Headache response rates at two hours, pain-free rates at two hours, sustained pain-free response Secondary: Adverse events	Primary: Headache response rates at two hours (mean percent) for sumatriptan 100 mg were 59.0 (95% CI, 7.3 to 60.8). Triptans with better efficacy than sumatriptan 100 mg were rizatriptan 10 mg (mean percent, 68.6; 95% CI, 66.9 to 70.4) and eletriptan 80 mg (mean percent, 65.8; 95% CI, 63.6 to 68.3). Triptans with similar efficacy to sumatriptan 100 mg were almotriptan 12.5 mg (mean percent, 61.2; 95% CI, 57.6 to 64.8), eletriptan 40 mg (mean percent, 60.2; 95% CI, 58.0 to 62.4), zolmitriptan 2.5 mg (mean percent, 63.5; 95% CI, 60.8 to 66.2), zolmitriptan 5 mg (mean percent, 62.8; 95% CI, 60.0 to 65.6) and rizatriptan 5 mg (mean percent, 62.4; 95% CI, 60.2 to 64.5). Triptans with lower efficacy compared to sumatriptan 100 mg were sumatriptan 25 mg (mean percent, 56.0; 95% CI, 53.1 to 58.9), naratriptan 2.5 mg (mean percent, 48.6; 95% CI, 45.7 to 51.4), eletriptan 20 mg (mean percent, 48.9; 95% CI, 44.5 to 53.3) and frovatriptan 2.5 mg (mean percent, 41.5; 95% CI, 39.3 to 43.8). Pain-free results at two hours (mean percent) for sumatriptan 100 mg was 28.9 (95% CI, 27.2 to 30.5).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sumatriptan 25 to 100 mg vs zolmitriptan 2.5 to 5 mg vs placebo				Triptans with higher rates compared to sumatriptan 100 mg were almotriptan 12.5 mg (mean percent, 61.2; 95% CI, not reported), eletriptan 80 mg (mean percent, 33.0; 95% CI, 30.5 to 35.4) and rizatriptan 10 mg (mean percent, 40.1; 95% CI, 38.3 to 42.0). Triptans with lower rates compared to sumatriptan 100 mg were sumatriptan 25 mg (mean percent, 23.4; 95% CI, 21.0 to 25.9), naratriptan 2.5 mg (mean percent, 22.4; 95% CI, 20.0 to 24.7) and eletriptan 20 mg (mean percent, 16.4; 95% CI, 13.2 to 19.7). All other triptans did not significantly differ from sumatriptan 100 mg. Sustained pain-free results (mean percent) for sumatriptan 100 mg were 20.0 (95% CI, 18.2 to 21.3). Triptans with higher rates compared to sumatriptan 100 mg were almotriptan 12.5 mg (mean percent, 25.9; 95% CI, 22.7 to 29.1), rizatriptan 10 mg (mean percent, 25.3; 95% CI, 23.7 to 26.9) and eletriptan 80 mg (mean percent, 25.0; 95% CI, 22.8 to 27.2). Triptans with lower rates compared to sumatriptan 100 mg were eletriptan 20 mg (mean percent, 10.6; 95% CI, 7.7 to 13.5), sumatriptan 25 mg (mean percent, 16.7; 95% CI, 14.5 to 18.9) and naratriptan 2.5 mg (mean percent, 15.9; 95% CI, 13.4 to 18.5). No differences were found with other triptan doses. Secondary: Placebo subtracted adverse events (mean) for sumatriptan 100 mg were 13.2 (95% CI, 8.6 to 17.8). Triptans with lower rates compared to sumatriptan 100 mg were almotriptan 12.5 mg (mean, 1.8; 95% CI, -2.5 to 6.2) and naratriptan 2.5 mg (mean, 2.4; 95% CI, -2.2 to 7.0). Central nervous system placebo subtracted adverse events (mean) for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sumatriptan 100 mg was 6.3 (95% CI, 3.2 to 9.5). Triptans with higher central nervous system adverse event rates than sumatriptan 100 mg was eletriptan 80 mg (mean, 14.6; 95% CI, 10.2 to 19.0). Rates for all other triptans and doses largely overlap. Triptans with lower central nervous system adverse event rates compared to sumatriptan 100 mg was almotriptan 12.5 mg (mean, -1.5; 95% CI%, -3.9 to 1.0). Rates for all other triptans and doses largely overlap.
Olesen et al.[38] (2004) Eletriptan 80 mg vs placebo	DB, PC, RCT Patients ≥18 years of age with migraine with aura every four weeks	N=123 24 hours	Primary: Proportion of patients not developing a migraine headache of moderate or severe intensity within six hours of dosing Secondary: Time to headache development, duration of aura symptoms, use of second dose, response to the second dose, use of rescue medication, treatment acceptability, time to rescue medication	Primary: Treatment with eletriptan during the aura phase was not effective in preventing the onset of moderate to severe headache post aura. There was no difference in the proportions of patients developing a headache on eletriptan and placebo (61 vs 46%; P value not reported). Secondary: Eletriptan did not increase the duration of the aura phase compared to placebo (0.7 vs 0.8 hour), nor was it associated with a significant delay in the median time to headache onset (1.3 vs 1.0 hour; P values not reported). A second dose of eletriptan was permitted for patients in both the eletriptan and placebo groups who developed a moderate to severe headache. Response rates to the 40 mg dose of eletriptan were similar (P value not reported). Additional rescue medication was taken by 28 and 17% of patients receiving eletriptan and placebo, respectively (P value not reported). The proportion of patients rating study medication as acceptable was comparable for both treatments (76 vs 72%; P value not reported). There was no difference between treatments on any efficacy measure.
Farkkila et al.[39] (2003) Eletriptan 40 to 80 mg	DB, MC, PC, RCT Patients ≥18 years of age with migraine with	N=446 3 migraine attacks	Primary: Two hour headache response rates	Primary: Two hour headache response, based on first dose, first attack data, was 59, 70 and 30% with eletriptan 40 mg, eletriptan 80 mg and placebo (P<0.0001 for both doses of eletriptan vs placebo; P<0.05 for eletriptan 80 vs 40 mg).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	or without aura		Secondary: Onset of action, freedom from pain at two hours, incidence of nausea, vomiting and headache recurrence and consistency of response	Secondary: Onset of action was rapid, with one hour headache response rates significantly higher with eletriptan 40 and 80 mg compared to placebo (40 and 48 vs 15%; P<0.0005 for both). Both eletriptan 40 and 80 mg were significantly better than placebo, based on first dose, first attack data, for freedom from pain at two hours (35 and 42 vs 7%; P<0.0001). Both eletriptan 40 and 80 mg demonstrated significant consistency of response, with headache relief rates at two hours on at least two of three attacks of 66 and 72%, respectively, compared to 15% with placebo (P<0.001).
Sheftell et al.[40] (2003) Eletriptan 20 to 80 mg vs placebo	DB, MC, PC, PG, RCT Patients >18 years of age with a history of at least one typical attack of migraine with or without aura every six weeks	N=1,334 3 migraine attacks	Primary: Headache response at two hours for the first attack Secondary: Incidence of associated symptom relief, pain-free, sustained pain-free and consistency of response	Primary: Eletriptan 20, 40, and 80 mg achieved significantly (P<0.001) better headache response rates compared to placebo at two (47, 62, and 59 vs 22%) and four hours (64, 76, and 79 vs 25%). Secondary: Two hour pain-free response rates for eletriptan 20, 40, and 80 mg were 14, 27, and 27%, respectively, compared to 4% with placebo (P<0.001). Sustained pain-free response rates for eletriptan 20, 40, and 80 mg were 10, 20, and 18%, respectively, compared to 3% with placebo (P<0.001). Eletriptan had a higher consistency of intra patient response compared to placebo in two of three and three of three attacks (68 to 82% and 32 to 60% vs 16 and 8%, respectively; P value not reported). All eletriptan doses yielded significant functional improvement at two hours (P<0.001).
Winner et al.[41] (2007) Eletriptan 40 mg	DB, MC, PC, PG, RCT Patients 12 to 17 years of age with	N=267 Single dose	Primary: Two-hour headache response Secondary:	Primary: There was no significant difference in two-hour headache response for eletriptan 40 mg vs placebo (57 vs 57%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	history of migraine at least every 6 weeks with mean duration of 4 hours minimum		Headache response at one-hour post-dose, absence of headache pain at one and two hours, absence of nausea, photophobia or phonophobia, change in functional impairment two hours post-dose, time to use of rescue meds, headache recurrence/time to headache recurrence two to 24 hours post-dose, sustained headache response/ pain-free response within two hours post-dose without recurrence or use of rescue meds within 24 hours following the first dose of study med	There were no significant improvements observed for any of the outcomes at one or two hours post-dose. There was a significant advantage for eletriptan 40 mg in reducing headache recurrence within 24 hours post-dose (11 vs 25%; P=0.028), Post-hoc analyses showed significant differences for sustained headache response rates (52 vs 39%; P=0.04) and sustained pain-free response rates (22 vs 10%; P=0.013).
Diener et al.[42] (2002) Eletriptan 40 to 80 mg vs	DB, MC, PC, PG, RCT Patients 18 to 65 years of age, with a history of migraine with or without aura	N=733 24 hours	Primary: Headache response (improvement from severe or moderate to mild or no pain) at two hours	Primary: The proportion of patients reporting headache response at two hours was significantly greater with eletriptan compared to ergotamine tartrate/caffeine (54 and 68 vs 33%; P<0.001). Secondary: Eletriptan headache response rates at one hour were significantly greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ergotamine tartrate 2 mg and caffeine 200 mg (Cafergot®) vs placebo	for at least one year; frequency of migraine attacks at least every six weeks but not more than six per month		Secondary: Headache response at one hour; pain-free rates at one and two hours, functional hour impairment, functional response, presence of migraine-associated symptoms or absence of nausea, vomiting, photophobia and phonophobia	compared to ergotamine tartrate/caffeine and placebo headache response rates (29 and 39 vs 29 vs 13%; P<0.002 for each comparison). The proportion of patients reporting no pain at two hours was significantly greater with eletriptan compared to ergotamine tartrate/caffeine (28 and 38 vs 10 vs 5%; P<0.001 for each comparison). Both doses of eletriptan were significantly more effective than ergotamine tartrate/caffeine in reducing nausea (P<0.0001), photophobia (80 mg; P<0.0001, 40 mg; P<0.002), phonophobia (80 mg; P<0.0001, 40 mg; P<0.003) and functional impairment (P≤0.001) at two hours.
Garcia-Ramos et al.[43] (2003) Eletriptan 40 mg vs naratriptan 2.5 mg vs placebo	DB, PC, PG, RCT Patients 18 to 80 years of age with migraine with or without aura reporting a minimum of one acute migraine attack every six weeks	N=548 Single migraine attack	Primary: Headache response at two hours Secondary: Headache response at one and four hours; pain-free response at one, two and four hours; presence or absence of associated symptoms at the same time points; functional status; headache recurrence and time to headache recurrence; use of	Primary: A significantly greater proportion of patients receiving eletriptan achieved headache response at two hours compared to patients receiving naratriptan (56 vs 42%; P<0.01). Both active treatments were significantly better than placebo (P<0.0001 and P<0.05). Secondary: A significantly greater proportion of patients receiving eletriptan achieved headache response at one and four hours compared to patients receiving naratriptan (34 vs 25%; P<0.05, 80 vs 67%; P<0.01) and patients receiving placebo (21%; P<0.01, 44%; P<0.0001). A significantly greater proportion of patients receiving eletriptan achieved a pain-free response at two and four hours compared to patients receiving naratriptan (35 vs 18%; P<0.001 and 56 vs 41%; P<0.01) and patients receiving placebo (19%; P<0.001 and 24%; P<0.0001). At one hour, freedom from pain was significantly greater with eletriptan (12%) compared to naratriptan (6%; P<0.05). Freedom from pain with naratriptan was significantly greater compared to placebo at four hours (P<0.01) but not at two hours (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			rescue medication, time to use of rescue medication; sustained headache; sustained pain-free response; global evaluation of medication and acceptability of study medication	Absence of nausea at two hours was not significantly different among the treatments (73 vs 68 vs 66%; P=0.09 vs naratriptan; P=0.07 vs placebo). Eletriptan resulted in significantly better functional improvement at two hours compared to naratriptan (60 vs 52%; P=0.014) and placebo (44%; P<0.001). No difference between naratriptan and placebo was noted (P value not reported). Among patients who achieved a two hour headache response, headache recurrence rates were consistently low with eletriptan (29%), naratriptan (26%) and placebo (28%), with no differences among the three (P values not reported). The proportion of patients taking a second dose of study medication for headache recurrence was lower for eletriptan and naratriptan (19 and 18%, respectively) compared to placebo (26%; P value not reported). Significantly less rescue medication was used with eletriptan compared to naratriptan (15 vs 27%; P<0.01). A significantly greater proportion of patients receiving eletriptan reported a sustained headache response (38%) compared to patients receiving naratriptan (27%; P<0.05) and patients receiving placebo (19%; P<0.01). No difference between naratriptan and placebo was noted (P value not reported). A significantly greater proportion of patients receiving eletriptan reported a sustained pain-free response (22%) compared to patients receiving naratriptan (11%; P<0.05) and patients receiving placebo (12%; P<0.05). Patient ratings of treatment acceptability were significantly higher for eletriptan compared to naratriptan (68 vs 50%; P<0.001) and placebo (31%; P<0.0001). Naratriptan was “superior” to placebo (P<0.05). The proportion of patients reporting treatment to be ‘good to excellent’ was significantly greater with eletriptan compared to naratriptan (70 vs 53%; P<0.001) and placebo (33%; P<0.0001). Naratriptan was “superior”

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to placebo (P<0.001).
Goadsby et al.[44] (2000) Eletriptan 20 to 80 mg vs sumatriptan 100 mg vs placebo	DB, PC, PG, RCT Patients ≥18 years of age with migraine with or without aura	N=692 Single migraine attack	Primary: Proportion of responders (any patient who within two hours after ingesting study drug, reported improvement in headache intensity to mild or pain-free levels from a pretreatment level of moderate or severe) Secondary: Not reported	Primary: The proportions of patients who responded were 24 (30/126), 55 (63/115), 54 (70/129), 65 (76/117) and 77% (91/118) for placebo, sumatriptan, eletriptan 20 mg, eletriptan 40 mg and eletriptan 80 mg, respectively. There was a significant difference compared to placebo for all doses of eletriptan (P<0.001). There was a significant difference between sumatriptan 100 mg and eletriptan 80 mg (P<0.001). Freedom from headache at two hours was significantly better with eletriptan 80 (37%) and 40 mg (29%) compared to placebo (6%; P<0.001). Eletriptan 80 mg was "superior" to sumatriptan (23%; P<0.05). Secondary: Not reported
Mandema et al.[45] (2005) Eletriptan 20 to 80 mg vs sumatriptan 25 to 300 mg vs placebo	MA (DB, PC, RCTs) Adult patients receiving treatment of moderate or severe migraine within eight hours of onset, with no re-medication or rescue before two hours	N=11,400 Duration not specified	Primary: Pain relief at four hours and proportion of patients that became pain-free Secondary: Not reported	Primary: A significant difference for eletriptan 40 mg for pain relief compared to sumatriptan 100 mg at any point in time up to four hours after treatment was observed (P value not reported). The benefit of eletriptan 40 mg is greatest around one and half to two hours after treatment. There was an absolute difference at two hours of 9.1% (7.4 to 11.5%) more patients achieving pain relief and 7.3% (5.8 to 8.6%) more patient achieving pain-free when compared to sumatriptan 100 mg (P values not reported). An absolute benefit of more than five percent of patients is maintained from 45 minutes up to four hours after treatment for pain relief and from one and half hours up to four hours for pain-free response (P values not reported). Eletriptan 20 mg was more efficacious than sumatriptan 50 mg and similar to sumatriptan 100 mg for pain relief, while it was similar to sumatriptan 50 mg for pain-free response (P values not reported). The benefit of eletriptan 20 mg when compared to sumatriptan 50 mg is

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				greatest around one and a half to two hours after treatment with an absolute difference at two hours of 5.0% (2.9 to 8.1%) more patients achieving pain relief (P value not reported). An absolute benefit of more than three percent of patients was maintained from one hour up to three hours after treatment. No difference was observed between eletriptan 20 mg and sumatriptan 50 mg for the fraction of patients that became pain-free (P value not reported). No significant effect of encapsulation of sumatriptan was found on the time course of response up to four hours after treatment when compared to commercial sumatriptan (P value not reported). Secondary: Not reported
Mathew et al.[46] (2003) Eletriptan 40 mg vs sumatriptan 100 mg vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age with migraine with or without aura	N=2,113 24 hours	Primary: Headache response at two hours Secondary: Headache response at one hour, pain-free rates, absence of associated symptoms, functional response at one and two hours and sustained headache response	Primary: Headache response at two hours was significantly greater for eletriptan compared to sumatriptan (67 vs 59%; P<0.001) and placebo (26%; P<0.0001). Secondary: Eletriptan consistently demonstrated significantly greater efficacy compared to sumatriptan across all secondary outcomes, including headache response at one hour, freedom from pain at two hours, absence of nausea, photophobia and phonophobia, functional improvement, use of rescue medication, treatment acceptability and sustained headache response (P<0.05 for all).
Schoenen et al.[47] (2005) Eletriptan 80 mg vs	OL, RCT, XO Patients 18 to 65 years of age with migraine with or without aura and suffering at least	N=311 3 migraine attacks	Primary: Patient preference Secondary: Change from pretreatment baseline in	Primary: Fifty one percent of patients preferred or greatly preferred eletriptan, while 43% of patients preferred sumatriptan SC (P value not reported). When permitted to choose between eletriptan and sumatriptan SC for subsequent treatment, 78% of patients who had preferred eletriptan took eletriptan during the extension phase for all three of their attacks, while only 37% of patients who preferred sumatriptan SC took sumatriptan SC for all of their

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sumatriptan 6 mg SC	one acute attack every six weeks		headache intensity; change from pretreatment baseline in a five-point patient-rated Global Impression of efficacy scale; the presence or absence of nausea, vomiting, photophobia and phonophobia; change in functional impairment scale; headache recurrence (and time to headache recurrence) between two and 24 hours; time to use of rescue medication; sustained relief and acceptability of study medication	extension phase attacks (P<0.05). Secondary: Secondary efficacy measures showed comparable efficacy for each study medication, except for faster headache response and pain-free rates in favor of sumatriptan SC, and a significantly lower recurrence rate with eletriptan (25 vs 40%; P<0.05).
Sandrini et al.[48] (2002) Eletriptan 40 to 80 mg vs sumatriptan 50 to 100 mg	DB, DD, MC, PC, PG, RCT Patients >18 years of age who were expected to have at least one attack of migraine with or without aura every six weeks	N=1,008 3 migraine attacks	Primary: Headache response at one and two hours Secondary: Headache response rates, functional improvement and patient acceptability	Primary: Headache response rates were 12% at one hour and 31% at two hours for placebo; 24 and 50% for sumatriptan 50 mg; 27 and 53% for sumatriptan 100 mg; 30 and 64% for eletriptan 40 mg and 37 and 67% for eletriptan 80 mg. Significantly more patients receiving eletriptan 80 mg achieved a one hour headache response compared to patients receiving sumatriptan 50 mg (P<0.05). All doses of eletriptan were more efficacious than sumatriptan at two hours for headache response and complete pain relief (P<0.05). Secondary: Significantly more patients receiving eletriptan 80 mg achieved headache

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				response in all attacks compared to sumatriptan (P values not reported). Eletriptan 40 mg was more efficacious than sumatriptan in functional improvement (P<0.005 for both). The higher efficacy of both eletriptan doses was associated with higher rates of patient acceptability than sumatriptan 50 mg (P<0.05).
Steiner et al.[49] (2003) Eletriptan 40 to 80 mg vs zolmitriptan 2.5 mg vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age with migraine with or without aura	N=1,312 Single migraine attack	Primary: Headache response within two hours Secondary: Headache response rates at one hour; pain-free rates at one and two hours, absence of associated symptoms at one-half, one, one and a half and two hours, functional recovery at one and two hours, headache recurrence rate, use of rescue medication, sustained headache response, patient's global evaluation of study medication at 24 hours on a seven-point Likert scale and acceptability of study medication	Primary: Significantly more patients receiving eletriptan 80 mg (74%) achieved a headache response within two hours compared to patients receiving zolmitriptan (60%; P<0.0001) and patients receiving placebo (22%; P<0.0001). Eletriptan 40 mg was "superior" to placebo (64 vs 28%; P value not reported). Eletriptan 80 mg was "superior" to eletriptan 40 mg at two hours (P<0.01). Secondary: A significantly greater proportion of patients receiving eletriptan 80 mg (40%) achieved a headache response at one hour compared to patients receiving zolmitriptan (25%; P<0.0001) and patients receiving placebo (5%; P<0.0001). Pain-free rates with eletriptan 80 mg were significantly higher at two (44%) and one hours (12%) compared to zolmitriptan (26%; P<0.0001 and 6%; P<0.01) and placebo (6%; P<0.0001 and <1%; P<0.01). Eletriptan 40 mg was "superior" compared to placebo (32%; P<0.0001, 6%; P<0.05). Eletriptan 80 mg was "superior" to eletriptan 40 mg at two hours (P<0.01). Eletriptan 80 mg was significantly better (P<0.01) than eletriptan 40 mg in pain-free rates at two hours. In patients with severe or moderate functional impairment at baseline, all active treatments were superior to placebo at bringing improvement (P<0.0001 for all). Response rates at one and two hours were significantly higher with eletriptan 80 mg (68 and 34%) compared to zolmitriptan (56%; P<0.05, 24%; P<0.05). There was no difference between eletriptan 40 mg (61 and 24%) and zolmitriptan (P values not reported). In patients achieving headache response by two hours, headache

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				recurrence rates were numerically lower with eletriptan 80 mg (33%; P=0.271) and significantly lower with eletriptan 40 mg (29%; P<0.05) compared to zolmitriptan (38%). Both doses of eletriptan had significantly lower recurrence rates than placebo (52%; P<0.05). Rescue medication was used significantly less with eletriptan 80 mg (14%) compared to zolmitriptan (26%; P<0.0001) and placebo (58%; P<0.0001). Similar results were observed with eletriptan 40 mg (20%; P<0.05 vs zolmitriptan; P<0.0001 vs placebo). Significantly greater proportions of patients receiving eletriptan 80 (47%; P<0.001) and 40 mg (44%; P<0.01) achieved sustained headache response compared to patients receiving zolmitriptan (35%). Eletriptan 80 (P<0.0001) and 40 mg (P<0.0001), as well as zolmitriptan (P<0.0001), were "superior" to placebo (11%). Sustained pain-free rates were higher with eletriptan 80 mg (29%) compared to zolmitriptan (17%; P<0.001). Eletriptan 80 (P<0.0001) and 40 mg (22%; P<0.0001), as well as zolmitriptan (P<0.01), were "superior" to placebo (5%). Patients' ratings of treatment acceptability ('would use again') showed significant preference for eletriptan 80 (61%; P<0.05) and 40 mg (64%; P<0.01) compared to zolmitriptan (53%). All active treatments were "superior" to placebo (19%; P<0.0001). On the seven-point global rating of study medication, analysis was of the percentage of patients in each group recording either "excellent" or "good". Eletriptan 80 (66%) and 40 mg (64%) were rated significantly higher than zolmitriptan (55%; P<0.01). All active treatments were "superior" to placebo (17%; P<0.0001).
Ryan et al.[50] (2002) Frovatriptan 2.5 mg	MA (3 DB, PC, PG, RCTs) Patients with migraine	N=2,676 24 hours (up to three migraine attacks)	Primary: Headache response at two hours Secondary: Time to headache	Primary: In all three trials, headache response two hours after frovatriptan was significantly greater compared to headache response two hours after placebo (P≤0.001), with approximately a twofold measure of effect over placebo for headache response at two and four hours.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			recurrence and headache recurrence	Secondary: Time to headache response occurred within one and half hours in a substantial proportion of patients. The incidence of 24-hour headache recurrence with frovatriptan was low (10 to 25%).
Cady et al.[51] (2004) Frovatriptan 2.5 mg early use vs frovatriptan 2.5 mg late use	DB, MC, PC, XO Patients with a history of migraine for more than one year and two to eight migraines in the previous two months	N=165 2 migraine attacks	Primary: The incidence of no headache at two hours Secondary: Comparison of early vs later use of frovatriptan	Primary: Twenty eight and 20% of early frovatriptan- and placebo-treated patients, respectively, were headache-free at two hours (P=0.04). Secondary: Fifty percent of early users were pain-free at three hours. Early use of frovatriptan prevented mild migraine headaches from progressing to moderate or severe headaches (P value not reported). Migraine recurrence was low, (four to six percent), regardless of treatment (P value not reported). During the 24 hours following the first dose, 64% of patients experienced nothing worse than mild functional impairment when frovatriptan was used early compared to 48% of patients when placebo was used early (P<0.001).
Gobel et al.[52] (2011) Frovatriptan 2.5 mg Patients were instructed to choose the time of self-administration and if migraine symptoms recurred, a second dose was permitted	OL, OS, PRO Patients 18 to 65 years of age with an established diagnosis of migraine with or without aura, age at migraine onset <50 years, at least one migraine attack per month and <10 days of non-migraine headache per month	N=2160 Patients were allowed to treat up to three migraine attacks during the study period; the third attack treated was evaluated	Primary: Headache response, defined as the length of time (in minutes) between medication consumption and the onset of headache relief Secondary: Time taken to achieve complete headache	Primary: Patients were divided into two groups: those that dosed frovatriptan with low symptom severity scores based on the MIS (severity one to five) and those that dosed with more severe symptoms based on the MIS (severity six to 10). Time to onset of efficacy was faster in the group with low symptom severity at dosing compared to those with more severe symptoms (42.06±32.33 vs 49.25±34.92 minutes; P=0.0023). Secondary: Patients with lower symptom severity scores at time of dose had an earlier time to pain-free response compared to those with more severe symptoms at dosing (79.33±65.33 vs 96.05±100.85 minutes; P=0.0109). A similar proportion of patients with lower symptom severity scores experienced headache recurrence compared to those with more severe symptoms at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
two to 24 hours later.	for the three months prior to study		relief, incidence of headache recurrence within 24 hours, the number of frovatriptan tablets required to treat each attack and the use of rescue medication	time of dose (224±29 [86.82%±11.24] vs 1053±176 [83.57%±13.97]; P=0.2711). Patients with lower symptom severity also required a similar number of frovatriptan tablets to treat each attack when compared to those patients that were dosed with a higher symptom severity score (1.17±0.42 vs 1.24±0.56 tablets; P=0.0575). Fewer patients that dosed frovatriptan with lower symptom severity scores required escape medication when compared to those patients in the group that dosed with higher symptom severity scores (10 [3.88%] vs 173 [13.73%]; P<0.0001).
Bartolini et al.[53] (2011) Frovatriptan 2.5 mg vs almotriptan 12.5 mg	DB, MC, RCT, XO Patients 18 to 65 years of age with a history of migraine with or without aura and six or fewer migraine attacks in the preceding six months	N=133 One to three migraine attacks	Primary: Between treatment comparison of the direction and average strength of preference Secondary: Pain-free and pain relief at two and four hours and recurrent and sustained pain-free episodes within 48 hours	Primary: There was no difference in average preference scores between the two treatments (3.1±1.3 vs 3.4±1.3; P value not significant). Sixty three percent of patients expressed a clear preference for a triptan, with 29 and 34% preferring frovatriptan and almotriptan, respectively (P value not significant). The most common reasons for preferring one triptan were the rapid action (54.4 vs 55.0%), prevention of aggravation (13.5 vs 2.5%) and reduction of severity (13.5 vs 15.0%; P values not significant). Secondary: At two hours, rates of pain-free (30 vs 32%) and pain relief episodes (54 vs 56%) were not significantly different between the two treatments (P value not significant). There was no difference in the rate of sustained pain-free episodes between the two treatments (P value not significant). Recurrent episodes within 48 hours occurred significantly less with frovatriptan compared to almotriptan (P<0.05).
Tullo et al.[54] (2010) Frovatriptan 2.5mg vs	DB, MC, RCT, XO Patients 18 to 65 years of age with current history of migraine with or without aura and at	N=107 6 months	Primary: Patient preference Secondary: Pain-free response at two hours, recurrence,	Primary: There was no difference between the two treatments in terms of patient preference (34 vs 43%; P value not significant). Secondary: There was no difference between the two treatments for rates of pain-free response at two hours (26 vs 31%; P value not significant).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
zolmitriptan 2.5mg Patients received 3 sequential treatments with one medication, then XO to 3 sequential treatments with the other treatment.	least one migraine attack per month for six months prior to enrollment		sustained pain-free episodes within 48 hours, pain relief episodes at two hours	There was no difference between the two treatments for rates of recurrent episodes (21 vs 24%), sustained pain-free episodes (18 vs 22%) and pain relief episodes at two hours (57 vs 58%; P values not significant).
Klassen et al.[55] (1997) Naratriptan 0.1 to 2.5 mg vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura at least one year	N=613 Single migraine attack	Primary: Proportion of patients who experienced headache relief at four hours Secondary: Proportion of patients with meaningful relief, proportions of patients with headache relief at eight, 12 and 24 hours, proportion of patients taking rescue medication within 24 hours and proportion of patients experiencing headache recurrence within 24 hours	Primary: Headache relief at four hours was reported in 60% of patients receiving naratriptan 2.5 mg compared to 50, 35, 32 and 34% of patients receiving naratriptan 1, 0.25, 0.1 mg and placebo, respectively (P<0.05 naratriptan 2.5 and 1 mg vs placebo, 1 vs 0.1 mg and 2.5 vs 0.1 and 0.25 mg). Secondary: Meaningful relief of headache at four hours occurred in 59% of patients receiving naratriptan 2.5 mg compared to 56, 38, 33 and 36% of patients receiving naratriptan 1, 0.25 and 0.1 mg and placebo (P≤0.006 vs 0.1 and 0.25 mg and placebo). The proportions of patients achieving headache relief at eight, 12 and 24 hours were significantly greater with naratriptan 2.5 mg compared to the lower doses of naratriptan (P<0.05) and placebo (P<0.001). Rescue medication was used significantly less with naratriptan 2.5 mg compared to the lower doses of naratriptan (P≤0.025 and 0.25 mg, P≤0.034 vs 0.1 mg) and placebo (P≤0.022). The proportions of patients reporting headache recurrence were not different among the treatments (39, 38, 39, 28 and 38%; P values not reported).
Stark et al.[56] (2000)	DB, PC, PG, RCT	N=347	Primary: Conversion from	Primary: Naratriptan was significantly more efficacious compared to placebo for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Naratriptan 2.5 mg vs sumatriptan 50 mg vs placebo	Self-described poor sumatriptan responders with a history of migraine for more than one year	2 migraine attacks	moderate or severe pain to mild or no pain at four hours for attack two Secondary: Headache relief at two hours, freedom from pain at two hours	relief of headache pain at four hours (P<0.001). Secondary: Naratriptan was more efficacious than placebo at two hours for relief of headache (P=0.005). There was no difference between naratriptan and placebo for freedom from pain at two hours (P>0.05).
Gobel et al.[57] (2000) Naratriptan 2.5 mg as a single dose vs sumatriptan 100 mg as a single dose	DB, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for more than one year	N=253 Single migraine attack	Primary: Headache recurrence and proportion of patients with 24-hour maintenance of headache relief Secondary: Proportion of patients experiencing headache relief, proportion of patients using rescue medication during the 24 hours after dosing and proportion of patients that took a second dose of study drug	Primary: The incidence of headache recurrence was numerically lower with naratriptan compared to sumatriptan (45 vs 57%; P value not reported). Twenty-four hour maintenance of headache relief was reported by 39 and 34% of patients receiving naratriptan and sumatriptan respectively (OR, 1.26; 95% CI, 0.86 to 1.85; P value not significant). Secondary: The proportions of patients experiencing headache relief were 76 and 84% with naratriptan and sumatriptan respectively (P value not significant). The proportions of patients who received rescue medications for inadequate relief up to 24 hours after dosing did not differ between the two treatments (21 vs 16%; OR, 1.47; 95% CI, 0.94 to 2.30; P value not reported). The proportions of patients that took a second dose of study drug was significantly less with naratriptan (40 vs 57%; OR, 0.51; 95% CI, 0.37 to 0.71; P<0.001).
Ashcroft et al.[58] (2004) Naratriptan 1 to 2.5 mg	MA Patients with moderate or severe migraine attacks	N=449 Single migraine attack	Primary: Response rate ratios for pain-free response	Primary: Pooled RRs compared to placebo for pain-free response at two and four hours for naratriptan 2.5 mg were 2.52 (95% CI, 1.78 to 3.57) and 2.58 (95% CI, 1.99 to 3.35), respectively. Naratriptan 2.5 mg was more effective than naratriptan 1 mg; the corresponding RRs for pain-free

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rizatriptan 10 mg vs sumatriptan 100 mg vs placebo			Secondary: Adverse events	response at two and four hours were 1.54 (95% CI, 1.28 to 1.86) and 1.35 (95% CI, 1.20 to 1.51), respectively. Naratriptan 2.5 mg was less effective in pain-free response than rizatriptan 10 mg (RR, 0.68; 95% CI, 0.55 to 0.85) or sumatriptan 100 mg at four hours (RR, 0.79; 95% CI, 0.67 to 0.93). Secondary: Significantly fewer patients experienced adverse events with naratriptan 2.5 mg compared to rizatriptan 10 mg (RR, 0.73; 95% CI, 0.56 to 0.97) or sumatriptan 100 mg (RR, 0.68; 95% CI, 0.55 to 0.86).
Mathew et al.[59] (2004) Rizatriptan 10 mg vs placebo	DB, PC, RCT Patients 20 to 64 years of age with migraine and a history of headache progressing to moderate or severe pain when no intervention was used	N=112 Three migraine attacks	Primary: Proportion of migraine attacks in which treatment produced a pain-free response at two hours Secondary: Pain-free response at one hour, percentage of migraine attacks in which treatment provided a sustained pain-free response lasting between two and 24 hours	Primary: Pain-free response at two hours occurred in 151 of 216 attacks (70%) with rizatriptan and 24 of 109 attacks (22%) with placebo (P<0.01). Secondary: Pain-free response at one hour occurred in more attacks treated with rizatriptan compared to placebo (45 vs 8%; P<0.01). When the attacks were categorized by headache severity at the time of treatment, the pain-free response at two hours was higher for mild attacks than for moderate or severe attacks (P<0.01). Sustained pain-free response rates were significantly higher with rizatriptan compared to placebo (60 vs 17%; P<0.001).
Ferrari et al.[60] (2001) Rizatriptan 5 to 10 mg	MA (DB, RCTs) Outpatients with a history of migraine for at least six	N=4,816 Single migraine attack	Primary: Pain relief, associated migraine symptoms and	Primary: At two hours, rizatriptan 10 mg was significantly more effective than placebo for pain relief (71 vs 38%; P<0.001), and for elimination of pain, nausea, photophobia, phonophobia and functional disability (P values not reported). The benefit was maintained over 24 hours; 37% of patients had

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	months		functional disability and headache recurrence Secondary: Not reported	sustained pain relief compared to 18% with placebo (P<0.001). Rizatriptan 10 mg was more effective than 5 mg, with a significant difference at two hours on all measures except for elimination of nausea (P values not reported). The benefit was maintained over 24 hours; 38% of patients had sustained pain relief vs 32% of patients with 5 mg (P=0.001). Secondary: Not reported
Oldman et al.[61] (2006) Rizatriptan 5 to 10 mg vs placebo	MA Patients >18 years of age with moderate or severe migraine with or without aura	N=2,626 Single migraine attack	Primary: Headache response at two hours, headache response at one hour, pain-free response at two hours and sustained relief over 24 hours Secondary: Not reported	Primary: Headache response at two hours was reported as follows: rizatriptan 5 mg: relative benefit, 1.8 (1.6 to 2.0); NNT, 3.9 (3.3 to 4.7); n=1,646 and rizatriptan 10 mg: relative benefit, 2.2 (2.0 to 2.4); NNT, 2.7 (2.4 to 2.9); n=2,770. Headache response at one hour was reported as follows: rizatriptan 5 mg: relative benefit, 1.6 (1.4 to 1.9); NNT, 7.2 (5.4 to 10); n=1,646 and rizatriptan 10 mg: relative benefit, 1.9 (1.6 to 2.1); NNT, 4.9 (4.2 to 6.0); n=2,770. Pain-free response at two hours was reported as follows: rizatriptan 5 mg: relative benefit, 3.4 (2.6 to 4.4); NNT, 4.7 (4.0 to 5.7); n=1,646 and rizatriptan 10 mg: relative benefit, 4.8 (3.8 to 5.9); NNT, 3.1 (2.9 to 3.4); n=2,770. Sustained-relief over 24 hours was reported as follows: rizatriptan 5 mg: relative benefit, 1.5 (1.3 to 1.8); NNT, 8.3 (6.0 to 14); n=1,450 and rizatriptan 10 mg: relative benefit, 1.7 (1.5 to 2.0); NNT, 5.6 (4.5 to 7.4); n=1,677. Secondary: Not reported
Cady et al.[62] (2006) Rizatriptan 10 mg	DB, MC, PC, PG, RCT Patients ≥18 years of age with at least a	N=1,030 Single dose	Primary: Pain freedom at two hours post-dose	Primary/Secondary: 57.3 vs 31.1% of patients reported pain freedom at two hours post-dose and 42.6 vs 23.2% reported 24-hour sustained pain freedom with rizatriptan vs placebo, respectively. (P<0.001 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	6-month history of 1 to 4 migraine attacks per month that were typically mild at onset		Secondary: Sustained pain freedom at 24 hours post-dose	58.9 vs 31.1% of patients reported pain freedom at two hours post-dose and 48.0 vs24.6% reported 24-hour sustained pain freedom with rizatriptan vs placebo, respectively (P<0.001 for both).
Martin et al.[63] (2008) Rizatriptan 10 mg vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with migraine, with or without aura with a history of 1 to 4 migraine attacks per month.	N=94 Single migraine attack	Primary: Two-hour pain freedom Secondary: 24-hour sustained pain-free response, need for rescue therapy, associated migraine symptoms	Primary: There was a significantly greater percentage of patients reporting pain freedom at 2 hours in the rizatriptan group (63.5%) compared to placebo (29%; OR, 4.54; 95% CI, 1.73 to 11.93; P=0.002). Secondary: Rizatriptan was significantly better than placebo with respect to time to pain freedom up to two hours (P=0.029), presence of nausea at two hours (P<0.001), and functional disability at two hours (P=0.025). There were no differences between rizatriptan and placebo with respect to 24-hour sustained pain freedom, need for rescue medication, photophobia or phonophobia.
Nett et al.[64] (2008) Rizatriptan 10 mg vs placebo	DB, PC, PG, RCT Women ≥18 years of age with a ≥6 month history of migraines, specifically the subgroup with pure menstrual migraines defined as having headaches only during menstruation	N=146 Single migraine attack	Primary: Two-hour pain relief Secondary: 24-hour pain relief, two-hour pain freedom or 24-hour sustained pain freedom	Primary: The percentage of patients reporting pain relief at two hours in the rizatriptan group (73%) was significantly greater than the placebo group (50%; OR, 2.74; 95% CI, 1.34 to 5.61; P=0.006). Secondary: Statistical analysis was not conducted for 24-hour pain relief, two hour pain freedom or 24-hour sustained pain freedom. Adverse events that occurred in ≥2% of patients in the rizatriptan group vs placebo were palpitations (3.1 vs 0%), fatigue (2.1 vs 0%), joint stiffness (2.1 vs 0%), dizziness (3.1 vs 0%) and somnolence (5.2 vs 0%).
Ng-Mak et al.[65] (2009) Rizatriptan 10 mg vs	MC, OL, PRO, XO Patients ≥18 years of age with more than one migraines per month who were rizatriptan naïve	N=79 2 migraine attacks	Primary: Mean time to onset of pain relief and pain freedom using a stopwatch Secondary:	Primary: More patients (88.6%) achieved onset of pain relief within two hours with rizatriptan than with almotriptan (73.4%; P=0.007). There was no significant difference in pain freedom within two hours after dosing with rizatriptan (55.7%) or almotriptan (45.6%; P=0.10).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
almotriptan 12.5 mg			Not reported	The mean time to pain relief was shorter with rizatriptan (69.7 minutes) than with almotriptan (178.8 minutes; P=0.065). The median time to relief was statistically shorter for rizatriptan (45 minutes) than for almotriptan (60 minutes; P=0.002). The mean time to pain freedom was shorter with rizatriptan (247.2 minutes) than with almotriptan (427.0 minutes; P=0.079). The median time to pain freedom was significantly shorter for rizatriptan (100 minutes) than for almotriptan (135 minutes; P=0.004). A greater proportion of patients indicated that they were very satisfied with rizatriptan compared to almotriptan (29.9 vs 16.7%). A smaller proportion of patients reported that they were dissatisfied (13.2 vs 23.1%) or very dissatisfied (9.2 vs 7.7%) with rizatriptan compared to almotriptan. Secondary: Not reported
Ng-Mak et al.[66] (1997) Rizatriptan 10 mg vs almotriptan 12.5 mg	MC, OL, XO Patients ≥18 years of age with migraine and a recent history of at least one migraine per month	N=146 Two migraine attacks	Primary: Mean and median times to onset of pain relief and pain-freedom Secondary: Patient satisfaction	Primary: The mean time to pain relief was numerically shorter with rizatriptan compared to almotriptan (69.7 vs 178.8 minutes; mean difference, 109 minutes; 95% CI, -6.8 to 224.8; P=0.065). The median time to pain relief was significantly shorter with rizatriptan (45 vs 60 minutes; P=0.002). The mean time to pain-freedom was numerically shorter with rizatriptan compared to almotriptan (247.2 vs 247.0 minutes; mean difference, 179.8 minutes; 95% CI, -21.8 to 381.4; P=0.079). The median time to pain-freedom was significantly shorter with rizatriptan (100 vs 135 minutes; P=0.004). Significantly more patients receiving rizatriptan achieved onset of pain relief within two hours compared to patients receiving almotriptan (88.6 vs 73.4%; P=0.007). More patients receiving rizatriptan achieved onset of pain-freedom within two hours compared to patients receiving almotriptan (55.7 vs 45.6%; P=0.10). Secondary: More patients indicated they were very satisfied when treating a migraine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with rizatriptan (29.9 vs 16.7%). Less patients indicated they were dissatisfied (13.2 vs 23.1%) or very dissatisfied (9.2 vs 7.7%) when treating a migraine attack with rizatriptan. Of the 39 patients who responded to the diary question regarding medication preference, 48.7 and 23.1% expressed preference for rizatriptan and almotriptan, while 28.2% expressed no preference.
Lainez et al.[67] (2006) Rizatriptan 10 mg vs eletriptan 40 mg	MC, OL, XO Patients 18 to 65 years of age with a history of migraine with or without aura for at least six months	N=372 Single migraine attack	Primary: Patient preference Secondary: Not reported	Primary: Significantly more patients preferred rizatriptan (61.1%; 95% CI, 55.7 to 66.3) compared to eletriptan (38.9%; 95% CI, 33.7 to 44.3; P≤0.001). The most common reason given for preference of either treatment was speed of headache relief. At two hours, 80 and 69% of patients reported that rizatriptan and eletriptan, respectively, were convenient or very convenient to take (mean convenience score, 1.99 vs 2.31, respectively; P≤0.001). Secondary: Not reported
Bomhof et al.[68] (1999) Rizatriptan 10 mg vs naratriptan 2.5 mg vs placebo	DB, DD, MC, PC, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for more than six months and experiencing up to eight attacks per month	N=552 Single migraine attack	Primary: Time to headache relief within two hours Secondary: Headache relief and pain-free up to two hours, associated symptoms, functional disability, satisfaction with medication at two hours, need for additional medication from two to 24 hours, 24-hour quality of life and safety	Primary: Rizatriptan was significantly more effective than naratriptan for time to headache relief within two hours (HR, 1.62; 95% CI, 1.26 to 2.09; P<0.001). Secondary: Headache relief at two hours was 68.7 and 48.4% with rizatriptan and naratriptan, respectively (P<0.001). In patients with migraine associated symptoms at baseline, rizatriptan gave earlier relief than naratriptan from nausea (HR, 1.53; 95% CI, 1.11 to 2.11; P=0.009), photophobia (HR, 1.57; 95% CI, 1.13 to 2.19; P=0.007) and phonophobia within two hours (HR, 1.61; 95% CI, 1.15 to 2.27; P=0.006), respectively. Rizatriptan was significantly better than naratriptan with regard to time to no functional disability (HR, 1.96; 95% CI, 1.36 to 2.82; P<0.001). Patients receiving rizatriptan were more satisfied with their medication compared to patients receiving naratriptan at two hours (means scores, 3.55 vs 4.21; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fewer patients receiving rizatriptan and naratriptan needed additional medications compared to patients receiving placebo (P<0.001); however, there was no difference between the two active treatments (P=0.068). Rizatriptan and naratriptan were significantly better than placebo on all five quality of life domains (P<0.01). The overall incidence of any clinical adverse event was significantly higher with rizatriptan compared to naratriptan and placebo (P<0.05).
Kolodny et al.[69] (2004) Rizatriptan 5 to 10 mg vs sumatriptan 25 to 50 mg vs placebo	DB, PC, RCT Patients >18 years of age with a history of migraine with or without aura for at least six months	N=1,447 5 days (2 migraine attacks)	Primary: Time to pain relief within two hours Secondary: Presence of associated symptoms at two hours and pain relief at two hours	Primary: The primary efficacy variable, expressed as the HR of rizatriptan 10 mg vs sumatriptan 50 mg, was 1.10 (95% CI, 0.96 to 1.26; P=0.161). Rizatriptan 5 mg was significantly (P=0.007) more efficacious than sumatriptan 25 mg; the HR of rizatriptan 5 mg vs sumatriptan 25 mg was 1.22 (95% CI, 1.06 to 1.41). Secondary: Rizatriptan 10 mg-treated patients had significantly less nausea compared to sumatriptan 50 mg-treated patients (P=0.004). For all other secondary measures at two hours, rizatriptan 10 mg was not different than sumatriptan 50 mg (P values not reported).
Lipton et al.[70] (2001) Rizatriptan 10 mg vs sumatriptan 25 to 100 mg vs naratriptan 2.5 mg	MA (5 trials) Patients >18 years of age with history of migraine with or without aura	N=4,097 Single migraine attack	Primary: Relief of nausea in those who had it at baseline, emergence of nausea in those who were free of it at baseline Secondary: Not reported	Primary: Approximately 60% of patients in each treatment group had nausea at baseline. Significantly more patients treated with rizatriptan 10 mg were free of nausea at two hours compared to patients treated with sumatriptan 100 mg (66 vs 58%; P=0.043), sumatriptan 50 mg (68 vs 57%; P=0.010), sumatriptan 25 mg (68 vs 59%; P=0.017) and naratriptan 2.5 mg (59 vs 45%; P=0.014). Averaging over the four post treatment time points in the first two hours, significantly more patients receiving rizatriptan 10 mg were free of nausea compared to patients treated with sumatriptan 100 mg (P=0.004), sumatriptan 50 mg (P=0.001) and naratriptan 2.5 mg (P=0.015).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs zolmitriptan 2.5 mg vs placebo				No differences in nausea relief were seen between rizatriptan 10 mg and zolmitriptan 2.5 mg, either at two hours (65 vs 61%; P=0.210) or over the first two hours (P=0.781). Rates of treatment-emergent nausea at two hours ranged from 11 to 18% with placebo, from 5 to 13% with rizatriptan 10 mg and from 10 to 20% with other comparator triptans (P values not reported). Secondary: Not reported
Adelman et al.[71] (2001) Rizatriptan 10 mg vs naratriptan 2.5 mg vs zolmitriptan 2.5 mg vs sumatriptan 25 to 100 mg	MA (5 DB, PC, RCTs) Outpatients with at least a six month history of migraine with or without aura	N=4,064 24 hours	Primary: Pain-free response at two hours, symptom-free response at two hours, 24-hour sustained pain-free response Secondary: Adverse events	Primary: Pain-free rates at two hours were significantly higher with rizatriptan compared to all other triptans. The proportions of patients who were pain-free ranged from 38 to 45% with rizatriptan 10 mg and 21 to 36% with all other triptans. The significance of these differences are noted as: rizatriptan vs sumatriptan 100 mg; P=0.019, rizatriptan vs sumatriptan 50 mg; P=0.009, rizatriptan vs sumatriptan 25 mg; P<0.001, rizatriptan vs naratriptan 2.5 mg; P<0.001 and rizatriptan vs zolmitriptan 2.5 mg; P=0.041. Symptom-free rates at two hours were significantly higher with rizatriptan compared to all other triptans. The proportions of patients with freedom from pain and associated symptoms ranged from 30 to 33% with rizatriptan and 11 to 28% with other triptans. The significance of these differences are noted as: rizatriptan vs sumatriptan 100 mg; P=0.002, rizatriptan vs sumatriptan 50 mg; P=0.003, rizatriptan vs sumatriptan 25 mg; P<0.001, rizatriptan vs naratriptan 2.5 mg; P<0.001 and rizatriptan vs zolmitriptan 2.5 mg; P=0.042. Sustained pain-free response rates were significantly higher with rizatriptan compared to all other triptans. The significance of these differences are noted as: rizatriptan vs sumatriptan 100 mg; P=0.112, rizatriptan vs sumatriptan 50 mg; P=0.015, rizatriptan vs sumatriptan 25 mg; P=0.005, rizatriptan vs naratriptan 2.5 mg; P=0.004 and rizatriptan vs zolmitriptan 2.5 mg; P=0.013. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Incidences of drug related adverse events were as follows: rizatriptan 10 mg vs sumatriptan 100 mg; 33 vs 41% (P=0.014), rizatriptan 10 mg vs sumatriptan 50 mg; 37 vs 35% (P=0.671), rizatriptan 10 mg vs sumatriptan 25 mg; 37 vs 31% (P=0.043), rizatriptan 10 mg vs naratriptan 2.5 mg; 27 vs 19% (P=0.079) and rizatriptan 10 mg vs zolmitriptan 2.5 mg; 25 vs 28% (P=0.410).
Seeburger et al.[72] (2012) Rizatriptan 10 mg ODT vs placebo Two migraine attacks were to be treated with rizatriptan and one with placebo, order of treatment was Rand DB.	DB, MC, PC, XO Patients were ≥18 years of age with a history of migraine for more than one year, with or without aura, a minimum of two moderate-to-severe migraine attacks per month during the three months prior to randomization while taking a stable dose of topiramate for migraine prophylaxis (minimum dose of 50 mg)	N=108 Patients treated up to three migraine attacks	Primary: Proportion of treated attacks resulting in pain relief at two hours postdose Secondary: Proportion of treated attacks resulting in: sustained pain relief from two to 24 hours postdose, pain-freedom two hours postdose, “normal” ratings of functional disability at two hours postdose, and satisfaction with treatment at 24 hours postdose	Primary: Significantly more rizatriptan-treated attacks resulted in pain relief at two hours post dose compared to placebo-treated attacks (55 vs 17%; OR, 5.80; 95% CI, 3.13 to 10.76; P<0.001). Secondary: Treatment with rizatriptan resulted in a greater proportion of attacks resulting in sustained pain relief from two to 24 hours postdose compared to treatment with placebo (33 vs 11%; P<0.001). Treatment with rizatriptan also resulted in a greater proportion of attacks resulting in pain-freedom two hours postdose compared to treatment with placebo (6 vs 36%; P<0.01), a greater proportion of “normal” ratings of functional disability at two hours postdose vs placebo (42 vs 13%; P<0.001), and a greater proportion of satisfaction with treatment at 24 hours postdose vs placebo (61 vs 34%; P<0.001).
Cady et al.[73] (2009) Rizatriptan 10 mg ODT vs	DB, MC, PC, PG, RCT Patients ≥18 years of age with a history of migraine with or without aura for at least one year and a	N=207 Single migraine attack	Primary: Proportion of patients free of pain at two hours and determination of whether treatment effects were consistent	Primary: Significantly more patients reported pain-freedom at two hours with rizatriptan compared to placebo (66 vs 26%; OR, 5.20; 95% CI, 2.75 to 9.80; P<0.001). The proportion reporting sustained pain-freedom between two and 24 hours was also significantly greater with rizatriptan (52 vs 18%; OR, 5.40; 95% CI, 2.71 to 10.79; P<0.001). A nonsignificant greater proportion of patients receiving rizatriptan plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Patients within each treatment group were also R to receive migraine education or to receive no migraine education.	history of one to four migraine attacks per month with attacks that were typically mild at onset and recognizable as migraine		across migraine education vs no migraine education with respect to pain-freedom at two hours Secondary: Use of rescue medication, elimination of photophobia, phonophobia, nausea and functional disability at two hours	migraine education reported pain-freedom at two hours compared to those receiving rizatriptan alone (72 vs 61%; P=0.430). Similar results were observed with patients receiving placebo with or without migraine education (28 vs 28%; P value not reported). Secondary: Significantly more patients reported no rescue medication use up to 24 hours with rizatriptan (71.7 vs 34.4%; P<0.001). Rizatriptan had significantly fewer patients reporting photophobia (P=0.002) and functional disability (P=0.001) at two hours. No difference in the incidence of phonophobia (P=0.110) and nausea (P=0.090) occurred.
Cady et al.[74] (1991) Sumatriptan 6 mg SC vs placebo	PC, RCT Adult patients with history of migraine with or without aura	N=1,104 Duration not specified	Primary: Headache response at one hour Secondary: Complete relief of headache, clinical disability and reduction in other migraine symptoms	Primary: Sumatriptan produced a response (mild pain or no pain) in 70% of patients compared to 22% with placebo (P<0.001). Secondary: Sumatriptan was significantly more effective than placebo in totally eliminating migraine headache by 60 minutes (49 vs 9%; P<0.001). Clinical disability improved significantly more with sumatriptan treatment compared to treatment with placebo (76 vs 34%; P<0.001). Sumatriptan was effective in reducing other symptoms such as nausea, vomiting and photophobia.
SC Sumatriptan International Study Group[75] (1991) Sumatriptan 6 to 8 mg SC	DB, PC, PG, RCT Adult patients with history of migraine with or without aura	N=639 Duration not specified	Primary: Severity of headache at 60 and 120 minutes Secondary: Not reported	Primary: After 60 minutes, the severity of headache pain declined in 72% of 422 patients receiving sumatriptan 6 mg, 79% of 109 patients receiving sumatriptan 8 mg and 25% of 105 patients receiving placebo (three patients were not evaluable; P values not reported). Compared to placebo, 47 and 54% more patients receiving sumatriptan 6

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				and 8 mg had less severe headaches (P<0.001). After 120 minutes, 86 to 92% of 511 patients receiving sumatriptan felt headache severity improve compared to 37% of 104 patients receiving placebo (P<0.001). Secondary: Not reported
Winner et al.[76] (2006) Sumatriptan 6 mg SC vs placebo	DB, PC, PG, RCT (2 studies) Patients 18 to 65 years of age with a history of migraine with moderate or severe pain on awakening	N=584 Single migraine attack	Primary: Pain free at two hours post-dose Secondary: Onset of efficacy and mean time to efficacy	Primary: Across the two studies, 48 to 57% of patients were pain free at two hours with sumatriptan compared to placebo (18 to 19%; both, P<0.001). Secondary: Onset of efficacy was observed beginning 10 minutes post-dose (P<0.05 sumatriptan vs placebo across pooled studies). The mean time to efficacy in the sumatriptan group was 10 minutes (P<0.05 vs controls).
Oral Sumatriptan International Multi-Dose Study Group[77] (1991) Sumatriptan 100 mg vs placebo One tablet at onset of headache, one tablet 2 hours later if migraine, and one tablet if the headache came	DB, PC, PG Adult patients with a history of migraine, with or without aura	N=233 24 hours	Primary: Headache relief at two and four hours Secondary: Pain free at two hours, improvement in headache severity at one hour postdose, number of patients needing two or three doses	Primary: Sumatriptan was significantly more effective than placebo at two hours (50 vs 19%; P<0.001) and at four hours (75 vs 30%; P<0.001). Secondary: In the sumatriptan group, 59% of the patients opted to take a second dose compared to 80% of the placebo arm (P<0.001). More patients treated with sumatriptan than with placebo were pain free by two hours (26 vs 5%; P<0.001) and by four hours (48 vs 13%; P<0.001). Improvement in headache severity by 1 hour postdose was seen in 42% of sumatriptan patients and 17% of placebo patients. There was no difference between groups in the number of patients who took a third tablet if the headache recurred within 24 hours (P=0.535).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
back within 24 hours.				
Cutler et al.[78] (1995) Sumatriptan 25 to 100 mg vs placebo	DB, PC, PG, RCT Adult patients with history of migraine with or without aura	N=259 Single migraine attack	Primary: Headache relief at two hours Secondary: Headache relief at four hours	Primary: By two hours, 50 to 56% of the patients who received sumatriptan (any dosage) experienced relief compared to 26% of the patients who received placebo (P<0.05). Secondary: By four hours, 68 to 71% of patients receiving sumatriptan experienced relief compared to 38% of the patients who received placebo (P<0.05).
Winner et al.[79] (2005) Sumatriptan 50 to 100 mg vs placebo	MA (6 DB, PC, RCTs) Patients 18 to 65 years of age with a history of migraine with or without aura for at least one year	N=2,297 Single migraine attack	Primary: Proportion of patients pain-free at two hours Secondary: Migraine-free at two hours, worsening pain at two hours and sustained pain-free results from two to 24 hours	Primary: Freedom from pain at two hours was reported by significantly more patients receiving either dose of sumatriptan compared to patients receiving placebo, and by significantly more patients receiving sumatriptan 100 mg compared to patients receiving sumatriptan 50 mg (50 mg, 49%; 100 mg, 58% and placebo, 24%; P<0.001, for both sumatriptan doses vs placebo and sumatriptan 100 vs 50 mg). Secondary: The proportions of patients who were migraine-free at two hours was 42, 47 and 20% with sumatriptan 50 mg, sumatriptan 100 mg and placebo (P<0.05 for both sumatriptan doses vs placebo). The proportions of patients reporting worsening of pain at two hours was 26, 21 and 46% with sumatriptan 50 mg, sumatriptan 100 mg and placebo (P<0.05 for both sumatriptan doses vs placebo). Sustained pain-free results from two through 24 hours were 30, 35 and 12% with sumatriptan 50 mg, sumatriptan 100 mg and placebo (P<0.05 for both sumatriptan doses vs placebo).
McCrory et al.[80] (2006) Sumatriptan 25 to 100 mg	MA (16 PC, RCTs) Adult patients with history of migraine with or without aura	N=16,200 Single migraine attack	Primary: Pain-free response at two hours, headache relief/ headache intensity, functional	Primary: Sumatriptan 100 (14 trials), 50 (five trials) and 25 mg (three trials) provided significantly better pain-free responses (100 and 25 mg only), headache relief and relief of disability at two hours compared to placebo (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			disability, headache recurrence, adverse events Secondary: Not reported	The NNT for pain-free response at two hours was 5.1 (3.9 to 7.1; n=2,221) and 7.5 (2.7 to 142.0; n=131) for sumatriptan 100 and 25 mg; there was no difference between sumatriptan 50 mg and placebo for this outcome (n=127). For headache relief at two hours, the NNT was 3.4 (3.0 to 4.0), 3.2 (2.4 to 5.1) and 3.4 (2.3 to 6.6) for sumatriptan 100 (n=2,940), 50 (n=420) and 25 mg (n=226), respectively. Adverse events were more common with sumatriptan 100 mg compared to placebo (RR, 0.14 [0.09 to 0.20]; NNH, 7.1 [5.0 to 11.1]; n=3172). The RR for sumatriptan 50 and 25 mg compared to placebo were not significant. Secondary: Not reported
Salonen et al.[81] (1994) Sumatriptan 1 to 40 mg administered IN vs placebo Study medication was taken as a single dose through one nostril in the first study and as a divided dose through two nostrils in the second study.	DB, MC, PC, PG, RCT (2 studies) Adult patients with a history of migraine, with or without aura	N=455 Single migraine attack	Primary: Headache relief at two hours Secondary: Not reported	Primary: In both studies, headache severity had significantly improved at 120 minutes after doses of 10 to 40 mg sumatriptan compared to placebo (P<0.05) and the greatest efficacy rates were obtained with 20 mg sumatriptan. With 20 mg sumatriptan, 78 and 74% of patients experienced headache relief in one- and two-nostril studies, respectively, compared to 35% and 42%, respectively, of those in the placebo groups. The 10-, 20-, and 40-mg doses were significantly more effective than placebo (P<0.01, P<0.001, P<0.05, respectively). Secondary: Not reported
Djupesland et al.[82]	DB, MC, PC, PG,	N=117	Primary:	Primary:

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(2010) Sumatriptan 10 or 20 mg IN vs placebo	RCT Patients 18 to 65 years of age with a developing or established attack of migraine with or without aura of moderate to severe intensity and no improvement in the attack at the time of assessment, migraine present for at least one year, age of diagnosis <50 years and up to six migraine attacks per month for the past six months	Single migraine attack	Proportion of patients free of pain at two hours, proportion of patients with pain relief at one and two hours, proportion of patients achieving sustained freedom from pain Secondary: Safety	A significantly greater proportion of patients were pain-free at two hours with sumatriptan compared to placebo (54 and 57 vs 25%; P<0.05 for both). A significantly greater proportion of patients receiving sumatriptan experienced pain relief at two (84 and 80 vs 44%; P<0.001 and P<0.01) and one hours (73 and 74 vs 38%; P<0.01 for both). A significantly greater proportion of patients achieved a sustained pain-free response with sumatriptan compared to placebo (P<0.05 for both). Secondary: Adverse events were rare, with a metallic taste being the most commonly reported (10 to 13% with sumatriptan).
Salonen et al.[83] (1994) Sumatriptan 1, 5, 10, 20 and 40 mg IN vs placebo Study medication taken as a single dose in the first trial and as a divided dose in the second trial.	2 DB, MC, PC, PG Adult patients with history of migraine with or without aura	N=245 (Trial 1) N=210 (Trial 2) Single migraine attack	Primary: Headache relief at two hours Secondary: Not reported	Primary: In both trials, headache severity had significantly improved by 120 minutes with sumatriptan 10 to 40 mg compared to placebo (P<0.05). The greatest efficacy rates were obtained with sumatriptan 20 mg. With sumatriptan 20 mg, 78 and 74% of patients experienced headache relief in trial one and two, respectively, compared to 35 and 42% of patients, respectively, with placebo. Sumatriptan 10, 20 and 40 mg were significantly more effective than placebo (P<0.01, P<0.001, P<0.05, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cady et al.[84] (2011) Sumatriptan 6 mg SC Patients were instructed to treat up to four migraine attacks of moderate to severe intensity.	MC, OL, PRO Patients 18 to 65 years of age with at least a one-year history of migraine with or without aura, with an average of two to six migraine episodes monthly, current triptan users, and a baseline score from satisfied to very dissatisfied on the Overall Satisfaction domain of the PPMQ-R	N=246 Patients were instructed to treat up to four migraine attacks and were followed until three to five days after the fourth treated attack or for 60 days, whichever came sooner	Primary: Change in score from baseline to end of treatment for the Overall Satisfaction item on the PPMQ-R Secondary: Not reported	Primary: The Overall Satisfaction domain score of the PPMQ-R increased from baseline to the end of treatment (65.7±19.8 vs 73.7±29.1; P=0.0007). Other satisfaction endpoints evaluated: The Efficacy domain score of the PPMQ-R increased from baseline to the end of treatment (62.2±17.6 vs 76.2±23.7; P<0.0001). Improvements were also seen on the Functionality domain score of the PPMQ-R (59.0±22.3 vs 73.8±25.3; P<0.0001). The Ease of Use domain score declined from baseline to the end of treatment (82.6±15.3 vs 67.8±27.6; P<0.0001). The total PPMQ-R score increased (63.9±16.5 vs 74.6±22.4; P<0.0001). The percentage of patients confident or very confident in treating repeated migraine attacks increased from 41.0% (95% CI, 35.4 to 46.9) to 64.6% (95% CI, 58.9 to 70.1) at the end of treatment. At the end of treatment, 35.1% of patients stated they preferred sumatriptan SC (Sumavel®) to treat their next migraine attack. Secondary: Not reported
Rothrock et al.[85] (2011) Sumatriptan 6 mg SC Patients were instructed to treat up to four migraine attacks of moderate to severe intensity.	MC, OL, PRO Patients 18 to 65 years of age with a history of migraine for at least one year with or without aura, with an average of two to six migraine episodes monthly, current triptan users, a baseline score from satisfied to very dissatisfied on the Overall Satisfaction domain of the PPMQ-R, and	N=90 Patients were instructed to treat up to four migraine attacks and were followed until three to five days after the fourth treated attack or for 60 days, whichever came sooner	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Across all of the treated attacks evaluated, the rates of attacks associated with pain relief were 30.7, 66.4, 80.1, 81.6, and 77.6% at 0.25, 0.5, 1, 2, and 24 hours after dosing, respectively. The rates for attacks associated with pain-free response were 0.7, 14.8, 35, 48, and 65.7% at 0.25, 0.5, 1, 2, and 24 hours after dosing, respectively. Sustained 24-hour pain relief and sustained 24-hour pain-free response was observed in 61.0 and 26.4% of attacks, respectively. The percentage of attacks requiring a second dose was 26%. Across attacks, PPMQ-R scores improved from baseline through the end of the treatment period for the Efficacy (52.5±17.8 vs 74.8±23.4; P<0.0001) and Functionality subscales (46.2±22.3 vs 71.3±25.2; P<0.0001). There was no decrease in the Tolerability subscale (80.6±14.7 vs 83.5±17.7; P=0.12). Scores declined for the Ease of Use

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	a baseline Migraine-ACT scores ≤2 (reflecting the need for a chance in acute migraine therapy)			subscale (79.6±16.0 vs 69.7±25.6; P=0.0007). The total PPMQ-R score and the PPMQ-R Overall Satisfaction score also increased over baseline (54.2±16.3 vs 73.3±22.1; P<0.0001 and 55.1±23.2 vs 74.6±27.7; P<0.0001, respectively). The percentage of patients satisfied or very satisfied increased from baseline to the end of treatment on the following global satisfaction domains: Overall Satisfaction (16.7 vs 62.2%; P value not reported), Satisfaction with Medication Effectiveness (17.8 vs 63.4%; P value not reported), and Satisfaction with Side Effects (35.5 vs 67.8%; P value not reported). The percentage of patients confident or very confident in treating repeated migraine attacks increased from 22.2% (90% CI, 15.2 to 30.6) at baseline to 57.8% (90% CI, 48.6 to 66.6) at the end of treatment.
Derry et al.[86] (2012) Sumatriptan vs placebo vs active control Results from the pooled analysis of PC trials and results of pooled analyses (including within-class, head-to-head trials not represented elsewhere in Table 4) have been reported.	MA (61 studies) Patients were at least 18 years of age with migraine	N=37,250 Duration varied	Primary: Pain-free at two hours without the use of rescue medication, reduction in headache pain at one and two hours, sustained pain-free during the 24 hours postdose, sustained headache relief during the 24 hours postdose, pain intensity and pain relief Secondary: Use of rescue medication, participants with any adverse events during the 24 hours postdose, participants with	Primary and Secondary: *Sumatriptan vs placebo* Sumatriptan surpassed placebo for all efficacy outcomes evaluated. For sumatriptan 50 mg, the NNTs were 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively. The NNTs for sustained pain-free and sustained headache relief during the 24 hours postdose were 9.5 and 6.0, respectively. For sumatriptan 100 mg compared to placebo the NNTs were 4.7, 6.8, 3.5, 6.5, and 5.2 for pain-free at two hours, headache relief at one hour, headache relief at two hours, sustained pain-free, and sustained headache relief during the 24 hours post dose, respectively. Results for the 25 mg dose were similar to the 50 mg dose, while sumatriptan 100 mg was significantly better than 50 mg for pain-free and headache relief at two hours, and for sustained pain-free during 24 hours. It was found that treating early, while pain was still mild, resulted in significantly better NNTs for pain-free at two hours and sustained pain-free during 24 hours when compared to treating established attacks with moderate or severe pain intensity. Relief of associated symptoms (including nausea, photophobia, and phonophobia) was greater and the use of rescue medication was lower with sumatriptan, compared to placebo. Adverse events were mostly transient and mild; however, they occurred with greater frequency with sumatriptan compared to placebo. Primary: *Sumatriptan 25 mg vs rizatriptan 5 mg* The proportion of participants pain-free at two hours with sumatriptan 25

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			particular adverse events during the 24 hours postdose, withdrawals due to adverse events, headache-associated symptoms (relief and/or presence at two hours), functional disability (relief and/or presence at two hours)	mg was 28% (310/1117; range, 27to 28%) compared to 33% with rizatriptan 5 mg (363/1093; range, 33 to 33%). The relative benefit of sumatriptan compared to rizatriptan was 0.84 (0.74 to 0.95; analysis, 2.1); the NNT was 18 (11 to 62) in favor of rizatriptan. The proportion of participants with headache relief at one hour with sumatriptan 25 mg was 34% (375/1117; range, 33 to 34%) compared to 27% with rizatriptan 5 mg (404/1093; range, 36 to 38%). The relative benefit of sumatriptan compared to rizatriptan was 0.91 (0.81 to 1.00; analysis, 2.2); the NNT was 29 (14 to 170) in favor of rizatriptan. The proportion of participants with headache relief at two hours with sumatriptan 25 mg was 35% (386/1117; range, 12 to 58%) compared to 67% with rizatriptan 5 mg (731/1093; range, 66 to 68%). The relative benefit of sumatriptan compared to rizatriptan was 0.90 (0.84 to 0.95; analysis, 2.3); the NNT was 14 (9.1 to 34.0) in favor of rizatriptan. *Sumatriptan 25 mg vs rizatriptan 10 mg* The proportion of participants pain-free at two hours with sumatriptan 25 mg was 28% (310/1117; range, 27 to 28%) compared to 39% with rizatriptan 10 mg (440/1114; range, 38 to 41%). The relative benefit of sumatriptan compared to rizatriptan was 0.70 (0.62 to 0.79; analysis, 3.1); the NNT was 8.5 (6.4 to 13.0) in favor of rizatriptan. The proportion of participants with headache relief at one hour with sumatriptan 25 mg was 34% (375/1117; range, 33 to 34%) compared to 41% with rizatriptan 10 mg (456/1114; range, 40 to 42%). The relative benefit of sumatriptan compared to rizatriptan was 0.82 (0.74 to 0.91; analysis, 3.2); the NNT was 14 (8.8 to 30.0) in favor of rizatriptan. The proportion of participants with headache relief at two hours with sumatriptan 25 mg was 35% (386/1117; range, 12 to 58%) compared to 70% with rizatriptan 10 mg (780/1114; range, 68 to 72%). The relative benefit of sumatriptan compared to rizatriptan was 0.86 (0.80 to 0.91; analysis, 3.3); the NNT was 9.9 (7.1 to 16.0) in favor of rizatriptan. *Sumatriptan 50 mg vs rizatriptan 5 mg* The proportion of participants pain-free at two hours with sumatriptan 50 mg was 35% (394/1116; range, 34 to 37%) compared to 33% with rizatriptan 5 mg (363/1093; range, 33 to 33%). The relative benefit of sumatriptan compared to rizatriptan was 1.1 (0.95 to 1.20; analysis, 8.1);

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				there was no significant difference between treatments. The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 37% (409/1116; range, 35 to 39%) compared to 37% with rizatriptan 5 mg (404/1093; range, 36 to 38%). The relative benefit of sumatriptan compared to rizatriptan was 0.99 (0.89 to 1.10; analysis, 8.2); there was no significant difference between treatments. The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 65% (949/1469; range, 62 to 67%) compared to 66% with rizatriptan 5 mg (951/1442; range, 63 to 68%). *Sumatriptan 50 mg vs rizatriptan 10 mg* The proportion of participants pain-free at two hours with sumatriptan 50 mg was 35% (394/1116; range, 34 to 37%) compared to 39% with rizatriptan 10 mg (440/1114; range, 38 to 41%). The relative benefit of sumatriptan compared to rizatriptan was 0.89 (0.80 to 1.00; analysis, 9.1); there was no significant difference between treatments. The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 37% (409/1116; range, 35 to 39%) compared to 41% with rizatriptan 10 mg (456/1114; range, 40 to 42%). The relative benefit of sumatriptan compared to rizatriptan was 0.9 (0.81 to 1.00; analysis, 9.2); there was no significant difference between treatments. The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 64% (710/1113; range, 62 to 66%) compared to 70% with rizatriptan 10 mg (780/1114; range, 68 to 72%). The relative benefit of sumatriptan compared to rizatriptan was 0.91 (0.86 to 0.97; analysis, 9.3); the NNT was 16 (9.9 to 43.0) in favor of rizatriptan. *Sumatriptan 50 mg vs zolmitriptan 2.5 mg* The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 41% (330/814; range, 35 to 44%) compared to 40% with zolmitriptan 2.5 mg (318/795; range, 35 to 43%). The relative benefit of sumatriptan compared to zolmitriptan was 1(0.90 to 1.10; analysis, 6.1); there was no significant difference between treatments. The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 67% (543/814; range, 59 to 71%) compared to 66% with zolmitriptan 2.5 mg (523/795; range, 65 to 67%). The relative benefit of sumatriptan compared to zolmitriptan was 1 (0.95 to 1.1;

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				analysis, 6.2); there was no significant difference between treatments. *Sumatriptan 50 mg vs zolmitriptan 5 mg* The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 41% (330/814; range 35 to 44%) compared to 39% with zolmitriptan 5 mg (320/819; range, 37 to 40%). The relative benefit of sumatriptan compared to zolmitriptan was 1 (0.90 to 1.2; analysis, 7.1); there was no significant difference between treatments. The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 67% (543/814; range, 59 to 71%). The proportion of participants with headache relief at two hours with zolmitriptan 5 mg was 66% (537/819; range, 65 to 66%). The relative benefit of sumatriptan compared to zolmitriptan was 1 (0.95 to 1.10; analysis, 7.2); there was no significant difference between treatments. *Sumatriptan 100 mg vs rizatriptan 10 mg* The proportion of participants pain-free at two hours with sumatriptan 100 mg was 31% (143/460; range, 22 to 33%) compared to 37% with rizatriptan 10 mg (178/476; range, 26 to 40%). The relative benefit of sumatriptan compared to rizatriptan was 0.82 (0.69 to 0.98; analysis, 15.1); the NNT was 16 (8.1 to 410.0) in favor of rizatriptan. The proportion of participants with headache relief at one hour with sumatriptan 100 mg was 26% (120/460; range, 24 to 27%) compared to 34% with rizatriptan 10 mg (163/476; range, 25 to 36%). The relative benefit of sumatriptan compared to rizatriptan was 0.76 (0.62 to 0.92; analysis, 15.2); the NNT was 12 (7.1 to 43.0) in favor of rizatriptan. *Sumatriptan 100 mg vs almotriptan 12.5 mg* The proportion of participants pain-free at two hours with sumatriptan 100 mg was 33% (129/387; range, 33 to 34%) compared to 28% with almotriptan 12.5 mg (102/367; range, 28 to 28%). The relative benefit of sumatriptan compared to almotriptan was 1.2 (0.97 to 1.50; analysis, 16.1); there was no significant difference between treatments. The proportion of participants with a 24-hour sustained pain-free response with sumatriptan 100 mg was 29% (111/387; range, 28 to 29%) compared to 30% with almotriptan 12.5 mg (110/367; range, 25 to 35%). The relative benefit of sumatriptan compared to almotriptan was 0.96 (0.77 to 1.20;

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				analysis, 16.2); there was no significant difference between treatments. Secondary: *Sumatriptan 25 mg vs rizatriptan 5 mg* Two studies provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity. The proportion of participants requiring rescue medication with sumatriptan 25 mg was 24% (207/853; range, 23 to 25%) compared to 25% with rizatriptan 5 mg (213/845; range, 23 to 30%). The relative benefit of sumatriptan compared to rizatriptan was 0.96 (0.82 to 1.10; analysis, 2.4); there was no significant difference between treatments. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 25 mg was 43% (250/587; range, 39 to 46%) compared to 41% with rizatriptan 5 mg (238/582; range, 38 to 44%). The relative harm of sumatriptan compared to rizatriptan was 1 (0.91 to 1.20; analysis, 2.5); there was no significant difference between the two treatments. *Sumatriptan 25 mg vs rizatriptan 10 mg* Two studies provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity. The proportion of participants requiring rescue medication with sumatriptan 25 mg was 24% (207/853; range, 23 to 25%) compared to 20% with rizatriptan 10 mg (175/863; range, 19 to 23%). The relative benefit of sumatriptan compared to rizatriptan was 1.2 (1.0 to 1.4; analysis, 3.4); there was no significant difference between treatments. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 25 mg was 43% (250/587; range, 39 to 46%) compared to 46% with rizatriptan 10 mg (276/599; range, 45 to 47%). The relative harm of sumatriptan compared to rizatriptan was 0.92 (0.81 to 1.10; analysis, 3.5); there was no significant difference between the two treatments. *Sumatriptan 50 mg vs rizatriptan 5 mg* Two studies provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity. The proportion of participants requiring rescue medication with sumatriptan 50 mg was 20% (167/851; range, 19 to 21%) compared

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				to 25% with rizatriptan 5 mg (213/845; range, 23 to 30%). The relative benefit of sumatriptan compared to rizatriptan was 0.78 (0.65 to 0.93; analysis, 8.4); the NNT was 18 (10 to 62). The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 48% (276/578; range, 46 to 49%) compared to 41% with rizatriptan 5 mg (238/582; range, 38 to 44%). The relative harm of sumatriptan compared to rizatriptan was 1.2 (1.0 to 1.3; analysis, 8.5); there was no significant difference between the two treatments. *Sumatriptan 50 mg vs rizatriptan 10 mg* Two studies provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity. The proportion of participants requiring rescue medication with sumatriptan 50 mg was 20% (167/851; range, 19 to 21%) compared to 20% with rizatriptan 10 mg (175/863; range, 19 to 23%). The relative benefit of sumatriptan compared to rizatriptan was 0.97 (0.80 to 1.20; analysis, 9.4); there was no significant difference between treatments. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 48% (276/578; range, 46 to 49%) compared to 46% with rizatriptan 10 mg (276/599; range, 45 to 47%). The relative harm of sumatriptan compared to rizatriptan was 1 (0.92 to 1.20; analysis, 9.5); there was no significant difference between the two treatments. *Sumatriptan 50 mg vs zolmitriptan 2.5 mg* Two studies in participants with moderate or severe baseline pain intensity provided data. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 32% (290/893; range, 29 to 34%) compared to 32% with zolmitriptan 2.5 mg (283/878; range, 28 to 35%). The relative harm of sumatriptan compared to zolmitriptan was 1 (0.88 to 1.20; analysis, 6.3); there was no significant difference between the two treatments. *Sumatriptan 50 mg vs zolmitriptan 5 mg* Two studies in participants with moderate or severe baseline pain intensity provided data. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 32% (290/893; range, 29 to 34%) compared to 36% with zolmitriptan 5 mg (322/897; range, 33 to

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				38%). The relative harm of sumatriptan compared to zolmitriptan was 0.91 (0.80 to 1.00; analysis, 7.3); there was no significant difference between the two treatments. *Sumatriptan 100 mg vs rizatriptan 10 mg* Two studies in participants with moderate or severe baseline pain intensity provided data regarding adverse events within 24 hours. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 100 mg was 52% (217/421; range, 45 to 52%) compared to 47% with rizatriptan 10 mg (203/435; range, 47 to 48%).
Derry et al.[87] (2012) Sumatriptan SC vs placebo vs active control Results from the pooled analysis of PC trials and results of within-class, head-to-head trials have been reported.	MA (32 studies) Patients were at least 18 years of age with migraine	N=9,365 Duration varied	Primary: Pain-free at two hours without the use of rescue medication, reduction in headache pain at one and two hours, sustained pain-free during the 24 hours postdose, sustained headache relief during the 24 hours postdose, pain intensity and pain relief Secondary: Use of rescue medication, participants with any adverse events during the 24 hours postdose, participants with particular adverse events during the	Primary and Secondary: *Sumatriptan vs placebo* Sumatriptan surpassed placebo for all efficacy outcomes evaluated. For sumatriptan 6 mg compared to placebo the NNTs were 2.9, 2.3, 2.2, and 2.1 for pain-free at one and two hours, and headache relief at one and two hours, respectively. The NNT for sustained pain-free vs placebo was 6.1. Results for sumatriptan 4 and 8 mg were similar to that seen with 6 mg, with 6 mg demonstrating significantly better results than 4 mg for pain-free at one hour, and 8 mg demonstrating significantly better results than 6 mg for headache relief at one hour. There was no evidence of increased migraine relief if a second dose of sumatriptan 6 mg was administered after an inadequate response to the first. Relief of headache-associated symptoms (nausea, photophobia, and phonophobia) was greater and use of rescue medication was lower with sumatriptan, compared to placebo. Adverse events were mostly transient and mild, and were more common with sumatriptan than placebo. Primary: *Sumatriptan 6 mg SC vs naratriptan* The proportion of participants pain-free at two hours after treating with sumatriptan was 55%, compared to 30, 44, 60, 79, and 88% of participants treating with SC naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. The proportion of participants with headache relief at one hour after treating with sumatriptan was 87%, compared to 60, 64, 81, 85, and 76% of participants treating with naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. The proportion of participants with headache relief at two hours after treating with sumatriptan was 89%, compared to 65, 75, 83, 94,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			24 hours postdose, withdrawals due to adverse events, headache-associated symptoms (relief and/or presence at two hours), functional disability (relief and/or presence at two hours)	and 91% of participants treating with naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. *Sumatriptan 6 mg SC vs dihydroergotamine SC* The proportion of participants with headache relief at one hour after treating with sumatriptan was 78%, compared to 57% of participants treating with dihydroergotamine. The proportion of participants with headache relief at one hour after treating with sumatriptan was 85%, compared to 73% of participants treating with dihydroergotamine. Secondary: *Sumatriptan 6 mg SC vs naratriptan* The proportion of participants requiring rescue medication within 24 hours of treating with sumatriptan was 4%, compared to 35, 22, 12, 6, and 3% of participants treating with naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. The proportion of participants with relief of nausea at two hours after treating with sumatriptan was 90%, compared to 74, 92, 91, 96, and 96% of participants treating with SC naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. No adverse event withdrawals were reported from any of the treatment arms. *Sumatriptan 6 mg SC vs dihydroergotamine SC* Neither treatment group reported any serious adverse events. The incidence of adverse event-related withdrawal was 0% (0/158) for sumatriptan and 1.3% (2/152) for SC dihydroergotamine.
Derry et al.[88] (2012) Sumatriptan IN vs placebo vs active control	MA (12 studies) Patients were ≥18 years of age with migraine	N=4,755 Duration varied	Primary: Pain-free at two hours without the use of rescue medication, reduction in headache pain at one and two hours, sustained pain-free during the 24 hours postdose, sustained headache relief	Primary and Secondary: *Sumatriptan vs placebo* Sumatriptan surpassed placebo for all efficacy outcomes evaluated. For sumatriptan 10 mg, the NNTs compared to placebo were 7.3, 7.4, and 5.5 for pain-free at two hours, and headache relief at one and two hours, respectively. For sumatriptan 20 mg compared to placebo, the NNTs were 4.7, 4.9, and 3.5 for pain-free at two hours, and headache relief at one and two hours, respectively. Sumatriptan 20 mg was significantly better than sumatriptan 10 mg for pain-free at two hours, and headache relief at one and two hours, respectively. Relief of headache-associated symptoms (nausea, photophobia, and phonophobia) was greater and use of rescue medication was lower with sumatriptan, compared to placebo. Adverse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Results from the pooled analysis of PC trials have been reported.			during the 24 hours postdose, pain intensity and pain relief Secondary: Use of rescue medication, participants with any adverse events during the 24 hours postdose, participants with particular adverse events during the 24 hours postdose, withdrawals due to adverse events, headache-associated symptoms (relief and/or presence at two hours), functional disability (relief and presence at two hours)	events were mostly transient and mild and occurred more frequently with sumatriptan than placebo.
Gershovich et al.[89] (2006) Sumatriptan vs rizatriptan ODT	RETRO Patients ≥18 years of age	N=457 (n=315 randomly sampled for a satisfaction questionnaire) 180 day medication conversion	Primary: Successful conversion rate, medication preference Secondary: Not reported	Primary: The total number of successful conversions from sumatriptan to rizatriptan (214/457; 47%) correlated to the number of successful conversions among the questionnaire group (173/315 [55%] returned the questionnaire; 82/173 [47%] had successful conversion; P=0.969). Among the patients that were successfully converted to rizatriptan and responded to the questionnaire, 68.0% preferred the rizatriptan compared to sumatriptan; whereas 8.5% of patients who failed conversion rated rizatriptan as their preferred medication (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
		period (plus an 180 day follow up period)		Successfully converted patients reported faster and more complete headache relief with rizatriptan (51.9 and 45.0% of the time, respectively; P<0.001). Failed conversion respondents reported that sumatriptan yielded faster and more complete headache relief 78.3 and 75.9% of the time, respectively (P<0.001). Secondary: Not reported
Loder et al.[90] (2001) Sumatriptan 50 mg tablet vs rizatriptan 10 mg ODT Patients treated first migraine with ODT and second migraine with sumatriptan	MC, OL, RCT, XO Patients ≥18 years of age	N=524 Two migraine attacks	Primary: Patient preference Secondary: Head pain severity, functional disability and headache recurrence	Primary: Significantly more patients preferred rizatriptan compared to sumatriptan (57 vs 43%; P=0.009). No preference was expressed by 2.6% of patients. Secondary: A significantly greater proportion of patients reported pain relief with rizatriptan compared to sumatriptan at 45 and 60 minutes (38 vs 29% and 58 vs 49%, respectively; P<0.01 for both). A significantly greater proportion of patients receiving rizatriptan reported a pain-free status at 60 and 120 minutes (23 vs 17%; P<0.05 and 60 vs 52%; P<0.01, respectively). Significantly more patients receiving rizatriptan reported normal function at 60 and 120 minutes (36 vs 27%; P=0.004 and 70 vs 64%; P=0.029). The overall rate of headache recurrence was similar with both treatments.
Cady et al.[91] (2000) Sumatriptan 25 to 100 mg vs ergotamine 2 mg and caffeine 200 mg	MA (DB, PC, RCTs) Patients with at least one headache which was treated early when pain was mild	N=92 (118 migraine attacks) Single migraine attack	Primary: Pain-free response at two and four hours Secondary: Use of a second dose of medication, clinical disability, migraine-	Primary: Pain-free responses were significantly higher two hours after dosing with sumatriptan 50 (51%) or 100 mg (67%; P<0.05) compared to placebo (28%), and were significantly higher with early treatment of mild pain compared to moderate to severe pain at two hours (sumatriptan 50 mg, 51 vs 31%; P<0.05, sumatriptan 100 mg, 67 vs 36%; P<0.05) and four hours (sumatriptan 50 mg, 75 vs 56% and sumatriptan 100 mg, 90 vs 61%; P<0.05). Secondary: Early intervention also resulted in less re-dosing with mild pain compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 900 mg and metoclopramide 10 mg vs placebo			associated symptoms, meaningful pain relief, time to meaningful relief, sustained pain-free response, proportion of attacks in which pain had worsened two and four hours after dosing; all compared in headaches treated during mild vs moderate to severe pain	to moderate to severe pain (sumatriptan 50 mg, 21 vs 32% and sumatriptan 100 mg, 20 vs 29%; P values not reported). More attacks treated early with sumatriptan 50 or 100 mg were associated with normal function at four hours compared to placebo (70 and 93 vs 46%, respectively; P value not reported). Sustained pain-free response rates two to 24 hours after mild pain with sumatriptan 50 or 100 mg were higher (34 and 53%, respectively) compared to treatment of moderate to severe pain (19 and 24%, respectively; P values not reported). Early treatment with sumatriptan 100 mg produced significantly higher pain-free rates at two hours compared to ergotamine/caffeine (69 vs 34%, respectively) or aspirin plus metoclopramide (73 vs 25%, respectively; P<0.001 for both).
Smith et al.[92] (2007) Sumatriptan-naproxen 85/500 mg taken at onset of migraine and repeated after at least 2 hours from the initial dose if response was unsatisfactory or incomplete	MC, OL Patients 18 to 35 years of age with first migraine attack before 50 years of age, with an average of two to eight moderate to severe attacks per month in six months prior to trial onset	N=600 12 months	Primary: Pain severity, change from baseline in PPMQ scores and change from baseline in MSQ scores Secondary: Not reported	Primary: A total of 81% of all attacks were reported pain-free at two hours post dose. At three months, the percentage of “satisfied” or “very satisfied” patients increased on all eight PPMQ items. At 12 months, PPMQ results remained high (P values not reported). Mean MSQ scores increased by 13 to 15 points at three months. Three and 12 month MSQ scores were significantly improved from baseline (P<0.001). Secondary: Not reported
Winner et al.[93] (2007) Sumatriptan-naproxen 85-500 mg	MC, OL Patients 18 to 35 years of age with first migraine attack before 50 years of	N=562 12 months	Primary: Clinical adverse events and clinical chemical analysis Secondary:	Primary: For overall safety data, 66% of patients reported at least one treatment emergent adverse event. A total of 41/565 patients withdrew from the trial due to an adverse event, 36 of which were not serious. Overall, 14 patients had one or more serious

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Administered at the onset of a moderate to severe migraine attack.	age, with an average of two to eight moderate to severe attacks per month in six months prior to trial onset		Not reported	adverse event; none were fatal or life-threatening. All were judged unrelated to treatment except one case of acute coronary syndrome. Clinical chemical analyses observed at 12 months were reported as follows: range of 0.3 to 1.7 decrease in hemoglobin levels, zero patients; minimal increases in ALT levels; nine patients (none greater than two times the upper limit of normal); minimal increases in serum creatinine levels, nine patients (none exceeded 1.2 times the upper limit of normal) and minimal increases in BUN; seven patients (the highest being 30 mg/dL [1.3 times the upper limit of normal]). Secondary: Not reported
Landy et al.[94] (2012) Sumatriptan-naproxen 85-500 mg Used to treat up to four migraine attacks over 12 weeks, administered within 30 minutes of the onset of pain while the pain was still mild.	OL, PRO Patients 18 to 65 years of age with a minimum of a one-year history of migraine with a positive screening for cutaneous allodynia; patients were required to have two to six migraines per month in the three months prior to screening	N=40 Patients could dose up to four migraine attacks over 12 weeks with a repeat dose after two hours was permitted for rescue	Primary: Percent of migraines with sustained pain-free response from two through 24 hours post dose and patients' overall satisfaction with sumatriptan/ naproxen from the PPMQ-R Secondary: Percentage of migraines pain-free at two hours, overall efficacy and overall adverse events from the PPMQ-R	Primary: Patients reported 78 (49%) migraines as sustained pain-free at 24 hours. Of the 40 included patients, 42.5% were satisfied for overall satisfaction. Secondary: Patients reported 94 (59%) migraines as pain-free at two hours. Of the 40 patients, 40 and 50% were satisfied for overall efficacy and overall adverse events, respectively.
Lipton et al.[95] (2009)	2 DB, PC, RCT, XO	N=4,145 Four migraine	Primary: Pain-free response at two hours and	Primary: Across attacks in both trials, pain-free response at two hours was reported in significantly more attacks treated with combination therapy compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sumatriptan-naproxen 85-500 mg vs placebo	Patients 18 to 65 years of age, history of migraine with or without aura for at least six months, an average of two to six migraine episodes monthly during the three months preceding enrollment, typically experienced moderate to severe headache pain preceded by an identifiable mild pain phase	attacks	24-hour sustained pain-free response Secondary: Migraine-free response at two and four hours	to attacks treated with placebo (Trial 1: 52 vs 25%; difference, 28%; 95% CI, 21 to 36; P<0.001, Trial 2: 50 vs 20%; difference, 30%; 95% CI, 24 to 36; P<0.001). Similar results were observed for each individual attack (P<0.001 for all). Across attacks in both trials, sustained pain-free response from two to 24 hours was reported in significantly more attacks treated with combination therapy compared to attacks treated with placebo (Trial 1: 37 vs 17%; difference, 20%; 95% CI, 15 to 27; P<0.001, Trial 2: 34 vs 12%; difference, 22%; 95% CI, 18 to 27; P<0.001). Similar results were observed for each individual attack (P<0.05 for all). Secondary: Across attacks in both trials, migraine-free response after two and four hours was reported in significantly more attacks treated with combination therapy (P<0.001 for both).
Silberstein et al.[96] (2008) Sumatriptan-naproxen 85-500 mg vs placebo	2 DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura of six months and an average of two to six attacks per month in three months prior to trial onset	N=658 (Trial 1) N=647 (Trial 2) Single migraine attack	Primary: Pain-free response at two hours Secondary: Pain-free responses at one-half, one and four hours; sustained pain-free response; migraine-free response at two and four hours; use of rescue medication within 24 hours postdose; nausea, photophobia and phonophobia rates	Primary: In Trial 1, sumatriptan-naproxen was significantly more effective than placebo at relieving pain at two hours (52 vs 17%; P<0.001). The corresponding rates in Trial 2 were 51 and 15%, respectively (P<0.001). Secondary: In Trial 1, combination therapy was significantly more effective at relieving pain after one-half (5 vs 2%; P=0.016), one (20 vs 7%; P<0.001) and four (70 vs 25%; P<0.001) hours. The corresponding rates in Trial 2 were 6 and 2% (P=0.021), 24 vs 7% (P<0.001) and 67 vs 25% (P<0.001), respectively. In Trial 1, combination therapy was significantly more effective at achieving a sustained pain-free response (45 vs 12%; P<0.001). The corresponding rate in Trial 2 was 40 vs 14% (P<0.001), respectively. In Trial 1, combination therapy was significantly more effective at achieving a migraine-free response at two and four hours (45 vs 15%; P value not reported and 63 vs 24%; P<0.05). The corresponding rates in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			at two and four hours; neck pain/discomfort and sinus pain/pressure at two and four hours	Trial 2 were 46 vs 14% (P value not reported) and 64 vs 25% (P<0.05). In Trial 1, combination therapy was significantly more effective in reducing the use of rescue medications within 24 hours post dose (20 vs 47%; P<0.001). The corresponding rate in Trial 2 was 16 vs 45% (P<0.001). In Trial 1, combination therapy was significantly more effective in reducing two and four hour nausea (P=0.018), photophobia (P<0.001) and phonophobia (P<0.001) Results were similar in Trial 2 (P<0.001 for all measures). In Trial 1, combination was significantly more effective at relieving two and four hour neck pain/discomfort and sinus pain/pressure (P<0.001 for all measures). Results were similar in Trial 2 (P<0.001 for all measures).
Matthew et al.[97] (2009) Sumatriptan-naproxen 85-500 mg vs placebo	2 DB, MC, PC, RCT, XO Patients 18 to 65 years of age with migraine with or without aura, up to eight migraine attacks during the three months preceding enrollment and <15 headache days monthly	N=283 Two migraine attacks	Primary: Sustained pain-free response Secondary: Proportion of patients with pain-free response at one-half, one, four and eight hours; proportion of patients with migraine-free response at two, four, eight and two to 24 hours; the proportion of patients with nausea, photophobia, phonophobia at two, four and eight	Primary: Combination therapy was “superior” to placebo for two to 24-hour sustained pain-free response (Trial 1: 26 vs 8%; OR, 4.50; 95% CI, 2.166 to 9.360; P<0.001, Trial 2: 31 vs 8%; OR, 5.63; 95% CI, 2.76 to 11.49; P<0.001). Secondary: Combination therapy was only “superior” to placebo for one (Trial 1: 19 vs 10%; OR, 2.20; 95% CI, 1.05 to 4.59; P<0.05, Trial 2: 25 vs 9%; OR, 3.19; 95% CI, 1.60 to 6.38; P≤0.001), two (Trial 1: 40 vs 17%; OR, 3.19; 95% CI, 1.80 to 5.65; P≤0.001, Trial 2: 44 vs 14%; OR, 4.69; 95% CI, 2.57 to 8.55; P≤0.001), four (Trial 1: 59 vs 23%; OR, 4.93; 95% CI, 2.85 to 8.54; P≤0.001, Trial 2: 62 vs 17%; OR, 8.12; 95% CI, 4.37 to 15.03; P≤0.001) and eight hour pain-free response (Trial 1: 65 vs 24%; OR, 5.81; 95% CI, 3.38 to 9.98; P≤0.001, Trial 2: 66 vs 24%; OR, 6.20; 95% CI, 3.58 to 10.76; P≤0.001). Combination therapy was “superior” to placebo for two (Trial 1: 35 vs 14%; OR, 3.18; 95% CI, 1.75 to 5.76; P≤0.001, Trial 2: 35 vs 11%; OR, 4.14; 95% CI, 2.20 to 7.80; P≤0.001), four (Trial 1: 53 vs 23%; OR, 3.88; 95% CI, 2.28 to 6.61; P≤0.001, Trial 2: 57 vs 15%; OR, 7.85; 95% CI, 4.17 to 14.77; P≤0.001) and eight hour migraine-free response (Trial 1: 59

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hours and recurrence	vs 22%; OR, 5.14; 95% CI, 2.99 to 8.89, Trial 2: 63 vs 23%; OR, 5.97; 95% CI, 3.42 to 10.39; P≤0.001). Combination therapy was "superior" to placebo for two through 24-hour sustained response (Trial 1: 24 vs 8; OR, 3.43; 95% CI, 1.63 to 7.20; P≤0.001, Trial 2: 25 vs 6%; OR, 5.45; 95% CI, 2.52 to 11.80; P≤0.001). In both trials, combination therapy was "superior" to placebo in the absence of photophobia at two, four and eight hours (P≤0.001 for all). Similar results were seen for the incidence of phonophobia (P≤0.001 for all; except P<0.05 at eight hours in Trial 1). Significance between the two treatments for nausea occurred only at four (Trial 2; P<0.05) and eight hours (Trial 1: P<0.05, Trial 2: P<0.05). Fewer patients receiving combination therapy had recurrence at 24 (Trial 1: 20 vs 52%, Trial 2: 22 vs 26%) and 48 hours (Trial 1: 20 vs 57%, Trial 2: 22 vs 32%; P values not significant).
Smith et al.[98] (2005) Sumatriptan-naproxen 50-500 mg vs sumatriptan 50 mg vs naproxen 500mg vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a history of migraine headache	N=972 Single migraine attack	Primary: 24-hour pain relief response Secondary: Two-hour headache response; two-hour pain free; sustained pain free (two to 24 hours); incidence of photophobia nausea at two hours; adverse events	Primary: 46% of sumatriptan-naproxen group, achieved 24-hour pain relief response, significantly more than sumatriptan alone (29%), naproxen alone (25%), or placebo (17%; P<0.001). Secondary: Two-hour headache response significantly favored sumatriptan-naproxen 500 mg therapy (65%) vs sumatriptan (49%), naproxen (46%), or placebo (27%; P<0.001). A similar pattern of between-group differences was observed for two-hour pain-free response and sustained pain-free response (P<0.001). Incidence of headache recurrence up to 24 hours after treatment was lowest in the sumatriptan-naproxen group (29%) vs sumatriptan alone (41%; P=0.048), vs naproxen alone (47%; P=0.0035), and vs placebo (38%; P=0.08). Incidences of photophobia, phonophobia or nausea were significantly lower at two hours following sumatriptan-naproxen vs placebo (P<0.001). Frequencies and types of adverse events reported did not differ between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment groups, with dizziness and somnolence being the most common.
Brandes et al.[99] (2007) Sumatriptan-naproxen 85-500 mg vs sumatriptan 85 mg vs naproxen 500 mg vs placebo	2 DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura six months and an average of two to six moderate or severe episodes monthly three months prior to trial onset	N=1,677 (Trial 1) N=1,736 (Trial 2) Single migraine attack	Primary: Headache relief at two hours; absence of photophobia, phonophobia and nausea at two hours; sustained pain-free response Secondary: Pain-free response at two hours; sustained headache relief; sustained absence of nausea, photophobia and phonophobia; use of rescue medications; headache recurrence and 24-hour incidence of vomiting	Primary: In Trial 1, sumatriptan-naproxen was significantly more effective than all other treatments for achieving relief at two hours (65 vs 55 [P=0.009], 44 [P<0.001] and 28% [P<0.001]). In Trial 2, the corresponding rates were 57 vs 50 (P=0.03), 43 (P<0.001) and 29% (P<0.001). In Trial 1, sumatriptan-naproxen was significantly more effective than placebo at achieving absence of photophobia (58 vs 36%), phonophobia (61 vs 38%) and nausea (71 vs 65%) (P<0.001 for all measures) at two hours. In Trial 2, the corresponding rates were (50 vs 32%, 56 vs 34% and 65 vs 64%) (P<0.001 for all measures). In Trial 1, sumatriptan-naproxen was significantly more effective than sumatriptan and naproxen for achieving a sustained pain-free response (25 vs 16 and 10%, respectively; P<0.01 for both]). In Trial 2, the corresponding rates were 23 vs 14 and 10%, respectively (P<0.001 for both). Secondary: In Trial 1, combination therapy was significantly more effective for achieving freedom from pain at two hours compared to sumatriptan, naproxen and placebo (34 vs 25, 15 and 9%; P≤0.009 for all). The corresponding rates in Trial 2 were 30 vs 23, 16 and 10%, respectively (P≤0.009 for all). In Trial 1, combination therapy was significantly more effective compared to sumatriptan, naproxen and placebo, respectively, for achieving sustained headache relief (48 vs 35, 30 and 18%; P<0.001 for all). In Trial 2, the corresponding rates were 44 vs 33, 28 and 17%, respectively (P≤0.002 for all). In Trial 1, patients receiving combination therapy experienced sustained benefit of absence of nausea, photophobia and phonophobia compared to patients receiving placebo (P<0.001 for all measures) and sumatriptan (P=0.002, P=002, P<0.001). In Trial 2, combination therapy exhibited significant sustained benefit compared to placebo (P<0.001 for all), and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to sumatriptan for only photophobia (P=0.05) and phonophobia (P=0.01). In Trial 1, patients receiving combination therapy used significantly less rescue medication compared to patients receiving sumatriptan (22 vs 32; P=0.004), naproxen (38; P value not reported) and placebo (53%; P<0.001]). In Trial 2, the corresponding rates were 23 vs 38 (P<0.001), 39 (P value not reported) and 58% (P<0.001), respectively. In Trial 1, the numbers of patients with headache recurrence were sumatriptan-naproxen, 30; sumatriptan, 47; naproxen, 25 and placebo, 26. In Trial 2, the corresponding numbers were 26, 34, 35 and 34 (P values not reported). In Trial 1, the 24-hour incidence of vomiting with combination treatment was no different than sumatriptan (4 vs 7%; P=0.14). Results were similar in Trial 2 (4 vs 9%; P=0.004).
Landy et al.[100] (2007) Sumatriptan-naproxen 85-500 mg vs sumatriptan 85 mg vs naproxen 500 mg vs placebo	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with 6-month history of migraine, first migraine before age 50 and 2 - 6 migraine attacks per month in the 3 months prior to screening	N=3,512 Single migraine attack	Primary: Ability to function; productivity-related impairment; patient satisfaction Secondary: Not reported	Primary: Significantly more patients in the sumatriptan-naproxen group reported no impairment vs naproxen and placebo groups. Median time to first report of normal function in Study 1 was four hours for the sumatriptan-naproxen group compared to four, seven, and 11 hours for the sumatriptan, naproxen (*P*<0.001), and placebo groups (*P*<0.001), respectively. Median time to first report of normal function in Study 2 was 3 hours for the sumatriptan-naproxen group compared to five, five, and 11 hours for the sumatriptan (*P*=0.002), naproxen (*P*<0.001), and placebo groups (*P*<0.001), respectively. Total lost productivity was 33 and 27% lower in the sumatriptan-naproxen group (4.7 and 4.5 hours) vs placebo group (7.0 and 6.2 hours; *P*<0.001) and 16 and 17% lower compared to the naproxen group (5.6 and 5.4 hours; *P*=0.016) for Studies 1 and 2, respectively. In Study 2, the sumatriptan-naproxen group was 20% lower compared to the sumatriptan group (5.6 hours; *P*=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For workplace productivity, the sumatriptan-naproxen group reported a mean of 3.2 hours of lost work productivity compared to 4.1 hours for the placebo group in Study 1 (*P*=0.024) and 2.8 vs 3.3 hours (*P*=0.008) in Study 2. For lost activity time, the sumatriptan-naproxen group reported losing 3.7 hours compared to 5.4 hours reported by the placebo group (*P*<0.001) in Study 1, and a loss of 3.6 hours compared to 4.7 for the placebo group (*P*=0.005) in Study 2. Patients in the sumatriptan-naproxen sodium group were significantly more satisfied with their treatment 24 hours post treatment than the other treatment groups in both studies. Secondary: Not reported
Diener et al.[101] (2005) Zolmitriptan 2.5 mg ODT	OS Patients nine to 95 years of age with migraines	N=14,543 2 years	Primary: Efficacy evaluation Secondary: Not reported	Primary: Headache pain improved in 96% of patients, and the mean time to headache improvement was 51±44 minutes (P value not reported). Physicians' assessment determined that 90% of patients had either 'good' or 'very good' efficacy with zolmitriptan ODT (P value not reported). Secondary: Not reported
Spierings et al.[102] (2004) Zolmitriptan 5 mg ODT vs placebo One dose was used	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with at least two migraine headaches per month of moderate to severe intensity, in addition to <10 days of non-	N=656 6 weeks	Primary: Migraine response at 30 minutes Secondary: Speed of onset of headache response, duration of response	Primary: Significantly more patients receiving zolmitriptan achieved migraine response at 30 minutes (16.5 vs 12.5%, respectively; P=0.048). Secondary: At one hour, the difference in the proportions of zolmitriptan- and placebo-treated patients with reduced migraine headache intensity was significant (41.1 vs 22.9%; P<0.0001). This difference was also consistent at two hours (59.0 vs 30.6%; P<0.0001). The proportions of patients that returned to normal activities at two hours was significantly greater with zolmitriptan (51.8 vs 25.7%, respectively; P<0.0001).

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to treat migraine headache; if there was inadequate relief or if the headache returned, a second dose was allowed 2 to 24 hours later.	migraine headaches per month for the three months prior to enrollment			A significantly greater proportion of patients receiving zolmitriptan achieved sustained headache response compared to placebo (42.5 vs 16.4%; P<0.0001).
Loder et al.[103] (2005) Zolmitriptan 2.5 mg ODT (studies A and B) or zolmitriptan 5 mg ODT (study C) vs placebo	DB, MC, PC, RXT Patients with moderate to severe headaches (study A and C); Patients who had a migraine attack and who were instructed to treat it as soon as possible (study B)	N=1,705 24 hours	Primary: Headache response (study A); pain-free rate at 2 hours (study B); migraine headache response at 30 minutes (study C); Secondary: Headache response at 30 minutes (study A); reduction of headache intensity (studies A and B); pain-free rate at 2 hours (studies A and C); resumption of normal activities (studies B and C)	Primary: In study A, headache response at two hours, or the reduction in headache intensity from “moderate” or “severe” to “mild” or “no pain,” was greater for the zolmitriptan 2.5 mg ODT group compared to placebo (63 vs 22%; P<0.0001). For study B, pain-free status at the two-hour interval was achieved in 40.1% of the zolmitriptan patients and 19.8% of the placebo group (P<0.001). At the 24-hour mark, this was maintained in 31.1% of the zolmitriptan patients and 14.6% of placebo patients (P<0.001). In study C, the percentage of zolmitriptan 5 mg ODT and placebo patients with reduced migraine headache intensity from “moderate” or “severe” to “mild” or “no pain” at 30 minutes were 16 and 13%, respectively (P<0.05). Secondary: In study A, the percentage of zolmitriptan 2.5 mg ODT and placebo patients with reduced migraine headache intensity from “moderate” or “severe” to “mild” or “no pain” at 30 minutes were 16 and 10%, respectively (P=0.054). Collective results data from studies A and B showed a greater reduction of headache intensity (excluding mild-intensity attacks) at 30 minutes for the zolmitriptan ODT group compared to placebo (20.1 vs 12.7%; P<0.005). In study A, pain-free status at the two-hour interval was achieved in 27% of the zolmitriptan 2.5 mg ODT patients and 7% of the placebo group (P<0.0001). In study C, pain-free status at the 2-hour interval was

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				achieved in 31% of the zolmitriptan 5 mg ODT patients and 11% of the placebo group (P<0.0001). Patients were able to resume normal activities two hours post-treatment in study B in 55.8% of the zolmitriptan ODT-treated cases compared to 34.0% of placebo-treated patients (P<0.001). In study C, there was a greater percentage of patients that were able to resume normal activities two hours post-treatment in the zolmitriptan group compared to placebo (51.8 vs 25.7%; P<0.0001).
Charlesworth et al.[104] (2003) Zolmitriptan 0.5 to 5 mg administered IN vs zolmitriptan 2.5 mg oral tablet vs placebo	DB, DD, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for at least one year, with an age of onset of migraine <50 years and an average of one to six migraine attacks per month during the two months preceding the trial	N=1,547 Duration not specified	Primary: Headache response at two hours Secondary: Early headache response at 15, 30 and 45 minutes; headache response at one and four hours; pain-free rates at 15, 30 and 45 minutes and one, two and four hours	Primary: Headache response at two hours was reported to be the following: 31, 70 (P≤0.01), 59 (P≤0.01), 55 (P≤0.01) and 42% (P≤0.0008) with placebo and zolmitriptan 0.5, 1, 2.5 and 5 mg IN, respectively. Zolmitriptan 5 mg IN was significantly more effective than zolmitriptan 2.5 mg (P<0.05). Secondary: Zolmitriptan 2.5 and 5 mg IN showed a rapid onset of action, with a significant difference in headache response compared to placebo from 15 minutes through four hours after administration. At 15 minutes, early headache response was 5, 11 (P=0.0115) and 8% (P=0.0261) with placebo, zolmitriptan 5 mg IN and zolmitriptan 2.5 mg IN. Zolmitriptan 5 mg IN produced a significantly faster headache response than zolmitriptan 2.5 mg from 15 minutes through two hours (P value not reported). Zolmitriptan IN resulted in pain-free rates that were dose-dependent. While all doses ≥1 mg produced significant pain-free outcomes from 30 minutes compared to placebo, only the 5 mg dose produced pain-free rates significantly better than the 2.5 mg tablet (P values not reported).
Dowson et al.[105] (2003) Zolmitriptan 5.0 mg administered IN	DB, PG, RCT, XO Patients 18 to 65 years of age with migraine with or without aura, previous participation in a	N=1,093 (n=783 entered the post XO phase) 1 year	Primary: Tolerability Secondary: Headache response at two hours, pain-free response rate	Primary: Adverse events occurred in 22.1% of attacks treated with zolmitriptan 5 mg, and the majority were of short duration and mild or moderate intensity. Unusual taste and nasopharyngeal events were reported in 11.0 and 5.5% of attacks, respectively. Only 1.9% of patients withdrew from the one year trial due to adverse events. Serious adverse events occurred in 0.2% of attacks treated. There

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	dose ranging trial, a one year history of migraine symptoms, with an age of onset of migraine <50 years and an average of one to six migraine attacks per month during the two months preceding the trial			was no evidence of increased incidence of adverse events with increasing duration of treatment. Secondary: Efficacy was consistent over time with two-hour headache response rates of 73, 74, 75 and 74% during the four 90-day periods. Long-term usage of zolmitriptan 5 mg was associated with a consistently effective response, with 58% of patients experiencing a two-hour headache response in >75% of attacks. Pain-free response rates were also consistent over each four 90-day period (52 to 56%).
Loder et al.[106] (2005) Zolmitriptan 2.5 mg ODT (Trials A and B) or zolmitriptan 5 mg ODT (Trial C) vs placebo	3 DB, MC, PC, RCTs Patients with moderate to severe headaches (Trials A and C) Patients who had a migraine attack and who were instructed to treat it as soon as possible (Trial B)	N=470 (Trial A) N=565 (Trial B) N=670 (Trial C) 24 hours	Primary: Headache response (Trial A), pain-free rates at two hours (Trial B), migraine headache response at 30 minutes (Trial C) Secondary: Headache response at 30 minutes (Trial A), reduction of headache intensity (Trials A and B), pain-free rates at two hours (Trials A and C), resumption of normal activities (Trials B and C)	Primary: In Trial A, headache response at two hours was significantly greater with zolmitriptan compared to placebo (63 vs 22%; P<0.0001). For Trial B, pain-free status at two hours was achieved in 40.1 and 19.8% of zolmitriptan- and placebo-treated patients (P<0.001). This was maintained at 24 hours (31.1 vs 14.6%; P<0.001). In Trial C, the proportions of zolmitriptan- and placebo-treated patients with reduced headache intensity at 30 minutes were 16 vs 13%, respectively (P<0.05). Secondary: In Trial A, the proportions of zolmitriptan- and placebo-treated patients with reduced headache intensity at 30 minutes were 16 vs 10%, respectively (P=0.054). Pooled data from Trials A and B showed a significantly greater reduction of headache intensity (excluding mild intensity attacks) at 30 minutes with zolmitriptan compared to placebo (20.1 vs 12.7%; P<0.005). In Trial A, pain-free status at two hours was achieved in 27 and 7% of zolmitriptan- and placebo-treated patients (P<0.0001). In Trial C, pain-free status at two hours was achieved in 31 and 11% of zolmitriptan- and placebo-treated patients (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In trial B, 55.8 vs 34.0% of zolmitriptan- and placebo-treated patients were able to resume normal activities at two hours (P<0.001). In Trial C, there was a significantly greater proportion of patients that were able to resume normal activities at two hours with zolmitriptan compared to placebo (51.8 vs 25.7%; P<0.0001).
Winner et al. (2016)[107] TEENZ Zolmitriptan 5 mg nasal spray vs zolmitriptan 2.5 mg nasal spray vs zolmitriptan 0.5 mg nasal spray vs placebo Patients completed a 30-day run-in period and received treatment with placebo for a single migraine. Patients were then randomized if they did not respond to placebo.	DB, MC, PC, PG, RCT Patients 12 to 17 years of age with migraine with or without aura that has been diagnosed for ≥1 year with ≥2 moderately-to-severely disabling migraines per month	N=798 10 weeks	Primary: Pain-free status two hours post-treatment Secondary: Pain-free status at three and four hours post-treatment, headache response, sustained headache response, presence/ resolution of associated symptoms, use of rescue medication, ability to perform normal activities, headache recurrence	Primary: The percentage of patients achieving pain-free status at two hours post-treatment was 29.7% (OR, 2.18; 95% CI, 1.40 to 3.39; P<0.001), 24.7% (OR, 1.76; 95% CI, 0.95 to 3.26; P=0.071), 22.0% (OR, 1.37; 95% CI 0.75 to 2.50; P=0.312), and 16.6% with zolmitriptan 5 mg, zolmitriptan 2.5 mg, zolmitriptan 0.5 mg, and placebo, respectively. Secondary: The percentage of patients achieving pain-free status at three and four hours post-treatment was significantly higher with zolmitriptan 5 mg compared to with placebo (45% vs 24% and 56% vs 39%, respectively; P<0.001 for both). Zolmitriptan 5 mg was more effective than placebo in achieving headache response two hours post-treatment (51% vs 39%; P=0.011). There was no statistically significant difference in sustained headache response between any zolmitriptan dose and placebo. There was no statistically significant reduction in the occurrence of nausea and vomiting symptoms with zolmitriptan 5 mg. The percentage of patients with a reduction in light sensitivity at two, three, and four hours post-treatment with zolmitriptan 5 mg compared to with placebo was 44% vs 56%, 32% vs 42%, and 20% vs 29%, respectively (P≤0.041 for all). There were significant reductions in sensitivity to sound at two and three hours post-treatment for patients treated with zolmitriptan 5 mg compared to with placebo (42% vs 52% and 30% vs 42%, respectively; P≤0.024 for both). The percentage of patients that required rescue medication during the first 24 hours was smaller in the zolmitriptan 5 mg than in the placebo group (20.3% vs 31.6%; P=0.004). At two hours, the percentage of patients able

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to perform normal activity was higher in the zolmitriptan 5 mg group than in the placebo group (55.0% vs 47.8%; P=0.117). Of the patients who were pain-free at two hours, fewer than 10% had headache recurrence between two and 24 hours post-treatment across all treatment groups.
Geraud et al.[108] (2000) Zolmitriptan 5 mg vs sumatriptan 100 mg vs placebo Use of escape medication was permitted 2 hours postdose if symptoms persisted.	DB, MC, PC, RCT Treatment naïve migraine patients 18 to 65 years of age with a history of migraine with or without aura for more than one year	N=1,058 24 hours	Primary: Complete headache response rates in acute treatment (defined as a reduction in headache pain from moderate to severe at baseline to mild or no pain two hours after taking study drug with no moderate or severe recurrences at 24 hours) Secondary: Headache responses at one, two and four hours	Primary: Complete headache response was 39, 38 and 32% with zolmitriptan, sumatriptan and placebo, respectively (P value not significant). In patients with moderate headache, response was significantly greater with zolmitriptan compared to placebo (48 vs 27%; P=0.01). In patients with a moderate headache, there was no difference in complete response with zolmitriptan and sumatriptan (48 vs 40%, respectively; P value not reported). In patients with a severe headache, there was no difference in complete response rates between placebo (44%) and zolmitriptan (27% and sumatriptan (35%; P values not reported). Secondary: Active treatment groups were significantly more effective than placebo for one, two and four hour headache responses (P<0.05).
Dowson et al.[109] (2005) Zolmitriptan 2.5 mg ODT vs sumatriptan 50 mg tablet	PC, RCT (vs placebo); OL, RCT, XO Patients with migraines	N=470 (vs placebo) N=168 (vs sumatriptan) N=171 (vs rizatriptan ODT)	Primary: Patient preference Secondary: Not reported	Primary: In the trial of zolmitriptan ODT vs placebo, 70% of patients preferred the ODT formation compared to conventional tablets (P value not reported). In terms of patient preference, a greater proportion of patients preferred zolmitriptan ODT compared to sumatriptan (60.1 vs 39.9%; P=0.013). Patients also found zolmitriptan ODT to be more efficacious compared to sumatriptan (76.7 vs 63.4%; P=0.006). Patient preference for zolmitriptan ODT was greater than that of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or rizatriptan 10 mg ODT or placebo		12 weeks (vs sumatriptan)		rizatriptan ODT (70 vs 27%; P<0.001). Secondary: Not reported
Chen et al.[110] (2008) Zolmitriptan 2.5 mg vs almotriptan 12.5 mg vs eletriptan 40 to 80 mg vs sumatriptan 50 to 100 mg vs naratriptan 2.5 mg vs rizatriptan 10 mg	MA Patients 18-65 years of age with migraine, with or without aura	N=15,408 (24 trials) Variable duration	Primary: Headache relief at one-hour and two-hours post-dose; one-hour and two-hour pain-free rate post-dose, sustained pain-free response over 24 hours post-dose Secondary: Not reported	Primary: All three formulations of zolmitriptan were found to be significantly more effective than placebo in achieving headache relief, pain free and sustained pain free responses. Zolmitriptan 2.5 and 5 mg tablets resulted in significantly more patients achieving headache relief (RR, 1.83; 95% CI, 1.46 to 2.29 and RR, 1.86; 95% CI, 1.19 to 2.90), pain free response at 2-hours post-dose (RR, 2.39; 95% CI, 1.75 to 3.27 and RR, 2.84; 95% CI, 1.17-6.89) and sustained pain-free response from two to 24-hours post-dose (2.5mg; RR, 4.10; 95% CI, 2.57 to 6.25). There were no significant differences between any of the active comparators and zolmitriptan. There was no significant difference between oral 2.5 and 5 mg zolmitriptan. There was a statistically significant difference between zolmitriptan 2.5 mg tablet and zolmitriptan 5 mg nasal spray (RR, 0.78; 95% CI, 0.65 to 0.94) and between zolmitriptan 2.5 mg nasal spray and zolmitriptan 5mg nasal spray (RR, 0.69; 95% CI, 0.57 to 0.84).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Sun et al.[111] (2013) Almotriptan, eletriptan, rizatriptan, sumatriptan, or zolmitriptan	SR Pediatric data submitted to the Food and Drug Administration from January 1, 1999, through December 31, 2011; efficacy trials used a R, DB, PC, PG trial design	N=3,732 (7 trials) Duration varied	Primary: Headache response, headache/pain relief, and headache/ pain freedom Secondary: Pharmacokinetic variables	Primary: Only almotriptan was significantly more effective than placebo among the trials conducted before 2008. Rizatriptan was not shown to be effective in the 1999 trial but demonstrated therapeutic effectiveness in the 2011 trial. Compared to the rizatriptan 1999 trial, the rizatriptan 2011 trial reported a 6% lower rate of placebo response. Placebo response rates for all trials were much higher than the corresponding rates in adult clinical trials. The placebo response rate for pain relief at two hours after treatment in pediatric trials ranged from 53.0 to 57.5%, in contrast to the placebo response rates ranging from 15.0 to 42.4% in adults. For almotriptan, the response rates for pain relief at two hours after treatment were higher in adolescents than in adults (71.8 vs 56.0% for the 6.25-mg dose; 72.9 vs 64.2% for the 12.5-mg dose); the response rates for the other drugs were comparable between adolescents and adults. Secondary: Although some numerical pharmacokinetic variable differences between adolescents and adults were noted, overall, the pharmacokinetic variables were statistically comparable between adolescents and adults.
Lipton et al.[112] (2013) Patients were taking NSAIDs and/or triptans	Longitudinal, OS, population-based Adult patients with EM or CM surveyed in the American Migraine Prevalence and Prevention study	N=9031 (537 CM onsets occurring in 507 distinct individuals) 5 years	Primary: NSAID and triptan combined use exposure, medication use and association with chronic migraine onset	Primary: Rates of NSAID and triptan use days per month were uniformly higher for those transitioning to CM compared with the reference. Results indicated that on average, 55% of the participants used NSAIDs in any given year and 2% transitioned to CM over subsequent years. Among the 20% using triptans, 3% per year transitioned to CM. Overall, regular use of NSAIDs lowers the risk of developing CM, but only in situations where headache frequency is less than 10 days per month. Increasing days

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	with data for at least two consecutive survey years		Secondary: Not reported	of triptan use per month were associated with a significant increased risk of CM onset in models that included headache days and headache by triptan day interactions. For triptans, the interaction term was never significant, indicating that the effect of triptans on CM onset is not significantly modified by attack frequency. While triptan monotherapy was associated with increased risk of CM onset, no significant increase was observed for CM onset when triptans were taken in concert with NSAIDs. Secondary: Not reported
Lipton et al.[113] (2018) Sumatriptan 10 mg nasal spray vs placebo	DB, MC, PG, RCT Adults with episodic migraine, at least a 12-month history of two to eight migraine attacks per month with 14 or fewer headache days monthly, and at least 48 hours of headache-free time between attacks	N=107 10 weeks	Primary: Proportion of subjects with moderate or severe pain pre-dose who were pain free at two hours post-dose in first double-blind treatment period Secondary: Pain relief, freedom from the most bothersome symptom, and freedom from nausea, photophobia, and phonophobia at two hours post-dose	Primary: The proportion of subjects who were free from headache pain at two hours-post dose was higher in the sumatriptan group than in the placebo in the last observation carried forward analysis (43.8% vs 22.5%; P=0.025) and in the observed cases analysis (43.8% vs 20.5%; P=0.025). <u>Secondary:</u> The proportion of subjects who experienced pain relief at two hours post-dose was higher in the sumatriptan group than in the placebo group (83.3% vs 55.0%; P=0.005). The proportion of subjects who experienced freedom from the most bothersome symptoms at two hours post-dose was higher in the sumatriptan group than in the placebo group (70.7% vs 39.5%; P=0.007). The proportion of subjects who were nausea-free at two hours post-dose was higher in the sumatriptan group than in the placebo group (78.3% vs 42.1%; P=0.026). The proportion of subjects who were photophobia-free at two hours post-dose was higher in the sumatriptan group than in the placebo group (71.8% vs 38.9%; P=0.005). The proportion of subjects who were phonophobia-free at two hours post-dose was higher in the sumatriptan group than in the placebo group (78.1% vs 40.0%; P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kuca et al.[114] (2018) Lasmiditan 200 mg vs lasmiditan 100 mg vs placebo	DB, PC, RCT Adults with a diagnosis of migraine with or without aura, had a history of disabling migraine for at least one year, a Migraine Disability Assessment total score of ≥11, migraine onset before 50 years of age, and a history of three to eight migraine attacks per month (<15 headache days per month)	N=1,856 8 weeks	<u>Primary:</u> Comparison between lasmiditan 200 mg and placebo in the proportion of patients who were headache pain free at two hours after the first dose <u>Secondary:</u> Comparison between lasmiditan 100 mg and placebo in the proportion of subjects who were headache pain free at two hours after the first dose and the comparison between lasmiditan (both doses) and placebo in the proportion of subjects who were free from the most bothersome symptom at two hours after the first dose	<u>Primary:</u> The proportion of subjects who were free from headache pain at two hours-post dose was higher in the lasmiditan 200 mg group than in the placebo group (32.2% vs 15.3%; P<0.001). <u>Secondary:</u> The proportion of subjects who were free from headache pain at two hours-post dose was higher in the lasmiditan 100 mg group than in the placebo group (28.2% vs 15.3%; P<0.001). The proportion of subjects who experienced freedom from the most bothersome symptoms at two hours post-dose was higher in the lasmiditan 200 mg (40.7%; P<0.001) and 100 mg groups (40.9%, P<0.001) than in the placebo group (29.5%).
Goadsby et al.[115] (2019) Lasmiditan 200 mg	PRO, DB, PC, RCT Adults who had at least a one-year history of disabling	N=2,583 1 week	<u>Primary:</u> Proportion of patients who were headache pain-free and most	<u>Primary:</u> The proportion of subjects who were free from headache pain at two hours-post dose was higher in the lasmiditan 200 mg (38.8%; P<0.001), 100 mg (31.4%; P<0.001), and 50 mg (28.6%; P=0.003) than in the placebo group (21.3%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs lasmiditan 100 mg vs lasmiditan 50 mg vs placebo	migraine with or without aura, a Migraine Disability Assessment score of ≥11, onset before 50 years of age, and three to eight migraine attacks per month		bothersome symptom-free at two hours after the first dose <u>Secondary:</u> Proportion of patients with headache pain relief; proportion of patients who had sustained pain freedom at 24 hours and 48 hours after the first dose; proportion of patients who were headache pain-free, most bothersome symptom-free, and headache pain relief at other time points; proportion of patients who were free from migraine symptoms; patient global impression change; level of disability; and proportion of patients who used a second dose of study drug for rescue or recurrence	The proportion of subjects who were free from the most bothersome symptom at two hours-post dose was higher in the lasmiditan 200 mg (48.7%; P<0.001), 100 mg (44.2%; P<0.001), and 50 mg (40.8%; P=0.009) than in the placebo group (33.5%). Subjects who received lasmiditan were less likely to use a second dose of study drug versus subjects who received placebo: 21.2% of the 200 mg group, 26.3% of the 100 mg group, 34.4% of the 50 mg group, and 29.5 mg of the placebo group took a second dose between two and 24 hour hours after the first dose. <u>Secondary:</u> In almost all secondary outcomes, the lasmiditan groups achieved more relief of symptoms than the placebo group and the difference was statistically significant. The benefits seen in nausea-free and vomiting-free at two hours were not statistically significant, where the proportions were higher in the placebo group than in the lasmiditan 50 mg group.
Ashina et al.[116]	DB, MC, RCT	N=1,471	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2021) CENTURION Lasmiditan 200 mg vs lasmiditan 100 mg vs control (placebo for three attacks and lasmiditan 50 mg for either the third or fourth attack)	Patients ≥18 year of age with migraine with or without aura fulfilling the International Headache Society diagnostic criteria 1.1 or 1.2.1; a history of disabling migraine of at least one year; Migraine Disability Assessment Test (MIDAS) score ≥11; migraine onset before the age of 50 years; and 3 to 8 migraine attacks per month, but <15 headache days per month during the past three months	Four migraine attacks or four months (whichever came sooner)	Pain freedom at 2 hours (first attack) and pain freedom at 2 hours in ≥2 of 3 attacks Secondary: Pain relief, sustained pain freedom and disability freedom	Both primary endpoints were met for lasmiditan 100 mg and 200 mg (P<0.001). Lasmiditan at either dose was superior to placebo for pain freedom at two hours, with therapeutic gains of 17.4% and 20.9% for lasmiditan 100 mg and 200 mg, respectively. Secondary: All gated secondary endpoints were met.
Menstrual Migraine				
Allais et al.[117] (2006) Almotriptan 12.5 mg vs zolmitriptan 2.5 mg	DB, MC, PC, RETRO, RCT Women with a history of migraine for more than one year and two to six migraine attacks in each of the two months preceding the trial	N=255 24 hours	Primary: Pain relief at one-half, one, one and one-half and two hours; pain-free at one-half, one, one and one-half and two hours; sustained pain-free at two hours with no recurrence and no rescue medication;	Primary: In the ITT analysis, almotriptan did not differ from zolmitriptan for any of the outcomes evaluated. Two hours after dosing, 67.9 and 68.6% of the women receiving almotriptan and zolmitriptan, respectively, had obtained pain relief (P=0.900). Evolution of pain from “moderate to severe” to “mild to no pain” was also similar between treatments at one-half hour post dose (14.9 vs 11.9%; P=0.477). A pain-free state at two hours was reported by 44.9 and 41.2% of women receiving almotriptan and zolmitriptan, respectively (P=0.554). Twenty-four hours after dosing 56.6 and 64.7% of patients, respectively, were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			recurrence within 24 hours of treatment; level of functional impairment before intake and after one-half, one, one and one-half and two hours Secondary: Tolerability	pain-free (P=0.187). Recurrences was reported in 32.8 and 34.7% of patients respectively (P=0.833). Use of rescue medication within two to 24 hours was reported by 21.8 and 25.4% of patients, respectively (P=0.499). A sustained pain-free response was reported by 29.3 and 27.1% of patients receiving almotriptan and zolmitriptan, respectively (P=0.698). Secondary: Adverse events occurring within 24 hours were reported in 19.8 and 23.1% of patients; with 13.2 and 17.6% (P=0.328), respectively, being considered triptan-related.
Marcus et al.[118] (2010) Eletriptan 20 mg three times daily starting 2 days prior to the expected onset of menstruation and continued for a total of 6 days	OL, PRO Women 18 to 45years of age with menstrual-related migraines experiencing >50% of migraine attacks during menses or increased severity by ≥50% during the menstrual week	N=71 3 months	Primary: Reduction in headache activity by ≥50% Secondary: Percentage of patients remaining migraine-free during menses; percentage of patients who were migraine-free but developed migraines after discontinuing eletriptan	Primary: Patients were categorized as Probability MM (those with migraines likely due to menses more than due to chance) and as Probability non-MM. The overall headache activity decreased significantly by 54% in the Probability MM group and by 34% in the Probability non-MM group (P=0.003). There was no difference in headache activity on non-menstrual days. Secondary: The mean percentage of treated menses without migraine was 71.3%. The percentage of patients with one, two and three migraine-free menstrual periods were 13.5, 19.4, and 53.2%, respectively. Migraine occurred during the three days immediately after discontinuing eletriptan in 8.8% of patients.
Bartolini et al.[119] (2011) Frovatriptan 2.5 mg	DB, MC, RCT, XO Women suffering from menstrual-related	N=114 Six months or six migraine attacks	Primary: Proportion of pain-relief episodes and pain-free episodes at two,	Primary: The proportions of pain-relief episodes were similar between patients treated with frovatriptan and almotriptan, respectively, at two hours (36 vs 41%; P=NS), four hours (53 vs 50%; P=NS) and 24 hours (62 vs 67%; P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs almotriptan 12.5 mg	migraine for at least six months		four and 24 hours and proportion of patients with migraine recurrence within 24 or 48 hours	The proportions of pain-free episodes were not significantly different between the frovatriptan and almotriptan groups, respectively, at two (19 vs 29%; P=NS), four (47 vs 54%; P=NS) and 24 hours (60 vs 67%; P=NS). The rate of migraine recurrence after 24 hours was significantly lower during frovatriptan treatment compared to almotriptan treatment (8 vs 21%; P<0.05). Similarly, there was a significantly lower incidence of recurrences at 48 hours with frovatriptan compared to almotriptan (9 vs 24%; P<0.05).
Silberstein et al.[120] (2004) Frovatriptan 2.5 mg daily vs frovatriptan 2.5 mg twice daily vs placebo	DB, MC, PC, XO Women >18 years of age with a history of migraine for more than one year and three to four attacks (perimenstrual period)	N=443 Three perimenstrual periods	Primary: Efficacy Secondary: Not reported	Primary: The incidence of menstrual migraine was 67% (n=468) with placebo compared to 52 (n=484; P<0.0001) and 41% (n=483; P<0.0001) with frovatriptan once and twice daily, respectively. Significant reductions in headache severity were observed in frovatriptan-treated patients (P<0.0001). Frovatriptan twice daily was more efficacious than once daily (P<0.0001). Secondary: Not reported
Brandes et al.[121] (2009) Frovatriptan 2.5 mg once daily vs frovatriptan 2.5 mg twice daily vs	DB, MC, PC, PG Women ≥15 years of age with menstrual-related migraines occurring in the perimenstrual period and menstrual-related migraines in 2 of the last 3 cycles; only women with	N=427 3 cycles	Primary: Number of headache-free perimenstrual periods Secondary: Time to use of rescue therapy, time to onset of symptoms	Primary: The mean number of headache-free perimenstrual periods was significantly higher in the frovatriptan treatment groups compared to placebo (daily group: 0.69 vs 0.42, respectively; P=0.0091; twice daily group: 0.92 vs 0.42, respectively; P<0.0001). Secondary: The percentage of patients with functional impairment decreased in the frovatriptan groups and was lower compared to placebo, with 78% (daily group) and 71% (twice daily group) of patients reporting functional impairment, compared to 93% of placebo-treated patients (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Therapy started 2 days prior to expected menstruation and continued for 6 days.	difficult to treat menstrual-related migraines (defined as exposure to non-triptan therapy and an inadequate response to triptan therapy for acute treatment over a minimum of 2 cycles) were included			Frovatriptan-treated patients experienced more headache-free days per perimenstrual period compared to placebo (daily group: ≤0.04; twice daily group: P≤0.01). Patients in the twice daily group experienced an increase in the number of headache-free days with each progressive perimenstrual period, increasing to 4.1 in perimenstrual period 1, 4.5 in perimenstrual period 2, and 4.7 days (P<0.001) in perimenstrual period 3. Over all perimenstrual periods, the mean number of headache-free days was 3.6 for placebo, 4.0 for frovatriptan 2.5 mg daily and 4.2 for frovatriptan 2.5 mg twice daily (both, P<0.0001 vs placebo). Frovatriptan decreased the severity of attacks during the three perimenstrual periods (P<0.01). The use of rescue medication was reported by 86% of patients receiving placebo, 67% of patients receiving daily frovatriptan, and 68% of patients receiving twice-daily frovatriptan (both, P<0.001 vs placebo).
Silberstein et al.[122] (2009) Frovatriptan 2.5 mg once daily vs frovatriptan 2.5 mg twice daily vs placebo Patients initiated treatment 2 days prior to the expected menstrual migraine and received each	DB, MC, PC, RCT, XO (Post-hoc analysis) Patients ≥18 years of age with a >1 year history of menstrual migraines, and had regular menstrual periods with predictable menstrual migraines; this post-hoc analysis was in women who reported a migraine occurring exclusively in association with menstruation	N=179 3 menstrual cycles	Primary: Percentage of patients who experienced menstrual migraine attacks Secondary: Severity and duration of menstrual migraine attacks, menstrual migraine-associated symptoms, functional disability, and rescue medication use	Primary: The percentage of patients with migraines occurring exclusively in the menstrual period who experienced an attack was significantly lower with frovatriptan daily and twice daily regimens (37.7 and 51.3%, respectively) compared to placebo (67.1%, twice daily vs placebo; P<0.001, daily vs placebo; P=0.002). There was a significant dose-dependent effect between the daily and twice daily frovatriptan treatment groups (P=0.01). Secondary: There was a significant reduction in moderate or severe migraines with frovatriptan twice daily (25.3%; P<0.001) and frovatriptan once daily (32.3%; P<0.01) compared to placebo (46%). There was a significant reduction in rescue medication use during treatment with frovatriptan twice daily (26.4%; P<0.001) and frovatriptan once daily (37.7%; P=0.04) compared to placebo (48.6%). There was a significant dose-dependent effect between frovatriptan once daily and twice daily regimens (P=0.02). There was a significant decrease in women with moderate or severe functional impairment during treatment with frovatriptan twice daily

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment sequentially over separate 6-day perimenstrual periods.				(13.6%; P<0.001) and frovatriptan once daily (24.1%; P<0.03) compared to placebo (35.4%). There was a significant dose-dependent effect between frovatriptan once daily and twice daily regimens (P=0.02). All menstrual-related migraine-related symptoms were lower during treatment with frovatriptan twice daily (P<0.001) and frovatriptan once daily (P=0.02) compared to placebo. There was a significant dose-dependent effect between frovatriptan once daily and twice daily regimens (P=0.02). Individually there were only significantly lower instances of photosensitivity, photosensitivity and nausea in the frovatriptan twice daily group.
MacGregor et al.[123] (2009) Study 1 Frovatriptan 2.5 mg once daily vs frovatriptan 2.5 mg twice daily vs placebo Study 2 Frovatriptan 2.5 mg daily Patients initiated treatment 2 days before the	Pooled data from 2 separate studies Study 1 DB, MC, PC, RCT Study 2 OL extension study Women ≥15 years of age with ≥12-month history menstrual migraine attacks	Study 1 N=427 3 menstrual cycles Study 2 N=549 12 to 15 months	Primary: Safety and tolerability Secondary: Not reported	Primary: In study 1, both frovatriptan groups had a higher proportion of patients with adverse events possibly or probably related to study drug (daily, 32%; 95% CI, 24.7 to 39.4; twice daily, 24%; 95% CI, 17.0 to 33.4; placebo, 19%; 95% CI, 13.3 to 25.4). In study 2, 60% of patients had an adverse event that was classified as probably or possibly related to treatment. In study 1, the most common adverse events were migraine-related or infection-related. The proportion of women reporting migraine as an adverse event was 4 to 8% (placebo, 4%; twice daily, 4%; once daily, 8%) in study 1 compared to 44% of patients in study 2. In study 2, migraine-associated adverse events (migraine, dizziness, headache, nausea and fatigue) numerically declined from perimenstrual periods one/cycle one to perimenstrual periods 11/cycle 11. Serious adverse events were reported by four patients in study 1, but none were thought to be related to study medication. In study 2, 14 serious adverse events were reported, with three being thought to be related to study drug. Flushing was reported in 1% of patients across both studies. Incidence of chest discomfort was similar between treatment groups during study 1. In

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
estimated start of a menstrual migraine headache and continued dosing for a total of 6 days.				study 2, 3% of patients reported chest pain and <1% reported tightness. Secondary: Not reported
Mannix et al.[124] (2007) Naratriptan 1 mg twice a day vs placebo	DB, MC, PC, PG, RCT Female patients ≥18 years of age with at least a 1-year history of migraine, a reported history of menstrual-related migraines, regular and predictable menstrual cycles and at least 1 menstrual-related migraine during the last menstrual cycle before the screening visit	N=633 4 to 6 months	Primary: Mean percentage of treated perimenstrual period with menstrual-related migraines per patient Secondary: Percentage of patients who were free of menstrual-related migraines during all treated perimenstrual periods, median number of days with menstrual-related migraines over four perimenstrual periods, patient satisfaction, safety and tolerability measures	Primary: Mean percentage of PMPs without menstrual-related migraines per patient was 38 and 34% in naratriptan groups, significantly higher than 29 and 24% in placebo groups (P<0.05 naratriptan vs placebo for both studies). More patients in naratriptan groups reported attacks post-treatment compared to patients in placebo groups. Secondary: Among patients treating at least one perimenstrual periods, the percentage of patients with no menstrual-related migraines in any treated perimenstrual periods was significantly (P=0.006) higher in the naratriptan group than the placebo group in study 2 only. The number of menstrual-related migraines days per patient across four perimenstrual periods was significantly lower in naratriptan group than in placebo group in both studies (median 5.0 vs 6.5 days in study 1 [P=0.005] and 5.3 vs 6.0 days in study 2 [P=0.018]). At visit five, significantly more naratriptan-treated patients reported greater overall satisfaction with the medication than placebo-treated patients. No serious drug-related adverse events were reported in either study. No individual drug-related adverse event was reported in more than 2% of patients in a group in either study, including days on which an additional naratriptan 2.5 mg tablet was taken to treat breakthrough headache. No drug-related effects or pattern of clinically significant changes in vital signs were noted.
Mannix et al.[125] (2009)	2 replicate studies: DB, MC, PC, R	N=621	Primary: Two hour pain-free	Primary: A significantly greater percentage of patients receiving sumatriptan-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sumatriptan-naproxen 85-500 mg vs placebo	Women ≥18 years of age with a 6-month history of migraine based on IHS criteria with attacks in at least 2 of the 3 perimenstrual periods prior to screening	1 menstrual cycle	response Secondary: 24-hour and 48-hour pain-free period	naproxen were pain free two hours post-dose compared to placebo (Study 1: 42 vs 23%, respectively; P<0.001; Study 2: 52 vs 22%, respectively; P<0.001). Secondary: A greater proportion of patients treated with sumatriptan-naproxen were pain free four hours post-dose in both studies compared to placebo (Study 1: 60 vs 36%, respectively; P<0.001; Study 2: 66 vs 30%, respectively; P<0.001). More participants treated with sumatriptan-naproxen had a sustained pain-free response two to 24 hours post-dose (Study 1: 29 vs 28%, respectively; P<0.001; Study 2: 38 vs 10%, respectively; P<0.001). The pain free response period from two to 48 hours post-dose was significantly higher in patients treated with sumatriptan-naproxen compared to placebo (Study 1: 26 vs 17%, respectively; P=0.04; Study 2: 28 vs 21%, respectively; P<0.001). Fewer patients treated with sumatriptan-naproxen required the use of rescue medication compared to placebo (Study 1: 37 vs 53%, respectively; P=0.005; Study 2: 31 vs 69%, respectively; P<0.001).
Mannix et al.[126] (2007) Rizatriptan 10 mg vs placebo	DB, PC, PG, RCT Female patients ≥18 years of age with at least a 6-month history of migraine, a reported history of menstrual-related migraine, regular and predictable menstrual cycles and at least 1 menstrual-related migraine during 2 of 3 previous	N=707 Single dose	Primary: Pain freedom at two hours post-dose Secondary: Sustained pain freedom at 24 hours post-dose	Primary/Secondary: Menstrual migraine one: 70 vs 53% of patients reported pain freedom at two hours post-dose (P=0.001) and 46 vs 33% reported 24-hour sustained pain freedom (P=0.016) with rizatriptan vs placebo, respectively. Menstrual migraine two: 73 vs 50% of patients reported pain freedom at two hours post-dose (P<0.001) and 46.0 vs33% reported 24-hour sustained pain freedom (P=0.024) with rizatriptan vs placebo, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	menstrual cycles before the screening visit			
Tuchman et al.[127] (2008) Zolmitriptan 2.5 mg three times daily vs zolmitriptan 2.5 mg twice daily vs placebo Treatments were given 2 days prior to expected onset of menstruation and continued for 5 days after the onset of menstruation.	DB, MC, PC, PG, R Women ≥18 years of age with a diagnosis of menstrual-related migraines with at least 3 menstrual-related migraines of moderate or severe intensity within the last 3 months and fewer than 15 days of non-migraine headaches	N=253 3 menstrual cycles	Primary: Proportion of patients with a ≥50% reduction in the frequency of menstrual migraine attacks per menstrual period Secondary: Mean number of menstrual migraine attacks per menstrual period, proportion of breakthrough migraine attacks treated with rescue medicine and their intensity, migraine associated symptoms	Primary: More patients receiving zolmitriptan (either regimen) experienced a ≥50% reduction in the frequency of menstrual migraine attacks compared to those receiving placebo (three times a day: 58.6 vs 37.8%, respectively; P=0.0007; twice daily regimen: 54.7 vs 37.8%; P=0.002). Secondary: The mean number of breakthrough attacks was significantly reduced in patients receiving zolmitriptan three times daily compared to placebo (0.56 vs 0.95; P=0.0002). There was no significant difference with zolmitriptan twice daily compared to placebo (0.75 vs 0.95; P=0.08). Both zolmitriptan regimens had less use of rescue medication compared to placebo during breakthrough attacks (three times daily regimen: 61.6 vs 74.4%; P=0.0004; twice daily regimen: 60.7 vs 74.4%; P=0.0055). More patients treated with zolmitriptan three times daily experienced no menstrual migraine attacks (39.8%) compared to zolmitriptan twice daily (21.3%) and placebo (6.2%). There was no effect on the incidence of migraine associated symptoms among the treatment groups.
Hu et al.[128] (2013) Triptan (frovatriptan, naratriptan, zolmitriptan) vs	MA All trials focused on a single dose of a triptan in the prevention of menstrual migraine and were MC; mean age of participants ranged from 36 to	N=1,999 6 trials 5 to 7 days	Primary: Proportion of patients free from menstrual migraine during the treated perimenstrual period Secondary: Menstrual	Primary: The relative benefit of frovatriptan once daily compared to placebo was 1.48 (1.27 to 1.72; number needed to treat to benefit, 7.22; 5.25 to 11.54); that of frovatriptan twice daily compared to placebo was 1.82 (1.58 to 2.09; number needed to treat to benefit, 3.90; 3.23 to 4.93). Patients with frovatriptan twice daily had a 23% increase in free from menstrual migraine per perimenstrual period 1.23 (1.10 to 1.39), giving a number needed to treat to benefit of 8.50 (5.77 to 16.19), compared to frovatriptan once daily.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	38 years, and all were women		migraine severity, need for rescue medication, adverse events	The relative benefit of naratriptan compared to placebo was 1.48 (1.20 to 1.83), giving a number needed to treat to benefit of 7.98 (5.24 to 16.71). Only one trial using naratriptan twice daily reported that naratriptan treated patients had fewer overall menstrual migraines and fewer menstrual migraine days compared to patients in the placebo group, however no significant differences were found. Zolmitriptan regimens were more efficacious vs placebo, as measured by ≥50% reduction in the frequency of menstrual migraine and the mean number of breakthrough menstrual migraines per menstrual cycle. There were insufficient data for MA. The number needed to treat to benefit for free from menstrual migraine per menstrual cycle for zolmitriptan twice daily vs placebo, three times daily vs placebo and three times daily vs twice daily were 4.98 (3.26 to 10.57), 2.52 (1.95 to 3.58) and 5.11 (2.95 to 18.93) respectively. Secondary: Patients with frovatriptan, both once and twice daily, had a reduction in menstrual migraine severity and need for rescue medication, and twice daily was more efficacious to once daily. Frovatriptan once daily had a reduction in moderate to severe menstrual migraine per perimenstrual period (0.75; 0.67 to 0.85) giving a number needed to treat to benefit of 7.70 (5.43 to 13.19), and in need for rescue medication per perimenstrual period (0.79; 0.70 to 0.89) giving a number needed to treat to benefit of 9.28 (6.17 to 18.72) when compared to placebo. Frovatriptan twice daily had a reduction in moderate to severe menstrual migraine per perimenstrual period (0.57; 0.50 to 0.66) giving an number needed to treat to benefit of 4.43 (3.58 to 5.81), and in need for rescue medication per perimenstrual period (0.64 [0.56 to 0.74]) giving a number needed to treat to benefit of 5.57 (4.28 to 7.99) when compared to placebo. Frovatriptan twice daily vs once daily had a reduction in moderate to severe menstrual migraine per perimenstrual period (0.77; 0.65 to 0.90) giving a number needed to treat to benefit of 10.45 (6.72 to 23.44), and in need for rescue medication per perimenstrual period (0.81 [0.70 to 0.94]) giving a number needed to treat to benefit of 13.93 (7.94 to 56.73). The adverse events in frovatriptan once daily vs placebo, frovatriptan

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				twice daily vs placebo and frovatriptan once daily vs twice daily were comparable. Most reported adverse events were mild to moderate. The incidence of severe adverse events was low and appeared to be unrelated to the treatments. After treatment with naratriptan twice daily, there was an increase in adverse events (1.37; 1.10 to 1.70) giving a number needed to treat to harm of 10.88 (6.46 to 34.38), but drug-related events (1.69; 0.98 to 2.90) were comparable to the placebo. In all studies, serious drug-related adverse events were not reported. It was reported that both zolmitriptan twice daily (0.82; 0.71 to 0.94, giving a number needed to treat to benefit of 7.31; 4.32 to 23.81) and zolmitriptan three times daily (0.83; 0.71 to 0.97, giving a number needed to treat to benefit of 7.81; 4.31 to 41.64) demonstrated a reduction in the need for rescue medication when compared to placebo. Zolmitriptan twice daily had an increase in any adverse event across four perimenstrual periods (1.44; 1.03 to 2.01), giving a number needed to treat to harm of 7.81 (4.31 to 41.64) when compared to placebo. Five serious adverse events were reported during the preventative therapy: two in the zolmitriptan three times daily group (pyelonephritis and endometrial disorder), two in the zolmitriptan twice daily group (uterine neoplasm and anxiety) and one in the placebo group. When drug-related adverse events were valued, no significant difference was found between treatment group and control group.
Safety				
Elkind et al.[129] (2004) Frovatriptan 2.5 mg daily vs placebo	DB, MC, PC, PG Men and women 18 years and older with a history of migraine with or without aura for longer than 1 year, with an attack frequency of 1 to 6 moderate or severe	N=75 Single migraine attack (follow-up at 36 hours)	Primary: Cardiovascular effects assessed by a 24-hour Holter monitor in patients administered frovatriptan 2.5 mg for the acute relief of migraine headache	Primary: Similar numbers of patients experienced ST segment changes indicative of ischemia on the 24-hour Holter monitor (11% frovatriptan-treated vs 13% placebo-treated). All episodes of myocardial ischemia or arrhythmias were asymptomatic and did not result in hemodynamic compromise. The incidence of arrhythmias was higher in the placebo-treated patients than frovatriptan group (11 vs 3%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	migraines per month		Secondary: Not reported	There were no differences in heart rate or diastolic or systolic blood pressure. The incidence of adverse events was similar in the frovatriptan treated and placebo-treated groups. Secondary: Not reported
Fleishaker et al.[130] (2002) Almotriptan 12.5 mg vs almotriptan 25 mg vs placebo	DB, R, 3-way, XO Patients with mild-to-moderate hypertension controlled by medications	N=20 Single dose	Primary: Assess cardiovascular effects of almotriptan in patients with mild-to-moderate hypertension controlled by antihypertensive medication Secondary: Plasma concentrations and cardiovascular effects	Primary: Almotriptan produced a dose-related change in systolic blood pressure for both four and 12 hours postdose. Mean changes from baseline from 0 to four hours were 1.59±3.88, 1.85±5.94, and 4.84±5.99 mm Hg for systolic blood pressure and 1.38±6.95, 6.25±9.54, and 11.0±10.6 mm Hg for diastolic blood pressure for placebo, almotriptan 12.5 mg, almotriptan 25 mg, respectively. Secondary: Plasma concentrations of almotriptan increased in a dose-related manner. There were no statistically significant differences in dose-related pharmacokinetic parameters between doses, indicating that the pharmacokinetics of almotriptan were linear for the dosage range studied for patients with controlled hypertension.

Drug regimen abbreviations: IN=intranasal, ODT=orally disintegrating tablets, SC=subcutaneous
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SR=systematic review, XO=crossover
Miscellaneous abbreviations: ALT=alanine transaminase, BUN=blood urea nitrogen, CM=chronic migraine, EM=episodic migraine, Migraine-ACT=Migraine assessment of current therapy, MqoLQ=Migraine Quality of Life Questionnaire, MSQ=Migraine-Specific Quality of Life Questionnaire, PPMQ=Patient Perception of Migraine Questionnaire, PPMQ-R=Revised Patient Perception of Migraine Questionnaire

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 10. Relative Cost of the Selective Serotonin Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Almotriptan	tablet	N/A	N/A	$$$$$
Eletriptan	tablet	Relpax®*	$$$$$	$$
Frovatriptan	tablet	Frova®*	$$$$$	$$$$$
Lasmiditan	tablet	Reyvow®	$$$$$	N/A
Naratriptan	tablet	Amerge®*	$$$$$	$
Rizatriptan	orally disintegrating tablet, tablet	Maxalt®*, Maxalt MLT®*	$$$$$	$
Sumatriptan	nasal powder, nasal spray, subcutaneous injection, tablet	Imitrex®*, Onzetra Xsail®, Tosymra®, Zembrace®	$$$$$	$$
Zolmitriptan	nasal spray, orally disintegrating tablet, tablet	Zomig®*, Zomig ZMT®*	$$$$$	$$$
Combination Products				
Sumatriptan and naproxen	tablet	Treximet®*	$$$$$	$$$$$

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

X. Conclusions

The selective serotonin agonists (triptans and lasmiditan) are approved for the treatment of acute treatment of migraine attacks with or without aura.[7-20] The subcutaneous formulation of sumatriptan is also approved for the treatment of cluster headaches.[7,8,14] Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, and sumatriptan-naproxen are available in a generic formulation.

For the acute treatment of migraine headaches, guidelines recommend the use of a nonsteroidal anti-inflammatory drug (NSAID) or triptan, depending on the severity of pain. NSAIDs are generally recommended for patients with mild pain, while the triptans are recommended for patients with moderate to severe pain. In very severe attacks, the use of subcutaneous sumatriptan is recommended as initial therapy. Patients experiencing nausea and vomiting may be better candidates for intranasal or subcutaneous formulations. The use of a second dose of a triptan is effective if a patient experiences a reoccurrence of their headache (new onset pain after symptoms had resolved); however, a second dose has not been shown to be useful if the first dose was ineffective. Although triptans can be taken any time during a migraine attack, evidence suggests they are more efficacious when taken early compared to later use.[1-6] Combining an NSAID with a triptan reduces headache recurrence. Guidelines also suggest that a triptan can be efficacious even if another triptan was not.[1-6] For the treatment of cluster headaches, the use of subcutaneous sumatriptan or intranasal zolmitriptan is recommended as initial therapy. For the prophylaxis of menstrual migraines, guidelines recommend the use of an NSAID; however, studies support the cyclical use of a triptan as well. In general, guidelines do not give preference to one triptan over another.[1-6]

Numerous clinical trials have evaluated the efficacy and safety of the triptans for the treatment of migraine headaches, cluster headaches and menstrual migraines.[21-130] Several studies have demonstrated similar efficacy among the agents. However, other studies have demonstrated greater efficacy with one agent over another. Sumatriptan-naproxen has been shown to be more effective than either drug administered alone. However, there is no data to suggest that the fixed-dose combination product is more efficacious than the coadministration of the individual components as separate formulations.[92-100,125] Some minor differences exist between the triptans with regards to their pharmacokinetic properties (e.g., onset and duration of action); however, this has not consistently resulted in differences in clinical outcomes.

Clinical trials evaluated lasmiditan and demonstrated lasmiditan had greater efficacy over placebo in achieving headache relief at two hours post-dose.[114-116] Lasmiditan has not yet been included in clinical guidelines.

There is insufficient evidence to support that one brand selective serotonin agonist is safer or more efficacious than another when administered at equipotent doses. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand selective serotonin agonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand selective serotonin agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, Antihistamines
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I. Overview

The pathophysiology of nausea and vomiting is complex and involves multiple neurotransmitters and organ systems. Five neurotransmitter receptor sites play a key role in the vomiting reflex. These receptor sites include M1 (muscarinic), D2 (dopamine), H1 (histamine), 5-HT_3 (serotonin), and NK_1 (substance P).[1] The available antiemetic drugs antagonize these receptors, leading to improvements in nausea and vomiting. Nausea and vomiting due to central or vestibular disorders respond well to anticholinergic agents and histamine H_1-receptor antagonists. However, nausea and vomiting due to cancer chemotherapy, radiation, and surgery tend to respond better to the 5-HT_3 receptor antagonists and the miscellaneous antiemetic, aprepitant.[2]

The antihistamine antiemetics are approved for the treatment of postoperative nausea and vomiting, general nausea and vomiting, motion sickness, and vertigo.[3-9] Prochlorperazine is also approved for the treatment of schizophrenia, as well as for the short-term treatment of generalized non-psychotic anxiety.[3,4,9] Conversely, the combination product of doxylamine succinate and pyridoxine is currently indicated for the treatment of nausea and vomiting in pregnancy.[7,8] These agents can be divided into two categories: antihistaminic-anticholinergic agents and phenothiazines. The antihistaminic-anticholinergic agents include dimenhydrinate, doxylamine succinate and pyridoxine, meclizine, and trimethobenzamide. They interrupt various visceral afferent pathways that stimulate nausea and vomiting. Prochlorperazine is the only phenothiazine in this class. Phenothiazines block dopamine receptors that are most likely located in the chemoreceptor trigger zone.[1,3,4]

The antihistamine antiemetics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in August 2020.

Table 1. Antihistamine Antiemetics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Dimenhydrinate	injection	N/A	dimenhydrinate
Meclizine	chewable tablet, tablet	Antivert®	meclizine
Prochlorperazine	injection, rectal suppository, tablet	N/A	prochlorperazine
Trimethobenzamide	capsule, injection	Tigan®*	trimethobenzamide
Combination Products			
Doxylamine succinate and pyridoxine	delayed-release tablet, extended-release tablet	Bonjesta®, Diclegis®*	doxylamine succinate and pyridoxine

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the antihistamine antiemetics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antihistamine Antiemetics

Clinical Guideline	Recommendation(s)
National Comprehensive Cancer Network: **Clinical Practice**	Principles of emesis control for the cancer patient: • Prevention of nausea/vomiting is the goal. The risk of nausea/vomiting (acute ≤24 hours vs delayed >24 hours) for persons receiving anticancer agents of high and moderate emetic risk lasts for at least three days for high and two days for

Clinical Guideline	Recommendation(s)
Guidelines in Oncology: Antiemesis (2022)[10]	moderate after the last dose of anticancer agents. Patients need to be protected throughout the full period of risk. • Oral and parenteral serotonin receptor antagonists (5-HT_3 RAs) have equivalent efficacy when used at the appropriate doses and intervals. • Consider the toxicity of the specific antiemetic(s). • Choice of antiemetic(s) used should be based on the emetic risk of the therapy, prior experience with antiemetics, and patient factors. Continuous infusion may make an agent less emetogenic. The emetic risk is expected to be the same for biosimilars as for the parent compound unless otherwise noted. • Patient risk factors for anticancer agent-induced nausea/vomiting include: o Younger age o Female sex o Previous history of anticancer agent-induced nausea/vomiting o Little or no previous alcohol use o Prone to motion sickness o History of morning sickness during pregnancy o Anxiety/high pretreatment expectation of nausea • There are other potential causes of emesis in patients with cancer (e.g., bowel obstruction, vestibular dysfunction, brain metastases, electrolyte imbalance, uremia, concomitant drugs, gastroparesis, cannabinoid hyperemesis syndrome, pancreatitis). For high emetic risk parenteral chemotherapy the following is recommended: • Preferred: combination of olanzapine, a neurokinin-1 receptor antagonist (NK1 RA), a 5-HT_3 RA, and dexamethasone. **OR** • Combination of olanzapine, palonosetron, and dexamethasone. **OR** • Combination of a NK1 RA, a 5-HT_3 RA, and dexamethasone. • The regimen and doses for each therapy are modified on days two to four after chemotherapy. For moderate emetic risk parenteral chemotherapy the following is recommended: • Combination of dexamethasone and a 5-HT_3 RA (palonosetron IV and granisetron SQ preferred). **OR** • Combination of olanzapine, palonosetron, and dexamethasone. **OR** • Combination of a NK1 RA, a 5-HT_3 RA, and dexamethasone. • The regimen and doses for each therapy are modified on days two and three after chemotherapy. For low emetic risk parenteral chemotherapy the following is recommended: • Dexamethasone; **OR** • Metoclopramide; **OR** • Prochlorperazine; **OR** • Dolasetron, granisetron or ondansetron (oral formulations). • Lorazepam PRN and H_2 blocker or PPI may be given with any regimen. For minimal emetic risk parenteral chemotherapy the following is recommended: • No routine prophylaxis For oral chemotherapy with moderate to high emetic risk the following is recommended: • A 5-HT_3 antagonist (dolasetron, granisetron, or ondansetron oral).

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	• Lorazepam may be given. • An H_2 receptor blocker or PPI may be given. For oral chemotherapy with low to minimal emetic risk the following is recommended: • Metoclopramide PRN; **OR** • Prochlorperazine PRN (maximum 40 mg/day); **OR** • Dolasetron, granisetron or ondansetron. • Lorazepam PRN and H_2 blocker or PPI may be given with any regimen. Principles for managing multiday emetogenic chemotherapy regimens • Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea/vomiting based on their chemotherapy regimen. It is therefore difficult to recommend a specific antiemetic regimen for each day, especially since acute and delayed emesis may overlap after the initial day of chemotherapy until the last day. • After chemotherapy administration concludes, the period of risk for delayed emesis also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen. • Practical issues also need to be considered when designing the antiemetic regimen, taking into consideration the administration setting, preferred route of administration, duration of action of the 5-HT_3 receptor agonist and associated dosing intervals, tolerability of daily antiemetics (e.g., steroids), compliance issues, and individual risk factors. • Steroids: o Dexamethasone should be administered once daily (either orally or intravenously [IV]) for moderately or highly emetogenic chemotherapy and for two to three days after chemotherapy for regimens likely to cause delayed emesis. o Dexamethasone dose may be modified or omitted when the chemotherapy regimen already includes a corticosteroid. • Serotonin antagonists: o A serotonin antagonist should be administered prior to the first (and subsequent) doses of moderately or highly emetogenic chemotherapy. o The frequency or need for repeated administration depends on the agent chosen and its mode of administration (IV, oral, or transdermal). o When palonosetron or granisetron extended-release injection is used as part of an antiemetic regimen that does NOT contain an NK1 antagonist, palonosetron or granisetron extended-release injection are the preferred 5-HT_3 receptor antagonists. • NK1 receptor antagonists: o NK1 antagonists may be used for multiday chemotherapy regimens likely to be moderately or highly emetogenic associated with significant risk for delayed nausea and emesis. Principles for managing breakthrough emesis • The general principle of treatment for breakthrough nausea and vomiting is to add one agent from a different drug class to the current regimen. • No one drug class has been shown to be superior for the management of breakthrough emesis. • Consider around-the-clock administration rather than PRN. • The oral route is not likely to be feasible due to vomiting, therefore rectal or IV therapy is often required. • Ensure adequate hydration.
European Society of	Prevention of acute and delayed nausea and vomiting induced by highly emetogenic

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Medical Oncology/ Multinational Association of Supportive Care in Cancer: **Consensus Guidelines for the Prevention of Chemotherapy and Radiotherapy-Induced Nausea and Vomiting (2016)[11]**	<u>chemotherapy</u>
	• For the prevention of cisplatin-containing highly emetogenic chemotherapy, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone, and an NK1 receptor antagonist (aprepitant, fosaprepitant, netupitant, or rolapitant), given before chemotherapy is recommended.
	• In patients receiving cisplatin-containing highly emetogenic chemotherapy treated with a combination of an NK1 receptor antagonist, a 5-HT_3 receptor antagonist and dexamethasone to prevent acute nausea and vomiting, dexamethasone on days two to four is suggested to prevent delayed nausea and vomiting.
	• In women with breast cancer receiving anthracycline/cyclophosphamide (AC) chemotherapy, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone, and an NK1 receptor antagonist (aprepitant, fosaprepitant, netupitant, or rolapitant), given before chemotherapy is recommended.
	• In women with breast cancer treated with a combination of a 5-HT_3 receptor antagonist, dexamethasone and an NK1 receptor antagonist to prevent acute nausea and vomiting, aprepitant or dexamethasone should be used on days two and three but not if fosaprepitant, netupitant, or rolapitant has been used on day one. If an NK1 receptor antagonist is not available for the prophylaxis of nausea and vomiting induced by AC chemotherapy, palonosetron is the preferred 5-HT_3 receptor antagonist.
	• For regimens including mechlorethamine, streptozocin, cyclophosphamide ≥1500 mg/m^2, carmustine, and dacarbazine, adding an NK1 receptor antagonist to the combination of a 5-HT_3 receptor antagonist and dexamethasone for all non-cisplatin and non-AC highly emetogenic chemotherapy is recommended.
	• Differences among the NK1 antagonists:
	  ○ Aprepitant and netupitant are inhibitors of CYP3A4 and as a consequence, both significantly increase the exposure to oral dexamethasone; hence, reduction in oral dexamethasone doses is recommended during co-administration (from 20 to 12 mg).
	  ○ Rolapitant is not an inhibitor or inducer of CYP3A4 and therefore does not require a reduced dose of dexamethasone when co-administered. However, rolapitant is a moderate inhibitor of CYP2D6.
	  ○ At present, no comparative studies have been carried out to identify differences in efficacy and toxicity between the three NK1 receptor antagonists.
	
	<u>Prevention of acute and delayed nausea and vomiting induced by moderately emetogenic chemotherapy (MEC)</u>
	• For the prevention of acute emesis in MEC-treated patients, a 5-HT_3 receptor antagonist plus dexamethasone is recommended.
	• There is no definitive evidence demonstrating an advantage of the use of palonosetron with respect to the other 5-HT_3 receptor antagonists, when both are combined with dexamethasone.
	• In patients receiving MEC with a known potential for delayed emesis (e.g. oxaliplatin, doxorubicin, cyclophosphamide), the use of dexamethasone for days two to three can be considered.
	• No routine prophylaxis for delayed emesis can be recommended for all other patients receiving MEC.
	• To prevent carboplatin-induced acute nausea and vomiting, a combination of an NK1 receptor antagonist, dexamethasone, and a 5-HT_3 receptor antagonist is recommended. If patients receive fosaprepitant, netupitant, or rolapitant on day one, no antiemetic prophylaxis for delayed emesis is required. If patients receive aprepitant on day one, aprepitant on days two and three is recommended.

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	Prevention of nausea and vomiting induced by multiple-day cisplatin chemotherapy • Patients affected by metastatic germ cell tumors receiving multiple-day cisplatin should receive a 5-HT_3 receptor antagonist plus dexamethasone plus aprepitant for the prevention of acute nausea and vomiting and dexamethasone for delayed nausea and vomiting. Prevention of acute and delayed nausea and vomiting induced by chemotherapy with low and minimal emetogenic potential • A single antiemetic agent, such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, such as metoclopramide may be considered for prophylaxis in patients receiving chemotherapy of low emetic risk. • No antiemetic should be routinely administered before chemotherapy to patients without a history of nausea and vomiting receiving minimally emetogenic chemotherapy. • No antiemetic should be administered for prevention of delayed nausea and vomiting induced by low or minimally emetogenic chemotherapy. • If a patient experiences acute or delayed nausea or vomiting after low or minimally emetogenic chemotherapy, it is advised that, with subsequent chemotherapy treatments, the regimen for the next higher emetic level be given. Breakthrough chemotherapy-induced emesis and refractory emesis • Antiemetics are most effective when used prophylactically. Therefore, it is preferable to use maximally effective antiemetics as first-line therapy rather than withholding more effective antiemetics for later use at the time of antiemetic failure. • For the treatment of breakthrough nausea and vomiting, it is recommended to use an antiemetic with a different mechanism of action than that of the antiemetic(s) used for prophylaxis. The available evidence for breakthrough nausea and vomiting suggests the use of olanzapine 10 mg orally daily for three days. The mild to moderate sedation in this patient population, especially elderly patients, is a potential problem with olanzapine. Prevention of nausea and vomiting induced by high-dose chemotherapy • For patients receiving high-dose chemotherapy for stem cell transplant, a combination of a 5-HT_3 receptor antagonist with dexamethasone and aprepitant (125 mg orally on day one and 80 mg on days two to four) is recommended before chemotherapy. Prevention of radiotherapy-induced nausea and vomiting • High emetic risk: prophylaxis with a 5-HT_3 receptor antagonist and dexamethasone is recommended. • Moderate emetic risk: prophylaxis with 5-HT_3 receptor antagonist and dexamethasone (optional) is recommended. • Low emetic risk with cranium area of treatment: prophylaxis or rescue with dexamethasone is recommended. • Low emetic risk with head/neck, thorax, or pelvis as area of treatment: prophylaxis or rescue with dexamethasone, a dopamine receptor antagonist, or a 5-HT_3 receptor antagonist is recommended. • Minimal emetic risk: rescue with dexamethasone, dopamine receptor antagonist, or 5-HT_3 receptor antagonists. Prevention of acute chemotherapy-induced nausea and vomiting in children • In children receiving chemotherapy of high emetic risk, an antiemetic prophylaxis with a 5-HT_3 receptor antagonist (granisetron, ondansetron, tropisetron or palonosetron) plus dexamethasone plus aprepitant is

Clinical Guideline	Recommendation(s)
	recommended. • Children who cannot receive dexamethasone should receive a $5HT_3$ receptor antagonist plus aprepitant. • When aprepitant administration is not feasible or desirable, the guideline recommends a 5-HT_3 receptor antagonist plus dexamethasone be given to children receiving highly emetogenic chemotherapy. • Children receiving MEC should receive antiemetic prophylaxis with a 5-HT_3 receptor antagonist plus dexamethasone. Furthermore, children who cannot receive receptor antagonist should receive a 5-HT_3 receptor antagonist and aprepitant. • In children receiving chemotherapy of low emetogenicity, antiemetic prophylaxis with a 5-HT_3 receptor antagonist is recommended. • In children receiving chemotherapy of minimal emetogenicity, no antiemetic prophylaxis is recommended.
Society for Ambulatory Anesthesia: **Consensus Guidelines for the Management of Postoperative Nausea and Vomiting (2020)[12]**	Pediatric postoperative nausea and vomiting (PONV) management • Low risk prophylaxis: No treatment or 5-HT_3 receptor antagonist or dexamethasone. • Medium risk prophylaxis: 5-HT_3 receptor antagonist + dexamethasone. • High risk prophylaxis: 5-HT_3 receptor antagonist + dexamethasone + consider total intravenous anesthesia. • Rescue treatment: Use anti-emetic from different class than prophylactic drug-droperidol, promethazine, dimenhydrinate, metoclopramide; may also consider acupuncture/acupressure. Adult PONV management • One to two risk factors prophylaxis: Give two agents (5-HT_3 receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • More than two risk factors prophylaxis: Give three or four agents (5-HT_3 receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • Rescue treatment: Use anti-emetic from different class than prophylactic drug.
American Society of Clinical Oncology: **Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update (2020)[13]**	High-emetic-risk antineoplastic agents in adult patients • Adults treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of an NK_1 receptor antagonist, a serotonin (5-HT_3) receptor antagonist, dexamethasone, and olanzapine (day 1). Dexamethasone and olanzapine should be continued on days two to four. • Adults treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine (day 1). Olanzapine should be continued on days two to four. Moderate-emetic-risk antineoplastic agents in adult patients • Adults treated with carboplatin area under the curve (AUC) ≥ 4 mg/mL/min should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone (day 1). • Adults treated with moderate-emetic-risk antineoplastic agents (excluding carboplatin AUC ≥ 4 mg/mL/min) should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone (day 1). • Adults treated with cyclophosphamide, doxorubicin, oxaliplatin, and other moderate-emetic-risk antineoplastic agents known to cause delayed nausea and vomiting may be offered dexamethasone on days two to three. Low-emetic-risk antineoplastic agents in adult patients

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	• Adults treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT_3 receptor antagonist or a single 8-mg dose of dexamethasone before antineoplastic treatment. Minimal-emetic-risk antineoplastic agents in adult patients • Adults treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis. Antineoplastic combinations in adult patients • Adults treated with antineoplastic combinations should be offered antiemetics appropriate for the component antineoplastic agent of greatest emetic risk. Adjunctive drugs in adult patients • Lorazepam is a useful adjunct to antiemetic drugs but is not recommended as a single-agent antiemetic. Cannabinoids in adult patients • Evidence remains insufficient for a recommendation regarding medical marijuana for the *prevention* of nausea and vomiting in patients with cancer receiving chemotherapy or radiation therapy. Evidence is also insufficient for a recommendation regarding the use of medical marijuana in place of the tested and US Food and Drug Administration–approved cannabinoids dronabinol and nabilone for the *treatment* of nausea and vomiting caused by chemotherapy or radiation therapy. Complementary and alternative therapies in adult patients • Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture/acupressure, and other complementary or alternative therapies for the *prevention* of nausea and vomiting in patients with cancer. High-dose chemotherapy with stem-cell or bone marrow transplantation in adult patients • Adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. • A four-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine may be offered to adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation. Multiday antineoplastic therapy in adult patients • Adults treated with multiday antineoplastic agents should be offered antiemetics before treatment that are appropriate for the emetic risk of the antineoplastic agent given on each day of the antineoplastic treatment and for two days after completion of the antineoplastic regimen. • Adults treated with four- or five-day cisplatin regimens should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. Breakthrough nausea and vomiting in adult patients • For patients with breakthrough nausea or vomiting, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; and ascertain that the best regimen is being administered for the emetic risk. • Adults who experience nausea or vomiting despite optimal prophylaxis and who did not receive olanzapine prophylactically should be offered olanzapine in addition to continuing the standard antiemetic regimen.

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	• Adults who experience nausea or vomiting despite optimal prophylaxis and who have already received olanzapine may be offered a drug of a different class (e.g., an NK1 receptor antagonist, lorazepam or alprazolam, a dopamine receptor antagonist, dronabinol, or nabilone) in addition to continuing the standard antiemetic regimen. Anticipatory nausea and vomiting in adult patients • All patients should receive the most active antiemetic regimen appropriate for the antineoplastic agents being administered. Clinicians should use such regimens with initial antineoplastic treatment rather than assessing the patient's emetic response with less-effective antiemetic treatment. If a patient experiences anticipatory emesis, clinicians may offer behavioral therapy with systematic desensitization. High-emetic-risk radiation therapy in adult patients • Adults treated with high-emetic-risk radiation therapy should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone before each fraction and on the day after each fraction, if radiation therapy is not planned for that day. Moderate-emetic-risk radiation therapy in adult patients • Adults treated with moderate-emetic-risk radiation therapy should be offered a 5-HT_3 receptor antagonist before each fraction, with or without dexamethasone, before the first five fractions. Low-emetic-risk radiation therapy in adult patients • Adults treated with radiation therapy to the brain should be offered breakthrough dexamethasone therapy. Patients who are treated with radiation therapy to the head and neck, thorax, or pelvis should be offered breakthrough therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine-receptor antagonist. Minimal-emetic-risk radiation therapy in adult patients • Adults treated with minimal-emetic-risk radiation therapy should be offered breakthrough therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine-receptor antagonist. Concurrent radiation and antineoplastic agent therapy in adult patients • Adults treated with concurrent radiation and antineoplastic agents should receive antiemetic therapy appropriate for the emetic risk level of the antineoplastic agents, unless the risk level of the radiation therapy is higher. During periods when prophylactic antiemetic therapy for the antineoplastic agents has ended and ongoing radiation therapy would normally be managed with its own prophylactic therapy, patients should receive prophylactic therapy appropriate for the emetic risk of the radiation therapy until the next period of antineoplastic therapy, rather than receiving breakthrough therapy for the antineoplastic agents as needed. High-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with high-emetic-risk antineoplastic agents should be offered a three-drug combination of a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant or fosaprepitant. • Pediatric patients treated with high-emetic-risk antineoplastic agents who are unable to receive aprepitant or fosaprepitant should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. • Pediatric patients treated with high-emetic-risk antineoplastic agents who are

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	unable to receive dexamethasone should be offered a two-drug combination of palonosetron and aprepitant or fosaprepitant. Moderate-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with moderate-emetic-risk antineoplastic agents should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. • Pediatric patients treated with moderate-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of a 5-HT_3 receptor antagonist and aprepitant or fosaprepitant. Low-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with low-emetic-risk antineoplastic agents should be offered ondansetron or granisetron. Minimal-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis.
American College of Obstetricians and Gynecologists: **Practice Bulletin No. 189: Nausea and Vomiting of Pregnancy (2018)**[14]	General considerations • Treatment of nausea and vomiting of pregnancy with vitamin B6 (pyridoxine) alone or vitamin B6 plus doxylamine in combination is safe and effective and should be considered first-line pharmacotherapy. • The standard recommendation to take prenatal vitamins for one month before fertilization may reduce the incidence and severity of nausea and vomiting of pregnancy. • The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis, or hyperemesis gravidarum, or both, includes supportive therapy, and antithyroid drugs are not recommended. • Treatment of nausea and vomiting of pregnancy with ginger has shown some beneficial effects in reducing nausea symptoms and can be considered as a nonpharmacologic option. • Treatment of severe nausea and vomiting of pregnancy or hyperemesis gravidarum with methylprednisolone may be efficacious in refractory cases; however, the risk profile of methylprednisolone suggests it should be a last-resort treatment. • Early treatment of nausea and vomiting of pregnancy may be beneficial to prevent progression to hyperemesis gravidarum. • Intravenous hydration should be used for the patient who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present. Correction of ketosis and vitamin deficiency should be strongly considered. Dextrose and vitamins should be included in the therapy when prolonged vomiting is present, and thiamine should be administered before dextrose infusion to prevent Wernicke encephalopathy. • Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as the first-line treatment to provide nutritional support to the woman with hyperemesis gravidarum who is not responsive to medical therapy and cannot maintain her weight. • Peripherally inserted central catheters should not be used routinely in women with hyperemesis gravidarum given the significant complications associated with this intervention. Peripherally inserted central catheters should be utilized only as a last resort in the management of a woman with hyperemesis gravidarum because of the potential of severe maternal morbidity.
Society of Obstetricians and	General considerations • Women experiencing nausea and vomiting of pregnancy may discontinue iron-

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Gynaecologists of Canada: **Clinical Practice Guideline: Management of Nausea and Vomiting of Pregnancy (2016)**[15]	containing prenatal vitamins during the first trimester and substitute them with folic acid or adult or children's vitamins low in iron. • Women should be counselled to eat whatever pregnancy-safe food appeals to them and lifestyle changes should be liberally encouraged. • Ginger may be beneficial in ameliorating the symptoms of nausea and vomiting of pregnancy. • Acupressure may help some women in the management of nausea and vomiting of pregnancy. • Mindfulness-based cognitive therapy as an adjunct to pyridoxine therapy may be beneficial. • Pyridoxine monotherapy or doxylamine/pyridoxine combination therapy is recommended as first line in treating nausea and vomiting of pregnancy due to their efficacy and safety. • Women with high risk for nausea and vomiting of pregnancy may benefit from preemptive doxylamine/pyridoxine treatment at the onset of pregnancy. • H1 receptor antagonists should be considered in the management of acute or chronic episodes of nausea and vomiting of pregnancy. • Metoclopramide can be safely used as an adjuvant therapy for the management of nausea and vomiting of pregnancy. • Phenothiazines are safe and effective as an adjunctive therapy for severe nausea and vomiting of pregnancy. • Despite potential safety concerns of ondansetron use in pregnancy, ondansetron can be used as an adjunctive therapy for the management of severe nausea and vomiting of pregnancy when other antiemetic combinations have failed. • Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. • When nausea and vomiting of pregnancy is refractory to initial pharmacotherapy, investigation of other potential causes should be undertaken.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antihistamine antiemetics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Antihistamine Antiemetics[3]

Indication	Single Entity Agents				Combination Products
	Dimen-hydrinate	Meclizine	Prochlor-perazine	Trimetho-benzamide	Doxylamine Succinate and Pyridoxine
Nausea and Vomiting					
Control of severe nausea and vomiting			✔		
Management of vertigo associated with diseases affecting the vestibular system		✔			
Prevention and treatment of symptoms associated with motion sickness (nausea, vomiting, and dizziness)	✔	✔			
Treatment of nausea and vomiting in pregnancy in women who do not respond to conservative management					✔
Treatment of nausea associated with gastroenteritis				✔	
Treatment of postoperative nausea and vomiting				✔	
Miscellaneous					
Short-term treatment of generalized non-psychotic anxiety			✔ *		
Treatment of schizophrenia			✔		

*Prochlorperazine is not the first drug to be used in therapy for most patients with non-psychotic anxiety, because certain risks associated with its use are not shared by common alternative treatments (e.g., benzodiazepines).

IV. Pharmacokinetics

The pharmacokinetic parameters of the antihistamine antiemetics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antihistamine Antiemetics[4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Dimenhydrinate	100	0	Liver (extensive)	Renal	1 to 4
Meclizine	Not reported	Not reported	Liver	Renal Feces	5 to 6
Prochlorperazine	IV: 100 PO: 12.5 PR: Not reported	Not reported	Not reported	Not reported	6 to 9
Trimethobenzamide	IV: 100 PO: 100	Not reported	Not reported	Renal	7 to 9

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Combination Products					
Doxylamine succinate and pyridoxine	Not reported	High (percent not reported)	Liver	Renal	12.5*, 0.5†

IV=intravenous, PO=oral, PR=per rectum
*Half-life of doxylamine succinate=12.5 hours.
†Half-life of pyridoxine=0.5 hours.

V. Drug Interactions

Major drug interactions with the antihistamine antiemetics are listed in Table 5.

Table 5. Major Drug Interactions with the Antihistamine Antiemetics[4]

Generic Name(s)	Interaction	Mechanism
Meclizine	CNS Depressants	Concurrent use of meclizine and CNS depressants may result in an increase in CNS or respiratory depression.
Prochlorperazine	Antiarrhythmic agents	Concurrent use of prochlorperazine and antiarrhythmic agents may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Prochlorperazine	Anticholinergics	Anticholinergics likely antagonize phenothiazines by direct central nervous system pathways involving cholinergic mechanisms. The therapeutic effects of phenothiazines may be decreased by anticholinergics.
Prochlorperazine	Cisapride	Concomitant use of prochlorperazine and cisapride may result in additive prolongation of the QT interval.
Prochlorperazine	Dofetilide	Prochlorperazine may decrease renal elimination of dofetilide, elevating plasma concentrations, which may increase the risk of ventricular arrhythmias.
Prochlorperazine	Tricyclic antidepressants	Concurrent use of phenothiazines and tricyclic antidepressants may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Doxylamine succinate and pyridoxine	CNS depressants	Concurrent use of doxylamine and CNS depressants may result in increased risk of CNS depression.
Doxylamine succinate and pyridoxine	Monoamine oxidase inhibitors	Concurrent use of doxylamine and monoamine oxidase inhibitors may result in prolonged and intensified anticholinergic effects (e.g., severe dry mouth, constipation, decreased urination or sweating).

VI. Adverse Drug Events

The most common adverse drug events reported with the antihistamine antiemetics are listed in Table 6. The boxed warning for prochlorperazine is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Antihistamine Antiemetics[3-9]

Adverse Events	Single Entity Agents				Combination Products
	Dimen-hydrinate	Meclizine	Prochlor-perazine	Trimetho-benzamide	Doxylamine Succinate and Pyridoxine
Cardiovascular					
Cardiac arrest	-	-	✔	-	-
Hypertension	✔	-	-	-	-

Adverse Events	Single Entity Agents				Combination Products
	Dimen-hydrinate	Meclizine	Prochlor-perazine	Trimetho-benzamide	Doxylamine Succinate and Pyridoxine
Hypotension	-	<1	✔	✔	-
Peripheral edema	-	-	✔	-	-
Q-wave distortions	-	-	✔	-	-
T-wave distortions	✔	-	✔	-	-
Tachycardia	✔	✔	-	-	✔
Central Nervous System					
Agitation	-	-	✔	-	-
Catatonia	-	-	✔	-	-
Cerebral edema	-	-	✔	-	-
Confusion	✔	-	-	-	-
Coma	-	-	-	✔	-
Cough reflex suppressed	-	-	✔	-	-
Decreased libido	-	-	✔	-	-
Depression	-	<1	-	✔	-
Disorientation	-	-	-	✔	✔
Dizziness	1 to 10	1 to 10	✔	✔	✔
Drowsiness	>10	>10	✔	✔	-
Excitability	✔	✔	✔	-	-
Fatigue	1 to 10	1 to 10	-	-	✔
Hallucination	✔	-	-	-	-
Headache	1 to 10	1 to 10	✔	✔	✔
Hyperactivity	-	-	✔	-	-
Hyperpyrexia	-	-	✔	-	-
Impaired cognition	✔	-	-	-	-
Insomnia	✔	✔	✔	-	✔
Migraine	✔	-	-	-	✔
Nervousness	1 to 10	1 to 10	-	-	-
Neuroleptic malignant syndrome	-	-	✔	-	-
Paresthesia	-	<1	-	-	✔
Restlessness	✔	✔	✔	-	-
Sedation	-	<1	-	-	>10
Seizure	-	-	✔	✔	-
Tremor	-	<1	✔	-	-
Vertigo	✔	✔	-	-	✔
Dermatological					
Angioedema	-	<1	✔	-	-
Contact dermatitis	-	-	✔	-	-
Discoloration of skin	-	-	✔	-	-
Eczema	-	-	✔	-	-
Epithelial keratopathy	-	-	✔	-	-
Erythema	-	-	✔	-	-
Exfoliative dermatitis	-	-	✔	-	-
Itching	-	-	✔	-	-
Photosensitivity	✔	<1	✔	-	-
Porphyria cutanea tarda	✔	-	-	-	-
Rash	✔	<1	✔	-	✔
Sweating	-	-	✔	-	-
Urticaria	✔	-	✔	-	-
Endocrine and Metabolic					
Amenorrhea	-	-	✔	-	-
Breast enlargement	-	-	✔	-	-

Adverse Events	Single Entity Agents				Combination Products
	Dimen-hydrinate	Meclizine	Prochlor-perazine	Trimetho-benzamide	Doxylamine Succinate and Pyridoxine
Galactorrhea	-	-	✔	-	-
Gynecomastia	-	-	✔	-	-
Hyperglycemia	-	-	✔	-	-
Hypoglycemia	-	-	✔	-	-
Menstrual irregularity	-	-	✔	-	-
Syndrome of inappropriate antidiuretic hormone secretion	-	-	✔	-	-
Gastrointestinal					
Abdominal pain	1 to 10	1 to 10	-	-	✔
Anorexia	✔	-	-	-	-
Atonic colon	-	-	✔	-	-
Constipation	✔	-	✔	-	✔
Diarrhea	1 to 10	1 to 10	-	✔	✔
Dyspepsia	✔	-	-	-	-
Ileus	-	-	✔	-	-
Nausea	1 to 10	1 to 10	✔	-	-
Taste alteration	1 to 10	1 to 10	-	-	-
Vomiting	✔	-	-	-	-
Xerostomia	1 to 10	1 to 10	✔	-	-
Genitourinary					
Dysuria	✔	-	-	-	✔
Ejaculating dysfunction	-	-	✔	-	-
Glucosuria	-	-	✔	-	-
Impotence	-	-	✔	-	-
Incontinence	-	-	✔	-	-
Polyuria	-	-	✔	-	-
Porphyria	✔	-	-	-	-
Priapism	-	-	✔	-	-
Urinary retention	-	<1	✔	-	✔
Hematologic					
Agranulocytosis	-	-	✔	-	-
Aplastic anemia	-	-	✔	-	-
Blood dyscrasias	-	-	-	✔	-
Eosinophilia	-	-	✔	-	-
Hemolytic anemia	-	-	✔	-	-
Leukopenia	-	-	✔	-	-
Pancytopenia	-	-	✔	-	-
Thrombocytopenic purpura	-	-	✔	-	-
Hepatic					
Cholestatic jaundice	-	-	✔	✔	-
Hepatitis	-	<1	-	-	-
Hepatoxicity	-	-	✔	-	-
Musculoskeletal					
Arthralgia	1 to 10	-	-	-	-
Dystonias	-	-	✔	-	-
Muscle cramps	-	-	-	✔	-
Myalgia	-	<1	-	-	-
Respiratory					
Asthma	-	-	✔	-	-
Bronchospasm	-	<1	-	-	-
Laryngeal edema	-	-	✔	-	-

Adverse Events	Single Entity Agents				Combination Products
	Dimen-hydrinate	Meclizine	Prochlor-perazine	Trimetho-benzamide	Doxylamine Succinate and Pyridoxine
Nasal congestion	-	-	✔	-	-
Pharyngitis	-	1 to 10	-	-	-
Thickening of bronchial secretions	>10	>10	-	-	-
Other					
Blurred vision	✔	<1	✔	✔	✔
Epistaxis	-	<1	-	-	-
Extrapyramidal symptoms	-	-	✔	-	-
Fever	-	-	✔	-	-
Hypersensitivity reaction	-	-	-	✔	✔
Opisthotonos	-	-	✔	✔	-
Parkinson-like syndrome	-	-	✔	✔	-
Retinopathy	-	-	✔	-	-
Weight alteration	-	1 to 10	✔	-	-

✔ Percent not specified.
- Event not reported.

Table 7. Boxed Warning for Prochlorperazine[3,9]

WARNING
Increased Mortality in Elderly Patients With Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Prochlorperazine maleate is not approved for the treatment of patients with dementia-related psychosis.

VII. Dosing and Administration

The usual dosing regimens for the antihistamine antiemetics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Antihistamine Antiemetics[3-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Dimenhydrinate	Motion sickness: Injection: 50 mg every four hours; maximum, 100 mg every four hours	Motion sickness: Injection: 1.25 mg/kg or 37.5 mg/m^2 intramuscularly every six hours	Injection: 50 mg/mL
Meclizine	Motion sickness: Tablet: 25 to 50 mg one hour prior to travel; may repeat every 24 hours Vertigo: Tablet: 25 to 100 mg daily in	Motion sickness in children ≥12 years of age: Tablet: 25 to 50 mg one hour prior to travel; may repeat every 24 hours Vertigo in children ≥12 years	Chewable tablet: 25 mg Tablet: 12.5 mg 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	divided doses	of age: Tablet: 25 to 100 mg daily in divided doses	
Prochlorperazine	Nausea and vomiting: Injection: 2.5 to 10 mg intramuscularly as a single dose; maximum, 40 mg/day Rectal Suppository: 25 mg twice daily Tablet: 5 to 10 mg three to four times daily Non-psychotic anxiety: Tablet: 5 mg three to four times daily; maximum, 20 mg/day Schizophrenia: Injection: 10 to 20 mg intramuscularly as a single dose; may repeat initial dose every two to four hours Tablet: 5 to 10 mg three to four times daily; titrate slowly every two to three days; doses up to 150 mg/day may be required	Nausea and vomiting in children ≥2 years of age: Injection: 0.06 mg intramuscularly per pound of body weight Tablet: 20 to 29 pounds, 2.5 mg orally or rectally one to two times per day; maximum, 7.5 mg/day; 30 to 39 pounds, 2.5 mg orally or rectally two to three times per day; maximum, 10 mg/day; 40 to 85 pounds, 2.5 mg orally or rectally three times per day or 5 mg orally or rectally two times per day; maximum, 15 mg/day Schizophrenia in children ≥2 years of age: Injection: 0.06 mg intramuscularly per pound of body weight; switch to oral once patient is controlled Schizophrenia in children two to five years of age: Tablet: 2.5 mg two to three times per day; maximum, 20 mg Schizophrenia in children six to 12 years of age: Tablet: 2.5 mg two to three times per day; maximum, 25 mg	Injection: 5 mg/mL Rectal Suppository: 25 mg Tablet: 5 mg 10 mg
Trimethobenzamide	Nausea and vomiting: Capsule: 300 mg three to four times daily Injection: 200 mg intramuscularly three to four times daily	Safety and efficacy in children have not been established.	Capsule: 300 mg Injection: 100 mg/mL
Combination Products			
Doxylamine succinate and pyridoxine	Nausea and Vomiting in Pregnancy: Delayed-release tablet: 20-20 mg as a single dose at bedtime; maximum, 40-40 mg daily in divided doses Extended-release tablet: 20-20	Safety and efficacy in children have not been established.	Delayed-release tablet: 10-10 mg Extended-release tablet: 20-20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg at bedtime; maximum, 20-20 mg in the morning and 20-20 mg at bedtime		

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antihistamine antiemetics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Antihistamine Antiemetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Acute Migraine				
Friedman et al.[16] (2008) Prochlorperazine plus diphenhydramine (both IV) vs metoclopramide plus diphenhydramine (both IV)	AC, DB, RCT Adult patients presenting to ED with headache disorder	N=77 24 hours	Primary: Change in numeric rating scale score between baseline and one hour Secondary: Sustained pain-free period (two to 24 hours), sustained headache relief (two to 24 hours), sustained normal functioning, need for rescue medication	Primary: The mean change in numeric rating scale scores at one hour was 5.5 and 5.2 in patients receiving prochlorperazine and metoclopramide, respectively (difference, 0.3; 95% CI, –1.0 to 1.6). Secondary: The mean change in numeric rating scale scores at two hours were 6.4 and 5.9 in patients receiving prochlorperazine and metoclopramide, respectively (difference, 0.6; 95% CI, –0.6 to 1.8). At 24 hours, the mean change in numeric rating scale scores were 6.3 and 5.3 in patients receiving prochlorperazine and metoclopramide, respectively (difference, 1.0; 95% CI, –0.6 to 2.5). Sustained pain-free state achieved within two hours in the ED and maintained for 24 hours without need of additional medication was achieved in 17 and 11% of patients receiving prochlorperazine and metoclopramide, respectively (difference, 6; 95% CI, -10 to 22). Sustained headache relief (pain level of mild or none) was achieved and maintained for 24 hours in 65 and 47% of patients receiving prochlorperazine and metoclopramide, respectively (95% CI, -5 to 41). Sustained normal functioning (no functional impairment by ED discharge and no functional impairment reported for the 24-hour follow-up period) was achieved in 47 and 36% of patients receiving prochlorperazine and metoclopramide, respectively (difference, 11; 95% CI, -12 to 34). The percentage of patients who requested additional medication for pain within one hour of investigational medication administration was 9 and 17%, respectively for prochlorperazine and metoclopramide (difference, 8; 95% CI, -8 to 24).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Miller et al.[17] (2009) Prochlorperazine 10 mg IV vs octreotide 100 µg IV	DB, RCT Patients 18 to 65 years of age presenting to the ED with diagnostic criteria for migraine	N=44 60 minutes	Primary: Clinical success as (defined as achievement of patient satisfaction and at least 50% decrease in pain scores) Secondary: Change in pain scale, change in nausea scale, change in sedation scale, occurrence of adverse effects	Primary: Significantly more patients in the prochlorperazine group (90%) achieved treatment success than the octreotide group (57%; P<0.01). Secondary: Patients in the prochlorperazine group had larger changes in pain scores (-50.5 vs -33.3 mm; P=0.03) and sedation scores (19.7 vs -2.7 mm; P=0.03) than the octreotide group. Significantly more patients in the octreotide group required rescue therapy than in the prochlorperazine group (48 vs 10%; P<0.01). Significantly more patients in the prochlorperazine group experienced akathisia than the octreotide group (35 vs 9%; P<0.01).
Chemotherapy-Induced Nausea and Vomiting (CINV)				
Lane et al.[18] (1991) Dronabinol 10 mg every 6 hours (group 1) vs prochlorperazine 10 mg every 6 hours (group 2) vs dronabinol and prochlorperazine, each 10 mg every 6 hours (group 3)	DB, MC, PG, RCT Patients 18 to 69 years of age with cancer who were receiving chemotherapy	N=62 Treatment began 24 hours prior to initiation of chemotherapy and continued for 24 hours after the last dose of chemotherapy	Primary: Duration per episode of vomiting Secondary: Side effects	Primary: The median duration per episode of vomiting was one minute in group 3 vs two minutes in group 1 and 4 minutes in group 2 (P<0.001). Secondary: Side effects, primarily central nervous system, were more common in group 1 than in group 2 (P<0.01); addition of prochlorperazine to dronabinol appeared to decrease the frequency of dysphoric effects seen with the latter agent. The combination was significantly more effective than either single agent in controlling CINV (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Machado et al.[19] (2008) Dronabinol or nabilone vs placebo or prochlorperazine	MA Patients with cancer who were receiving chemotherapy	N=1,719 (18 trials) Variable duration	Primary: Anti-emetic efficacy and patient preference Secondary: Not reported	Primary: The anti-emetic efficacy of dronabinol was not significantly different than placebo (RR, 0.47; 95% CI, 0.19 to 1.16; P=0.10). The anti-emetic efficacy of dronabinol was significantly greater than prochlorperazine (RR, 0.67; 95% CI, 0.47 to 0.96; P=0.03). The anti-emetic efficacy of nabilone was not significantly different than prochlorperazine (RR, 0.88; 95% CI, 0.72 to 1.08; P=0.21). Patients preferred dronabinol or nabilone over prochlorperazine (RR, 0.33; 95% CI, 0.24 to 0.44; P<0.00001). Secondary: Not reported
Niiranen et al.[20] (1985) Nabilone 2 mg every 12 hours vs prochlorperazine 15 mg every 12 hours	DB, RCT, XO Lung cancer patients receiving chemotherapy with cisplatinum, vincristine, cyclophosphamide, adriamycin, vindesine, and etoposide	N=24 Two consecutive chemotherapy cycles	Primary: Reduction of vomiting episodes; adverse events; patient preference Secondary: Not reported	Primary: Nabilone was significantly more effective than prochlorperazine in the reduction of vomiting episodes. Adverse events (mainly vertigo) were seen in ~50% of nabilone-treated patients. Three patients were withdrawn from the study due to decreased coordination and hallucinations after nabilone. Adverse events were limited to mild drowsiness in one patient receiving prochlorperazine. Two-thirds of the patients preferred nabilone to prochlorperazine. Secondary: Not reported
Einhorn et al.[21] (1981) Nabilone vs	DB, PRO, RCT Patients receiving chemotherapy	N=80 Two consecutive chemotherapy cycles	Primary: Relief of nausea and vomiting; adverse events Secondary: Not reported	Primary: Sixty patients (75%) reported nabilone to be more effective than prochlorperazine for relief of nausea and vomiting. Forty-six patients required further chemotherapy and continued taking nabilone as the antiemetic of choice. Adverse events consisted of hypotension and lethargy, which were more

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prochlorperazine				pronounced with nabilone. Secondary: Not reported
Tramer et al.[22] (2001) Cannabinoids (dronabinol 13 trials, levonantradol 1 trial and nabilone 16 trials) vs conventional anti-emetics (alizapride 1 trial, chlorpromazine 2 trials, domperidone 2 trials, haloperidol 1 trial, metoclopramide 4 trials, prochlorperazine 12 trials and thiethylperazine 1 trial) or placebo (12 trials) (trials may have >1 treatment arm)	MA of RCT published between 1975 and 1997 (literature search of databases including Medline, Embase and Cochrane library to August 2000) Patients receiving chemotherapy	N=1,366 (30 trials [average trial size N=46]) 24 hours	Primary: Anti-emetic efficacy (absence of nausea or vomiting in the first 24 hours of chemotherapy) Secondary: Number of patients who expressed preference for cannabis for control for future chemotherapy cycles and adverse effects	Primary: Cannabinoids were more effective anti-emetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone or alizapride for complete control of nausea (RR, 1.38; 95% CI, 1.18 to 1.62; NNT, 6) and for complete control of vomiting (RR, 1.28; 95% CI, 1.08 to 1.51; NNT, 8). Cannabinoids were not more effective in patients receiving very low or very high emetogenic chemotherapy. Secondary: In XO trials, patients preferred cannabinoids for future chemotherapy cycles (RR, 2.39; 95% CI, 2.05 to 2.78; NNT, 3). Side effects that were considered “potentially beneficial” that were observed more frequently in patients receiving cannabinoids were a “high”, sedation, drowsiness and euphoria. Side effects that were considered harmful that were reported more often with cannabinoids were dizziness, dysphoria, depression, hallucinations, paranoia and arterial hypotension. Patients on given cannabinoids were more likely to withdraw due to side effects (RR, 4.67; 95% CI, 3.07 to 7.09; NNT, 11).
Lindley et al.[23] (2005) Prochlorperazine	MC, RCT Chemotherapy-naive patients	N=232 5 days	Primary: Number of vomiting episodes, average nausea	Primary: The treatment regimen for delayed CINV did not affect the percentage of patients reporting one or more vomiting episodes on days two through five (prochlorperazine, 24%; ondansetron, 22%; and dexamethasone, 21%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SR 15 mg BID vs dexamethasone 8 mg BID vs ondansetron 8 mg BID All patients received ondansetron 24 mg and dexamethasone 20 mg orally before chemotherapy.	scheduled to receive moderately high to highly emetogenic chemotherapy		score reported on days two through five Secondary: Not reported	P=0.86). The average severity of nausea during days two through five was lower in patients receiving prochlorperazine, whereas patients receiving ondansetron reported the highest severity of nausea, but this difference was not significant (P=0.055). Forty-seven of the 49 patients who reported one or more vomiting episodes also experienced some degree of nausea. Secondary: Not reported
Friedman et al.[24] (2000) Prochlorperazine SR 10 mg BID vs granisetron 1 mg BID All medications given one hour prior to and 12 hours after chemotherapy.	CS, DB, MC, PG Patients ≥18 years of age who were scheduled to receive their first cycle of moderately emetogenic chemotherapy	N=230 5 to 11 days	Primary: Proportion of patients with no emesis, no nausea, moderate or severe nausea and no antiemetic rescue at 48 hours Secondary: Safety and tolerability	Primary: Females and all patients combined who received granisetron had significantly higher no-emesis rates at 48 hours (P=0.010 for females and P=0.016 for all patients combined) than those receiving prochlorperazine. No-nausea rates at 48 hours were numerically higher for all patients who received granisetron rather than prochlorperazine (P=0.629). No-nausea rates at 48 hours were numerically higher for female patients in the granisetron group compared to the prochlorperazine group (P=0.501). No-nausea rates at 72 hours were similar between the granisetron group and the prochlorperazine group for all patients (P=0.057), but were significantly higher in female patients in the granisetron group compared to female patients in the prochlorperazine group (P=0.050). Response rates for no nausea or mild nausea were also numerically higher in females treated with granisetron compared to prochlorperazine at 48

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				hours, but this did not reach statistical significance (P=0.184). Significantly more patients (P<0.001) and females (P<0.001) in the granisetron group than in the prochlorperazine group did not require rescue antiemetics at 48 hours, but the use of rescue antiemetics was comparable at 72 hours. Secondary: Incidence of severe adverse effects was similar for granisetron and prochlorperazine (12.6 vs 13.5%).
Hickok et al.[25] (2005) Day one: Any 5-HT_3 receptor antagonist plus dexamethasone (or equivalent dose of methyl-prednisolone) Days two and three: prochlorperazine by mouth 10 mg every eight hours vs Day one: Any 5-HT_3 receptor antagonist plus dexamethasone (or equivalent dose of methyl-	OL, RCT Patients >18 years of age scheduled to receive their first treatment with a chemotherapy regimen containing doxorubicin and antiemetic prophylaxis with ondansetron, granisetron, or dolasetron plus dexamethasone or equivalent methyl-prednisolone	N=691 3 days	Primary: Mean severity of delayed nausea Secondary: Severity of acute nausea, frequency of acute and delayed nausea, frequency of acute and delayed vomiting, compliance	Primary: Delayed nausea was reported in 71% of patients treated with prochlorperazine every eight hours, 79% of patients treated with 5-HT_3 receptor antagonist and 82% of patients treated with prochlorperazine as needed. The groups did not differ significantly in the mean severity of delayed nausea. Patients treated with prochlorperazine every eight hours had less delayed nausea than patients treated with a 5-HT_3 receptor antagonist (P=0.05) and those treated with prochlorperazine as needed (P=0.009). Secondary: The severity of acute nausea did not differ between groups. The frequency of acute vomiting or delayed vomiting did not differ between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prednisolone) Day two and three: ondansetron 8 mg BID, granisetron 1 mg BID, dolasetron 100 mg QD or 50 mg BID vs Day one: Any 5-HT_3 receptor antagonist plus dexamethasone (or equivalent dose of methyl-prednisolone) Day two and three: prochlorperazine 10 mg as needed				
General Nausea and Vomiting				
Braude et al.[26] (2006) Prochlorperazine 10 mg vs droperidol 1.25 mg vs	DB, PRO, RCT Patients 18 to 65 years of age admitted to emergency department complaining of moderate to severe nausea of any etiology	N=97 24 hours	Primary: Reduction in visual analogue scale scores for nausea at 30 minutes Secondary: Change in visual analogue scale scores for sedation and anxiety, need for rescue	Primary: Droperidol was significantly better than metoclopramide or prochlorperazine at reducing nausea at 30 minutes (P=0.04). Secondary: No significant differences between groups at 30 minutes with respect to subjective anxiety (P=0.7), sedation (P=0.17), or the need for rescue medications (P=0.23) were noted. Droperidol had significantly higher akathisia (71.4 vs 23.5%) at 24-hour follow up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metoclopramide 10 mg vs placebo			antiemetic administration, adverse medication effects, patient satisfaction	No significant differences between groups with respect to patient satisfaction were reported (95% of all patients were satisfied). Metoclopramide and prochlorperazine were not more efficacious at 30 minutes compared to placebo.
Headache				
Callan et al.[27] (2008) Prochlorperazine 10 mg IV vs promethazine 25 mg IV	AC, DB, RCT Patients 18 to 65 years of age presenting to the ED with a benign headache (potentially undiagnosed migraine)	N=70 60 minutes	Primary: Difference in pain scores at 30 and 60 minutes Secondary: Rate of akathisia, need for rescue medication, nausea resolution in ED, recurrence of headache within five days, drowsiness within one day, and patient satisfaction	Primary: At 30 minutes, 69% of patients receiving prochlorperazine had a reduction in visual analogue scale >25 mm compared to 39% of patients in the promethazine group (P=0.006). At 60 min, 91% of patients in the prochlorperazine group and 47% of patients in the promethazine group had a visual analogue scale reduction >25 mm (P=0.133). Secondary: Headache recurrence, rates of akathisia, need for rescue medications in the ED, patient satisfaction, nausea resolution, and rates of agitation were all similar between the groups. The rate of drowsiness after discharge from the ED was greater in the promethazine group (P=0.002).
Infectious Gastroenteritis				
Uhlig et al.[28] (2009) Dimenhydrinate suppository 40 mg (weight-based dosing) vs placebo	DB, MC, PC, RCT Patients six months to six years of age with suspected infectious gastroenteritis, acute vomiting (≥2 episodes in 24 hours) and body weight >7 kg	N=237 24 hours	Primary: Relative weight gain from randomization to follow-up visit Secondary: Number of episodes of vomiting; number of diarrheal episodes; volume of fluid intake;	Primary: The mean relative gain of body weight was -0.14% in the dimenhydrinate group and 0.06% in the placebo group (P=0.452). Secondary: The mean number of episodes of vomiting between randomization and follow-up visit was 0.64 in the dimenhydrinate group and 1.36 in the placebo group (95% CI, -1.16 to -0.29). At the follow-up visit, 69.6% in the dimenhydrinate vs 47.4% in the placebo group were free of vomiting (P=0.001). The NNTs were two (95% CI, 1 to 4) to avoid one episode of vomiting and five (95% CI, 3 to 12) for complete cessation of vomiting. Additional use of the study medication was reported in 30.4% of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hospitalization as a result of gastroenteritis; well being of child (6-point smiley scale); adverse events	in the dimenhydrinate group and in 54.6% of the placebo group (P<0.001). The mean frequencies of diarrheal episodes were 1.75 and 1.74, respectively (P=0.720). The amount of fluid intake and the improvement of well-being of the child according to parents' assessment were similar in both groups. Sedation occurred in 21.6% children who received dimenhydrinate and in 18.6% children who received placebo. One (1%) child in each group had rash, and drowsiness was reported for one (1%) child in the dimenhydrinate group.
Motion Sickness				
Paul et al.[29] (2005) Dimenhydrinate 50 mg vs meclizine 50 mg vs promethazine 25 mg vs promethazine 25 mg plus dextro-amphetamine 10 mg vs	RCT Aircrew personnel 22 to 59 years of age	N=21 7 hours	Primary: Serial reaction time, logical reasoning time, serial subtraction time and multitask scores Secondary: Not reported	Primary: The serial reaction time was significantly impaired by dimenhydrinate (P<0.023), promethazine (P<0.000001), and meclizine (P<0.00001). The addition of dextroamphetamine to promethazine abolished the effect on serial reaction time (P<0.901), but the addition of pseudoephedrine to promethazine did not abolish effect on serial reaction time (P<0.00001). Impairment on logical reasoning time was significant for promethazine (P<0.000001) and meclizine (P<0.00004), but not significant for dimenhydrinate (P<0.516). The addition of dextroamphetamine to promethazine abolished the effect on logical reasoning time (P<0.77) but pseudoephedrine did not (P<0.007). Impairment on serial subtraction time was significant for promethazine (P<0.001) and meclizine (P<0.006). The addition of dextroamphetamine to promethazine abolished the effect on serial subtraction time (P<0.99), but the addition of pseudoephedrine did not (P<0.006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
promethazine 25 mg plus pseudoephedrine 60 mg vs placebo				Impairment on multitask was significant for promethazine (P<0.001) and meclizine (P<0.00002), but not significant for dimenhydrinate (P<0.20). The addition of dextroamphetamine to promethazine abolished the effect on multitask (P<0.25), but the addition of pseudoephedrine did not (P<0.0003). Recovery times to baseline sleepiness levels for promethazine, meclizine, dimenhydrinate, and promethazine plus pseudoephedrine were 7.25, >7.25, 6.25, and >7.25 hours, respectively. Secondary: Not reported
Spinks et al.[30] (2007) Scopolamine transdermal patch, tablet, capsule, oral solution or intravenous vs placebo, antihistamines (cinnarizine, dimenhydrinate, meclizine, promethazine) and other drugs (calcium channel antagonists, lorazepam, methscopolamine) vs	MA Patients with motion sickness	N=1,025 (14 trials) Duration varied	Primary: Prevention and treatment of clinically defined motion sickness Secondary: Task ability, psychological tests and adverse effects	Primary: Scopolamine was more effective than placebo in the prevention of motion sickness symptoms (RR, 0.47; 95% CI, 0.31 to 0.71). Scopolamine transdermal patch was more effective than methscopolamine in preventing motion sickness (RR, 0.33; 95% CI, 0.09 to 1.19). Compared to meclizine, scopolamine showed a greater decrease in mean motion sickness score (89%) than meclizine (59%) (P value not reported), and delayed the onset of symptoms for longer than meclizine (mean time and percentage increase from baseline, scopolamine 4.32 minutes [32.47%] vs meclizine 0.58 seconds [8.66%]; P value not reported). Scopolamine transdermal patch was equivalent to other antihistamines such as promethazine and dimenhydrinate in preventing motion sickness. Studies comparing the effectiveness of scopolamine with cinnarizine produced mixed results. When scopolamine alone or in combination with ephedrine was studied, the MA showed no statistically significant results, although; fewer participants treated with scopolamine alone reported symptoms (RR, 0.70; 95% CI, 0.39 to 1.26). Scopolamine was more effective at delaying the onset of motion sickness than lorazepam, which was found to hasten the onset of symptoms. The mean time and percentage change from baseline was 4.32 minutes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination of scopolamine with cyclizine, ephedrine or placebo				(32.47%) with scopolamine compared to –1.35 minutes [–1.65%] with lorazepam (P values not reported). Secondary: There was no marked difference in performance (task ability and psychological tests) between scopolamine and placebo (P values not reported). Scopolamine was no more likely to induce drowsiness (RR, 1.42; 95% CI, 0.79 to 2.56; P value not reported), dizziness (10 to 27% vs 0 to 26%; P value not reported) or blurring of vision (RR, 2.73; 95% CI, 0.89 to 8.37; P=0.08) than placebo. Scopolamine (35 to 50%) was associated with more reports of dry mouth than placebo (5%), dimenhydrinate (0%) and methscopolamine (10%). No studies were available relating to the therapeutic effectiveness of scopolamine in the management of established symptoms of motion sickness.
Dahl et al.[31] (1984) Scopolamine transdermal patch (0.5 mg) vs meclizine 25 mg tablet vs placebo	DB, DD, PC, RCT, XO Patients 20 to 39 years of age with no concomitant medication use that could influence trial outcome or recent travel by air or sea	N=36 Each subject went through 3 times with 70 hours between experiments	Primary: Self reported nausea score, mean motion sickness score, adverse reactions Secondary: Not reported	Primary: Mean motion sickness scores were highest during the placebo period and decreased with the use of scopolamine and meclizine. There was a significant difference between the scopolamine and placebo groups, the scopolamine and meclizine groups, but not the meclizine and placebo groups. However there was a statistical difference between meclizine and placebo for the last half of the trial period. The number of patients experiencing dry mouth was 21 for the scopolamine groups, eight for placebo, and six for meclizine. Secondary: Not reported
Nausea and Vomiting in Pregnancy				
Koren et al.[32] (2010) DIC-301	DB, MC, PC, RCT Pregnant women	N=298 15 days	Primary: Change from baseline to day-15	Primary: There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day-15 in the doxylamine succinate-pyridoxine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doxylamine succinate-pyridoxine hydrochloride, two tablets QHS, up to a maximum dose of four tablets per day vs placebo	≥18 years of age in the gestational age range of 7 to 14 weeks with nausea and vomiting in pregnancy and a PUQE score ≥6 and had not responded to conservative management consisting of dietary/lifestyle advice		in symptom and quality of life domain PUQE scores Secondary: Day-by-day area under the curve for change in PUQE from baseline, time loss from employment, number of women in each arm who continued with blinded compassionate use of their medication, number of patients who reported concurrent use of alternate therapy for nausea and vomiting in pregnancy, safety	hydrochloride group compared to 3.9 point decrease in the placebo group (P=0.006). There was a 2.8 point mean increase from baseline in quality of life domain PUQE score at day 15 in the doxylamine succinate-pyridoxine hydrochloride group compared to 1.8 point decrease in the placebo group (P=0.005). Secondary: The mean area under the curve of the change in PUQE from baseline as measured day-by-day was significantly larger in the doxylamine succinate-pyridoxine hydrochloride combination group compared (61.5) to placebo (53.5) with the difference being statistically significant (P<0.001). There was a trend toward more time lost from employment in the placebo group (2.37 days) compared to the doxylamine succinate-pyridoxine hydrochloride combination group compared (0.92); however, it should be noted that this difference was no statistically significant (P=0.06). At the end of the 15-day trial, 48.9% of patients in the doxylamine succinate-pyridoxine hydrochloride combination group compared to 32.8% in the placebo group requested to continue compassionate use of their medication (P=0.009). Significantly more women receiving placebo (36%), requested alternate therapies for nausea and vomiting in pregnancy compared to the doxylamine succinate-pyridoxine hydrochloride combination group (23.7%). The difference was statistically significant (P=0.04). For the doxylamine succinate-pyridoxine hydrochloride combination group and placebo group respectively the most common treatment emergent adverse events included somnolence (14.5 vs 2%; P=0.54), dry mouth (3.0 vs 0.8%; P=0.37), hypersensitivity (0.8 vs 0%; P>0.99), dizziness (6.0 vs 6.4%; P=0.94), headache (13.0 vs 16.0%; P=0.51), and loss of consciousness (0 vs 0.8%; P=0.49).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Persaud et al.[33] (2018) Doxylamine succinate-pyridoxine hydrochloride, two tablets QHS, up to a maximum dose of four tablets per day vs placebo	DIC-301 re-analysis Pregnant women ≥18 years of age in the gestational age range of 7 to 14 weeks with nausea and vomiting in pregnancy and a PUQE score ≥6 and had not responded to conservative management consisting of dietary/lifestyle advice	N=280	Primary: Change from baseline to day-15 in symptom and quality of life domain PUQE scores Secondary: Day-by-day area under the curve for change in PUQE from baseline, time loss from employment, number of women in each arm who continued with blinded compassionate use of their medication, number of patients who reported concurrent use of alternate therapy for nausea and vomiting in pregnancy, safety	Primary: Doxylamine-pyridoxine use led to a larger reduction in symptoms compared with placebo in the prespecified imputation using last observation carried forward analysis (P=0.006) but no significant difference using the prespecified complete data sensitivity analysis (P=0.107). Secondary: The results in this clinical study re-analysis showed that there were statistically significant differences based on a P=0.05 threshold for global well-being but not for the other ten secondary outcomes. There were four (3.0%) serious adverse events in the doxylamine-pyridoxine group and five (3.9%) in the placebo group. The same numbers are reported on the registration website.
Sullivan et al.[34] (1996) Ondansetron 10 mg IV for one dose (mandatory), then every eight hours as needed	RCT Patients with hyperemesis gravidarum during the first and early second trimesters of pregnancy that had	N=30 Single hospital admission	Primary: Length of hospitalization, treatment failures (defined as no change in nausea or emesis was observed after 48	Primary: On average, patients receiving ondansetron and promethazine remained in the hospital for 4.47 days each (P=1.00). There were two treatment failures in patients receiving ondansetron and three treatment failures in patients receiving promethazine (P=1.00). After the mandatory initial dose, the antiemetic medication usage was not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(optional) vs promethazine 50 mg IV for one dose (mandatory), then every eight hours as needed (optional)	not been previously treated by IV medication or hospitalization who required hospital admission		hours of medication and hydration), antiemetic usage, severity of nausea, weight gain, and adverse events Secondary: Not reported	different between patients receiving ondansetron and promethazine (2.1 vs 1.93 doses, respectively; P=0.71). There was a progressive decline in the severity of nausea, but there was no significant differences observed among the treatment groups. Daily weight gain was similar among the treatment groups. Eight patients receiving promethazine reported sedation compared to no patients in the ondansetron group (P=0.002). There were no other adverse events observed. Secondary: Not reported
Postoperative Nausea and Vomiting (PONV)				
Loewen et al.[35] (2000) 5-HT_3 antagonists vs traditional agents (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol)	MA Patients undergoing surgery who received an antiemetic agent	N=6,638 (41 trials) Variable duration	Primary: PONV that occurred within 48 hours after surgery Secondary: 5-HT3 receptor antagonists compared to traditional antiemetics for rates of vomiting	Primary: 5-HT_3 receptor antagonists showed a 46% reduction in the odds of PONV (OR, 0.54; 95% CI, 0.42 to 0.71; P<0.001). 5-HT_3 receptor antagonists showed a 39% reduction in PONV over droperidol (OR, 0.61; 95% CI, 0.42 to 0.89; P<0.001). 5-HT_3 receptor antagonists showed a 56% reduction in PONV over metoclopramide (OR, 0.44; 95% CI, 0.31 to 0.62; P<0.001). Secondary: 5-HT_3 receptor antagonists showed a 38% reduction in vomiting compared to traditional antiemetics (OR, 0.62; 95% CI, 0.48 to 0.81; P<0.001). 5-HT_3 antagonists showed a beneficial effect over droperidol in rate of vomiting (OR, 0.56; 95% CI, 0.41 to 0.76; P<0.001). 5-HT_3 antagonists showed a beneficial effect over metoclopramide in rate of vomiting (OR, 0.50; 95% CI, 0.32 to 0.77; P<0.001). Sedation was more common in the traditional group (11.9%) compared to 5-HT_3 receptor antagonists (5.6%; (OR, 0.7; 95% CI, 0.32 to 0.64;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P<0.001). Headache was more common in the 5-HT_3 receptor antagonist group (17.0%) than in the traditional antiemetic group (13.0%; (OR, 1.65; 95% CI, 1.35 to 2.02; P<0.001).
Turner et al.[36] (2004) Dimenhydrinate LA capsule vs droperidol IV vs dimenhydrinate LA capsule and droperidol 0.625 mg IV	DB, RCT Women 27 to 40 years of age scheduled for elective outpatient gynecologic laparoscopic surgery	N=141 Until lunchtime the day after discharge	Primary: Complete treatment therapy defined as the administration of rescue medication in post-anesthesia care unit or nausea, vomiting, or retching at any time during the study Secondary: Treatment failure vomiting defined as the administration of rescue medication in post-anesthesia care unit or vomiting or retching at any time point during the study	Primary: The incidence of complete treatment therapy was not significantly different among the three treatment groups. Secondary: The incidence of treatment failure vomiting was significantly less in the combination group vs droperidol (P=0.007). The treatment failure vomiting in patients receiving dimenhydrinate alone was less than with droperidol (35 vs 25%), but was not statistically significant.
Eberhart et al.[37] (2000) Dimenhydrinate 1 mg/kg vs	DB, RCT Men undergoing endonasal surgery (e.g., septoplasty, rhinoplasty, septorhinoplasty)	N=160 24 hours	Primary: Number of men free from nausea and vomiting; severity of PONV during the 24 hour observation interval; episodes	Primary: Incidence of patients free from PONV was 62.5% in the placebo group and increased to 72.5% in the metoclopramide group (P=0.54), 75.0% in the dimenhydrinate group (P=0.34), and 85.0% in the combination group (P=0.025). In the latter group, the severity of PONV was reduced compared to placebo treatment (P=0.017).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metoclopramide 0.3 mg/kg vs dimenhydrinate 1 mg/kg plus metoclopramide 0.3 mg/kg vs placebo Administered after induction of anesthesia and six hours later.			of vomiting, retching, nausea; need for additional antiemetics Secondary: Side effects	Secondary: The incidence of side effects was the same in all four groups.
Kothari et al.[38] (2000) Dimenhydrinate 50 mg IV vs ondansetron 4 mg IV All medications administered before induction of anesthesia.	DB, PRO, RCT Patients undergoing laparoscopic cholecystectomy	N=128 24 hours after discharge	Primary: Frequency of PONV, need for rescue antiemetics, need for overnight hospitalization secondary to persistent nausea and vomiting, frequency PONV 24 hours after discharge Secondary: Not reported	Primary: Need for rescue medication occurred in 34% of ondansetron group and 29% of dimenhydrinate group (P=0.376). Postoperative vomiting occurred in 6% of ondansetron group and 12% of dimenhydrinate group (P=0.228). Postoperative nausea and vomiting occurred in 42% of ondansetron group and 34% of dimenhydrinate group (P=0.422). One patient in the ondansetron group and two patients in the dimenhydrinate group required overnight hospitalization for persistent nausea and vomiting (P=NS). Rates of postoperative nausea and vomiting 24 hours after discharge were similar between the ondansetron and dimenhydrinate groups (10 and 14%; P=0.397 and 2 and 5%; P=0.375, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
McCall et al.[39] (1999) Dimenhydrinate 0.5 mg/kg vs ondansetron 0.1 mg/kg vs placebo Study drugs were given at the end of surgery and again four hours later	DB, PC, PRO, RCT Patients undergoing reconstructive burn surgery with general anesthesia	N=100 8 hours	Primary: Incidence of PONV, POV Secondary: Not reported	Primary: Statistically significant reductions in the incidence of PONV in the patients who received ondansetron or dimenhydrinate were found, as compared to the results of patients who received placebo. The incidence of POV was reduced from 61% in the placebo group to 29% and 40% in the ondansetron and dimenhydrinate groups, respectively, and PONV was similarly reduced from 69% to 47% and 40%, respectively. The differences between ondansetron and dimenhydrinate were not statistically significant. Secondary: Not reported
Hamid et al.[40] (1998) Dimenhydrinate 0.5 mg/kg vs ondansetron 0.1 mg/kg IV vs placebo All given at induction of	DB, PC, PRO, RCT Children 2 to 10 years of age scheduled for adenotonsillectomy	N=47 24 hours	Primary: Incidence of retching and vomiting observed first 24 hours post surgery Secondary: Not reported	Primary: The incidence of POV during the first 24 hours after surgery in the ondansetron group (42%) was significantly less than in the dimenhydrinate (79%; P<0.02) and placebo (82%; P<0.01) groups. The number of episodes of POV in the first 24 hours differed significantly between the ondansetron and placebo groups only. The number of children whose discharges from hospital were delayed secondary to POV in the ondansetron group (0 of 25) was significantly less than in the placebo group (4 of 22; P<0.04). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
anesthesia				
Bopp et al.[41] (2010) Meclizine 50 mg the night before surgery and 30 to 45 minutes prior to surgery vs placebo	DB, PG, RCT Patients ≥18 years of age undergoing elective surgery with general anesthesia and who had ≥3 risk factors for PONV	N=70 24 hours	Primary: PONV incidence, severity, and treatment; time in the surgical ward; anesthesia satisfaction scores; analgesic requirements Secondary: Not reported	Primary: The incidence of PONV was higher in the placebo group (both in Same Day Surgery Unit and at home after discharge; P<0.05). Time to first complaint of PONV was longer in meclizine group at all time points (in post-anesthesia care unit, same-day surgical unit, and home; P<0.05). There was no significant difference in the time to the second or third complaint of PONV. The two antiemetic agents used to treat PONV were ondansetron and promethazine. Ondansetron was administered in only 7% of the meclizine group compared to 37% in the placebo group (P<0.05). Promethazine was used in 18% of the meclizine group compared to 44% of the placebo group (P<0.05). The total time in the post-anesthesia care unit and same-day surgical unit was similar between groups. The post-anesthesia care unit time requirement was 50.9 minutes in the meclizine group compared to 54.8 minutes in the placebo group (P=0.535). In the same-day surgical unit, an average of 226.9 minutes was required before discharge in the placebo group compared to 167.8 minutes in the meclizine group (P=0.269). Overall anesthesia satisfaction scores were significantly higher in the meclizine group compared to the placebo group; 85% of the meclizine group reported a score of five (completely satisfied) compared to only 54% of the placebo group (P=0.004). No difference in analgesic requirements in any setting was noted between groups. Secondary: Not reported
Layeeque et al.[42] (2006) Dronabinol 5 mg	RETRO Patients undergoing surgery	N=242 Variable duration	Primary: Rate and severity of PONV	Primary: The rate of nausea (59 vs 15%; P<0.001) and vomiting (29 vs 3%; P<0.001) were significantly better in the patients treated prophylactically with dronabinol and prochlorperazine compared to those receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
as prophylaxis and prochlorperazine 25 mg rectal suppository after anesthesia vs standard preoperative care (which excludes prophylactic use of antiemetics)			Secondary: Not reported	standard preoperative care. Secondary: Not reported
Jamil et al.[43] (2005) Prochlorperazine 0.1 to 0.2 mg/kg IM vs metoclopramide 0.1 to 0.2 mg/kg IV vs placebo All treatments were injected 10 minutes before the induction of general anesthesia.	PC, RCT Adults undergoing tonsillectomy	N=150 4 hours from the end of the surgical procedure	Primary: Episodes of nausea, retching, and vomiting, adverse events, vital signs, the need for rescue antiemetic drug (metoclopramide 0.1 to 0.2 mg/kg IV) Secondary: Not reported	Primary: Overall frequencies of PONV were 18, 16, and 24% in the metoclopramide, prochlorperazine and placebo groups, respectively. Rescue antiemetics were needed in 8, 2, and 12% in the metoclopramide, prochlorperazine, and placebo groups, respectively. These differences did not reach statistical significance (P>0.05). During the study period 82, 84 and 76% of patients in the metoclopramide, prochlorperazine and placebo groups, respectively, were found free from PONV. No adverse events related to either of the test medications were noted in any patient. Secondary: Not reported
Chen et al.[44] (1998)	DB, RCT	N=78	Primary: Incidence and	Primary: The incidence of nausea was significantly greater in the ondansetron group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prochlorperazine maleate 10 mg IM vs ondansetron 4 mg IV All administered at end of surgical procedure.	Patients ≥18 years of age undergoing elective, primary or revisionary total hip or total knee replacement procedures	48 hours post-operatively	severity of PONV Secondary: Number of rescue antiemetic doses required, number of physical therapy cancellations because of PONV, length of hospital stay	compared to the prochlorperazine group (P=0.02), as was the severity of nausea (P=0.04). The incidence (P=0.13) and severity (P=0.51) of vomiting were similar between the two groups. Secondary: The need for rescue antiemetic therapy was greater in the ondansetron group compared to the prochlorperazine group, but the difference was not statistically significant (P=0.08). The mean number of rescue antiemetic doses required was 2.1 in the ondansetron group and 1.7 in the prochlorperazine group, but the difference did not reach statistical difference (P=0.50).
Van den Berg et al.[45] (1996) Prochlorperazine 0.2 mg/kg IM vs ondansetron 0.06 mg/kg IV vs prochlorperazine 0.2 mg/kg IV vs placebo All given with induction of	DB, PRO, RCT Patients 9 to 61 years of age who received standardized general anesthesia for tympanoplasty	N=148 24 hours	Primary: Incidence of retching and vomiting in the post-anesthesia care unit, during first 24 hours post surgery Secondary: Postoperative headache	Primary: Nausea alone during the first 24-hour postoperative period was infrequent in each treatment group with a similar incidence (3 to 8%). The incidence of vomiting alone (without accompanied nausea) during this time was also similar between groups (11 to 24%). The incidence of vomiting or retching immediately after extubation or during recovery occurred in 16% of placebo patients, 5% of patients in the IM prochlorperazine group, and 8% in the prochlorperazine and ondansetron IV groups, but the differences between groups was not significant (P>0.05 for all groups). The incidence of nausea accompanied by vomiting occurred in 53% of the placebo group and 16 and 19% in those given prochlorperazine IM and ondansetron IV, respectively (P<0.0005), and 30% in those given prochlorperazine IV (P<0.05). The study was not powered to detect a difference between groups. The percent of patients who experienced no nausea or vomiting was 27% for placebo, 57% for prochlorperazine IM, 43% for prochlorperazine IV, and 62% for ondansetron IV. Only the prochlorperazine IM and ondansetron IV groups achieved significance compared to placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
anesthesia				(P<0.01 and P=0.005, respectively). Secondary: Incidence of headache reported in the first 24 hours after surgery (placebo 56%, prochlorperazine IM 41%, prochlorperazine IV 43% and ondansetron IV 49%) was similar in the four groups.
Vertigo				
Schmitt et al.[46] (1986) Meclizine by mouth for one week vs scopolamine TD for one week vs placebo	DB, RCT, XO Healthy subjects	N=12 7 days	Primary: Effect on vertigo symptoms Secondary: Side effects	Primary: Vertigo symptoms on day one of treatment were significantly less with transdermal scopolamine than oral meclizine or placebo and on day seven were significantly less with both scopolamine and meclizine compared to placebo. On day one, meclizine did not reduce vertigo symptoms significantly when compared to placebo. Secondary: Drowsiness was greater with use of oral meclizine than transdermal scopolamine.
Shih et al.[47] (2017) Meclizine 25 mg vs diazepam 5 mg	DB, RCT Patients with peripheral vertigo in the emergency department	N=40 60 minutes	Primary: Mean change in visual analog scale score from 0 to 60 minutes Secondary: Not reported	Primary: The mean baseline score was 55 mm for the diazepam group and 62 mm for the meclizine group (−6.7; 95% CI −18.2 to 4.8; P=0.24). Both agents were associated with rapid significant improvement (P<0.001) in vertigo scores (t0 to t60 visual analog scale scores). However, no significant differences were seen when comparing mean decrease in visual analog scale between diazepam versus meclizine at any time points. At 60 minutes, the mean improvement in the diazepam and meclizine groups were 36 mm and 40 mm, respectively (difference, −4; 95% CI, −20 to 12; P=0.60). Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, LA=long-acting, QD=once daily, QHS=at bedtime, SR=sustained release, TD=transdermal

Study abbreviations: AC=active-controlled, CI=confidence interval, CS=controlled study, DB=double-blind, MC=multicenter, NNT=number needed to treat, NS=not significant, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: CINV=chemotherapy induced nausea and vomiting, ED=emergency department, PONV=postoperative nausea and vomiting, PUQE=pregnancy-unique quantification of emesis

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Chen et al. evaluated the efficacy and safety of antiemetics on hospital stays and cancellations of physical therapy visits in patients undergoing total hip or total knee replacement surgeries.[44] Patients were randomized to receive ondansetron 4 mg intravenously or prochlorperazine 10 mg intramuscularly in the operating room after the completion of surgery. They were permitted the same medication on a rescue basis every 4 hours for 48 hours if vomiting occurred or if the medication was requested by the patient. Results showed that the length of hospital stay was similar between both groups and averaged 5.1 days for ondansetron treated patients and 4.9 days for the prochlorperazine treated patients (P=0.50). The proportion of patients who canceled a physical therapy appointment due to nausea and vomiting was also similar in both groups, occurring in 11% of ondansetron treated patients and 7% of prochlorperazine treated patients (P=0.70).

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 10. Relative Cost of the Antihistamine Antiemetics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Dimenhydrinate	injection	N/A	N/A	$$$$$
Meclizine	chewable tablet, tablet	Antivert®	N/A	$
Prochlorperazine	injection, rectal suppository, tablet	N/A	N/A	$
Trimethobenzamide	capsule, injection	Tigan®*	$$$$-$$$$$	$$
Combination Products				
Doxylamine succinate and pyridoxine	delayed-release tablet, extended-release tablet	Bonjesta®, Diclegis®*	$$$$$	$$$$

*Generic is available in at least one dosage form or strength.

N/A=Not available

X. Conclusions

The antihistamine antiemetics are approved for the treatment of postoperative nausea and vomiting, general nausea and vomiting, motion sickness, and vertigo.[3-9] The combination product of doxylamine succinate and pyridoxine is approved for nausea and vomiting associated with pregnancy.[7,8] Prochlorperazine is also approved for the treatment of schizophrenia, as well as for the short-term treatment of generalized non-psychotic anxiety.[3,4,9] All of the products are available in a generic formulation.

The antihistamine antiemetics are effective for the treatment of nausea and vomiting associated with motion sickness, vertigo, and other related disorders.[10-15] They may also be considered in the management of acute or breakthrough episodes of nausea and vomiting of pregnancy.[14-15] For nausea and vomiting associated with chemotherapy and radiation, the selection of therapy depends on the relative emetogenic potential of the regimen.[10,13] Prochlorperazine is recommended as one of several options to treat acute nausea and vomiting induced by low or minimal emetogenic chemotherapy.[10] There are limited studies directly comparing the efficacy and safety of the antihistamine antiemetics.

There is insufficient evidence to support that one brand antihistamine antiemetic is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand antihistamine antiemetics within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand antihistamine antiemetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, 5-HT$_3$ Receptor Antagonists
AHFS Class 562220
November 9, 2022

I. Overview

The pathophysiology of nausea and vomiting is complex and involves multiple neurotransmitters and organ systems. Five neurotransmitter receptor sites play a key role in the vomiting reflex. These receptor sites include M1 (muscarinic), D2 (dopamine), H1 (histamine), 5-HT$_3$ (serotonin), and NK$_1$ (substance P).[1] The available antiemetic drugs antagonize these receptors, leading to improvements in nausea and vomiting. Nausea and vomiting due to central or vestibular disorders respond well to anticholinergic agents and histamine H$_1$-receptor antagonists. However, nausea and vomiting due to cancer chemotherapy, radiation, and surgery tend to respond better to 5-HT$_3$ receptor antagonists and the NK$_1$ antagonists.[2]

The 5-HT$_3$ receptor antagonists are approved for the prevention and treatment of chemotherapy-induced nausea and vomiting, postoperative nausea and vomiting, and radiation-induced nausea and vomiting.[3-8] They block the 5-HT$_3$ receptors in the gastric area and the chemoreceptor trigger zone located in the central nervous system. This disrupts the signal to vomit and reduces the sensation of nausea.[8-11]

The 5-HT$_3$ receptor antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents are available in a generic formulation, with the exception of dolasetron. This class was last reviewed in August 2020.

Table 1. 5-HT$_3$ Receptor Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dolasetron	tablet	Anzemet®	none
Granisetron	extended-release injection, injection*, tablet*, transdermal patch	Kytril®*, Sancuso®, Sustol®	granisetron
Ondansetron	injection*, orally disintegrating tablet*, solution*, tablet*	N/A	ondansetron
Palonosetron	injection*	N/A	palonosetron

*Generic is available in at least one dosage form or strength.
ODT=orally disintegrating tablet, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the 5-HT$_3$ receptor antagonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the 5-HT$_3$ Receptor Antagonists

Clinical Guideline	Recommendation(s)
National Comprehensive Cancer Network: **Clinical Practice Guidelines in Oncology: Antiemesis (2022)**[12]	Principles of emesis control for the cancer patient: • Prevention of nausea/vomiting is the goal. The risk of nausea/vomiting (acute ≤24 hours vs delayed >24 hours) for persons receiving anticancer agents of high and moderate emetic risk lasts for at least three days for high and two days for moderate after the last dose of anticancer agents. Patients need to be protected throughout the full period of risk. • Oral and parenteral serotonin receptor antagonists (5-hT$_3$ RAs) have equivalent efficacy when used at the appropriate doses and intervals. • Consider the toxicity of the specific antiemetic(s). • Choice of antiemetic(s) used should be based on the emetic risk of the therapy, prior experience with antiemetics, and patient factors. Continuous infusion may

Clinical Guideline	Recommendation(s)

	make an agent less emetogenic. The emetic risk is expected to be the same for biosimilars as for the parent compound unless otherwise noted.
	• Patient risk factors for anticancer agent-induced nausea/vomiting include:
	  ○ Younger age
	  ○ Female sex
	  ○ Previous history of anticancer agent-induced nausea/vomiting
	  ○ Little or no previous alcohol use
	  ○ Prone to motion sickness
	  ○ History of morning sickness during pregnancy
	  ○ Anxiety/high pretreatment expectation of nausea
	• There are other potential causes of emesis in patients with cancer (e.g., bowel obstruction, vestibular dysfunction, brain metastases, electrolyte imbalance, uremia, concomitant drugs, gastroparesis, cannabinoid hyperemesis syndrome, pancreatitis).
	
	For high emetic risk parenteral chemotherapy the following is recommended:
	• Preferred: combination of olanzapine, a neurokinin-1 receptor antagonist (NK1 RA), a 5-HT$_3$ RA, and dexamethasone.
	OR
	• Combination of olanzapine, palonosetron, and dexamethasone.
	OR
	• Combination of a NK1 RA, a 5-HT$_3$ RA, and dexamethasone.
	• The regimen and doses for each therapy are modified on days two to four after chemotherapy.
	
	For moderate emetic risk parenteral chemotherapy the following is recommended:
	• Combination of dexamethasone and a 5-HT$_3$ RA (palonosetron IV and granisetron SQ preferred).
	OR
	• Combination of olanzapine, palonosetron, and dexamethasone.
	OR
	• Combination of a NK1 RA, a 5-HT$_3$ RA, and dexamethasone.
	• The regimen and doses for each therapy are modified on days two and three after chemotherapy.
	
	For low emetic risk parenteral chemotherapy the following is recommended:
	• Dexamethasone; **OR**
	• Metoclopramide; **OR**
	• Prochlorperazine; **OR**
	• Dolasetron, granisetron or ondansetron (oral formulations).
	• Lorazepam PRN and H$_2$ blocker or PPI may be given with any regimen.
	
	For minimal emetic risk parenteral chemotherapy the following is recommended:
	• No routine prophylaxis
	
	For oral chemotherapy with moderate to high emetic risk the following is recommended:
	• A 5-HT$_3$ antagonist (dolasetron, granisetron, or ondansetron oral).
	• Lorazepam may be given.
	• An H$_2$ receptor blocker or PPI may be given.
	
	For oral chemotherapy with low to minimal emetic risk the following is recommended:
	• Metoclopramide PRN; **OR**
	• Prochlorperazine PRN (maximum 40 mg/day); **OR**
	• Dolasetron, granisetron or ondansetron.

Clinical Guideline	Recommendation(s)
	• Lorazepam PRN and H_2 blocker or PPI may be given with any regimen. Principles for managing multiday emetogenic chemotherapy regimens • Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea/vomiting based on their chemotherapy regimen. It is therefore difficult to recommend a specific antiemetic regimen for each day, especially since acute and delayed emesis may overlap after the initial day of chemotherapy until the last day. • After chemotherapy administration concludes, the period of risk for delayed emesis also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen. • Practical issues also need to be considered when designing the antiemetic regimen, taking into consideration the administration setting, preferred route of administration, duration of action of the 5-HT$_3$ receptor agonist and associated dosing intervals, tolerability of daily antiemetics (e.g., steroids), compliance issues, and individual risk factors. • Steroids: o Dexamethasone should be administered once daily (either orally or intravenously [IV]) for moderately or highly emetogenic chemotherapy and for two to three days after chemotherapy for regimens likely to cause delayed emesis. o Dexamethasone dose may be modified or omitted when the chemotherapy regimen already includes a corticosteroid. • Serotonin antagonists: o A serotonin antagonist should be administered prior to the first (and subsequent) doses of moderately or highly emetogenic chemotherapy. o The frequency or need for repeated administration depends on the agent chosen and its mode of administration (IV, oral, or transdermal). o When palonosetron or granisetron extended-release injection is used as part of an antiemetic regimen that does NOT contain an NK1 antagonist, palonosetron or granisetron extended-release injection are the preferred 5-HT$_3$ receptor antagonists. • NK1 receptor antagonists: o NK1 antagonists may be used for multiday chemotherapy regimens likely to be moderately or highly emetogenic associated with significant risk for delayed nausea and emesis. Principles for managing breakthrough emesis • The general principle of treatment for breakthrough nausea and vomiting is to add one agent from a different drug class to the current regimen. • No one drug class has been shown to be superior for the management of breakthrough emesis. • Consider around-the-clock administration rather than PRN. • The oral route is not likely to be feasible due to vomiting, therefore rectal or IV therapy is often required. • Ensure adequate hydration.
European Society of Medical Oncology/ Multinational Association of Supportive Care in Cancer: **Consensus Guidelines for the Prevention of Chemotherapy and**	Prevention of acute and delayed nausea and vomiting induced by highly emetogenic chemotherapy • For the prevention of cisplatin-containing highly emetogenic chemotherapy, a three-drug regimen including single doses of a 5-HT$_3$ receptor antagonist, dexamethasone, and an NK1 receptor antagonist (aprepitant, fosaprepitant, netupitant, or rolapitant), given before chemotherapy is recommended. • In patients receiving cisplatin-containing highly emetogenic chemotherapy treated with a combination of an NK1 receptor antagonist, a 5-HT$_3$ receptor antagonist and dexamethasone to prevent acute nausea and vomiting, dexamethasone on days two to four is suggested to prevent delayed nausea and vomiting.

Clinical Guideline	Recommendation(s)
Radiotherapy-Induced Nausea and Vomiting (2016)[13]	• In women with breast cancer receiving anthracycline/cyclophosphamide (AC) chemotherapy, a three-drug regimen including single doses of a 5-HT$_3$ receptor antagonist, dexamethasone, and an NK1 receptor antagonist (aprepitant, fosaprepitant, netupitant, or rolapitant), given before chemotherapy is recommended. • In women with breast cancer treated with a combination of a 5-HT$_3$ receptor antagonist, dexamethasone and an NK1 receptor antagonist to prevent acute nausea and vomiting, aprepitant or dexamethasone should be used on days two and three but not if fosaprepitant, netupitant, or rolapitant has been used on day one. If an NK1 receptor antagonist is not available for the prophylaxis of nausea and vomiting induced by AC chemotherapy, palonosetron is the preferred 5-HT$_3$ receptor antagonist. • For regimens including mechlorethamine, streptozocin, cyclophosphamide ≥1500 mg/m^2, carmustine, and dacarbazine, adding an NK1 receptor antagonist to the combination of a 5-HT$_3$ receptor antagonist and dexamethasone for all non-cisplatin and non-AC highly emetogenic chemotherapy is recommended. • Differences among the NK1 antagonists: o Aprepitant and netupitant are inhibitors of CYP3A4 and as a consequence, both significantly increase the exposure to oral dexamethasone; hence, reduction in oral dexamethasone doses is recommended during co-administration (from 20 to 12 mg). o Rolapitant is not an inhibitor or inducer of CYP3A4 and therefore does not require a reduced dose of dexamethasone when co-administered. However, rolapitant is a moderate inhibitor of CYP2D6. o At present, no comparative studies have been carried out to identify differences in efficacy and toxicity between the three NK1 receptor antagonists. <u>Prevention of acute and delayed nausea and vomiting induced by moderately emetogenic chemotherapy (MEC)</u> • For the prevention of acute emesis in MEC-treated patients, a 5-HT$_3$ receptor antagonist plus dexamethasone is recommended. • There is no definitive evidence demonstrating an advantage of the use of palonosetron with respect to the other 5-HT$_3$ receptor antagonists, when both are combined with dexamethasone. • In patients receiving MEC with a known potential for delayed emesis (e.g. oxaliplatin, doxorubicin, cyclophosphamide), the use of dexamethasone for days two to three can be considered. • No routine prophylaxis for delayed emesis can be recommended for all other patients receiving MEC. • To prevent carboplatin-induced acute nausea and vomiting, a combination of an NK1 receptor antagonist, dexamethasone, and a 5-HT$_3$ receptor antagonist is recommended. If patients receive fosaprepitant, netupitant, or rolapitant on day one, no antiemetic prophylaxis for delayed emesis is required. If patients receive aprepitant on day one, aprepitant on days two and three is recommended. <u>Prevention of nausea and vomiting induced by multiple-day cisplatin chemotherapy</u> • Patients affected by metastatic germ cell tumors receiving multiple-day cisplatin should receive a 5-HT$_3$ receptor antagonist plus dexamethasone plus aprepitant for the prevention of acute nausea and vomiting and dexamethasone for delayed nausea and vomiting. <u>Prevention of acute and delayed nausea and vomiting induced by chemotherapy with low and minimal emetogenic potential</u> • A single antiemetic agent, such as dexamethasone, a 5-HT$_3$ receptor antagonist or a dopamine receptor antagonist, such as metoclopramide may be considered for

Clinical Guideline	Recommendation(s)
	prophylaxis in patients receiving chemotherapy of low emetic risk. • No antiemetic should be routinely administered before chemotherapy to patients without a history of nausea and vomiting receiving minimally emetogenic chemotherapy. • No antiemetic should be administered for prevention of delayed nausea and vomiting induced by low or minimally emetogenic chemotherapy. • If a patient experiences acute or delayed nausea or vomiting after low or minimally emetogenic chemotherapy, it is advised that, with subsequent chemotherapy treatments, the regimen for the next higher emetic level be given. <u>Breakthrough chemotherapy-induced emesis and refractory emesis</u> • Antiemetics are most effective when used prophylactically. Therefore, it is preferable to use maximally effective antiemetics as first-line therapy rather than withholding more effective antiemetics for later use at the time of antiemetic failure. • For the treatment of breakthrough nausea and vomiting, it is recommended to use an antiemetic with a different mechanism of action than that of the antiemetic(s) used for prophylaxis. The available evidence for breakthrough nausea and vomiting suggests the use of olanzapine 10 mg orally daily for three days. The mild to moderate sedation in this patient population, especially elderly patients, is a potential problem with olanzapine. <u>Prevention of nausea and vomiting induced by high-dose chemotherapy</u> • For patients receiving high-dose chemotherapy for stem cell transplant, a combination of a 5-HT$_3$ receptor antagonist with dexamethasone and aprepitant (125 mg orally on day one and 80 mg on days two to four) is recommended before chemotherapy. <u>Prevention of radiotherapy-induced nausea and vomiting</u> • High emetic risk: prophylaxis with a 5-HT$_3$ receptor antagonist and dexamethasone is recommended. • Moderate emetic risk: prophylaxis with 5-HT$_3$ receptor antagonist and dexamethasone (optional) is recommended. • Low emetic risk with cranium area of treatment: prophylaxis or rescue with dexamethasone is recommended. • Low emetic risk with head/neck, thorax, or pelvis as area of treatment: prophylaxis or rescue with dexamethasone, a dopamine receptor antagonist, or a 5-HT$_3$ receptor antagonist is recommended. • Minimal emetic risk: rescue with dexamethasone, dopamine receptor antagonist, or 5-HT$_3$ receptor antagonists. <u>Prevention of acute chemotherapy-induced nausea and vomiting in children</u> • In children receiving chemotherapy of high emetic risk, an antiemetic prophylaxis with a 5-HT$_3$ receptor antagonist (granisetron, ondansetron, tropisetron or palonosetron) plus dexamethasone plus aprepitant is recommended. • Children who cannot receive dexamethasone should receive a 5HT$_3$ receptor antagonist plus aprepitant. • When aprepitant administration is not feasible or desirable, the guideline recommends a 5-HT$_3$ receptor antagonist plus dexamethasone be given to children receiving highly emetogenic chemotherapy. • Children receiving MEC should receive antiemetic prophylaxis with a 5-HT$_3$ receptor antagonist plus dexamethasone. Furthermore, children who cannot receive receptor antagonist should receive a 5-HT$_3$ receptor antagonist and aprepitant. • In children receiving chemotherapy of low emetogenicity, antiemetic prophylaxis with a 5-HT$_3$ receptor antagonist is recommended.

Clinical Guideline	Recommendation(s)
	• In children receiving chemotherapy of minimal emetogenicity, no antiemetic prophylaxis is recommended.
Society for Ambulatory Anesthesia: **Consensus Guidelines for the Management of Postoperative Nausea and Vomiting (2020)**[14]	Pediatric postoperative nausea and vomiting (PONV) management • Low risk prophylaxis: No treatment or 5-HT$_3$ receptor antagonist or dexamethasone. • Medium risk prophylaxis: 5-HT$_3$ receptor antagonist + dexamethasone. • High risk prophylaxis: 5-HT$_3$ receptor antagonist + dexamethasone + consider total intravenous anesthesia. • Rescue treatment: Use anti-emetic from different class than prophylactic drug-droperidol, promethazine, dimenhydrinate, metoclopramide; may also consider acupuncture/acupressure. Adult PONV management • One to two risk factors prophylaxis: Give two agents (5-HT$_3$ receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • More than two risk factors prophylaxis: Give three or four agents (5-HT$_3$ receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • Rescue treatment: Use anti-emetic from different class than prophylactic drug.
American Society of Clinical Oncology: **Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update (2020)**[10]	High-emetic-risk antineoplastic agents in adult patients • Adults treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of an NK$_1$ receptor antagonist, a serotonin (5-HT$_3$) receptor antagonist, dexamethasone, and olanzapine (day 1). Dexamethasone and olanzapine should be continued on days two to four. • Adults treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK$_1$ receptor antagonist, a 5-HT$_3$ receptor antagonist, dexamethasone, and olanzapine (day 1). Olanzapine should be continued on days two to four. Moderate-emetic-risk antineoplastic agents in adult patients • Adults treated with carboplatin area under the curve (AUC) ≥ 4 mg/mL/min should be offered a three-drug combination of an NK$_1$ receptor antagonist, a 5-HT$_3$ receptor antagonist, and dexamethasone (day 1). • Adults treated with moderate-emetic-risk antineoplastic agents (excluding carboplatin AUC ≥ 4 mg/mL/min) should be offered a two-drug combination of a 5-HT$_3$ receptor antagonist and dexamethasone (day 1). • Adults treated with cyclophosphamide, doxorubicin, oxaliplatin, and other moderate-emetic-risk antineoplastic agents known to cause delayed nausea and vomiting may be offered dexamethasone on days two to three. Low-emetic-risk antineoplastic agents in adult patients • Adults treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT$_3$ receptor antagonist or a single 8-mg dose of dexamethasone before antineoplastic treatment. Minimal-emetic-risk antineoplastic agents in adult patients • Adults treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis. Antineoplastic combinations in adult patients • Adults treated with antineoplastic combinations should be offered antiemetics appropriate for the component antineoplastic agent of greatest emetic risk. Adjunctive drugs in adult patients

Clinical Guideline	Recommendation(s)
	• Lorazepam is a useful adjunct to antiemetic drugs but is not recommended as a single-agent antiemetic. Cannabinoids in adult patients • Evidence remains insufficient for a recommendation regarding medical marijuana for the *prevention* of nausea and vomiting in patients with cancer receiving chemotherapy or radiation therapy. Evidence is also insufficient for a recommendation regarding the use of medical marijuana in place of the tested and US Food and Drug Administration–approved cannabinoids dronabinol and nabilone for the *treatment* of nausea and vomiting caused by chemotherapy or radiation therapy. Complementary and alternative therapies in adult patients • Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture/acupressure, and other complementary or alternative therapies for the *prevention* of nausea and vomiting in patients with cancer. High-dose chemotherapy with stem-cell or bone marrow transplantation in adult patients • Adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. • A four-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine may be offered to adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation. Multiday antineoplastic therapy in adult patients • Adults treated with multiday antineoplastic agents should be offered antiemetics before treatment that are appropriate for the emetic risk of the antineoplastic agent given on each day of the antineoplastic treatment and for two days after completion of the antineoplastic regimen. • Adults treated with four- or five-day cisplatin regimens should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. Breakthrough nausea and vomiting in adult patients • For patients with breakthrough nausea or vomiting, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; and ascertain that the best regimen is being administered for the emetic risk. • Adults who experience nausea or vomiting despite optimal prophylaxis and who did not receive olanzapine prophylactically should be offered olanzapine in addition to continuing the standard antiemetic regimen. • Adults who experience nausea or vomiting despite optimal prophylaxis and who have already received olanzapine may be offered a drug of a different class (e.g., an NK1 receptor antagonist, lorazepam or alprazolam, a dopamine receptor antagonist, dronabinol, or nabilone) in addition to continuing the standard antiemetic regimen. Anticipatory nausea and vomiting in adult patients • All patients should receive the most active antiemetic regimen appropriate for the antineoplastic agents being administered. Clinicians should use such regimens with initial antineoplastic treatment rather than assessing the patient's emetic response with less-effective antiemetic treatment. If a patient experiences anticipatory emesis, clinicians may offer behavioral therapy with systematic desensitization. High-emetic-risk radiation therapy in adult patients

Clinical Guideline	Recommendation(s)
	• Adults treated with high-emetic-risk radiation therapy should be offered a two-drug combination of a 5-HT$_3$ receptor antagonist and dexamethasone before each fraction and on the day after each fraction, if radiation therapy is not planned for that day. Moderate-emetic-risk radiation therapy in adult patients • Adults treated with moderate-emetic-risk radiation therapy should be offered a 5-HT$_3$ receptor antagonist before each fraction, with or without dexamethasone, before the first five fractions. Low-emetic-risk radiation therapy in adult patients • Adults treated with radiation therapy to the brain should be offered breakthrough dexamethasone therapy. Patients who are treated with radiation therapy to the head and neck, thorax, or pelvis should be offered breakthrough therapy with a 5-HT$_3$ receptor antagonist, dexamethasone, or a dopamine-receptor antagonist. Minimal-emetic-risk radiation therapy in adult patients • Adults treated with minimal-emetic-risk radiation therapy should be offered breakthrough therapy with a 5-HT$_3$ receptor antagonist, dexamethasone, or a dopamine-receptor antagonist. Concurrent radiation and antineoplastic agent therapy in adult patients • Adults treated with concurrent radiation and antineoplastic agents should receive antiemetic therapy appropriate for the emetic risk level of the antineoplastic agents, unless the risk level of the radiation therapy is higher. During periods when prophylactic antiemetic therapy for the antineoplastic agents has ended and ongoing radiation therapy would normally be managed with its own prophylactic therapy, patients should receive prophylactic therapy appropriate for the emetic risk of the radiation therapy until the next period of antineoplastic therapy, rather than receiving breakthrough therapy for the antineoplastic agents as needed. High-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with high-emetic-risk antineoplastic agents should be offered a three-drug combination of a 5-HT$_3$ receptor antagonist, dexamethasone, and aprepitant or fosaprepitant. • Pediatric patients treated with high-emetic-risk antineoplastic agents who are unable to receive aprepitant or fosaprepitant should be offered a two-drug combination of a 5-HT$_3$ receptor antagonist and dexamethasone. • Pediatric patients treated with high-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of palonosetron and aprepitant or fosaprepitant. Moderate-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with moderate-emetic-risk antineoplastic agents should be offered a two-drug combination of a 5-HT$_3$ receptor antagonist and dexamethasone. • Pediatric patients treated with moderate-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of a 5-HT$_3$ receptor antagonist and aprepitant or fosaprepitant. Low-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with low-emetic-risk antineoplastic agents should be offered ondansetron or granisetron.

Clinical Guideline	Recommendation(s)
	Minimal-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis.
American College of Obstetricians and Gynecologists: **Practice Bulletin No. 189: Nausea and Vomiting of Pregnancy (2018)**[15]	General considerations • Treatment of nausea and vomiting of pregnancy with vitamin B6 (pyridoxine) alone or vitamin B6 plus doxylamine in combination is safe and effective and should be considered first-line pharmacotherapy. • The standard recommendation to take prenatal vitamins for one month before fertilization may reduce the incidence and severity of nausea and vomiting of pregnancy. • The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis, or hyperemesis gravidarum, or both, includes supportive therapy, and antithyroid drugs are not recommended. • Treatment of nausea and vomiting of pregnancy with ginger has shown some beneficial effects in reducing nausea symptoms and can be considered as a nonpharmacologic option. • Treatment of severe nausea and vomiting of pregnancy or hyperemesis gravidarum with methylprednisolone may be efficacious in refractory cases; however, the risk profile of methylprednisolone suggests it should be a last-resort treatment. • Early treatment of nausea and vomiting of pregnancy may be beneficial to prevent progression to hyperemesis gravidarum. • Intravenous hydration should be used for the patient who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present. Correction of ketosis and vitamin deficiency should be strongly considered. Dextrose and vitamins should be included in the therapy when prolonged vomiting is present, and thiamine should be administered before dextrose infusion to prevent Wernicke encephalopathy. • Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as the first-line treatment to provide nutritional support to the woman with hyperemesis gravidarum who is not responsive to medical therapy and cannot maintain her weight. • Peripherally inserted central catheters should not be used routinely in women with hyperemesis gravidarum given the significant complications associated with this intervention. Peripherally inserted central catheters should be utilized only as a last resort in the management of a woman with hyperemesis gravidarum because of the potential of severe maternal morbidity.
Society of Obstetricians and Gynaecologists of Canada: **Clinical Practice Guideline: Management of Nausea and Vomiting of Pregnancy (2016)**[16]	General considerations • Women experiencing nausea and vomiting of pregnancy may discontinue iron-containing prenatal vitamins during the first trimester and substitute them with folic acid or adult or children's vitamins low in iron. • Women should be counselled to eat whatever pregnancy-safe food appeals to them and lifestyle changes should be liberally encouraged. • Ginger may be beneficial in ameliorating the symptoms of nausea and vomiting of pregnancy. • Acupressure may help some women in the management of nausea and vomiting of pregnancy. • Mindfulness-based cognitive therapy as an adjunct to pyridoxine therapy may be beneficial. • Pyridoxine monotherapy or doxylamine/pyridoxine combination therapy is recommended as first line in treating nausea and vomiting of pregnancy due to their efficacy and safety. • Women with high risk for nausea and vomiting of pregnancy may benefit from preemptive doxylamine/pyridoxine treatment at the onset of pregnancy. • H1 receptor antagonists should be considered in the management of acute or

Clinical Guideline	Recommendation(s)
	chronic episodes of nausea and vomiting of pregnancy. • Metoclopramide can be safely used as an adjuvant therapy for the management of nausea and vomiting of pregnancy. • Phenothiazines are safe and effective as an adjunctive therapy for severe nausea and vomiting of pregnancy. • Despite potential safety concerns of ondansetron use in pregnancy, ondansetron can be used as an adjunctive therapy for the management of severe nausea and vomiting of pregnancy when other antiemetic combinations have failed. • Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. • When nausea and vomiting of pregnancy is refractory to initial pharmacotherapy, investigation of other potential causes should be undertaken.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the 5-HT$_3$ receptor antagonists are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the 5-HT$_3$ Receptor Antagonists[3-8]

Indication	Dolasetron	Granisetron	Ondansetron	Palonosetron
Chemotherapy-Induced Nausea and Vomiting				
Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy	✔		✔ *	
Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide combination chemotherapy regimens		✔ ^		
Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin		✔ *†	✔ *†	
Prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to five consecutive days duration		✔ ‡		
Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy				✔
Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy				✔
Postoperative Nausea and Vomiting				
Prevention of postoperative nausea and vomiting		✔ †	✔ *†	
Prevention of postoperative nausea and vomiting for up to 24 hours following surgery				✔
Treatment of postoperative nausea and/or vomiting		✔ †		
Radiation-Induced Nausea and Vomiting				

Indication	Dolasetron	Granisetron	Ondansetron	Palonosetron
Prevention of nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation		✔ *		
Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen			✔ *	

*Oral formulations
†Injection formulation.
‡Transdermal formulation.
^Extended-release subcutaneous injection formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the 5-HT$_3$ receptor antagonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the 5-HT$_3$ Receptor Antagonists[4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Dolasetron	75	69 to 77	Glucuronidation and hydroxylation	Renal (61)	5.5 to 8.1
Granisetron	PO: 60 TD: 66	65	Liver (89)	Renal (12)	ER: 24 IV: 5 to 9 PO: 1 to 20
Ondansetron	56 to 71	70 to 76	Liver (90 to 95)	Renal (44 to 60)	3 to 6
Palonosetron	97	62	Liver (50 to 60)	Renal (80)	37 to 48

ER-extended-release, IV=intravenous, PO=oral, TD=transdermal

V. Drug Interactions

Major drug interactions with the 5-HT$_3$ receptor antagonists are listed in Table 5.

Table 5. Major Drug Interactions with the 5-HT$_3$ Receptor Antagonists[4]

Generic Name(s)	Interaction	Mechanism
Granisetron, ondansetron	Vandetanib	Concomitant administration of vandetanib with 5-HT3 antagonists may result in synergistic or additive prolongation of the QT interval.
Granisetron, ondansetron	Ziprasidone	Concomitant administration of ziprasidone with 5-HT3 antagonists may result in synergistic or additive prolongation of the QT interval.
5-HT$_3$ receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron)	Apomorphine	Significant adverse reactions, including profound hypotension and loss of consciousness, may occur when apomorphine is administered with 5-HT3 antagonists. The mechanism is unknown.
Dolasetron, granisetron, ondansetron	QT prolonging agents	Concurrent use of 5-HT3 antagonists and QT prolonging agents may result in increased risk of QT-interval prolongation and torsade de pointes.

VI. Adverse Drug Events

The most common adverse drug events reported with the 5-HT$_3$ receptor antagonists are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the 5-HT$_3$ Receptor Antagonists[3-8]

Adverse Events	Dolasetron	Granisetron	Ondansetron	Palonosetron
Cardiovascular				
Angina	-	<1	<1	-
Arrhythmia	-	<1	<1	<1
Atrial fibrillation	-	<1	<1	-
Atrial flutter	-	-	-	-
Atrioventricular block	-	-	<1	-
Bradycardia	4 to 5	-	<1	1 to 4
Bundle branch block	-	-	-	-
Cardiopulmonary arrest	-	-	<1	-
Chest discomfort	-	-	<1	-
ECG changes	-	<1	<1	<1
Edema	<2	-	-	-
Flushing	<2	-	-	-
Extrasystole	-	-	-	<1
Hypertension	-	1 to 2	2	<1
Hypotension	<2	<1	3 to 5	<1
Myocardial ischemia	-	-	-	<1
Orthostatic hypotension	-	-	-	-
Peripheral ischemia	<2	-	-	-
Phlebitis	<2	-	-	-
Palpitation	-	-	<1	-
PR prolongation	-	-	-	-
Premature ventricular contractions	-	-	<1	-
QRS prolongation	-	-	-	-
QT prolongation	-	2 to 3	<1	1 to 5
Shock	-	-	<1	-
ST-T wave change	-	-	-	-
Supraventricular extrasystoles	-	-	-	<1
Supraventricular tachycardia	-	-	<1	-
Syncope	-	-	<1	-
T wave change	-	-	-	-
Tachycardia	3	-	<1	<1
Thrombophlebitis	<2	-	-	-
Torsades de pointes	-	-	<1	-
U wave change	-	-	-	-
Ventricular arrhythmia	-	-	<1	-
Ventricular fibrillation	-	-	<1	-
Ventricular tachycardia	-	-	<1	-
Central Nervous System				
Abnormal dreams	<2	-	-	-
Agitation	<2	<2	-	-
Anxiety	<2	2	6	1
Ataxia	<2	-	-	-
Chills	<2	5	7	<1
Central nervous system stimulation	-	<2	-	-
Cold sensation	-	-	2	-
Confusion	<2	-	-	-
Depersonalization	<2	-	-	-
Dizziness	1 to 3	4 to 5	4 to 7	<1

Adverse Events	Dolasetron	Granisetron	Ondansetron	Palonosetron
Drowsiness	-	-	8	-
Euphoria	-	-	-	<1
Extrapyramidal symptoms	-	<1	<1	-
Fatigue	3 to 6	-	-	<1
Fever	-	3 to 9	2 to 8	<1
Headache	18 to 23	3 to 21	9 to 27	3 to 9
Hypersomnia	-	-	-	<1
Insomnia	-	<2 to 5	-	<1
Malaise/fatigue	-	-	9 to 13	<1
Motion sickness	-	-	-	<1
Paresthesia	<2	-	2	<1
Seizure	-	-	<1	<1
Shivering	<2	-	-	-
Sleep disorder	<2	-	-	-
Somnolence	-	1 to 4	-	<1
Syncope	-	<1	-	-
Tremor	<2	-	-	-
Vertigo	<2	-	-	-
Dermatological				
Allergic dermatitis	-	-	-	<1
Diaphoresis	<2	-	-	-
Erythema	-	-	-	<1
Hyperhidrosis	-	-	<1	-
Pruritus	-	-	2 to 5	<1
Rash	<2	1	1	<1
Urticaria	<2	-	<1	-
Gastrointestinal				
Abdominal pain	<2	4 to 6	3	<1
Anorexia	<2	-	-	<1
Appetite decreased	-	-	-	<1
Constipation	<2	3 to 18	6 to 11	2 to 5
Diarrhea	2 to 5	3 to 9	2 to 7	<1
Dyspepsia	2 to 3	3 to 6	-	<1
Flatulence	-	-	-	<1
Hiccups	-	-	<1	<1
Pancreatitis	<2	-	-	-
Taste perversion	-	2	-	-
Xerostomia	-	-	2	<1
Genitourinary				
Acute renal failure	<2	-	-	-
Dysuria	<2	-	-	-
Glycosuria	-	-	-	<1
Gynecological disorder	-	-	7	-
Hematuria	<2	-	-	-
Oliguria	-	2	-	-
Polyuria	<2	-	-	-
Urinary retention	-	-	5	<1
Hematologic				
Metabolic acidosis	-	-	-	<1
Partial thromboplastin time prolonged	<2	-	-	-
Thrombocytopenia	<2	-	-	<1
Hepatic				
Alanine aminotransferase increased	-	5 to 6	1 to 5	<1
Aspartate aminotransferase increased	-	5 to 6	1 to 5	<1

Adverse Events	Dolasetron	Granisetron	Ondansetron	Palonosetron
Hepatic failure	-	-	<1	-
Hepatic necrosis	-	-	<1	-
Hepatitis	-	-	<1	-
Jaundice	-	-	<1	-
Laboratory Test Abnormalities				
Alkaline phosphatase increased	<2	-	-	-
Bilirubin increased	<2	-	-	<1
Hyperglycemia	-	-	-	<1
Hyperkalemia	-	-	-	<1
Hypokalemia	-	-	<1	<1
Increased gamma-glutamyl transferase	<2	-	-	-
Musculoskeletal				
Arthralgia	<2	-	<1	<1
Asthenia	-	14	-	-
Myalgia	<2	-	-	-
Respiratory				
Bronchospasm	<2	-	<1	-
Cough	-	2	-	-
Dyspnea	<2	-	<1	-
Hypoventilation	-	-	-	<1
Hypoxia	-	-	9	-
Laryngeal edema	-	-	<1	-
Laryngospasm	-	-	<1	<1
Stridor	-	-	<1	-
Other				
Abnormal vision	<2	-	-	-
Allergic reaction	-	<1	-	-
Amblyopia	-	-	-	<1
Anaphylaxis	<2	<1	<1	-
Anemia	<2	-	-	<1
Angioedema	-	-	<1	-
Application site reaction (patch)	-	<1	-	-
Ataxia	-	-	-	-
Blurred vision	-	-	<1	-
Dystonic reaction	-	-	<1	-
Edema	-	-	-	<1
Epistaxis	<2	-	-	<1
Eye irritation	-	-	-	<1
Facial edema	-	-	-	-
Flu-like syndrome	-	-	-	<1
Flushing	-	-	<1	-
Hematoma	<2	-	-	-
Hot flashes	-	<1	-	<1
Hypersensitivity	-	<1	<1	<1
Infection	-	3	-	-
Injection site reaction	-	-	4	<1
Lethargy	-	-	<1	-
Oculogyric crisis	-	-	<1	-
Pain	3	10	2	<1
Photophobia	<2	-	-	-
Tinnitus	<2	-	-	<1
Twitching	<2	-	-	-
Weakness	-	5 to 18	2	1

- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the 5-HT$_3$ receptor antagonists are listed in Table 7.

Table 7. Usual Dosing Regimens for the 5-HT$_3$ Receptor Antagonists[3-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Dolasetron	Chemotherapy induced nausea and vomiting: Tablet: 100 mg within one hour before chemotherapy	Chemotherapy induced nausea and vomiting in children two to 16 years of age: Tablet: 1.8 mg/kg as a single dose within one hour before chemotherapy; maximum, 100 mg	Tablet: 50 mg
Granisetron	Chemotherapy induced nausea and vomiting: Extended-release injection: 10 mg administered subcutaneously at least 30 minutes before chemotherapy; readminister not more frequently than once every seven days Injection: 10 µg/kg intravenously within 30 minutes before chemotherapy Tablet: 2 mg up to one hour before chemotherapy or 1 mg up to one hour before chemotherapy and 1 mg 12 hours after the first dose Transdermal patch: one patch applied at a minimum of 24 hours prior to starting chemotherapy; remove patch at a minimum of 24 hours after chemotherapy regimen is complete; may be worn for up to seven days Postoperative nausea and vomiting: Injection: 1 mg intravenously before induction of anesthesia or immediately before reversal of anesthesia Radiation induced nausea and vomiting Tablet: 2 mg within one hour of radiation	Chemotherapy induced nausea and vomiting in children two to 16 years of age: Injection: 10 µg/kg intravenously	Extended-release injection: 10 mg/ 0.4 mL Injection: 100 µg/mL 1 mg/mL Tablet: 1 mg Transdermal patch: 3.1 mg/24 hours
Ondansetron	Chemotherapy induced nausea and vomiting:	Chemotherapy induced nausea and vomiting in children six	Injection: 2 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: three 0.15 mg/kg intravenous doses (first dose prior to chemotherapy, then repeated four and eight hours after first dose); maximum, 16 mg per dose Chemotherapy induced nausea and vomiting with highly emetogenic chemotherapy: Orally disintegrating tablet: 24 mg 30 minutes prior to chemotherapy Solution: 24 mg 30 minutes prior to chemotherapy Tablet: 24 mg 30 minutes prior to chemotherapy Chemotherapy induced nausea and vomiting with moderately emetogenic chemotherapy: Orally disintegrating tablet: 8 mg orally twice daily Solution: 8 mg orally twice daily Tablet: 8 mg orally twice daily Postoperative nausea and vomiting Injection: 4 mg intravenously immediately before induction of anesthesia, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery Orally disintegrating tablet: 16 mg one hour before induction of anesthesia Solution: 16 mg one hour before induction of anesthesia Tablet: 16 mg one hour before induction of anesthesia Radiation induced nausea and vomiting: Orally disintegrating tablet: 8 mg three times daily	months to 18 years of age: Injection: three 0.15 mg/kg intravenous doses (first dose prior to chemotherapy, then repeated four and eight hours after first dose); maximum, 16 mg per dose Chemotherapy induced nausea and vomiting in children four to 11 years of age: Orally disintegrating tablet: 4 mg three times daily Solution: 4 mg three times daily Tablet: 4 mg three times daily Chemotherapy induced nausea and vomiting in children ≥12 years of age: Orally disintegrating tablet: 8 mg twice daily Solution: 8 mg twice daily Tablet: 8 mg twice daily Postoperative nausea and vomiting in children one month to 12 years of age: Injection: ≤40 kg, 0.1 mg/kg intravenous; >40 kg, 4 mg intravenous	4 mg/2 mL Orally disintegrating tablet: 4 mg 8 mg Solution: 4 mg/5 mL Tablet: 4 mg 8 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Solution: 8 mg three times daily Tablet: 8 mg three times daily		
Palonosetron	Chemotherapy induced nausea and vomiting: Injection: 0.25 mg intravenously 30 minutes prior to chemotherapy Postoperative nausea and vomiting: Injection: 0.075 mg intravenously immediately before the induction of anesthesia	Chemotherapy induced nausea and vomiting in patients one month to <17 years of age: Injection: 20 µg/kg infused intravenously over 15 minutes 30 minutes prior to chemotherapy, maximum 1.5 mg	Injection: 0.25 mg/2 mL 0.25 mg/5 mL

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the 5-HT$_3$ receptor antagonists are summarized in Table 8.

Table 8. Comparative Clinical Trials with the 5-HT$_3$ Receptor Antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting (CINV)				
Billio et al.[17] (2010) 5-HT$_3$ receptor antagonist vs a different 5-HT$_3$ receptor antagonist or 5-HT$_3$ receptor antagonist in combination with corticosteroids vs a different 5-HT$_3$ receptor antagonist in combination with corticosteroids or 5-HT$_3$ receptor antagonist in combination with	MA Patients ≥16 years old receiving highly emetic chemotherapy for a malignant neoplasm	N=7,808 (16 trials) 7 days	Primary: Prevention of acute emesis induced by highly emetic chemotherapy Secondary: Prevention of delayed emesis induced by highly emetic chemotherapy, adverse events	Primary: In eight studies comparing granisetron to ondansetron, treatment with granisetron was favored for the prevention of acute vomiting (OR, 0.89; 95% CI, 0.78 to 1.02). In seven studies comparing granisetron to ondansetron, treatment with ondansetron was favored for the complete absence of acute nausea (OR, 0.97; 95% CI, 0.85 to 1.10). One study comparing palonosetron plus dexamethasone to granisetron plus dexamethasone for the prevention of acute vomiting found no significant difference between treatments (OR, 0.95; 95% CI, 0.75 to 1.21). In six studies comparing granisetron to ondansetron, the treatments were found to be similar for the complete absence of combined acute nausea and vomiting (OR, 1.00; 95% CI, 0.85 to 1.16). One study comparing palonosetron plus dexamethasone to granisetron plus dexamethasone for complete response for acute nausea and vomiting found no significant difference between treatment groups (OR, 1.11; 95% CI, 0.85 to 1.45). Secondary: Three studies comparing granisetron to ondansetron for the complete absence of delayed vomiting found no significant difference between treatments (OR, 1.00; 95% CI, 0.74 to 1.34). In one study comparing palonosetron plus dexamethasone to granisetron plus dexamethasone, treatment with palonosetron was found to be more efficacious for the prevention of delayed vomiting (OR, 1.45; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
corticosteroids plus aprepitant vs a different 5-HT$_3$ receptor antagonist in combination with corticosteroids plus aprepitant or 5-HT$_3$ receptor antagonist vs the same 5-HT$_3$ receptor antagonist with different dose/dosing schedule 5-HT$_3$ receptor antagonists may include dolasetron, granisetron, ondansetron, palonosetron, ramosetron and tropisetron.				1.14 to 1.85). The proportion of patients with complete control of delayed vomiting in the palonosetron treatment group was 63.2% compared to 54.2% in the palonosetron group. For two studies that were analyzed for the complete absence of delayed nausea, the pooled OR was 0.96 (95% CI, 0.75 to 1.24) in favor of treatment with ondansetron. One studied comparing palonosetron plus dexamethasone to granisetron plus dexamethasone found that treatment with palonosetron was more efficacious in the prevention of delayed nausea (OR, 1.63; 95% CI, 1.27 to 2.10). The proportion of patients with complete control of delayed nausea for the palonosetron and granisetron groups was 37.8 and 27.2%, respectively. One study comparing palonosetron plus dexamethasone to granisetron plus dexamethasone found that treatment with palonosetron was more efficacious in achieving complete response for delayed nausea and vomiting (OR, 1.63; 95% CI, 1.29 to 2.07). The proportion of patients with complete control of delayed nausea and vomiting in the palonosetron group was 53.0% compared to 42.4% in the granisetron group. There was no significant difference in the incidence of headache or diarrhea between the ondansetron and granisetron treatment groups. The incidence of constipation was higher in the ondansetron group compared to the granisetron group. There was no significant difference between treatment with ondansetron and granisetron for cumulative adverse effects. There were no significant differences in cumulative treatment-related and severe adverse events between the palonosetron plus dexamethasone and the granisetron plus dexamethasone treatment groups.
Hickok et al.[18] (2005) Day one:	OL, RCT Patients >18 years of age scheduled to	N=691 3 days	Primary: Mean severity of delayed nausea	Primary: Delayed nausea was reported in 71% of patients treated with prochlorperazine every eight hours, 79% of patients treated with 5-HT$_3$ receptor antagonist and 82% of patients treated with prochlorperazine as

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Any 5-HT$_3$ receptor antagonist plus dexamethasone (or equivalent dose of methyl-prednisolone) Days two and three: prochlorperazine by mouth 10 mg every eight hours vs Day one: Any 5-HT$_3$ receptor antagonist plus dexamethasone (or equivalent dose of methyl-prednisolone) Day two and three: ondansetron 8 mg two times a day, granisetron 1 mg two times a day, dolasetron 100 mg QD or 50 mg two times a day vs Day one:	receive their first treatment with a chemotherapy regimen containing doxorubicin and antiemetic prophylaxis with ondansetron, granisetron, or dolasetron plus dexamethasone or equivalent methyl-prednisolone		Secondary: Severity of acute nausea, frequency of acute and delayed nausea, frequency of acute and delayed vomiting, compliance	needed. The groups did not differ significantly in the mean severity of delayed nausea. Patients treated with prochlorperazine every eight hours had less delayed nausea than patients treated with a 5-HT$_3$ receptor antagonist (P=0.05) and those treated with prochlorperazine as needed (P=0.009). Secondary: The severity of acute nausea did not differ between groups. The frequency of acute vomiting or delayed vomiting did not differ between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Any 5-HT$_3$ receptor antagonist plus dexamethasone (or equivalent dose of methyl-prednisolone) Day two and three: prochlorperazine 10 mg as needed				
Rapoport et al.[19] (2010) Aprepitant 125 mg one hour prior to chemotherapy followed by 80 mg on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later,	DB, MC, PG, RCT Adult patients who were naïve to moderate or highly emetogenic chemotherapy and were scheduled to receive treatment with one or more moderately emetogenic agents	N=848 120 hours	Primary: Proportion of patients reporting no vomiting Secondary: Overall complete response (no emesis and no use of rescue therapy)	Primary: Significantly more patients in the aprepitant (triple therapy) group reported no vomiting (76.2%) compared to patients receiving dual therapy (62.1%) during the 120 hour study period (P<0.001). Secondary: Significantly more patients in the aprepitant (triple therapy) group reported complete response (68.7%) compared to patients receiving dual therapy (56.3%; P<0.001). There were no significant differences in adverse events between the two groups; however, the overall incidence of adverse events in the entire study population was 65%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy				
Yeo et al.[20] (2009) Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to	DB, PC, RCT Breast cancer patients ≥18 years of age who were naïve to chemotherapy and were receiving a moderately emetogenic regimen (doxorubicin and cyclophosphamide)	N=127 120 hours	Primary: Complete response (no vomiting and no rescue therapy used) during the overall period (0 to 120 hours) Secondary: Proportion of patients with no vomiting, no nausea, no significant nausea, no rescue therapy, complete protection, and total control during the acute (0 to 24 hour), delayed (24 to 120 hours), and overall periods	Primary: There was no significant difference in the complete response rates for patients receiving aprepitant (triple therapy) compared to patients receiving dual therapy during the overall period (46.8 vs 41.9%, respectively; P=0.58). Secondary: During the overall period, there was no significant difference among the treatment groups in the proportion of patients reporting complete protection (P=0.71), total control (P=0.55), no vomiting (P=0.58), no significant nausea (P=0.71) and no nausea (P=0.57). Rescue medication use was lower in the aprepitant group than the control group (11 vs 20%; P=0.06). There was no significant difference between the two groups with respect to all the parameters of emesis control in the acute and delayed time frames. The median time to first vomiting after the initiation of chemotherapy was 64.4 hours for the aprepitant arm and 52.6 hours in the control arm (P=0.78).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chemotherapy				
Herrstedt et al.[21] (2005) Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy	DB, MC, PG, RCT Patients with breast carcinoma who were naïve to emetogenic chemotherapy and treated with cyclophosphamide alone or in combination with doxorubicin or epirubicin	N=866 3 days of treatment during cycles 1 to 4 of chemotherapy	Primary: Proportion of patients with a complete response (no emesis or use of rescue therapy) in cycle one, efficacy end points for the multiple-cycle extension were the probabilities of a complete response in cycles two to four and a sustained complete response rate across multiple cycles Secondary: Not reported	Primary: Overall, the complete response was greater with the aprepitant regimen over the four cycles: 50.8 vs 42.5% for cycle one, 53.8 vs 39.4% for cycle two, 54.1 vs 39.3% for cycle three, and 55.0 vs 38.4% for cycle four. The cumulative percentage of patients with a sustained complete response over all four cycles was greater with the aprepitant regimen (P=0.017). The aprepitant regimen was more effective than a control regimen for the prevention of nausea and emesis induced by moderately emetogenic chemotherapy over multiple chemotherapy cycles. Secondary: Not reported
Warr et al.[22] (2005) Aprepitant 125 mg	DB, PG, RCT Patients with breast cancer who were	N=857 120 hours	Primary: Proportion of patients with complete response	Primary: Overall complete response was greater with the aprepitant regimen than with the control regimen (50.8 vs 42.5%; P=0.015).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy	naïve to emetogenic chemotherapy and who were treated with a regimen of cyclophosphamide alone, cyclophosphamide plus doxorubicin, or cyclophosphamide plus epirubicin		(defined as no vomiting and no use of rescue therapy) 120 hours after initiation of chemotherapy in cycle one Secondary: Proportion of patients with an average item score higher than 6 of 7 on the Functional Living Index-Emesis questionnaire	Secondary: More patients in the aprepitant group reported minimal or no impact of CINV on daily life (63.5 vs 55.6%; P=0.019). Both treatments were generally well tolerated. The aprepitant regimen was more effective than the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide.
Gralla et al.[23] (2005) Aprepitant 125 mg plus ondansetron 32 mg and dexamethasone 12 mg on day one;	DB, PG, RCT (pooled analysis) Patients >18 years of age receiving their first cisplatin-based chemotherapy	N=1,043 120 hours	Primary: Complete response (defined as no vomiting and no rescue therapy) on days one to five Secondary:	Primary: In the total combined study population, regardless of treatment group or use of concomitant chemotherapy, complete response was achieved in 58% of patients. Analysis by treatment group showed a 20% greater efficacy with the aprepitant regimen (68 vs 48%; P<0.001). Among 13% of patients who received additional emetogenic chemotherapy (doxorubicin or cyclophosphamide), the aprepitant regimen

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aprepitant 80 mg and dexamethasone 8 mg on days two to three; and dexamethasone 8 mg on day four vs ondansetron 32 mg IV and dexamethasone 20 mg orally on day one; dexamethasone 8 mg twice daily on days two to four			Not reported	provided a 33% improvement in the complete response rate compared to the control regimen (P<0.001). Secondary: Not reported
De Wit et al.[24] (2004) Aprepitant 125 mg, ondansetron 32 mg IV, dexamethasone 12 mg on day one, aprepitant 80 mg and dexamethasone 8 mg on days two to three, dexamethasone 8 mg on day four vs ondansetron 32 mg	DB, MC, RCT Patients with cancer who were receiving their first cycle of cisplatin-based chemotherapy	N=1,038 120 hours	Primary: No emesis and no significant nausea over the five days following cisplatin, for up to six cycles of chemotherapy Secondary: Not reported	Primary: In every cycle, the estimated probabilities (rates) of no emesis and no significant nausea were significantly higher (P<0.006) in the aprepitant group. In the first cycle, rates were 61% in the aprepitant group and 46% in the standard therapy group. Thereafter, rates for the aprepitant regimen remained higher throughout (59 vs 40% for the standard therapy by cycle six). Repeated dosing with aprepitant over multiple cycles was generally well tolerated. Those who received aprepitant in addition to standard therapy had consistently better antiemetic protection that was well maintained over multiple cycles of highly emetogenic chemotherapy. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV and dexamethasone 20 mg on day one, dexamethasone 8 mg twice daily on days two to four				
Poli-Bigelli et al.[25] (2003) Aprepitant 125 mg, ondansetron 32 mg IV, and dexamethasone 12 mg orally on day one; aprepitant 80 mg and dexamethasone 8 mg orally on days two to three; and dexamethasone 8 mg orally on day four vs ondansetron 32 mg IV and dexamethasone 20 mg orally on day one, followed by dexamethasone 8 mg orally twice daily on days two to four	DB, MC, PG, RCT Patients with cancer who were scheduled to receive treatment with high-dose cisplatin chemotherapy	N=1,091 120 hours	Primary: Complete response (no emesis and no rescue therapy) during the five-day period post cisplatin therapy Secondary: Not reported	Primary: During the five days after chemotherapy, the percentages of patients who achieved a complete response were 62.7% in the aprepitant group compared to 43.3% in the standard therapy group (P<0.001). For day one, the complete response rates were 82.8% for the aprepitant group and 68.4% for the standard therapy group (P<0.001); for days two to five, the complete response rates were 67.7% in the aprepitant group and 46.8% in the standard therapy group (P<0.001). The overall incidence of adverse events was similar between the two treatment groups (72.8% in the aprepitant group and 72.6% in the standard therapy group) as were rates of serious adverse events, discontinuations due to adverse events, and deaths. In patients with cancer who were receiving high-dose cisplatin-based chemotherapy, therapy consisting of aprepitant (125 mg on day one and 80 mg on days two to three) plus a standard regimen of ondansetron and dexamethasone provided greater antiemetic protection compared to standard therapy alone and was generally well tolerated. Secondary: Not reported
Hesketh et al.[26] (2003)	DB, MC, PG, RCT Patients with cancer	N=530 120 hours	Primary: Complete response (no emesis and no	Primary: The percentage of patients with complete response was significantly higher in the aprepitant group (72.7 vs 52.3% in the standard therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aprepitant plus ondansetron and dexamethasone on day one; aprepitant and dexamethasone on days two to three; dexamethasone on day four vs ondansetron and dexamethasone on day one; dexamethasone on days two to four	who were receiving cisplatin for the first time		rescue therapy) on days one to five post cisplatin therapy Secondary: Not reported	group), as were the percentages on day one, and especially on days two to five (P<0.001 for all three comparisons). Compared to standard dual therapy, addition of aprepitant was generally well tolerated and provided consistent protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy. Secondary: Not reported
Martin et al.[27] (2003) Aprepitant and dexamethasone plus ondansetron on day one, followed by aprepitant and dexamethasone on days two to five vs dexamethasone and ondansetron on day one, followed by dexamethasone on days two to five	DB, RCT Patients with cancer who were receiving cisplatin	N=381 5 days	Primary: Complete response, the Functional Living Index-Emesis Secondary: Not reported	Primary: Compared to standard therapy, significantly more patients treated with the high-dose aprepitant regimen achieved a complete response (71 vs 44%; P<0.001) and also reported no impact on daily life as indicated by the Functional Living Index-Emesis total score (84 vs 66%; P<0.01). Use of the Functional Living Index-Emesis demonstrated that improved control of emesis was highly effective in reducing the impact of CINV on patients' daily activities. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gore et al.[28] (2009) Aprepitant 125 mg one hour prior to chemotherapy followed by 80 mg on days two to three, plus ondansetron 0.15 mg/kg for three doses on days one to two, plus dexamethasone 8 mg on day one followed by 4 mg on days two to four vs ondansetron 0.15 mg/kg for three doses on days one to two, plus dexamethasone 16 mg on day one followed by 8 mg on days two to four	DB, MC, RCT Patients 11 to 19 years of age who were receiving emetogenic chemotherapy or who had experienced intolerable CINV with previous chemotherapy	N=46 120 hours	Primary: Complete response (no vomiting and no rescue therapy used), as well as the proportion of patients with no vomiting and/or no rescue therapy during the overall period (0 to 120 hours), acute period (0 to 24 hour), and delayed (24 to 120 hours) period Secondary: Not reported	Primary: There was no significant difference among the treatment groups with regards to the complete response rates, proportion of patients reporting no vomiting, or the proportion of patients reporting no nausea during the overall period, acute period, or delayed period. There were no significant differences in adverse event rates between the two groups. Secondary: Not reported
Jordan et al.[29] (2009) Aprepitant 125 mg prior to chemotherapy, then 80 mg on	PRO Adult patients undergoing multiple-day chemotherapy of moderate or high	N=78 Variable duration	Primary: Complete response (no vomiting or use of rescue therapy) at the end of the treatment cycle	Primary: The percentage of patients with a complete response was 57.9% in those who were receiving highly emetogenic chemotherapy and 72.5% in those who were receiving moderately emetogenic chemotherapy. Secondary: During the acute and delayed phases, the complete response in patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days two to three, plus granisetron 1 mg on day one, plus dexamethasone 8 mg on days one to three	emetogenic potential		Secondary: Complete response in the acute and delayed phase of the treatment cycle	receiving highly emetogenic chemotherapy was 65.8 and 68.5%, respectively. During the acute and delayed phases, the complete response in patients receiving moderately emetogenic chemotherapy was 72.5 and 82.5%, respectively. The most common adverse events were related to chemotherapy, not antiemetic therapy.
Grunberg et al.[30] (2009) Aprepitant 285 mg plus dexamethasone 20 mg plus palonosetron 0.25 mg prior to chemotherapy (single dose therapy)	MC, PRO Adult patients with documented solid tumor who were naïve to chemotherapy and were receiving a moderately emetogenic regimen	N=41 120 hours	Primary: Complete response (no vomiting or use of rescue therapy) during the overall period (0 to 120 hours) during the first chemotherapy cycle Secondary: Proportion of patients with no vomiting, no nausea, and no significant nausea during the acute (0 to 24 hour), delayed (24 to 120 hours), and overall periods	Primary: Complete response was seen in 51% of patients during the overall period. A total of 76% of patients experienced a complete response during the acute period and 66% of patients experienced a complete response during the delayed period. Secondary: No emesis was seen in 95% of patients during the overall period. No emesis was reported for 100% of patients during the acute period and for 95% of patients during the delayed period. No nausea was seen in 32% of patients during the overall period and 56% of patients had no significant nausea. During the acute period, 59% of patients had no nausea and 79% of patients had no significant nausea. During the delayed period, 41% of patients had no nausea and 59% of patients had no significant nausea. There were no major adverse events seen during the study period that were attributed to the antiemetic regimen.
Gao et al.[31] (2013) Aprepitant 125 mg 1 hour before chemotherapy on day 1, and 80 mg once daily on the	OS, PRO Patients were consecutively included if they received 3-day cisplatin-based (25 mg/m^2/day)	N=41 8 days	Primary: Complete response in the overall phase of CINV Secondary: Complete response in the acute and	Primary and Secondary: Seven (17.1%) patients had no nausea, 22 (53.7%) experienced grade 1 nausea and 12 (29.2%) experienced grade 2 nausea. With regard to acute and delayed phase, 24.4 and 36.6% of patients were prevented from nausea. The complete response rate in the acute, delayed and overall phases was achieved in 63.4, 78.0 and 58.5% of patients respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
following 2 days, palonosetron 0.5 mg IV once daily on the days 1 and 3, and dexamethasone 5 mg IV once daily from day 1 to day 3	chemotherapy and had never treated with aprepitant before		delayed phases, safety and the severity of nausea	Regarding single days of the acute phase, the complete response rate decreased from 85.4% on day one to 65.8% on day three. In 23 patients (56.1%) who received the study treatment more than one cycle, the cumulative emetic protection rate after five cycles was 0.82. Regardless of cause, the most common side effects were hiccups (31.7%), fatigue (17.1%), headache (14.6%) and constipation (12.2%).
Hesketh et al.[32] (2012) All patients received the following antiemetics: day 1: aprepitant 125 mg 1 hours before chemotherapy; dexamethasone 8 to 10 mg IV or orally 30 minutes before chemotherapy; palonosetron 0.25 mg IV 30 minutes before chemotherapy; on days 2 to 3, dexamethasone 4 mg orally and aprepitant 80 mg orally each morning	OS, PRO Patients were required to have pathologically documented breast cancer and be ≥18 years of age, chemotherapy naïve, have a Karnofsky performance status of ≥60, and scheduled to receive their first course of chemotherapy with cyclophosphamide (≥500 mg/m^2) and doxorubicin (60 mg/m^2)	N=36 5 days	Primary: Proportion of patients achieving complete response during the 120-hour study period Secondary: Acute complete response (no emesis, no rescue antiemetics during the 24 hours following chemotherapy); acute complete control (no emesis, no nausea, no rescue antiemetics during the 24 hours following chemotherapy); delayed complete response (no emesis, no rescue antiemetics during hours 24–120 following	Primary: Complete response for the 120-hour study period was achieved in 18 (50%) patients. Secondary: Acute and delayed complete response rates were 81 (27/36) and 61% (22/36), respectively. No emesis rates for the acute, delayed, and overall study periods were 97 (35/36), 94 (34/36), and 92% (33/36), respectively. Complete control rates for the acute, delayed, and overall study periods were 53 (19/36), 36 (13/36), and 31% (11/36), respectively. No nausea rates for the acute, delayed, and overall study periods were 53 (19/36), 42 (15/36), and 36% (13/36), respectively. Overall 22 patients (61%) experienced some degree of nausea. Six patients (17%) noted moderate nausea. Antiemetic therapy was well tolerated overall. The most common treatment-related adverse events were headache in five patients (15%) and fatigue in four patients (10%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			chemotherapy); delayed complete control (no emesis, no nausea, no rescue antiemetics during hours 24–120 following chemotherapy); and safety	
Mandanas et al.[33] (2005) Dolasetron 100 mg IV prior to chemotherapy, then 100 mg by mouth eight to 12 hours afterward on each day of chemotherapy vs ondansetron 32 mg IV prior to chemotherapy, then 8 mg by mouth eight to 12 hours afterward on each day of chemotherapy Other antiemetic medications were allowed.	MC, OL, RCT Patients receiving high-dose myeloablative chemotherapy	N=197 24 hours	Primary: Total response (no emetic episodes and no nausea); complete response (no emetic episodes with no rescue antiemetic medication); major response (one to two emetic episodes with no rescue antiemetic medications; failure (≥2 emetic episodes in any 24-hour period) Secondary: Not reported	Primary: There was no significant difference in the prevention of nausea and vomiting associated with high-dose chemotherapy with dolasetron compared to ondansetron (P=0.956). Total response: Dolasetron (9.6%) vs ondansetron (7.4%) Complete response: Dolasetron (36.1%) vs ondansetron (39.5%) Major response: Dolasetron (26.5%) vs ondansetron (25.9%) Treatment failure: Dolasetron (27.7%) vs ondansetron (27.2%) Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lofters et al.[34] (1997) Dolasetron 2.4 mg/kg IV followed by dolasetron 200 mg by mouth (arm one) vs dolasetron 2.4 mg/kg IV plus dexamethasone 8 mg IV followed by dexamethasone 8 mg by mouth (arm two) vs dolasetron 2.4 mg/kg IV plus dexamethasone 8 mg IV followed by dexamethasone 8 mg by mouth and dolasetron 200 mg by mouth (arm three) vs ondansetron 32 mg IV or 8 mg by mouth twice daily without	DB, PG, RCT Patients receiving seven days of moderately emetogenic chemotherapy	N=696 7 days	Primary: Control of nausea and vomiting in the first 24 hours, complete response was no episode of emesis Secondary: Mean nausea score based on a visual analog scale, rates of complete protection after seven days of treatment	Primary: In the dolasetron arms, 57% had complete protection for the first 24 hours compared to the ondansetron arms which had 67% (P=0.013). Secondary: The mean nausea score was more pronounced on the dolasetron arm, but the difference did not reach statistical significance (P=0.051). The mean nausea score was significantly reduced with the addition of dexamethasone to either dolasetron or ondansetron (P=0.001). Complete protection rates over seven days was not statistically different (P=0.459) between dolasetron (36%) and ondansetron (39%). The addition of dexamethasone to both dolasetron and ondansetron showed statistical improvement compared to no dexamethasone in protection from emesis over seven days (P<0.001). Dizziness and vision abnormalities were more common in the ondansetron group compared to dolasetron (P<0.001). Diarrhea was more common in the dolasetron group (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dexamethasone followed by ondansetron 8 mg by mouth twice daily (arm four) vs ondansetron 32 mg IV or 8 mg by mouth twice daily with dexamethasone 8 mg IV followed by ondansetron 8 mg by mouth twice daily and dexamethasone 8 mg by mouth (arm five) vs ondansetron 32 mg IV or 8 mg by mouth twice daily with dexamethasone 8 mg IV followed by dexamethasone 8 mg by mouth (arm six)				
Eisenberg et al.[35] (2003) Dolasetron 100 mg IV	DB, MC, PG, RCT Patients receiving moderately emetogenic	N=592 5 days	Primary: Complete response (no emetic episodes and no need for rescue	Primary: The proportion of patients with complete response was not statistically different between the two palonosetron doses and dolasetron [palonosetron 0.25 mg 63% vs dolasetron 100 mg 52.9% (97.5% CI, -1.7 to 21.9; P=0.049)], [palonosetron 0.75 mg, 57.1% vs dolasetron 100 mg, 52.9%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs palonosetron 0.25 mg IV vs palonosetron 0.75 mg IV	chemotherapy, study drug given 30 minutes before chemotherapy, dexamethasone could be added 15 minutes before chemotherapy		medication) during the first 24 hours after chemotherapy Secondary: Complete response during hours 24 to 120	(97.5% CI, -7.7 to 16.2; P=0.412)]. (Note: Significance was P<0.025 using the one-sided Fisher exact test). Secondary: Complete response with palonosetron 0.75 and 0.25 mg were significantly higher in the delayed phase (hours 24 to 120) compared to dolasetron (palonosetron 0.75 mg vs dolasetron 100 mg; P<0.001 and palonosetron 0.25 mg vs dolasetron 100 mg; P=0.004). Adverse effects were similar and mild for all three groups.
Meiri et al.[36] (2007) <u>Day two (fixed dose)</u> Dronabinol 2.5 mg by mouth four times daily vs ondansetron 8 mg by mouth twice daily vs dronabinol 2.5 mg by mouth four times daily plus ondansetron 8 mg by mouth twice daily vs placebo	DB, PC, PG, RCT Patients ≥18 years of age with malignancy that did not involve the bone marrow and be undergoing chemotherapy including a moderately to highly emetogenic regimen	N=64 5 days	Primary: Total response two to five days after moderately to highly emetogenic chemotherapy (no vomiting and/or retching, intensity of nausea <5 mm, and no use of rescue medication) Secondary: Complete response rate, nausea status, episodes of vomiting and/or retching, duration of nausea and vomiting and/or retching, intensity of nausea, Eastern Cooperative Oncology Group score, and quality of life	Primary: Total response during active treatment did not differ between treatment groups (P=NS) due to small sample size. Improvement (range 47 to 58%) in three active treatment groups compared to placebo (20%) implies clinically relevant improvement (days two to five). Secondary: Overall response to treatment: dronabinol (71%), ondansetron (64%), combination (53%), placebo (15%). Combination therapy did not provide benefit beyond that observed with either agent alone. Complete responder rate was 62% with dronabinol, 60% with combination therapy, 58% with ondansetron, and 20% with placebo (P<0.005 vs placebo). All active treatments reduced the intensity of nausea vs placebo (P<0.05). No significant difference was observed among groups for mean number of episodes of vomiting and/or retching. Active treatments reduced the number of episodes of vomiting to 0 by days four and five. Active treatment reduced the duration of vomiting/retching to 0 hours in all groups by days four and five.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<u>Days three to five (flexible dose)</u> dronabinol 2.5-5 mg by mouth four times daily vs ondansetron 4 to 8 mg by mouth twice daily vs dronabinol 2.5 to 5 mg by mouth four times daily plus ondansetron 4 to 8 mg by mouth twice daily vs placebo Day one regimen consisted of dexamethasone 20 mg and ondansetron 16 mg administered to all study participants. Dronabinol 2.5 mg was also administered on				Duration of nausea was comparable among all groups. Changes from baseline in Eastern Cooperative Oncology Group score were significant in patients receiving dronabinol vs placebo (P=0.036, in favor of placebo) and in patients receiving dronabinol vs combination therapy (p=0.028). Improvement in quality of life was observed only in patients receiving dronabinol vs combination therapy (3.6; P=0.033, in favor of dronabinol).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
day one in the three active treatment arms.				
Jaing et al.[37] (2004) Granisetron 0.5 to 1 mg by mouth vs ondansetron 0.15 mg/kg IV for two doses (one hour prior to chemotherapy and four hours later) and then a single oral dose (eight hours after first dose)	OL, PRO, RCT, XO Patients three to 18 years of age receiving chemotherapy	N=33 24 hours	Primary: Number of emetic episodes within 24 hours of chemotherapy Secondary: Therapeutic success (defined as 0 to 2 emetic episodes), therapeutic failure (defined as ≥3 vomiting episodes)	Primary: Complete efficacy for granisetron and ondansetron was 60.6 and 45.5%, respectively (P=0.227). Secondary: Therapeutic success was 84.8% in the granisetron group and 87.9% in the ondansetron group (P=1.00). Therapeutic failure for granisetron and ondansetron was 15.2 and 12.1%, respectively (P=1.00).
Kalaycio et al.[38] (1998) Granisetron 0.5 mg IV bolus then 1 mg/24 hour continuous infusion vs ondansetron 8 mg IV bolus then 24 mg/24 hour continuous infusion	DB, PRO, RCT Breast cancer patients receiving cyclophosphamide, thiotepa and carboplatin, in addition to dexamethasone	N=45 7 days	Primary: Incidence and severity of nausea Secondary: Incidence of emesis, number of patients experiencing no emetic episodes	Primary: There was no difference in the incidence of nausea between the ondansetron and granisetron treatment groups (P=0.86). Secondary: The incidence of emesis was not statistically different between the granisetron and ondansetron treatment groups (P=0.67). There was no statistical difference between treatment groups in regard to the number of patients experiencing no emetic episodes (granisetron 9.1% vs ondansetron 17.4%; P=0.67). There were no significant differences in adverse effects between the granisetron and ondansetron treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dempsey et al.[39] (2004) Granisetron 10 µg/kg or 1 mg IV vs ondansetron 8 mg IV vs ondansetron 32 mg IV	RETRO Prophylactic efficacy in patients with breast cancer treated with cyclophosphamide	N=224 72 hours	Primary: Incidence of acute nausea or vomiting occurring within 24 hours of completion of chemotherapy Secondary: Incidence of delayed emesis (occurring 25 to 72 hours after chemotherapy), total control of CINV with or without dexamethasone	Primary: The incidence of acute nausea was statistically greater with ondansetron 8 mg IV (50%) than ondansetron 32 mg IV (26%) or granisetron (25%; P<0.01 for both comparisons). The incidence of acute emesis was not different among the three groups. Secondary: The incidence of delayed nausea was 6% for ondansetron 8 mg IV, 9% for ondansetron 32 mg, and 9% for granisetron; the incidences were not statistically different among treatment groups. The incidence of delayed emesis was not different among the three groups. Total control of CINV without dexamethasone was 35% for ondansetron 8 mg, 33% for ondansetron 32 mg and 69% for granisetron (P=0.05 for granisetron compared to ondansetron 8 mg). With the addition of dexamethasone, total control of CINV was not significantly different among the three groups.
Lacerda et al.[40] (2000) Granisetron 3 mg IV vs ondansetron 16 mg IV vs ondansetron 24 mg IV vs	DB, PG, RCT Patients undergoing autologous or allogenic stem cell transplantation received daily IV doses of 5-HT_3 antagonist during days of chemotherapy	N=100 Treatment duration not reported	Primary: Complete response (no episodes of nausea or vomiting) Secondary: Major response (one episode), minimal response (two to four episodes) and failure (more than four episodes of nausea or vomiting)	Primary: When comparing rates of complete response, there was a significant difference in the ondansetron 24 mg group (62.5%) compared to the granisetron group (27.8%; P=0.015) and tropisetron (16.7%; P=0.003). (Complete response for ondansetron 16 mg was 31.3%, but statistical difference from ondansetron 24 mg was not reported.) There were no statistical differences in complete response rates between ondansetron 16 mg (31.3%), granisetron and tropisetron. Secondary: There was a trend in the major response of ondansetron 24 mg vs granisetron (P=0.064). A significant difference was not observed with ondansetron 16 mg. No statistically significant differences were found between ondansetron 16 mg, granisetron or tropisetron.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tropisetron 5 mg IV				
Walsh et al.[41] (2004) Granisetron 10 µg/kg IV daily vs ondansetron 0.15 mg/kg IV every eight hours	DB, PG, PRO, RCT Patients undergoing nontotal body irradiation-containing conditioning agents in hematopoietic stem cell transplant, in addition to dexamethasone and lorazepam	N=96 24 hours after completion of chemotherapy	Primary: Number of emetic episodes, nausea report until 24 hours after cessation of chemotherapy Secondary: Rates of complete response or major response	Primary: The median number of emetic episodes for the granisetron arm was three and for the ondansetron arm was one (P=0.228). Rating of nausea was equal between the groups on all days of measurement (P=0.563 to P=1.0). Secondary: On day one, complete response for the granisetron group was 83% and major response was 13%. Complete response for the ondansetron group was 90% and major response was 6%. These differences were not statistically significant (P=1.00). There were no differences in adverse effects.
Orchard et al.[42] (1999) Granisetron 7.5 µg/kg/dose (≥18 years) or 10 µg/kg/dose (<18 years) every 12 hours vs ondansetron 8 mg IV bolus then 0.015 mg/kg/hour (≥18 years) or 0.15mg/kg bolus then 0.03 mg/kg/hour (<18 years)	DB, PRO, RCT Patients 2 to 65 years of age undergoing hematopoietic cell transplantation, in addition to dexamethasone	N=187 9 days	Primary: Number of emetic episodes Secondary: Mean nausea score, complete control over emesis as defined by no emetic episodes and major control over emesis as defined by emetic episodes in 24 hours	Primary: There were no statistical differences between granisetron (0.73) and ondansetron (0.86) for episodes of emesis (P=0.32). Secondary: There were no statistical differences in the mean nausea scores between granisetron and ondansetron (1.17 vs 1.29; P=0.32). When stratified by age: there were no statistical differences in the <18 year old group between granisetron (0.54) and ondansetron (0.87) in mean episodes of emesis per day (P=0.08) or for mean nausea score per day (granisetron 0.82, ondansetron 1.14; P=0.09). There were no statistical differences in the ≥18 year old group between granisetron (0.80) and ondansetron (0.86) in mean episodes of emesis per day (P=0.71) or for mean nausea score per day (granisetron 1.29, ondansetron 1.36; P=0.65). There were no differences between granisetron and ondansetron in number of days in which emesis control was complete (P=0.68) or major (P=0.68).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
del Giglio et al.[43] (2000) Granisetron various IV and oral regimens vs ondansetron various IV and oral regimens	MA Patients receiving highly or moderately emetogenic chemotherapy	N=6,467 (14 trials) Variable duration	Primary: Comparison of prophylaxis of acute or delayed nausea and vomiting in highly or moderately emetogenic chemotherapy Secondary: Not reported	Primary: For all scenario comparisons (acute highly emetogenic, acute moderately emetogenic, delayed highly emetogenic, delayed moderately emetogenic), there were no statistical differences in efficacy between granisetron and ondansetron for rates of nausea or vomiting. There was only one study that showed differences in toxicity between granisetron and ondansetron. In this study, ondansetron was associated with more dizziness and abnormal vision than granisetron. Secondary: Not reported
Suzuki et al.[44] (2016) TRIPLE Granisetron (1 mg IV) vs palonosetron (0.75 mg IV) Both arms were treated with dexamethasone (12 mg on day 1 and 8 mg on days 2 to 4) and aprepitant (125 mg on day 1 and 80 mg on days 2 to 3)	DB, RCT Patients with cisplatin-naïve solid tumor were eligible if they were to receive a cisplatin (≥50 mg/m^2)-based highly emetogenic chemotherapy regimen in hospital admission	N=827 5 days	Primary: Complete response (no vomiting/ retching and no rescue medication) at the 0 to 120 h period Secondary: Complete control (no vomiting/ retching, no rescue medication, and no more than mild nausea) and total control (no vomiting/retching, no rescue medication, and no nausea).	Primary: Of 827 total evaluable patients, 65.7% in the palonosetron group had a complete response at the 0 to 120 hour period when compared with 59.1% in the granisetron group (P=0.0539). Both arms had the same complete response rate of 91.8% at the acute (0 to 24 h) period, while at the delayed (24 to 120 h) period, the palonosetron group had a significantly higher complete response rate than the granisetron group (67.2 vs 59.1%, P=0.0142). Secondary: In secondary end points, the palonosetron group had significantly higher rates than the granisetron group at the 0 to 120 h period (complete control rate: 63.8 vs 55.9%, P=0.0234; total control rate: 47.6 vs 40.7%, P=0.0369) and delayed periods (complete control rate: 65.2 vs 55.9%, P=0.0053; total control rate: 48.6 vs 41.4%, P=0.0369). For comparisons in the acute period, P=1.0000.
Saito et al.[45] (2013) Granisetron 40	DB, MC, PC, RCT Patients ≥20 years of age who received	N=347 3 days	Primary: Percentage of patients who achieved a	Primary: The percentage of patients who achieved a complete response (no emesis and no rescue therapy) in the overall phase (0–120 h) was significantly higher in the fosaprepitant group (64%; 95% CI, 16 to 46 vs 47%; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/kg IV and dexamethasone (20 mg) on day 1 and dexamethasone (8 mg) on days 2 and 3 vs fosaprepitant (150 mg), granisetron (40 µg/kg), and dexamethasone (10 mg) on day 1, dexamethasone (4 mg) on day 2, and dexamethasone (8 mg) on day 3	cancer chemotherapy containing cisplatin (≥70 mg/m^2)		complete response (no emesis and no rescue therapy) in the overall phase Secondary: In the acute and delayed phases, the percentages of patients with a complete response, the percentages of patients with complete protection (no emesis, no rescue therapy, and no significant nausea) in the overall, acute, and delayed phases, with no emesis in the overall, acute, and delayed phases, and with no rescue therapy in the acute phase, percentages of patients with no rescue therapy in the overall phase	10 to 36; P=0.0015. Secondary: In the acute and delayed phases, the percentages of patients with a complete response were significantly higher in the fosaprepitant group (acute phase, 94 vs 81%; P=0.0006, delayed phase, 65 vs 49%; P=0.0025). Among the patients who had previously been treated with cisplatin and experienced vomiting, the complete response rates in the overall phase were higher in the fosaprepitant group (60.0 vs 30.3%). The percentages of patients with complete protection (no emesis, no rescue therapy, and no significant nausea) in the overall, acute, and delayed phases, with no emesis in the overall, acute, and delayed phases, and with no rescue therapy in the acute phase were significantly higher in the fosaprepitant group. The percentages of patients with no rescue therapy in the overall phase also did not differ significantly.
Jordan et al.[45] (2007) Granisetron vs ondansetron	MA Patients receiving prophylaxis of acute CINV	N=12,343 (44 trials) <24 hours	Primary: Complete acute response or complete absence of vomiting within first 24 hours after	Primary: Granisetron vs ondansetron: Pooled ORs (including all dose schedules) revealed an overall equivalence of granisetron and ondansetron (OR, 1.033; 95% CI, 0.93 to 1.142). Low-dose granisetron (3 mg IV) showed a possible advantage in non-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
granisetron vs tropisetron ondansetron vs tropisetron ondansetron vs dolasetron			chemotherapy Secondary: Not reported	cisplatin-based studies compared to low-dose ondansetron (8 mg IV) (P=0.015). Granisetron (2 or 3 mg) was similar in efficacy to high-dose ondansetron (24 or 32 mg) for both cisplatin-based and non-cisplatin-based studies (OR, 1.053; 95% CI, 0.916 to 1.211). Granisetron and ondansetron demonstrated similar efficacy in trials that did not include administration of dexamethasone. Granisetron demonstrated a significant advantage over tropisetron (OR, 1.463; 95% CI, 1.069 to 2.002). Ondansetron was similar in efficacy to tropisetron (OR, 1.103; 95% CI, 0.835 to 1.458). No difference in efficacy was demonstrated with ondansetron vs dolasetron in one cisplatin-based study. There was a significant advantage for ondansetron vs dolasetron in one of two non-cisplatin-based studies (P=0.01). Secondary: Not reported
Schnadig et al.[47] (2016) Granisetron injection extended-release 500 mg subcutaneously vs ondansetron 0.15 mg/kg intravenously	DB, DD, PRO, RCT Patients 18 to 80 years of age with a histologically or cytologically confirmed malignancy, scheduled to receive single-day highly emetogenic chemotherapy, and entering the first cycle of their	N=942 6 days	Primary: Delayed-phase (24 to 120 hours) complete response (no emesis or rescue medication) Secondary: Overall-phase complete response and rate of no emetic episodes	Primary: The proportion of patients with delayed-phase complete response was significantly greater with the granisetron (291/450, 64.7%) versus ondansetron regimen (256/452, 56.6%); the absolute treatment difference was 8.0% (95% CI, 1.7 to 14.4; P=0.014). Secondary: Overall-phase complete response was numerically higher with the granisetron (263/450, 58.4%) versus ondansetron regimen (239/452, 52.9%), but not statistically significantly (treatment difference: 5.6%; 95% CI, -0.9 to 12.1; unadjusted P=0.092). Rates of no emetic episodes in granisetron and ondansetron arms were 82.2% (370/450) and 79.2% (358/452), respectively (unadjusted P=0.254). Controlling for overall type I error (Hochberg model) resulted in no secondary end points achieving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Both treatments were given with dexamethasone and fosaprepitant	regimen			statistical significance.
Raftopoulos et al.[48] (2015) Granisetron injection extended-release 250 or 500 mg subcutaneously vs palonosetron 0.25 mg intravenously	DB, DD, MC, NI, RCT Patients ≥18 years of age with histologically or cytologically confirmed malignancy and scheduled to receive single-day moderately or highly emetogenic chemotherapy	N=1395 5 days	Primary: Percentage of patients achieving a complete response (no emetic episodes and no use of rescue medications) during the acute (0 to 24 h) and delayed (24 to 120 h) phases after chemotherapy cycle one Secondary: Safety and percentage of patients with complete response over the entire (0 to 120 h) period during cycle one	Primary: Both granisetron doses were noninferior to palonosetron in preventing acute CINV after moderately emetogenic chemotherapy (complete response, 74.8%; 97.5% CI, -9.8 to 9.3 and 76.9%; 97.5% CI, -7.5 to 11.4, respectively, vs 75.0% palonosetron) and after highly emetogenic chemotherapy (complete response, 77.7%; 98.33% CI, -11.5 to 5.5 and 81.3%; 98.33% CI, -7.7 to 8.7, respectively, vs 80.7% palonosetron). Granisetron 500 mg was noninferior to palonosetron in preventing delayed CINV after moderately emetogenic chemotherapy (complete response, 58.5%; 98.33% CI, -9.5 to 12.1; vs 57.2% palonosetron) but not superior in preventing delayed CINV after highly emetogenic chemotherapy. Secondary: After administration of moderately emetogenic chemotherapy, overall complete response rates (95% CI difference vs palonosetron) with granisetron 250 and 500 mg were 48.6% (−2.9 to 6.2) and 53.8% (−7.8 to 11.4), respectively, versus 51.9% for palonosetron 0.25 mg. After administration of highly emetogenic chemotherapy, complete response rates (95% CI difference vs palonosetron) with granisetron 250 and 500 mg were 57.6% (−11.8 to 6.1) and 63.3% (−5.9 to 11.6), respectively, versus 60.5% for palonosetron 0.25 mg over the entire treatment period (0 to 120 h).
Yang et al.[49] (2016) Granisetron transdermal patch for seven days vs	AC, DB, RCT Cancer patients who were administrated to multiday (≥2 days) moderately or highly emetogenic chemotherapy	N=313 14 days	Primary: Percentage of patients achieving complete control from chemotherapy initiation until 24 hours after final administration	Primary: Complete control was achieved by 67 (47.52%) patients in the granisetron transdermal group and 83 (59.29%) patients in the oral granisetron group (P=0.0559) in the per-protocol set. The difference of the complete control percentage mainly occurred on the first day of chemotherapy between the groups. The complete control was 70.13% on day one in the granisetron transdermal group, which was significantly lower than that of 91.03% in the oral granisetron group in the full analysis set. In the following days of chemotherapy, the complete control percentage was similar between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
granisetron oral 2 mg/day, ≥2 days			Secondary: Safety and tolerability	groups. In the full analysis set, the number of patients who achieved complete control was 72 (46.75%) in the granisetron transdermal group and 92 (58.97%) in the oral granisetron group (P=0.0404). Secondary: A total of 313 patients were included in the safety population, of whom 212 experienced adverse events. The main adverse events included constipation, anorexia, cough, and fatigue.
Seol et al.[50] (2016) Granisetron transdermal patch for 7 days vs palonosetron intravenous 0.25 mg/day for 1 day All patients received both treatments on separate chemo cycles	AC, MC, OL, RCT, XO Patients ≥20 years of age who were scheduled to receive a moderately emetogenic chemotherapy	N=196 348 chemo cycles	Primary: Percentage of chemotherapy cycles achieving complete response (CR; defined as no emetic episodes and no rescue medication use) during the acute phase (0 to 24 h in post-chemotherapy) Secondary: Complete response at various time periods, total control (defined as no emetic episode, no nausea and no need for rescue medication)	Primary: The granisetron transdermal cycles showed non-inferiority to palonosetron cycles during the acute phase: CR was achieved by 124 (75.2 %) patients in the granisetron transdermal cycles, and 134 (79.8 %) patients in the palonosetron cycles (treatment difference, −4.6%; 95% CI, −13.6 to 4.4). The stratified analysis showed that granisetron transdermal was not different to palonosetron in terms of the risk factors of CINV, such as female sex, age, alcohol history. Secondary: For secondary efficacy analyses, similar proportions of cycles with a complete response were noted in the palonosetron cycle and granisetron transdermal cycle during the overall 0 to 72 hour period. Response was assessed every day; the proportion of cycles with a CR was not significantly different in the palonosetron cycle and granisetron transdermal cycle. The proportion of cycles with complete control and total control was not significantly different in the palonosetron cycle and granisetron transdermal cycle during the acute period and the overall period. The severity of nausea, vomiting, and/or retching per day and total days of treatment was not different between the groups. In the both groups, small portion of patients had severe nausea during acute phase (3 of 175 patients in the granisetron transdermal cycle and 1 of 173 patients in the palonosetron cycle).
Abali et al.[51] (2007) Ondansetron 8 mg IV	OL, PRO Patients receiving highly and moderately emetogenic	N=158 5 days	Primary: Emesis control and nausea control in acute (within 24 hours of chemotherapy) and	Primary: During the acute period, there were no significant differences between the treatment groups with respect to the following outcomes (P=0.877): • Tropisetron: complete response (80.4%), major response (13.7%), minor response (3.9%). • Ondansetron: complete response (72.1%), major response (18%),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs granisetron 3 mg IV vs tropisetron 5 mg IV Dexamethasone 8 mg IV was coadministered with all treatments.	chemotherapy		delayed periods (between 25 and 120 hours), nausea, complete response (no emetic episodes), major response (≤2 emetic episodes), minor response (two to five emetic episodes), failure (≥5 emetic episodes or rescue medication) Secondary: Not reported	mR (4.9%). • Granisetron: complete response (71.7%), major response (21.7%), minor response (2.2%). During the delayed period, there were no significant differences between the treatment groups with respect to the following outcomes (P=0.527): • Tropisetron: complete response (68.6%), major response (19.6%), minor response (7.8%). • Ondansetron: complete response (68.9%), major response (11.5%), minor response (6.6%). • Granisetron: complete response (76.1%), major response (10.9%), minor response (4.3%). During the acute period, there were no significant differences between the treatment groups with respect to nausea (P=0.995): • Tropisetron: severe (11.8%), moderate (13.7%), mild (35.3%). • Ondansetron: severe (14.8%), moderate (14.8%), mild (34.4%). • Granisetron: severe (10.9%), moderate (13.0%), mild (39.1%). During the delayed period, there were no significant differences between the treatment groups with respect to nausea (P=0.527): • Tropisetron: severe (23.5%), moderate (13.7%), mild (25.5%). • Ondansetron: severe (19.7%), moderate (19.7%), mild (23.0%). • Granisetron: severe (19.6%), moderate (17.4%), mild (23.9%). Secondary: Not reported
Gralla et al.[52] (2003) Ondansetron 32 mg IV vs palonosetron 0.25	DB, PRO, RCT Patients receiving moderately emetogenic chemotherapy	N=570 5 days	Primary: Proportion of patients with no emetic episodes and no rescue medication (complete response) during the 24 hour period	Primary: Complete response rates were significantly higher for palonosetron 0.25 mg (81.0%) than ondansetron (68.6%) during the acute period (P<0.01). Secondary: Complete response rates were significantly higher for palonosetron than ondansetron at 24 to 120 hours (74.1 vs 55.1%; P<0.01) and overall 0 to 120 hours (69.3 vs 50.3%; P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV vs palonosetron 0.75 mg IV			after chemotherapy (acute period) Secondary: Efficacy in treatment of delayed CINV (≤5 days post chemotherapy), overall tolerability	Complete response rates achieved with palonosetron 0.75 mg were numerically higher but not statistically different from ondansetron during all time intervals. Both treatments were well tolerated with adverse events reported in 16% of patients receiving palonosetron vs 13.9% of patients receiving ondansetron. Post hoc analysis revealed no differences in the duration of adverse events in patients treated with ondansetron vs palonosetron.
Mattiuzzi et al.[53] (2010) Ondansetron 8 mg IV followed by 24-hour continuos infusion 30 minutes before high-dose cytarabine until 12 hours after infusion end vs palonosetron 0.25 mg IV 30 minutes before chemotherapy, daily from day one of high-dose cytarabine up to day five vs palonosetron 0.25	DB, RCT Patients ≥18 years of age with acute myelogenous leukemia receiving high-dose cytarabine-containing chemotherapy	N=143 7 days	Primary: Prevention of emesis episodes, use of rescue medication during administration of chemotherapy (assessed as complete response) Secondary: Not reported	Primary: A numerically greater proportion of patients treated with palonosetron achieved a complete response, however, this difference was not significant. On day one, >77% of patients in each treatment arm were nausea-free. On days two through five, the proportion of patients who were nausea-free declined similarly across all three groups. On days six and seven, significantly more patients treated with palonosetron on days one through five were free from nausea compared to patients treated with ondansetron (P=0.001 and P=0.0247, respectively). Daily assessment of emesis did not show significant differences across treatment arms in terms of the number of patients without emesis. Fewer patients in the palonosetron treatment groups reported emesis compared to the ondansetron group. A significantly greater proportion of patients treated with palonosetron on days one through five reported having no or mild nausea on days six and seven compared to the ondansetron group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV 30 minutes before high-dose cytarabine on days one, three and five				
Kovács et al.[54] (2016) Ondansetron 150 µg/kg x 3 doses on day 1, each 4 hours apart vs palonosetron 10 µg/kg on day one vs palonosetron 20 µg/kg on day one	DB, DD, MC, NI, RCT Pediatric patients newborn to <17 years of age who were naive or non-naive to chemotherapy, and scheduled to undergo moderately or highly emetogenic chemotherapy for the treatment of malignant disease	N=493 120 hours post-chemotherapy	Primary: Complete response (no vomiting, retching, or use of rescue drugs) during the acute phase (0 to 24 h post-chemotherapy) of the first on-study chemotherapy cycle Secondary: Proportion of patients who achieved a complete response during the delayed (defined as >24 to 120 h after the start of chemotherapy on day 1) and overall phases (defined as 0 to 120 h after the start of chemotherapy on day 1)	Primary: During the acute phase, complete responses were recorded in 90 (54%) of 166 patients receiving 10 µg/kg palonosetron, 98 (59%) of 165 receiving 20 µg/kg palonosetron, and 95 (59%) of 162 receiving ondansetron. The complete response rate in the acute phase was therefore lower in the 10 µg/kg palonosetron group than in the ondansetron group (ΔCR −4.41%; 97.5% CI, −16.4 to 7.6; P=0.024). According to the preset margin, non-inferiority versus ondansetron was not shown for this dose. For the 20 µg/kg palonosetron and ondansetron groups, the ΔCR was 0.36%, with non-inferiority shown for this dose of palonosetron as the lower bound of the 97.5% CI of this difference (−11.7 to 12.4; P=0.0022) was greater than the preset non-inferiority margin (δ = –15%). Secondary: During the delayed phase, complete responses were recorded in 48 (29%) of 166 patients who received 10 µg/kg palonosetron, 64 (39%) of 165 who received 20 µg/kg palonosetron, and 46 (28%) of 162 who received ondansetron. The complete responses were therefore comparable for the 10 µg/kg palonosetron and ondansetron groups (ΔCR 0.42%; 95% CI, −9.4 to 10.3), and higher for the 20 µg/kg palonosetron group versus the ondansetron group (ΔCR 10.17%; 95% CI, −0.1 to 20.4). The proportional differences in complete responses recorded during the overall phase were similar to those recorded during the delayed phase, with the 20 µg/kg dose of palonosetron being more effective at achieving a complete response than ondansetron.
Tan et al.[55] (2018) Ondansetron 150 µg/kg x 3 doses	DB, PRO, RCT Pediatric patients newborn to <18 years of age who	N=565 120 hours post-chemotherapy	Primary: Complete response (no nausea and no emesis, no rescue antiemetics) during	Primary: There were no significant differences of complete response rates during the acute phase among three groups (palonosetron 5 µg/kg: 69.1%, palonosetron 10 µg/kg: 69.7%, ondansetron: 64.6%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs palonosetron 5 µg/kg on day one vs palonosetron 10 µg/kg on day one All patients across the three groups received intravenous dexamethasone	were naive or non-naive to chemotherapy, and scheduled to undergo moderately or highly emetogenic chemotherapy for the treatment of cancer		the acute phase Secondary: Complete response during the delayed and overall phases	Secondary: In the delayed phase, 10 µg/kg palonosetron showed superiority (P<0.017) to 5 µg/kg palonosetron and ondansetron (complete response: 53.5% vs 39.8% vs 32.8%, respectively); however, there was no difference between the 5 µg/kg palonosetron and ondansetron groups (P value not reported). In the overall phase, both palonosetron groups (10 µg/kg: 42.7%; 5 µg/kg: 36.5%) had higher control rates than ondansetron group (21.7%); no statistically significant difference was observed between the palonosetron groups.
Nakagaki et al.[56] (2017) Ondansetron 32 mg infusion over 24 hours vs palonosetron 0.25 mg IV single-dose vs olanzapine 10 mg by mouth (while continuing ondansetron IV 8 mg three times a day)	OL, PRO, RCT Patients 18 to 70 years of age receiving allogeneic or autologous HSCT following high-dose chemotherapy experiencing emesis or moderate to severe nausea despite prophylactic anti-emetics	N=62 48 hours	Primary: Composite outcome of no emesis, no use of rescue medication, and nausea score reduction of ≥50% Secondary: Nausea score reduction of ≥50%	Primary: The primary endpoint was achieved in 6% (1/18) of patients on ondansetron, 45% (10/22) of patients on olanzapine, and 18% (4/22) of patients on palonosetron at 24 hours. At 48 hours, it was achieved in 6% (1/17), 64% (14/22), and 18% (4/22), respectively. Overall, olanzapine was significantly more effective at controlling breakthrough CINV compared to ondansetron at both 24 and 48 hours (P=0.01 and 0.0002, respectively). Olanzapine was also more effective than palonosetron at 48 hours (P=0.005). Palonosetron failed to show statistically significant benefits above ondansetron at 24 hours (P=0.36) and at 48 hours (P=0.36). Secondary: Nausea score reduction of ≥50% was observed in 17% (3/18) of patients on ondansetron, 60% (12/20) of patients on olanzapine, and 62% (13/21) of patients on palonosetron, and 35% (6/17), 71% (15/21), and 43% (9/21) at 24 and 48 hours, respectively. Olanzapine was more effective than ondansetron at controlling nausea at both 24 and 48 hours (P=0.0009 and P=0.048, respectively). However, there was no significant difference between olanzapine and palonosetron in reduction of nausea score ≥50% at either time point. Palonosetron was superior to ondansetron at nausea control at 24 hours (P=0.008) but not at 48 hours.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were administered the standard prophylaxis of IV ondansetron 8 mg three times a day plus a single dose of oral aprepitant 165 mg				
Davidson et al.[57] (1999) Ondansetron 8 mg oral tablet twice daily for three days vs ondansetron 8 mg orally disintegrating tablet twice daily for three days	DB, MC, RCT Patients receiving cyclophosphamide	N=427 3 days	Primary: Complete or major control of emesis on their worst of days one through three Secondary: Not reported	Primary: Complete or major control of emesis was achieved by 80% of patients treated with the oral tablet and 78% of patients treated with the orally disintegrating tablet (90% CI -8.6 to 4.4 with $\pm$15% limit for equivalence). Complete control of emesis for days one through three was not significantly different between the treatment groups (63 vs 64% for patients treated with the oral tablet and orally disintegrating tablet, respectively). There was no significant difference in overall incidence of adverse effects between the two formulations. The most common adverse effects reported and those most frequently assessed as drug-related were headache (11 vs 9% for patients treated with the oral tablet and orally disintegrating tablet, respectively) and constipation (both 10%). Secondary: Not reported
Yu et al.[58] (2009) Palonosetron 0.25 mg IV as a single dose vs granisetron 3 mg	DB, MC, PG, RCT Chinese patients undergoing highly emetogenic chemotherapy regimens	N=240 120 hours	Primary: Complete response rate (defined as no emetic episodes and no rescue medication) during the first 24 hours after chemotherapy Secondary:	Primary: The complete response rate for acute vomiting during the first 24 hours after chemotherapy was not significantly different with palonosetron (82.7%) compared to granisetron (72.1%; P=NS). Secondary: The complete response rates for delayed vomiting were not significantly different among the treatment groups (24 to 48 hours; P=0.3279, 48 to 72 hours; P=0.8897, 72 to 96 hours; P=0.7815, 96 to 120 hours; P=0.0738).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV as a single dose Rescue medication was permitted.			Complete response rates during successive 24 hour time periods (24 to 48, 48 to 72, 72 to 96 and 96 to 120); safety	There were no clinically relevant differences between groups with regard to overall incidence of adverse events.
Tian et al.[59] (2011) Palonosetron 0.25 mg IV for first cycle followed by granisetron 3 mg IV for second cycle vs granisetron 3 mg for first cycle followed by palonosetron 0.25 mg IV for second cycle	DB, RCT, XO Patients 18 to 69 years of age with histologically or cytologically confirmed malignant disease who were chemotherapy naïve or non-naïve, having a Karnofsky score ≥60, scheduled to receive two courses of moderately emetogenic chemotherapy	N=144 120 hours	Primary: Proportion of patients with complete response 0 to 24 hours post-chemotherapy administration Secondary: Proportion of patients with complete response at 24 to 120 hours and 0 to 120 hours post-chemotherapy administration	Primary: Treatment with palonosetron and granisetron resulted in similar complete response rates (75.0 vs 69.4%, 58.3 vs 56.9% and 55.6 vs 52.8% for 0 to 24 hours, 24 to 120 hours and 0 to 120 hours following chemotherapy, respectively). Treatment with palonosetron resulted in numerically higher complete response rates compared to granisetron in the acute phase (0 to 24 hours, 71.1 vs 65.5%), the delayed phase (24 to 120 hours, 60.2 vs 55.8%) and overall (0 to 120 hours, 53.1 vs 50.0%), although the difference were not significant. The NI of palonosetron compared to granisetron was established, as the lower boundaries of the 95% Cis of the difference in complete response rates were greater than the pre-set threshold of -15% (-3.54, -5.61 and -6.96 for 0 to 24, 24 to 120 and 0 to 120 hours following chemotherapy, respectively). Secondary: Treatment with palonosetron and granisetron resulted in comparable results for major protection from vomiting, major protection from nausea, total control and complete control in the acute phase, delayed phase and overall following chemotherapy. The time to the first emetic episode was comparable for the palonosetron and granisetron treatment groups. Although the first quartile time to the first emetic episode was longer for the palonosetron treatment group compared to the granisetron group (19 vs 16 hours, respectively), this difference was not significant.
Saito et al.[60] (2009) Palonosetron 0.75 mg IV as a single	DB, DD, MC, PG, RCT Patients ≥20 years of age who were	N=1,114 120 hours	Primary: Proportion of patients with a complete response during the acute	Primary: There was no difference in the proportion of patients achieving a complete response in the acute phase (75.3 vs 73.3% for the palonosetron and granisetron treatment groups, respectively; P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose vs granisetron 40 µg/kg IV as a single dose Administration of prophylactic dexamethasone (16 mg IV) within 45 minutes before palonosetron or granisetron on day one was required. Additionally, dexamethasone (8 mg IV for patients receiving cisplatin or 4 mg orally for patients receiving an anthracycline and cyclophosphamide, was administered on days two (24 to 26 hours after chemotherapy) and three (48 to 50 hours after chemotherapy).	scheduled to receive a single dose of highly emetogenic chemotherapy on day one (cisplatin >50 mg/m^2, doxorubicin-cyclophosphamide, or epirubicin-cyclophosphamide)		phase (0 to 24 hours post-chemotherapy) and the proportion with complete response during the delayed phase (24 to 120 hours post-chemotherapy) Secondary: Complete response during the entire 0 to 120 hours study period, proportion of patients with complete control, number of emetic episodes, time to first emetic episode, time to administration of rescue antiemetic	A significantly greater proportion of patients in the palonosetron group achieved a complete response compared to the granisetron group (56.8 vs 44.5%, respectively; P<0.0001) during the delayed phase. Secondary: There was a greater proportion of patients with a complete response in the palonosetron group compared to the granisetron group (54.5 vs 40.4%; P=0.0001). More patients achieved complete control in the palonosetron group compared to the granisetron group (47.9 vs 38.1%; P=0.0007). The proportion of patients with no nausea or no emetic episodes was similar during the acute phase among the treatment groups. The proportion of patients with no nausea during the delayed and overall phases was higher in the palonosetron group compared to the granisetron group (37.8 and 31.8% vs 27.2 and 25%, respectively; P=0.0002 and P=0.117, respectively). The proportion of patients with no emetic episodes during the delayed and overall phases was higher in the palonosetron group compared to the granisetron group (63.2 and 57.5% vs 54.2 and 49.2%, respectively; P=0.0023 and P=0.0058, respectively). Time to treatment failure was longer in the palonosetron group than in the granisetron group. Time to first emetic episode was longer in the palonosetron group compared to the granisetron group, as was the time to first use of rescue medication.
Aapro et al.[61] (2006) Palonosetron 0.25	DB, DD, MC, PG, RCT Patients ≥18 years	N=673 5 days	Primary: Complete response (no emetic episodes and no	Primary: Complete response rates during the acute phase were 59.2% for palonosetron 0.25 mg, 65.5% for palonosetron 0.75 mg, and 57.0% for ondansetron (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV vs palonosetron 0.75 mg IV vs ondansetron 32 mg IV	of age with histologically or cytologically confirmed malignant disease, naïve or non-naïve to chemotherapy, with a Karnofsky index ≥50%, scheduled to receive a single dose of highly emetogenic chemotherapy on day one		rescue medication use) during the acute phase (0 to 24 hours post-chemotherapy) Secondary: Complete response for the delayed (24 to 120 hour post-chemotherapy) and overall (0 to 120 hour post-chemotherapy) phases; complete control rates; number of emetic episodes; time to first emetic episode; time to first administration of rescue medication	Secondary: Complete response rates during the delayed phase were 45.3% for palonosetron 0.25 mg, 48.0% for palonosetron 0.75 mg, and 38.9% for ondansetron (P=NS). Complete response rates during the overall phase were 40.8% for palonosetron 0.25 mg, 42.2% for palonosetron 0.75 mg, and 33.0% for ondansetron (P=NS). Complete control rates were comparable with the treatments during the acute, delayed, and overall phases. Time to first emetic episode was longer for patients treated with palonosetron 0.25 mg (median >120 hours) and palonosetron 0.75 mg (median >120 hours) compared to patients treated with ondansetron (median 42.7 hours) (P=0.023 and P=0.006, respectively), with no difference between palonosetron doses. There was no significant difference in the use of rescue medication during the acute, delayed, or overall phases.
Aapro et al.[62] (2005) Palonosetron 0.25 mg IV vs ondansetron 32 mg IV or dolasetron 100 mg IV	RETRO post hoc analysis of studies by Eisenberg et al. and Gralla et al. Patients ≥65 years receiving moderately emetogenic chemotherapy	N=171 5 days	Primary: Complete response during the acute period (0 to 24 hours after chemotherapy), delayed period (24 to 120 hours), and over all period (0 to 120 hours) with significance P<0.025 Secondary:	Primary: During the overall post chemotherapy period, complete response rate was significantly higher in the palonosetron group than in the ondansetron /dolasetron group (70.9 vs 51.2%; P=0.011). The proportion of patients with complete response during the acute time period was not significantly different between the palonosetron and ondansetron/dolasetron groups (84.8 vs 74.4%; P>0.025). Complete response was significantly higher in the palonosetron group compared to the ondansetron/dolasetron group during the delayed period (72.2 vs 53.5%; P=0.016). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	Not reported
Botrel et al.[63] (2010) Palonosetron 0.25 mg IV vs palonosetron 0.75 mg IV vs dolasetron 100 mg IV palonosetron 0.25 mg IV vs granisetron 3 mg IV palonosetron 0.25 mg IV vs ondansetron 8 mg/m^2 IV every eight hours palonosetron 0.25 mg IV vs palonosetron 0.75 mg IV vs ondansetron IV 32 mg palonosetron 0.25 mg IV vs palonosetron 0.75 mg IV vs ondansetron 32 mg IV	MA Patients receiving prophylaxis of acute CINV	N=2,057 (5 trials) 120 hours	Primary: Emetic events, intensity of nausea, complete response during acute phase Secondary: Not reported	Primary: Treatment with palonosetron was significantly better for the prevention of both acute (RR, 0.86; 95% CI, 0.76 to 0.96; P=0.007; NNT, 14) and late nausea (RR, 0.82; 95% CI, 0.75 to 0.89; P=0.00001; NNT, 8) compared to dolasetron, granisetron and ondansetron. During the entire evaluated period (0 to 120 hours), treatment with palonosetron was more efficacious in preventing nausea (RR, 0.87; 95% CI, 0.81 to 0.95; P=0.008; NNT, 11). Treatment with palonosetron was significantly more effective than dolasetron, granisetron and ondansetron in preventing acute vomiting (RR, 0.76; 95% CI, 0.66 to 0.88; P=0.0002; NNT, 11) as well as the late vomiting (RR, 0.76; 95% CI, 0.68 to 0.85; P<0.00001; NNT, 8). During the entire evaluated period (0 to 120 hours), treatment with palonosetron was more efficacious in the prevention of vomiting (RR, 0.79; 95% CI, 0.72 to 0.88; P<0.00001). Secondary: Not reported
Likun et al.[64] (2011)	MA, SR (8 DB, RCTs including 6	N=3,592	Primary: Complete response	Primary: Treatment with palonosetron reduced the risk of acute CINV by 24% (OR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Palonosetron 0.25 mg IV vs palonosetron 0.75 mg IV vs palonosetron 0.25 mg IV plus dexamethasone 20 mg before chemotherapy vs palonosetron 0.75 mg IV plus dexamethasone before chemotherapy vs palonosetron 0.75 mg IV plus dexamethasone (16 mg IV on day one, 8 mg IV for cisplatin chemotherapy on days two and three and 4 mg orally for anthracycline plus	NI and 2 XO) Adults with cancer receiving chemotherapy	5 days	of the acute, delayed and overall phases of CINV (complete response defined as no emetic episodes and no rescue medication; overall phase defined as 0 to 120 hours after chemotherapy) Secondary: Not reported	0.62; 95% CI, 0.66 to 0.88; P=0.0003). Subgroup analyses demonstrated a difference in favor of treatment with palonosetron 0.25 mg (OR, 0.68; 95% CI, 0.56 to 0.83; P=0.0001) and 0.75 mg (OR, 0.82; 95% CI, 0.69 to 0.99; P=0.03). In seven studies, patients treated with palonosetron had a reduced risk of delayed CINV compared to patients treated with other 5-HT$_3$ receptor antagonists (OR, 0.62; 95% CI, 0.54 to 0.71; P<0.00001). Subgroup analyses demonstrated a difference in favor of treatment with palonosetron 0.25 mg (OR, 0.62; 95% CI, 0.51 to 0.75; P<0.00001) and palonosetron 0.75 mg (OR, 0.61; 95% CI, 0.52 to 0.72; P<0.00001). In seven studies, patients treated with palonosetron had a reduced risk of CINV in the overall phase compared to patients treated with other 5-HT$_3$ receptor antagonists (OR, 0.64; 95% CI, 0.56 to 0.74; P<0.00001). Subgroup analyses demonstrated a difference in favor of treatment with palonosetron 0.25 mg (OR, 0.62; 95% CI, 0.51 to 0.75; P<0.00001) and palonosetron 0.75 mg (OR, 0.65; 95% CI, 0.55 to 0.76; P<0.00001). In three studies, there was no statistically significant difference observed between patients treated with palonosetron 0.25 and 0.75 mg for the prevention of CINV (OR, 1.09; 95% CI, 0.85 to 1.38; P=0.5), delayed CINV (OR, 1.05; 95% CI, 0.83 to 1.32; P=0.68) or overall phase CINV (OR, 1.11; 95% CI, 0.88 to 1.4; P=0.38). Two studies compared treatment with palonosetron plus dexamethasone to a 5-HT$_3$ receptor antagonist plus dexamethasone in patients receiving highly emetic chemotherapy. Although not statistically significant, a trend in favor of treatment with palonosetron plus dexamethasone was observed in the prevention of acute CINV (OR, 0.84; 95% CI, 0.67 to 1.05; P=0.36). Treatment with palonosetron plus dexamethasone resulted in a significant reduction in the risk of delayed and overall phase CINV by 40 and 38%, respectively (P<0.0001). Treatment with palonosetron reduced the risk of acute CINV (OR, 0.70; 95% CI, 0.64 to 0.91; P=0.008), delayed CINV (P<0.00001) and overall phase CINV (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cyclophosphamide chemotherapy on days two and three) vs dolasetron 100 mg IV vs granisetron 40 µg/kg plus dexamethasone (16 mg IV on day one, 8 mg IV for cisplatin chemotherapy on days two and three and 4 mg orally for anthracycline plus cyclophosphamide chemotherapy on days two and three) vs granisetron 3 mg IV vs ondansetron 16 mg IV				In patients receiving highly emetic chemotherapy, treatment with palonosetron reduced the risk of acute CINV (OR, 0.70; 95% CI, 0.64 to 0.96; P=0.02), delayed CINV (P<0.00001) and overall phase CINV (P<0.00001). In two studies, there was a difference observed in favor of palonosetron 0.25 mg for the prevention of acute CINV in highly emetic chemotherapy (OR, 0.58; 95% CI, 0.36 to 0.93; P=0.02). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ondansetron 32 mg IV vs ondansetron 32 mg IV plus dexamethasone 20 mg before chemotherapy				
Aapro et al.[65] (2017) Palonosetron 0.5 mg by mouth vs netupitant-palonosetron 300-0.5 mg by mouth (Akynzeo®) Both treatment groups were also given dexamethasone	DB, ES, MC, RCT Patients ≥18 years, naïve to chemotherapy, and scheduled to receive their first course of an anthracycline/ cyclophosphamide regimen for treatment of a solid malignant tumor	N=1286 5969 chemotherapy cycles; 120 hours post-chemotherapy	Primary: Proportion of patients with an overall (0 to 120 h) complete response Secondary: Safety	Primary: The proportion of patients with an overall (0 to 120 h) complete response was significantly greater for netupitant-palonosetron compared with oral palonosetron during cycle one, and this was maintained in subsequent cycles. The incremental benefit of netupitant-palonosetron over oral palonosetron in cycles two through four was greater than that seen in cycle one (7.7% in cycle one, 13.6% in cycle two, 13.5% in cycle three, and 9.2% in cycle four). Complete response rates were similar for netupitant-palonosetron and oral palonosetron during the acute phase but higher for netupitant-palonosetron compared with oral palonosetron during the delayed phase. Secondary: There were no serious treatment-related adverse events during cycle one or during the multiple-cycle extension for either treatment group. There were also no treatment-related adverse events leading to discontinuation and no deaths for netupitant-palonosetron treated patients.
Schwartzberg et al.[66] (2014) Palonosetron 0.25 or 0.75 mg vs	MA (4 DB, RCTs) Patients ≥18 years of age with histologically or cytologically confirmed malignancy	N=2,962 120 hours post-chemotherapy	Primary: Complete response (no emesis and no rescue antiemetics) Secondary: Complete control (emesis, no rescue	Primary: Complete response rates were significantly higher for palonosetron (pooled doses) relative to older 5-HT$_3$ antagonists during the delayed phase (P<0.0001), and overall phase (P<0.0001), but not the acute phase (P=0.091) Secondary: Palonosetron provided higher complete control rates than older 5-HT$_3$

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
other 5-HT_3 antagonists (ondansetron 32 mg, dolasetron 100 mg, or granisetron 40 μg/kg)			antiemetics, and no more than mild nausea), number of emetic episodes, nausea severity	antagonists in the delayed (P<0.0001) and overall (P<0.0001) phases, but not the acute phase (P=0.137). The frequency of emetic episodes was significantly different for palonosetron and older 5-HT_3 antagonists during the acute (P=0.007), delayed (P<0.0001), and overall (P<0.0001) phases. The severity of nausea episodes was not significantly different with palonosetron and older 5-HT_3 antagonists during the acute postchemotherapy phase (P=0.165). However, there were significant differences in the delayed (P=0.0002) and overall phases (P=0.011).
Longo et al.[67] (2011) Palonosetron 0.25 mg IV, dexamethasone IV 20 mg, and aprepitant 125 mg 1 hour before chemotherapy on day 1; aprepitant 80 mg and dexamethasone on day 2; aprepitant 80 mg and dexamethasone 4 mg on day 3	MC, PRO Chemotherapy-naïve patients with histologically or cytologically proven solid or blood tumors	N=220 5 days	Primary: Proportion of patients who achieved a complete response (defined as no emetic episodes and no use of rescue therapy), during the overall phase Secondary: Complete control (defined as no emesis, no rescue therapy, and no more than mild nausea), complete response, and proportion of patients with no emesis, during the acute, delayed, and overall phases, proportion of	Primary: 70.3% of patients had complete response during the overall phase. An analysis of each component of the primary end point showed that 92.8% of patients did not experience any vomiting, while 70.3% of patients did not use rescue medication throughout the entire observation period. Secondary: The majority of patients (59.9%) did not experience any nausea; 31.1% of patients experienced mild nausea, 8.1% moderate nausea, and 0.9% severe nausea. Nausea experience was the main reason for use of rescue medication: 53 patients (23.9%) due to nausea and 13 (5.9%) due to vomiting. None of the patients with complete response experienced more than mild nausea and then complete control rates coincided with the complete response rates. No major adverse events were recorded due to antiemetic therapy. The most commonly reported side effects were constipation (39% of patients) and headache (5%). Laxative therapy was allowed in patients who reported constipation. 41% of patients reported fatigue, 23% reported some grade of pain, and 33% reported a reduction in their social activity.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patients with no nausea, nausea severity, no use of rescue medication, and causes for the use of rescue therapy were assessed during the overall phase, quality of life during the whole study observation period, safety	
Choi et al.[68] (2014) Single IV bolus injection of 0.25 mg palonosetron and chemotherapy on day one of the first chemotherapy cycle, and up to three further consecutive cycles	MC, OL, uncontrolled Chemotherapy-naïve patients being treated for non-Hodgkin lymphoma receiving moderately emetogenic chemotherapy	N=88 2 to 4 chemotherapy cycles	Primary: Complete response rate (defined as no emetic episode and no rescue medication for the overall phase; endpoints based on diary data) Secondary: Complete protection (defined as no vomiting, no rescue therapy, and no nausea), safety	Primary: Complete response was observed for 76.7% (95% CI, 71.7 to 81.0) of treatment cycles. Across all four cycles, for the acute and delayed phases, 81.7 and 90.5% of patients, respectively, were complete responders. Secondary: Complete protection was achieved in 79.2% (95% CI, 74.4 to 83.3), 86.4% (95% CI, 82.2 to 89.8), and 72.2% (95% CI, 67.1 to 76.9) of all cycles during the acute, delayed and overall phases, respectively. No emesis was observed in 90.5% (95% CI, 86.8 to 93.3) of all cycles, and no rescue medication was used in 81.7% (95% CI, 77.1 to 85.6) of all cycles. Overall, 78.4% of patients experienced 301 treatment-emergent adverse events. A total of 17 patients (19.3%) experienced 26 serious treatment-emergent adverse events. None of the serious treatment-emergent adverse events were considered to be study-drug related. Constipation and fatigue (2.3% each) were the most frequently reported adverse events.
Lindley et al.[69] (2005) Prochlorperazine sustained release 15 mg two times a day	MC, RCT Chemotherapy-naïve patients scheduled to receive moderately high to highly emetogenic	N=232 5 days	Primary: Number of vomiting episodes, average nausea score reported on days two through five	Primary: The treatment regimen for delayed CINV did not affect the percentage of patients reporting one or more vomiting episodes on days two through five (prochlorperazine, 24%; ondansetron, 22%; and dexamethasone, 21%; P=0.86). The average severity of nausea during days two through five was lower in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dexamethasone 8 mg two times a day vs ondansetron 8 mg two times a day All patients received ondansetron 24 mg and dexamethasone 20 mg orally before chemotherapy.	chemotherapy		Secondary: Not reported	patients receiving prochlorperazine, whereas patients receiving ondansetron reported the highest severity of nausea, but this difference was not significant (P=0.055). Forty-seven of the 49 patients who reported one or more vomiting episodes also experienced some degree of nausea. Secondary: Not reported
Friedman et al.[70] (2000) Prochlorperazine sustained release 10 mg two times a day vs granisetron 1 mg two times a day All medications given one hour prior to and 12 hours after chemotherapy.	DB, MC, PG Patients ≥18 years of age who were scheduled to receive their first cycle of moderately emetogenic chemotherapy	N=230 5 to 11 days	Primary: Proportion of patients with no emesis, no nausea, moderate or severe nausea and no antiemetic rescue at 48 hours Secondary: Safety and tolerability	Primary: Females and all patients combined who received granisetron had significantly higher no-emesis rates at 48 hours (P=0.010 for females and P=0.016 for all patients combined) than those receiving prochlorperazine. No-nausea rates at 48 hours were numerically higher for all patients who received granisetron rather than prochlorperazine (P=0.629). No-nausea rates at 48 hours were numerically higher for female patients in the granisetron group compared to the prochlorperazine group (P=0.501). No-nausea rates at 72 hours were similar between the granisetron group and the prochlorperazine group for all patients (P=0.057), but were significantly higher in female patients in the granisetron group compared to female patients in the prochlorperazine group (P=0.050). Response rates for no nausea or mild nausea were also numerically higher in females treated with granisetron compared to prochlorperazine at 48

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				hours, but this did not reach statistical significance (P=0.184). Significantly more patients (P<0.001) and females (P<0.001) in the granisetron group than in the prochlorperazine group did not require rescue antiemetics at 48 hours, but the use of rescue antiemetics was comparable at 72 hours. Secondary: Incidence of severe adverse effects was similar for granisetron and prochlorperazine (12.6 vs 13.5%).
Nausea and Vomiting of Pregnancy				
Oliveira et al.[71] (2014) Ondansetron 4 mg plus placebo tablet every eight hours vs pyridoxine 25 mg plus doxylamine 12.5 mg every eight hours	DB, RCT Women requesting treatment for nausea with or without vomiting associated with pregnancy who were at least 18 years of age and at <16 weeks of gestation	N=36 5 days	Primary: Improvement in nausea as reported on a 100-mm visual analog scale Secondary: Reduction in vomiting on the visual analog scale and the proportion of patients reporting sedation or constipation while using either study regimen	Primary: Patients using ondansetron reported a greater reduction in nausea than those using pyridoxine and doxylamine (median 51 mm [interquartile range 37 to 64] compared with 20 mm [interquartile range 8 to 51]; P=0.019). Secondary: Patients using ondansetron reported less vomiting on the visual analog scale as compared with the pyridoxine and doxylamine group (median 41 [interquartile range 17 to 57] compared with 17 [interquartile range -4 to 38]; P=0.049). This study was adequately powered to detect only differences in the primary outcome and no differences were found between the groups with respect to sedation or constipation.
Sullivan et al.[72] (1996) Ondansetron 10 mg IV for one dose (mandatory), then every eight hours as needed (optional)	RCT Patients with hyperemesis gravidarum during the first and early second trimesters of pregnancy that had not been previously treated by IV	N=30 Single hospital admission	Primary: Length of hospitalization, treatment failures (defined as no change in nausea or emesis was observed after 48 hours of medication and	Primary: On average, patients receiving ondansetron and promethazine remained in the hospital for 4.47 days each (P=1.00). There were two treatment failures in patients receiving ondansetron and three treatment failures in patients receiving promethazine (P=1.00). After the mandatory initial dose, the antiemetic medication usage was not different between patients receiving ondansetron and promethazine (2.1 vs 1.93 doses, respectively; P=0.71).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs promethazine 50 mg IV for one dose (mandatory), then every eight hours as needed (optional)	medication or hospitalization who required hospital admission		hydration), antiemetic usage, severity of nausea, weight gain, and adverse events Secondary: Not reported	There was a progressive decline in the severity of nausea, but there was no significant differences observed among the treatment groups. Daily weight gain was similar among the treatment groups. Eight patients receiving promethazine reported sedation compared to no patients in the ondansetron group (P=0.002). There were no other adverse events observed. Secondary: Not reported
Einarson et al.[73] (2004) Ondansetron vs diclectin, metoclopramide, phenothiazines and ginger (group one) vs drugs considered to be safe to use during pregnancy or no medication use (group two)	OBS, PRO Pregnant women exposed to ondansetron, other antiemetic drugs, or non-teratogen exposures	N=491 4 to 6 months following delivery	Primary: Safety Secondary: Not reported	Primary: In the ondansetron group, there were six major malformations reported (three cases of hypospadias, double urinary collecting system in kidney, mild pulmonary stenosis and a duodenal atresia). In group one, there were three major malformations (hydrocephalus, kidney anomaly and aortic stenosis). In group two, there were three malformations (one case of hypospadias and two congenital heart defects). There were no significant differences between the three groups in terms of live births, miscarriages, stillbirths, therapeutic abortions, birthweight or gestational age. The rate of hypospadias live births in the ondansetron group was not significantly different from the combined control group (3/169 vs 1/322; P=0.25). Secondary: Not reported
Postoperative Nausea and Vomiting (PONV)				
Hartrick et al.[74] (2010) Aprepitant 40 mg by mouth	OL, PRO Patients undergoing total knee arthroplasty	N=24 48 hours	Primary: Presence or absence of PONV during the postoperative	Primary: The percentage of patients experiencing PONV was significantly lower with aprepitant (25%) compared to the multimodal analgesia group (75%; P=0.039).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ondansetron 4 mg and dexamethasone (4 to 6 mg) plus either metoclopramide 10 mg, diphenhydramine 25 mg, or prochlorperazine 5 mg	receiving extended-release morphine for postoperative pain management		period Secondary: Not reported	There were no significant differences in pain scores, need for rescue therapy, or adverse events among the treatment groups. Secondary: Not reported
Diemunsch et al.[75] (2007) Aprepitant 40 mg by mouth vs aprepitant 125 mg mouth vs ondansetron 4 mg IV	DB, MC, PC, RCT Patients ≥18 years of age (ASA I or III status) undergoing open abdominal surgery requiring at least one overnight hospital stay and receiving volatile-agent-based general anesthesia including nitrous oxide	N=922 48 hours	Primary: Complete response (no vomiting and no use of rescue therapy) over 0 to 24 hours after surgery; no vomiting over 0 to 24 hours after surgery Secondary: No vomiting in the first 48 hours after surgery	Primary: Complete response was achieved in 64% of patients in the aprepitant 40 mg group, 63% in the aprepitant 125 mg group, and 55% in the ondansetron group, indicating NI of the aprepitant treatment compared to ondansetron treatment. The percentage of patients with no vomiting over 0 to 24 hours was 84% with aprepitant 40 mg, 86% with aprepitant 125 mg, and 71% with ondansetron 4 mg (P<0.001 for both doses of aprepitant vs ondansetron). Secondary: The percentage of patients with no vomiting over 0 to 48 hours was 82% with aprepitant 40 mg, 85% with aprepitant 125 mg, and 66% with ondansetron 4 mg (P<0.001 for both doses of aprepitant vs ondansetron).
Gan et al.[76] (2007) Aprepitant 40 mg by mouth vs	DB, MC, PC, RCT Patients ≥18 years of age (ASA I or III status) scheduled to undergo open abdominal surgery requiring an	N=805 48 hours	Primary: Complete response (no vomiting and no use of rescue therapy in the 24 hours after surgery)	Primary: Complete response was achieved in 45% of patients in the aprepitant 40 mg group, 43% in the aprepitant 125 mg group, and 42% in the ondansetron group, indicating NI of the aprepitant treatment compared to ondansetron treatment (P>0.5 for both doses of aprepitant vs ondansetron). Secondary: Over 0 to 24 hours, there was no significant difference in the proportion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aprepitant 125 mg by mouth vs ondansetron 4 mg IV	overnight hospital stay and who were scheduled to receive general anesthesia including nitrous oxide with volatile anesthetics		Secondary: No rescue therapy 0 to 24 hours; no vomiting 0 to 48 hours	patients who did not need rescue therapy (45, 44, and 46% for aprepitant 40 mg, 125 mg, and ondansetron, respectively). More patients in both aprepitant groups reported no vomiting for the 0 to 48 hour time interval compared to the ondansetron group (OR, 2.7 for aprepitant 40 mg vs ondansetron and 6.9 for aprepitant 125 mg vs ondansetron; P<0.001 for both ratios).
Moon et al.[77] (2014) Aprepitant 40 mg by mouth vs palonosetron 0.075 mg IV	DB, RCT Patients 20 to 60 years of age who were scheduled to undergo laparoscopic gynecologic surgery under general anaesthesia	N=93 48 hours	Primary: Complete response (visual analogue scale nausea score <4 and no use of rescue therapy) 0 to 48 h after surgery Secondary: Effect of aprepitant quantified using a 10-point visual analog scale for pain, consumption of intravenous patient-controlled analgesia, and use of rescue analgesics	Primary: Aprepitant was non-inferior to palonosetron in terms of complete response 0 to 48 hours after surgery (74 vs 77%). The nausea intensity in the recovery room and two hours after surgery assessed using the 10-point visual analog scale was significantly lower in the aprepitant group (11.2 ± 2.1 and 9.7 ± 2.1, respectively) than in the palonosetron group (19.0 ± 2.2 and 19.4 ± 3.5, respectively; P<0.05). However, the results at 6, 24, and 48 h after surgery did not differ significantly. Secondary: The pain intensity was also not significantly different throughout the study period. Fentanyl consumption via automated IV-PCA was significantly lower in the aprepitant group than in the palonosetron group at two and six hours after surgery (P<0.05). No significant differences were observed in the incidence and number of additional fentanyl administrations between the two groups.
Tang et al.[78] (2012) Dolasetron, granisetron, ondansetron or tropisetron vs	DB, MA, RCT Patients at risk of PONV undergoing general anesthesia	N=15,269 (85 trials) 24 hours	Primary: Proportion of patients free from PONV and POV from 0 to 24 hours after anesthesia/ surgery Secondary: Not reported	Primary: Treatment with ondansetron, granisetron, tropisetron and dolasetron was associated with significantly better efficacy compared to placebo for the prevention of PONV. Treatment with granisetron was significantly better compared to ondansetron (OR, 1.53; 95% CI, 1.15 to 2.0) and dolasetron (OR, 1.67; 95% CI, 1.12 to 2.38). No other statistical differences between treatment arms were observed. In terms of median ranking for the prevention of PONV, granisetron ranked first, followed by tropisetron, ondansetron, dolasetron and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
a different 5-HT$_3$ receptor antagonist (dolasetron, granisetron, ondansetron or tropisetron) or placebo				Granisetron was ranked at least second within the scope of a 95% CI. All four 5-HT$_3$ receptor antagonists were significantly more effective than placebo for the prevention of POV, however, no differences were observed between the 5-HT$_3$ receptor antagonist treatment arms. After controlling for the drug dose and administration route, treatment with the 5-HT$_3$ receptor antagonists resulted in comparable efficacy for the prevention of PONV or POV. Secondary: Not reported
Birmingham et al.[79] (2006) Dolasetron 12.5 mg IV vs ondansetron 4 mg IV	DB, PRO, RCT Patients >18 years of age at high risk for PONV undergoing general anesthesia	N=100 24 hours	Primary: Satisfaction with medication (visual analog score, 0 to 100 mm), overall satisfaction (visual analog score, 0 to 100 mm) Secondary: Complete response; emetic episodes; post-discharge emesis; delay in post-anesthesia care unit discharge attributable to PONV	Primary: Satisfaction with the medication used to prevent PONV was not different between the groups (dolasetron, 70.9; ondansetron, 67.0; P=0.69). Overall satisfaction with surgery, anesthesia, and hospital experience was not different between the groups (dolasetron, 87.9; ondansetron, 85.3; P=0.51) Secondary: Complete response (40 vs 50%), emetic episodes (44 vs 34%), post-discharge emesis (30 vs 26%), and delay in the post-anesthesia care unit discharge attributable to PONV (41 vs 21 minutes) were not different in patients receiving dolasetron compared to ondansetron (P=0.36, P=0.32, P=0.79 and P=0.12, respectively).
Olutoye et al.[80] (2003) Dolasetron 45 µg/kg IV	DB, PG, PRO, RCT Patients 2 to 12 years of age undergoing day surgery	N=204 24 hours	Primary: Complete response (no postoperative emetic symptoms) Secondary:	Primary: There were no significant differences in complete response between ondansetron 100 µg/kg, dolasetron 700 µg/kg and dolasetron 350 µg/kg. Ondansetron, dolasetron 700 µg/kg and dolasetron 350 µg/kg were all statistically more efficacious to dolasetron 175 µg/kg and dolasetron 45

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dolasetron 175 µg/kg IV vs dolasetron 350 µg/kg IV vs dolasetron 700 µg/kg IV vs ondansetron 100 µg/kg IV			Not reported	µg/kg (P<0.05). Secondary: Not reported
Meyer et al.[81] (2005) Dolasetron 12.5 mg IV vs ondansetron 4 mg IV	DB, PRO, RCT Patients undergoing day surgery	N=92 24 hours	Primary: Need for antiemetic rescue medication Secondary: Evaluation of nausea and vomiting within 24 hours of surgery, overall time until discharge-ready in day surgery, overall time spent in post-anesthesia care unit	Primary: The need for rescue antiemetic in the dolasetron group was 40% compared to 70% in the ondansetron group (P<0.004). Secondary: There was no significant difference between the two groups in regards to the number of patients who actually vomited (P=0.34). The overall time until discharge-ready in day surgery was 131 minutes for dolasetron and 158 minutes for ondansetron (P=0.17). The overall time spent in the post-anesthesia care unit was similar between groups (P=0.99).
Walker[82] (2001)	RETRO	N=59	Primary: Number of	Primary: PONV occurred in 44% patients receiving dolasetron and 53% patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dolasetron 12.5 mg IV vs ondansetron 4 mg IV	Patients who underwent total abdominal hysterectomy or laparoscopic cholecystectomy	24 hours	recorded episodes of PONV in 24 hours after surgery; time to occurrence of PONV Secondary: Not reported	receiving ondansetron. Four patients (36%) receiving dolasetron experienced PONV in the first two hours after surgery, compared to seven patients (39%) receiving ondansetron. Differences in primary endpoints did not reach statistical significance.
Karamanlioglu et al.[83] (2003) Dolasetron 1.8 mg/kg by mouth vs ondansetron 0.15 mg/kg by mouth vs placebo Medications were given one hour before induction of surgery.	DB, PRO, RCT Children undergoing elective strabismus surgery, middle ear surgery, adenotonsillectomy or orchiopexy	N=150 24 hours	Primary: Total nausea and vomiting scores Secondary: Not reported	Primary: Over the 0 to 24 hour period, both dolasetron and ondansetron were significantly better than placebo with regard to nausea (16 vs 26 vs 40%, respectively), vomiting (8 vs 16 vs 30%, respectively), and total nausea and vomiting scores (32 vs 48 vs 78%, respectively; P<0.05 compared to placebo). There were no significant differences between dolasetron and ondansetron. There were no important adverse events. Secondary: Not reported
Eberhart et al.[84] (2004) Dolasetron 12.5 mg IV vs	DB, PG, RCT Patients undergoing vitreoretinal surgery	N=304 24 hours	Primary: Mean PONV score Secondary: Complete prevention of PONV	Primary: Droperidol was significantly better than placebo in reduction of mean PONV score (P<0.0001). Dolasetron was not significantly better than placebo (P=0.017). Combination therapy was significantly better than placebo in reduction of mean PONV score (P<0.0001). Droperidol and dolasetron were not significantly different (P=0.096).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
droperidol 10 µg/kg IV vs dolasetron 12.5 mg and droperidol 10 µg/kg IV vs placebo				Secondary: Droperidol was significantly more efficacious to placebo in complete prevention of PONV (P<0.0006). Dolasetron was not significantly better than placebo (P=0.038). Combination therapy was statistically better than placebo in complete prevention of PONV (P<0.0001). Droperidol and dolasetron were not significantly different from each other in complete prevention of PONV (P=0.17).
Bhatnagar et al.[85] (2007) Granisetron 2 mg by mouth vs ondansetron 4 mg by mouth vs placebo	DB, RCT Hospitalized female patients 18 to 65 years of age (ASA I and II) scheduled for modified radical mastectomies	N=90 24 hours	Primary: Complete response (no nausea, vomiting/retching, and no need for rescue antiemetic); PONV score: Grade 1 (no nausea/vomiting); Grade 2 (nausea only); Grade 3 (vomiting once); Grade 4 (vomiting more than once) Secondary: Not reported	Primary: Complete response (0 to 2 hours): Placebo (43%), granisetron (63%), ondansetron (90%); ondansetron was found to be significantly better than granisetron. Rescue medication use (0 to 2 hours): Placebo (40%), granisetron (17%), ondansetron (7%); ondansetron was found to be significantly better than granisetron. Observation of PONV score and requirement of antiemetics at other time intervals (2 to 6, 6 to 12, and 12 to 24 hours) did not significantly differ among the three groups. Secondary: Not reported
Metaxari et al.[86] (2011) Granisetron 3 mg IV vs	DB, RCT Female patients 20 to 65 years of age who were scheduled to undergo elective partial or total thyroidectomy.	N=203 24 hours	Primary: Incidence of nausea of any degree, incidence of moderate to severe nausea (defined as visual analog score >4	Primary: In the post-anesthesia care unit, there was no significant difference in the incidence of nausea and vomiting observed between the placebo, granisetron, ondansetron or tropisetron groups. A significantly greater proportion of patients treated with tropisetron reported nausea compared to the granisetron group (50 vs 24%, respectively). At six hours post-surgery, significantly fewer patients treated with granisetron or ondansetron reported nausea or vomiting compared to the placebo group (P=0.0011

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron 4 mg IV vs tropisetron 5 mg IV vs placebo All patients were premedicated with midazolam 0.07 mg/kg IM 1 to 1.5 hours before surgery.			cm) requiring rescue medication, incidence of vomiting episodes among four treatment groups Secondary: Not reported	and P=0.0023, respectively). There were no significant differences observed between the tropisetron and placebo groups. At 12 and 18 hours, treatment with granisetron was found to be more efficacious to placebo in the prevention of PONV (P=0.0014 and P=0.0001, respectively). At 24 hours, there were no significant differences among the treatment groups. Secondary: Not reported
Oksuz et al.[87] (2007) Granisetron 40 µg/kg IV vs ondansetron 15 µg/kg IV vs metoclopramide 10 mg IV	DB, PRO, RCT Patients 21 to 72 years of age and weighing 52 to 102 kg (ASA I and II) with planned elective laparoscopic cholecystectomy	N=75 24 hours	Primary: Nausea/vomiting using Bellville's four-stage score chart (0=no symptoms; 1=nausea; 2=retching; 3=vomiting); nausea/vomiting incidence, and antiemetic rescue Secondary: Not reported	Primary: Prophylactic antiemetic treatment with granisetron resulted in a lower incidence (0%) of PONV than with ondansetron (3%) and metoclopramide (3%) during the first three hours. Granisetron resulted in a lower incidence (1%) of PONV in the four to 24 hour period than with ondansetron (3%) or metoclopramide (11%). Nausea and vomiting scores in the first three-hour period revealed that each of the drugs had a similar antiemetic effect (P>0.05). Scores between four to 24 hours were higher with metoclopramide than granisetron or ondansetron (P<0.001). There was no significant difference in nausea and vomiting scores between granisetron and ondansetron (P=NS). Secondary: Not reported
Candiotti et al.[88] (2007) Granisetron 0.1 mg	DB, RCT Patients 18 to 64 years of age with	N=88 24 hours	Primary: Complete response (no further PONV and no requests for	Primary: Complete response occurred in 57, 60 and 68% of patients in the ondansetron 4 mg, granisetron 1 mg, and granisetron 0.1 mg groups, respectively (P=0.773).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV vs granisetron 1 mg IV vs ondansetron 4 mg IV	ASA I and II status who were scheduled to undergo nonemergency surgery, requiring general anesthesia of at least 30 minutes; women who developed PONV following surgery were enrolled		further medication) Secondary: Not reported	There were no significant differences between the treatment groups for nausea scores, breakthrough rate of vomiting with or without nausea in the 30 minutes after rescue, and efficacy between rescue arms relating to vomiting. Secondary: Not reported
White et al.[89] (2006) Granisetron 1 mg by mouth one hour before surgery vs ondansetron 4 mg IV at the end of surgery	DB, MC, RCT Patients undergoing laparoscopic surgery	N=220 24 hours	Primary: Postoperative episodes of emesis, patient report of nausea, need for rescue antiemetic medication Secondary: Not reported	Primary: PONV <4 hours post surgery: nausea was reported in 47 and 43% of ondansetron and granisetron patients, respectively. Vomiting was noted in 22% of both ondansetron and granisetron patients. Rescue antiemetics were used in 34 and 39% of ondansetron and granisetron patients, respectively. PONV four to 24 hours post surgery: nausea was reported in 46 and 38% of ondansetron and granisetron patients, respectively. Vomiting was noted in 23 and 13% of ondansetron and granisetron patients, respectively. Rescue antiemetics were used in 25 and 24% of ondansetron and granisetron patients, respectively. None of these comparisons were significantly different from each other. Secondary: Not reported
Riad et al.[90] (2009) Granisetron 10 µg/kg IV vs	DB, PC, RCT Patients 4 to 12 years of age (ASA class I) who were undergoing elective strabismus surgery using general	N=100 24 hours	Primary: Incidence of PONV Secondary: Safety	Primary: The incidence of PONV was significantly higher in the placebo group compared to the treatment groups (P<0.01). No significant differences in the incidence of PONV were seen among the treatment groups (granisetron: 8 and 12%, respectively; ondansetron: 16 and 3%, respectively; midazolam: 0 and 0%, respectively; P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron 50 µg/kg IV vs midazolam 50 µg/kg IV vs placebo All three treatment regimens included dexamethasone 0.5 mg/kg.	anesthesia			Secondary: No major respiratory or hemodynamic adverse effects were observed in the treatment groups.
Dabbous et al.[91] (2010) Granisetron 1mg IV vs ondansetron 4 mg IV Both groups received dexamethasone 8 mg IV.	DB, RCT Patients (ASA I or II) undergoing laparoscopic surgery	N=84 24 hours	Primary: Incidence of PONV Secondary: Patient satisfaction, safety	Primary: No significant differences were seen between the two groups during the three time intervals (0 to 1, 1 to 6, 6 to 24 hours) with respect to total response, number of patients who vomited, and the use of antiemetics (P>0.05). Secondary: Approximately 90% of patients in the granisetron group and 88% of patients in the ondansetron group were satisfied with the antiemetic prophylaxis. There was no significant difference between the two groups concerning the side effects and pain scores.
Gan et al.[92] (2005) Granisetron 0.1 mg IV and dexamethasone 8	DB, MC, PG, RCT Patients undergoing abdominal hysterectomy	N=176 24 hours	Primary: Proportion of patients with no vomiting during 0 to two hours post surgery	Primary: From 0 to two hours post surgery, the granisetron group had no emesis in 94% of patients and the ondansetron group had no emesis in 97% of patients. The difference was not statistically significant (95% CI, -8.5 to 3.8).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV vs ondansetron 4 mg IV and dexamethasone 8 mg IV			Secondary: Proportion of patients with no vomiting during 0 to six hours and overall 0 to 24 hours post surgery	Secondary: From 0 to six hours post surgery, the granisetron group had no emesis in 87% of patients and the ondansetron group had no emesis in 93% of patients. This difference was not statistically significant (95% CI, -14.6 to 2.8). From 0 to 24 hours post surgery, the granisetron and ondansetron groups had no emesis in 83 and 87% of its patients, respectively. The difference was not statistically significant (95% CI, -14.4 to 6.9). There were no differences in adverse effects between the groups.
Gan et al.[93] (2002) Ondansetron orally disintegrating tablet 8 mg before discharge and 12 hours later vs placebo	DB, PC, RCT Patients undergoing outpatient gynecological laparoscopy	N=60 24 hours	Primary: Incidence of PONV, severity of nausea, rescue antiemetic, side effects, satisfaction PONV management assessed at two and 24 hours post surgery Secondary: Not reported	Primary: Patients treated with ondansetron orally disintegrating tablets had significantly less post discharge emesis (3 vs 23%) and less severe nausea after discharge compared to placebo patients (P<0.05). The ondansetron orally disintegrating tablet group was more satisfied with PONV control than placebo (90 vs 63%; P<0.05). Treatment with ondansetron orally disintegrating tablets was less acceptable to patients, although they would use it again (P<0.01). Secondary: Not reported
Grover et al.[94] (2009) Ondansetron 4 mg IV vs ondansetron 8 mg orally disintegrating tablet	DB, PC, RCT Patients 18 to 65 years of age (ASA I or II status) undergoing an elective laparoscopic cholecystectomy under general anesthesia	N=103 24 hours	Primary: Incidence of PONV Secondary: Use of rescue antiemetics, patient satisfaction	Primary: The incidence of PONV 0 to 24 hours postoperatively was significantly reduced in the IV and orally disintegrating tablet ondansetron groups compared to placebo (33.3 vs 26.5 vs 94.5%, respectively). The incidence of PONV 0 to 6 hours post-operatively was significantly less in the IV and orally disintegrating tablet ondansetron group compared to placebo (23.4 vs 20.6 vs 77.7%, respectively). There was no statistical difference in PONV six to 24 hours post-operatively between the three groups; however, the overall incidence was lower in the ondansetron groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Secondary: Use of rescue antiemetics did not significantly differ between the three groups during the entire study period. The overall patient satisfaction scores were significantly higher in the orally disintegrating tablet and IV ondansetron groups compared to placebo (P=0.001), with no significant difference between the orally disintegrating tablet and IV ondansetron groups.
Jain et al.[95] (2009) Ondansetron 4 mg IV vs granisetron 1 mg IV vs placebo	DB, PC, RCT Patients (ASA I or II status) scheduled for supratentorial craniotomy for intracranial tumor excision	N=90 24 hours	Primary: Episodes of PONV within 24 hours Secondary: Requirement of rescue antiemetic	Primary: The overall incidence of emesis within 24 hours after surgery was significantly lower in the ondansetron group (14.8%) and granisetron group (10%) compared to placebo (53%; P<0.001). The incidence was not significantly different between ondansetron and granisetron (P=NS). The overall incidence of nausea within 24 hours after surgery was comparable between the groups. Secondary: The requirement of rescue antiemetics was significantly reduced in patients who received ondansetron (14.8%) and granisetron (13.3%) compared to placebo (53.3%; P<0.001).
Erhan et al.[96] (2008) Ondansetron 4 mg IV vs granisetron 3 mg IV vs dexamethasone 8	DB, PC, RCT Patients 21 to 75 years of age (ASA I or II status) scheduled for laparoscopic cholecystectomy	N=80 24 hours	Primary: Incidence of nausea and vomiting at intervals 0 to six hours, six to 12 hours, and 12 to 24 hours; rescue antiemetic use Secondary: Not reported	Primary: <u>0 to six hour nausea/vomiting:</u> Control 70%, ondansetron 30%, granisetron 20%, dexamethasone 15% (P<0.05 for all treatment groups vs control). <u>0 to six hour rescue antiemetic:</u> Control 55%, ondansetron 15%, granisetron 10%, dexamethasone 10% (P<0.05 for all treatment groups vs control). <u>Six to 12 hour nausea/vomiting:</u> Control 20%, ondansetron 5%, granisetron 10%, dexamethasone 15%. <u>Six to 12 hour rescue antiemetic:</u> Control 15%, ondansetron 5%, granisetron 0%, dexamethasone 10%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV vs placebo				<u>12 to 24 hour nausea/vomiting:</u> Control 10%, ondansetron 0%, granisetron 0%, dexamethasone 0%. <u>12 to 24 hour rescue antiemetic:</u> Control 10%, ondansetron 0%, granisetron 0%, dexamethasone 0%. The total incidence of PONV during 24 hours was 75% in the control group, 35% in the ondansetron group, 30% in the granisetron group, and 25% in the dexamethasone group (P<0.05 for all treatment groups vs control). There was no difference in the antiemetic effect between the ondansetron, granisetron, and dexamethasone groups. Secondary: Not reported
Hamid et al.[97] (1998) Ondansetron 0.1 mg/kg IV vs dimenhydrinate 0.5 mg/kg vs placebo	DB, PC, PRO, RCT Children 2 to 10 years of age scheduled for adenotonsillectomy	N=47 24 hours	Primary: Incidence of retching and vomiting observed first 24 hours post surgery Secondary: Not reported	Primary: The incidence of POV during the first 24 hours after surgery in the ondansetron group (42%) was significantly less than in the dimenhydrinate (79%; P<0.02) and placebo (82%; P<0.01) groups. The number of episodes of POV in the first 24 hours differed significantly between the ondansetron and placebo groups only. The number of children whose discharges from hospital were delayed secondary to POV in the ondansetron group (0 of 25) was significantly less than in the placebo group (4 of 22, P<0.04). Secondary: Not reported
Kothari et al.[98] (2000) Ondansetron 4 mg IV vs	DB, PRO, RCT Patients undergoing laparoscopic cholecystectomy	N=128 24 hours	Primary: Frequency of PONV, need for rescue antiemetics, need for overnight hospitalization secondary to persistent nausea	Primary: Need for rescue medication occurred in 34% of ondansetron group and 29% of dimenhydrinate group (P=0.376). POV occurred in 6% of ondansetron group and 12% of dimenhydrinate group (P=0.228). PONV occurred in 42% of ondansetron group and 34% of dimenhydrinate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dimenhydrinate 50 mg IV			and vomiting, frequency PONV 24 hours after discharge Secondary: Not reported	group (P=0.422). One patient in the ondansetron group and 2 patients in the dimenhydrinate group required overnight hospitalization for persistent nausea and vomiting (P=NS). Rates of PONV 24 hours after discharge were similar between the ondansetron and dimenhydrinate groups (10 and 14%; P=0.397 and 2 and 5%; P=0.375, respectively). Secondary: Not reported
McCall et al.[99] (1999) Ondansetron 0.1 mg/kg vs dimenhydrinate 0.5 mg/kg vs placebo	DB, PC, PRO, RCT Patients with a mean age of 11.8 years undergoing reconstructive burn surgery with general anesthesia	N=100 8 hours	Primary: Incidence of PONV, POV Secondary: Not reported	Primary: Statistically significant reductions in the incidence of PONV in the patients who received ondansetron or dimenhydrinate were found, compared to the results of patients who received placebo. POV was reduced from 61% in the placebo group to 29 and 40% in the ondansetron and dimenhydrinate groups, respectively, and PONV was similarly reduced from 69 to 47 and 40%, respectively. The differences between ondansetron and dimenhydrinate were not statistically significant. Secondary: Not reported
Tsutsumi et al.[100] (2014) Ondansetron 4 mg IV vs fosaprepitant 150 mg IV	DB, PRO, RCT Patients between 20 and 80 years of age undergoing elective craniotomy under general anesthesia	N=64 48 hours	Primary: Incidence of nausea and vomiting, use of rescue antiemetics, and severity of pain Secondary: Not reported	Primary: For the period from 0 to 24 hours, the percentage of patients who experienced vomiting (6 vs 50%, P<0.001; OR, 0.067; 95% CI, 0.014 to 0.327) and the complete response rate (66 vs 41%, P=0.045; OR, 2.790; 95% CI, 1.011 to 7.698) were significantly different in the fosaprepitant group compared to the ondansetron group. However, there were no statistically significant differences between the groups in the incidence of PONV or the need for rescue antiemetics during this time period. The incidence of vomiting and complete response from 0 to 48 hours were similar to rates from 0 to 24 hours (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Kakuta et al.[101] (2015) Ondansetron 4 mg IV vs fosaprepitant 150 mg IV	DB, PRO, RCT Patients 20 to 80 years of age scheduled to undergo lower limb surgery (total hip arthroplasty, total knee arthroplasty, and rotational acetabular osteotomy) under general anesthesia	N=38 48 hours	Primary: Incidence of nausea and vomiting, use of rescue antiemetics, and severity of pain Secondary: Not reported	Primary: The incidence of PONV, complete response rate, rescue antiemetic use, nausea score, and visual analog scale score for pain were not significantly different between the two groups at all time points during the 48 hours after surgery. During the periods from 0 to 24 and 0 to 48 hours, the proportion of patients who experienced vomiting was significantly different between the groups (0 versus 26%; P=0.046). Secondary: Not reported
Van den Berg[102] (1996) Ondansetron 0.06 mg/kg IV vs prochlorperazine 0.2 mg/kg IM vs prochlorperazine 0.2 mg/kg IV vs placebo	DB, PRO, RCT Patients 9 to 61 years of age who received standardized general anesthesia for tympanoplasty	N=148 24 hours	Primary: Incidence of retching and vomiting in the post-anaesthesia care unit during first 24 hours post surgery Secondary: Postoperative headache	Primary: Nausea alone during the first 24-hour postoperative period was infrequent in each treatment group with a similar incidence (3 to 8%). The incidence of vomiting alone (without accompanied nausea) during this time was also similar between groups (11 to 24%). The incidence of vomiting or retching immediately after extubation or during recovery occurred in 16% of placebo patients, 5% of patients in the IM prochlorperazine group, and 8% in the prochlorperazine and ondansetron IV groups, but the differences between groups was NS (P>0.05 for all groups). The incidence of nausea accompanied by vomiting occurred in 53% of the placebo group and 16 and 19% in those given prochlorperazine IM and ondansetron IV, respectively (P<0.0005), and 30% in those given prochlorperazine IV (P<0.05). The study was not powered to detect a difference between groups. The percent of patients who experienced no nausea or vomiting was 27% for placebo, 57% for prochlorperazine IM, 43% for prochlorperazine IV, and 62% for ondansetron IV. Only the prochlorperazine IM and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ondansetron IV groups achieved significance compared to placebo (P<0.01 and P=0.005, respectively). Secondary: Incidence of headache reported in the first 24 hours after surgery (placebo 56%, prochlorperazine IM 41%, prochlorperazine IV 43% and ondansetron IV 49%) was similar in the four groups.
Chen et al.[103] (1998) Ondansetron 4 mg IV vs prochlorperazine maleate 10 mg IM	DB, RCT Patients ≥17 years of age undergoing elective, primary or revisionary total hip or total knee replacement procedures	N=78 48 hours	Primary: Incidence and severity of PONV Secondary: Number of rescue antiemetic doses required, number of physical therapy cancellations because of PONV, length of hospital stay	Primary: The incidence of nausea was significantly greater in the ondansetron group compared to the prochlorperazine group (P=0.02), as was the severity of nausea (P=0.04). The incidence (P=0.13) and severity (P=0.51) of vomiting were similar between the two groups. Secondary: The need for rescue antiemetic therapy was greater in the ondansetron group compared to the prochlorperazine group, but the difference was not statistically significant (P=0.08). The mean number of rescue antiemetic doses required was 2.1 in the ondansetron group and 1.7 in the prochlorperazine group, but the difference did not reach statistical difference (P=0.50).
White et al.[104] (2007) Ondansetron 4 mg vs scopolamine 1.5 mg transdermal patch	DB, PC, RCT Patients 18 to 65 years of age scheduled to undergo major laparoscopic (e.g., bariatric surgery) or plastic (e.g., abdominoplasty, reduction mammoplasty) surgery procedures	N=77 72 hours	Primary: PONV or retching; need for rescue antiemetics, complete response rates (i.e., absence of protracted nausea or repeated episodes of emesis requiring antiemetic rescue medication) Secondary:	Primary: There were no differences between the transdermal scopolamine and ondansetron treatment groups with respect to the incidence of PONV symptoms or need for rescue medications. Complete response rates did not differ significantly between the transdermal scopolamine and ondansetron treatment groups (51 and 47%, respectively). The requirement for rescue antiemetics was not significantly reduced in the transdermal scopolamine group compared to the ondansetron group during the 24 to 48 hour period (21 vs 40%; P=0.07). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	Not reported
Gan et al.[105] (2009) Scopolamine 1.5 mg transdermal patch applied two hours prior to surgery and ondansetron 4 mg IV two to five minutes prior to induction of anesthesia vs ondansetron 4 mg IV two to five minutes prior to induction of anesthesia	DB, MC, RCT Adult female patients (ASA I or III status) at high risk for PONV who were undergoing outpatient gynecological laparoscopy, laparoscopic cholecystectomy, or breast augmentation surgery with an anticipated duration of one to three hours	N=620 24 hours	Primary: Complete antiemetic response through 24 hours postoperatively Secondary: Time elapsed between surgery and first episode of nausea or use of antiemetic medication, vomiting/retching or use of rescue medication, and vomiting/retching, nausea, or use of rescue medication	Primary: There was a significant increase in complete response rate in patients receiving combination therapy vs ondansetron alone (48 vs 39%; P=0.021). Secondary: The incidence of nausea, vomiting, or the use of rescue antiemetics was significantly less frequent in the post-anesthesia care unit and at 24 and 48 hours after surgery in the combination group compared to ondansetron monotherapy; however, there was no difference in these outcomes at hospital discharge. The time that elapsed before the first episode of nausea, vomiting, or the use of rescue antiemetic was significantly longer in the combination group compared to ondansetron monotherapy. The cumulative number of times rescue medication was given at 24 hours was less frequent with combination therapy compared to ondansetron monotherapy (P=0.047). The mean maximum severity of the nausea was significantly lower in the combination group than in the ondansetron group for those patients who experienced one or more nausea episodes at any time point during the 48 hours after surgery (P<0.05). The combination group had a significantly higher patient mean satisfaction score than the ondansetron monotherapy group (P=0.049). The overall incidence of adverse effects was significantly decreased in the combination therapy group (36.7 vs 49%; P<0.01).
Sah et al.[106] (2009) Scopolamine 1.5 mg transdermal patch applied two	DB, RCT Patients (ASA I or II status) at high risk for PONV who were undergoing	N=126 24 hours	Primary: Presence of vomiting, severity of nausea, rescue medications for nausea, and	Primary: Transdermal scopolamine significantly decreased the frequency of postoperative nausea between eight and 24 hours; however, there was no significant reduction in the frequency of vomiting during any time period assessed.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours prior to surgery and ondansetron 4 mg 30 minutes prior to the end of surgery vs ondansetron 4 mg 30 minutes prior to the end of surgery	outpatient plastic surgery		adverse events Secondary: Not reported	There was no significant difference in the use of rescue medications between the treatment groups (P=0.388). The most common adverse event was dry mouth (70%) for patients in the transdermal scopolamine group, but frequency of dry mouth was also high in the placebo group (63%). Sedation was seen in 40% of patients receiving transdermal scopolamine compared to 33% of patients in the placebo group. Secondary: Not reported
Loewen et al.[107] (2000) 5-HT$_3$ antagonists vs traditional agents (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol)	MA Patients undergoing surgery who received an antiemetic agent	N=6,638 (41 trials) Variable duration	Primary: PONV that occurred within 48 hours after surgery Secondary: 5-HT3 receptor antagonists compared to traditional antiemetics for rates of vomiting	Primary: 5-HT$_3$ receptor antagonists showed a 46% reduction in the odds of PONV (OR, 0.54; 95% CI, 0.42 to 0.71; P<0.001). 5-HT$_3$ receptor antagonists showed a 39% reduction in PONV over droperidol (OR, 0.61; 95% CI, 0.42 to 0.89; P<0.001). 5-HT$_3$ receptor antagonists showed a 56% reduction in PONV over metoclopramide (OR, 0.44; 95% CI, 0.31 to 0.62; P<0.001). Secondary: 5-HT$_3$ receptor antagonists showed a 38% reduction in vomiting compared to traditional antiemetics (OR, 0.62; 95% CI, 0.48 to 0.81; P<0.001). 5-HT$_3$ antagonists showed a beneficial effect over droperidol in rate of vomiting (OR, 0.56; 95% CI, 0.41 to 0.76; P<0.001). 5-HT$_3$ antagonists showed a beneficial effect over metoclopramide in rate of vomiting (OR, 0.50; 95% CI, 0.32 to 0.77; P<0.001). Sedation was more common in the traditional group (11.9%) compared to 5-HT$_3$ receptor antagonists (5.6%; (OR, 0.7; 95% CI, 0.32 to 0.64; P<0.001). Headache was more common in the 5-HT$_3$ receptor antagonist group (17.0%) than in the traditional antiemetic group (13.0%; (OR, 1.65; 95% CI, 1.35 to 2.02; P<0.001).
Kovac et al.[108]	DB, MC, PC, PRO,	N=544	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) palonosetron 0.025 mg IV vs palonosetron 0.050 mg IV vs palonosetron 0.075 mg IV vs placebo	RCT Female patients with an ASA status I-III, greater than 18 years old, scheduled to undergo elective inpatient gynecological or breast surgery that was expected to last a minimum of 1 hour and were scheduled to be hospitalized for at least 72 hours after surgery	Monitored over 72 hour time period	Complete response (no postoperative emetic symptoms) over 0 to 24 hours and 24 to 72 hours Secondary: Time to treatment failure, use of rescue therapy, emetic episodes, nausea and safety	Compared to placebo (36%), complete response was 46% for palonosetron 0.025 mg (P=0.069), 47% for palonosetron 0.05 mg (P=0.069) and 56% for palonosetron 0.075 mg (P=0.001) when evaluated at the 0 to 24 hour time interval after surgery. Complete response for placebo and palonosetron 0.075 mg were 52% and 70% for the 24 to 74 hour time interval (P=0.002). Complete response rates for palonosetron 0.025 mg and 0.050 mg were not statistically different than placebo. Secondary: A significantly longer time to treatment failure was observed in the palonosetron 0.075 mg group vs placebo (P=0.004). No significant time difference was seen between placebo and palonosetron 0.025 mg group (P=0.112) and palonosetron 0.05 mg group (P=0.060). During the 0 to 72 hour study period 62/136 (46%) placebo patients compared to 36/135 (27%) palonosetron 0.075 mg patients required rescue medication (P<0.001). During the 0 to 24 hour time block 82/136 (60%) placebo patients compared to 54/136 (46%) palonosetron 0.075 mg patients experience an emetic episode (P<0.001). During the 24 to 72 hour time block there was no significant difference between the placebo (10%) and palonosetron 0.075 mg groups (4%; P=0.061). During the 0 to 24 hour time block significantly fewer patient treated with palonosetron 0.075 mg (50%) compared to placebo (71%) experienced nausea (P<0.001). All doses of palonosetron were well tolerated in this study. Percentages of severe adverse events were 5% in the placebo group, 4% in the palonosetron 0.075 mg group, and 7% in both the palonosetron 0.025 mg and 0.05 mg groups. Not all values were reported in secondary end points.
Candiotti et al.[109]	DB, MC, PC, PRO,	N=546	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Palonosetron 0.025 mg IV vs palonosetron 0.05 mg IV vs palonosetron 0.075 mg IV vs placebo	RCT Patients at least 18 years old with an ASA physical status of I-III and scheduled to undergo elective laparoscopic abdominal or gynecological surgery and had to have at least two of the following risk factors: female gender, history of PONV and/or motion sickness, or nonsmoking status	Monitored over 72 hour time period	Complete response (no postoperative emetic symptoms) over 0 to 24 hours and 24 to 72 hours Secondary: Emetic episodes, nausea, interference of PONV with patient functions and safety	Complete response at 0-24 hours was 26% in the placebo group compared with 33% of the palonosetron 0.025 mg group (P=0.187), 39% in the palonosetron 0.050 mg group (P=0.017) and 43% in the palonosetron 0.075 mg group (P=0.004). Complete response at 24 to 72 hours was 41% in the placebo group compared to 44% in the palonosetron 0.025 mg group (P=0.638), 47% in the palonosetron 0.050 mg group (P=0.249) and 49% in the palonosetron 0.075 mg group (P=0.188). Secondary: Emetic episodes at 0 to 72 hours were 33% in the palonosetron 0.075 mg group compared to 44% in the placebo group (P=0.075). During the 0 to 24 hour time period more patients receiving palonosetron 0.075 mg did not experience nausea (P=0.033) or experienced less intense nausea (P=0.0504) compared to placebo. Total Osoba questionnaire scores (evaluating interference of PONV with patient function) were better with palonosetron 0.075 mg than placebo (P=0.004). Adverse events were reported in 7% of patients in the palonosetron 0.075 mg group and 10% in placebo group (P values not reported). Only values of palonosetron 0.075 mg group were reported for the secondary end points.
Chun et al.[110] (2014) Palonosetron 0.075 mg IV vs placbeo	DB, PC, RCT Healthy inpatients 20 to 70 years of age who were undergoing elective surgery with general anaesthesia	N=204 72 hours	Primary: Incidence of PONV 0 to 24 hours after operation Secondary: Incidence of PONV 24 to 72 hours after	Primary: The incidence of PONV was significantly lower in the palonosetron group than in the placebo group during the 0 to 24 hour (33 vs 47%) and the 0 to 72 hours postoperative period (33 vs 52%; P<0.05). Secondary: The incidence of PONV was not significantly different in the 24 to 72 hour period between the palonosetron and placebo groups (6 vs 11%). The severity of nausea during the 0 to 24 hours postoperative period was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			operation, severity of nausea, use of rescue medication, patient satisfaction	less in the palonosetron group compared with the placebo group, but the difference was not statistically significant (P=0.08). There was no significant difference in rescue anti-emetics used between the groups. There was no significant difference with regard to patient satisfaction between the groups.
Bang et al.[111] (2016) Palonosetron 0.075 mg IV vs placbeo	DB, PRO, RCT Women 20 to 60 years of age with an ASA physical status of I or II undergoing elective gynecological laparoscopic surgery under total intravenous anesthesia	N=100 24 hours	Primary: Overall incidence of nausea and vomiting during the first 24 h after anesthesia Secondary: Severity of nausea, the need for a rescue drug, patient satisfaction, and the incidence of adverse events	Primary: The overall incidence of PONV (0 to 24 h) was significantly lower in the palonosetron group than in the placebo group (34 vs 58%, P=0.027). During the six to 24 hour period following surgery, the incidence of PONV (12 vs 30%, P=0.030) and the incidence of moderate to severe nausea (6 vs 22%, P=0.041) were significantly lower in the palonosetron group than in the placebo group. In contrast, at zero to two hours and two to six hours following surgery, the incidence of PONV and the severity of nausea were not significantly different between the two groups. Secondary: There were no significant differences with respect to the use of rescue antiemetics, adverse effects, or patient satisfaction.
Radiation-Induced Nausea and Vomiting (RINV)				
Spitzer et al.[112] (2000) Granisetron 2 mg by mouth vs ondansetron 8 mg by mouth vs historical control	DB, PG, PRO, RCT Patients ≥18 years of age diagnosed with malignant disease or aplastic anemia receiving 11 fractions of radiation over the course of 4 days	N=34 4 days	Primary: Number of patients who had no emetic episodes over four days Secondary: Percent of patients with no emetic episodes and no rescue medication over 24 hours and four days	Primary: Significantly more patients given granisetron (33.3%) and ondansetron (26.7%) experienced no episodes of emesis than the historical control (0%; P<0.01 for both granisetron and ondansetron compared to historical control). Secondary: During the first 24 hours, significantly more patients receiving granisetron (61.1%) and ondansetron (46.7%) had no emetic episodes than the historical control group (6.7%; P<0.01). Within the first four days, fewer patients in the granisetron (27.8%) and ondansetron groups (26.7%) had no emetic episodes and needed no rescue medication compared to historical controls (0%; P<0.01).
Ades et al.[113] (2017) AVERT	MC, PRO Patients ≥18 years	N=52 Period of	Primary: Complete response defined as no	Primary: Complete response was achieved by 58% of patients (95% CI, 43.2 to 71.3). This study was powered to demonstrate an absolute 15%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ondansetron 8 mg by mouth every 12 hours and aprepitant 125/80/80 mg on a Monday, Wednesday, Friday schedule throughout radiotherapy	of age requiring radiotherapy, with or without radiosensitizing chemotherapy for a malignancy localized to the upper abdomen	radiotherapy until 72 h beyond the final fraction	vomiting or rescue therapy during the entire observation period of radiotherapy Secondary: Nausea, vomiting, and use of rescue medication	improvement in complete response compared to a baseline efficacy of 65%, but failed to attain this threshold. Secondary: For secondary outcomes, 73.1% (95% CI, 59.0 to 84.4) of patients did not vomit, and 71.2% (95% CI, 56.9 to 82.9) did not use rescue medication during the observation period. Overall, participants vomited or experienced significant nausea for an average of 6.8% (95% CI ,11.4 to 21.0) and 8.4% (95% CI, 4.2 to 12.7) of time on study, respectively. Nausea was common with 32 (61.5%) reporting significant nausea at any time during the observation period.

Drug regimen abbreviations: IM=intramuscular, IV=intravenous
Study abbreviations: CI=confidence interval, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multi-center, NI=non-inferiority, NNT=number needed to treat, NS=not significant, OBS=observational, OL=open label, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SR=systematic review, XO=crossover
Miscellaneous abbreviations: ASA=American Society of Anesthesiologists, CINV=chemotherapy induced nausea and vomiting, PONV=postoperative nausea and vomiting, POV=postoperative vomiting

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the 5-HT$_3$ Receptor Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Dolasetron	tablet	Anzemet®	$$$	N/A
Granisetron	extended-release injection, injection*, tablet*, transdermal patch	Kytril®*, Sancuso®, Sustol®	$$$$$	$
Ondansetron	injection*, orally disintegrating tablet*, solution*, tablet*	N/A	$$$$$	$
Palonosetron	injection*	N/A	$$$	$$$

*Generic is available in at least one dosage form or strength.
ODT=orally disintegrating tablet, PDL=Preferred Drug List

X. Conclusions

The 5-HT$_3$ receptor antagonists are approved for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), and radiation-induced nausea and vomiting (RINV).[3-10] All agents are available in a generic formulation with the exception of dolasetron.

The use of multiple antiemetic agents is generally required for the prevention of CINV. The selection of therapy depends on the emetogenic potential of the chemotherapy regimen. Guidelines recommend the use of 5-HT$_3$

receptor antagonists to prevent acute nausea and vomiting associated with moderately or highly emetogenic chemotherapy (generally in combination with an NK1 antagonist and/or dexamethasone).[10,12,13] The 5-HT$_3$ receptor antagonists are also recommended as one of several options to prevent delayed nausea and vomiting, as well as to treat breakthrough nausea and vomiting.[12] Clinical trials have demonstrated similar efficacy and safety with the 5-HT$_3$ receptor antagonists for the prevention of CINV.[12,13,33,35,37,38,41-46,52,58,60,61] Intravenous and oral formulations are equally effective when used at the appropriate dose.[10,12,13] A limited body of evidence suggests that palonosetron improves CINV more that the first-generation agents, which is thought to be due to its higher receptor binding affinity and longer half-life.[1,35,52,66] Guidelines do not give preference to one 5-HT$_3$ receptor antagonist over another. However, the National Comprehensive Cancer Network guidelines specifically recommend palonosetron IV or granisetron SQ in combination with dexamethasone for CINV prevention in moderate emetic risk chemotherapy.[12] In contrast, the European Society of Medical Oncology/Multinational Association of Supportive Care in Cancer guidelines state that there is no definitive evidence demonstrating an advantage of the use of palonosetron with respect to the other 5-HT$_3$ receptor antagonists, when both are combined with dexamethasone.[13] For the prevention of RINV, guidelines recommend the use of a 5-HT$_3$ receptor antagonist (with or without dexamethasone) before each fraction.[10,12,13]

According to the Society for Ambulatory Anesthesia guidelines, not all surgical patients will benefit from prophylactic antiemetic therapy.[14] Prophylaxis is recommended for adult patients who have at least one risk factor for PONV. These patients should receive treatment with two or three antiemetic agents from different classes.[14] The 5-HT$_3$ receptor antagonists can effectively be combined with droperidol, dexamethasone, or promethazine. In general, patients at low risk for PONV are not given prophylactic therapy unless they are at risk for complications from vomiting.[14] For patients who do not receive prophylaxis, a small-dose of a 5-HT$_3$ receptor antagonist should be administered upon the first signs of PONV.[14] Clinical trials have demonstrated similar efficacy and safety among the 5-HT$_3$ receptor antagonists for the prevention and treatment of PONV.[79-80,82-83,89-92,95-96]

Nausea and vomiting associated with pregnancy is a common condition that can significantly impact a woman's quality of life.[15] Mild symptoms can often be treated with lifestyle and dietary modifications. However, some women may experience severe nausea and vomiting (hyperemesis gravidarum), which may require hospitalization. Despite the paucity of data, the 5-HT$_3$ receptor antagonists have been used to treat nausea and vomiting during pregnancy when other antiemetic combinations have failed.[15] The American College of Obstetricians and Gynecologists and Society of Obstetricians and Gynaecologists of Canada guidelines recommend the use of vitamin B$_6$, with or without doxylamine, as first-line therapy for the treatment of pregnancy induced nausea and vomiting.[15,16] If there is no improvement, the addition of promethazine, dimenhydrinate, metoclopramide, or trimethobenzamide is recommended.[16] Ondansetron is considered an alternative treatment option for women who are dehydrated and have symptoms that are not relieved by other treatments. Ondansetron has been shown to be safe and effective in a few published trials.[71,72] One randomized trial demonstrated that intravenous ondansetron was as effective as intravenous promethazine for the treatment of hyperemesis gravidarum.[71] Another demonstrated a greater reduction in nausea in women using ondansetron as compared to pyridoxine plus doxylamine as reported on a visual analog scale.[73]

There is insufficient evidence to support that one brand 5-HT$_3$ receptor antagonist is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand 5-HT$_3$ receptor antagonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand 5-HT$_3$ receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, Neurokinin-1 Receptor Antagonists
AHFS Class 562232
November 9, 2022

I. Overview

The pathophysiology of nausea and vomiting is complex and involves multiple neurotransmitters and organ systems. Five neurotransmitter receptor sites play a key role in the vomiting reflex. These receptor sites include M1 (muscarinic), D2 (dopamine), H1 (histamine), 5-HT_3 (serotonin), and NK1 (substance P). The available antiemetic drugs antagonize these receptors, leading to improvements in nausea and vomiting. Nausea and vomiting due to central or vestibular disorders respond well to anticholinergic agents and histamine H_1-receptor antagonists.[1-7]

The neurokinin-1 (NK1) receptor antagonists are Food and Drug Administration (FDA)-approved for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), and aprepitant is also indicated for prevention of post-operative nausea and vomiting.[1-7] Single-entity products include aprepitant (Emend®) and its prodrug, fosaprepitant dimeglumine (Emend®). Aprepitant is now also available under the brand name Cinvanti® as an injectable emulsion formulation. Fosaprepitant is rapidly converted to aprepitant when administered intravenously. There is an NK1 antagonist combination product currently available, netupitant-palonosetron (Akynzeo®), along with the injectable version fosnetupitant-palonosetron (Akynzeo®). With this combination, netupitant, a NK1 antagonist is co-formulated with palonosetron, a 5-HT_3 receptor antagonist.[1-7]

The NK1 receptor antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Aprepitant and fosaprepitant are available in a generic formulation. This class was last reviewed in August 2020.

Table 1. NK1 Receptor Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Aprepitant	capsule*, capsule dose pack*, injectable emulsion, powder packet	Cinvanti®, Emend®*	aprepitant
Fosaprepitant	injection*	Emend®*	fosaprepitant
Combination Products			
Netupitant and palonosetron	capsule, injection	Akynzeo®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the NK1 receptor antagonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the NK1 Receptor Antagonists

Clinical Guideline	Recommendation(s)
National Comprehensive Cancer Network: **Clinical Practice Guidelines in Oncology: Antiemesis (2022)**[9]	Principles of emesis control for the cancer patient: • Prevention of nausea/vomiting is the goal. The risk of nausea/vomiting (acute ≤24 hours vs delayed >24 hours) for persons receiving anticancer agents of high and moderate emetic risk lasts for at least three days for high and two days for moderate after the last dose of anticancer agents. Patients need to be protected throughout the full period of risk. • Oral and parenteral serotonin receptor antagonists (5-HT_3 RAs) have equivalent efficacy when used at the appropriate doses and intervals.

Clinical Guideline	Recommendation(s)

	• Consider the toxicity of the specific antiemetic(s).
	• Choice of antiemetic(s) used should be based on the emetic risk of the therapy, prior experience with antiemetics, and patient factors. Continuous infusion may make an agent less emetogenic. The emetic risk is expected to be the same for biosimilars as for the parent compound unless otherwise noted.
	• Patient risk factors for anticancer agent-induced nausea/vomiting include:
	  ○ Younger age
	  ○ Female sex
	  ○ Previous history of anticancer agent-induced nausea/vomiting
	  ○ Little or no previous alcohol use
	  ○ Prone to motion sickness
	  ○ History of morning sickness during pregnancy
	  ○ Anxiety/high pretreatment expectation of nausea
	• There are other potential causes of emesis in patients with cancer (e.g., bowel obstruction, vestibular dysfunction, brain metastases, electrolyte imbalance, uremia, concomitant drugs, gastroparesis, cannabinoid hyperemesis syndrome, pancreatitis).
	
	For high emetic risk parenteral chemotherapy the following is recommended:
	• Preferred: combination of olanzapine, a neurokinin-1 receptor antagonist (NK1 RA), a 5-HT_3 RA, and dexamethasone.
	OR
	• Combination of olanzapine, palonosetron, and dexamethasone.
	OR
	• Combination of a NK1 RA, a 5-HT_3 RA, and dexamethasone.
	• The regimen and doses for each therapy are modified on days two to four after chemotherapy.
	
	For moderate emetic risk parenteral chemotherapy the following is recommended:
	• Combination of dexamethasone and a 5-HT_3 RA (palonosetron IV and granisetron SQ preferred).
	OR
	• Combination of olanzapine, palonosetron, and dexamethasone.
	OR
	• Combination of a NK1 RA, a 5-HT_3 RA, and dexamethasone.
	• The regimen and doses for each therapy are modified on days two and three after chemotherapy.
	
	For low emetic risk parenteral chemotherapy the following is recommended:
	• Dexamethasone; **OR**
	• Metoclopramide; **OR**
	• Prochlorperazine; **OR**
	• Dolasetron, granisetron or ondansetron (oral formulations).
	• Lorazepam PRN and H_2 blocker or PPI may be given with any regimen.
	
	For minimal emetic risk parenteral chemotherapy the following is recommended:
	• No routine prophylaxis
	
	For oral chemotherapy with moderate to high emetic risk the following is recommended:
	• A 5-HT_3 antagonist (dolasetron, granisetron, or ondansetron oral).
	• Lorazepam may be given.
	• An H_2 receptor blocker or PPI may be given.
	
	For oral chemotherapy with low to minimal emetic risk the following is recommended:
	• Metoclopramide PRN; **OR**
	• Prochlorperazine PRN (maximum 40 mg/day); **OR**

Clinical Guideline	Recommendation(s)
	• Dolasetron, granisetron or ondansetron. • Lorazepam PRN and H_2 blocker or PPI may be given with any regimen. Principles for managing multiday emetogenic chemotherapy regimens • Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea/vomiting based on their chemotherapy regimen. It is therefore difficult to recommend a specific antiemetic regimen for each day, especially since acute and delayed emesis may overlap after the initial day of chemotherapy until the last day. • After chemotherapy administration concludes, the period of risk for delayed emesis also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen. • Practical issues also need to be considered when designing the antiemetic regimen, taking into consideration the administration setting, preferred route of administration, duration of action of the 5-HT_3 receptor agonist and associated dosing intervals, tolerability of daily antiemetics (e.g., steroids), compliance issues, and individual risk factors. • Steroids: o Dexamethasone should be administered once daily (either orally or intravenously [IV]) for moderately or highly emetogenic chemotherapy and for two to three days after chemotherapy for regimens likely to cause delayed emesis. o Dexamethasone dose may be modified or omitted when the chemotherapy regimen already includes a corticosteroid. • Serotonin antagonists: o A serotonin antagonist should be administered prior to the first (and subsequent) doses of moderately or highly emetogenic chemotherapy. o The frequency or need for repeated administration depends on the agent chosen and its mode of administration (IV, oral, or transdermal). o When palonosetron or granisetron extended-release injection is used as part of an antiemetic regimen that does NOT contain an NK1 antagonist, palonosetron or granisetron extended-release injection are the preferred 5-HT_3 receptor antagonists. • NK1 receptor antagonists: o NK1 antagonists may be used for multiday chemotherapy regimens likely to be moderately or highly emetogenic associated with significant risk for delayed nausea and emesis. Principles for managing breakthrough emesis • The general principle of treatment for breakthrough nausea and vomiting is to add one agent from a different drug class to the current regimen. • No one drug class has been shown to be superior for the management of breakthrough emesis. • Consider around-the-clock administration rather than PRN. • The oral route is not likely to be feasible due to vomiting, therefore rectal or IV therapy is often required. • Ensure adequate hydration.
European Society of Medical Oncology/ Multinational Association of Supportive Care in Cancer: **Consensus Guidelines for the**	Prevention of acute and delayed nausea and vomiting induced by highly emetogenic chemotherapy • For the prevention of cisplatin-containing highly emetogenic chemotherapy, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone, and an NK1 receptor antagonist (aprepitant, fosaprepitant, netupitant, or rolapitant), given before chemotherapy is recommended. • In patients receiving cisplatin-containing highly emetogenic chemotherapy treated with a combination of an NK1 receptor antagonist, a 5-HT_3 receptor antagonist and dexamethasone to prevent acute nausea and vomiting, dexamethasone on days two

Clinical Guideline	Recommendation(s)
Prevention of Chemotherapy and Radiotherapy-Induced Nausea and Vomiting (2016)[10]	to four is suggested to prevent delayed nausea and vomiting. • In women with breast cancer receiving anthracycline/cyclophosphamide (AC) chemotherapy, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone, and an NK1 receptor antagonist (aprepitant, fosaprepitant, netupitant, or rolapitant), given before chemotherapy is recommended. • In women with breast cancer treated with a combination of a 5-HT_3 receptor antagonist, dexamethasone and an NK1 receptor antagonist to prevent acute nausea and vomiting, aprepitant or dexamethasone should be used on days two and three but not if fosaprepitant, netupitant, or rolapitant has been used on day one. If an NK1 receptor antagonist is not available for the prophylaxis of nausea and vomiting induced by AC chemotherapy, palonosetron is the preferred 5-HT_3 receptor antagonist. • For regimens including mechlorethamine, streptozocin, cyclophosphamide ≥1500 mg/m^2, carmustine, and dacarbazine, adding an NK1 receptor antagonist to the combination of a 5-HT_3 receptor antagonist and dexamethasone for all non-cisplatin and non-AC highly emetogenic chemotherapy is recommended. • Differences among the NK1 antagonists: o Aprepitant and netupitant are inhibitors of CYP3A4 and as a consequence, both significantly increase the exposure to oral dexamethasone; hence, reduction in oral dexamethasone doses is recommended during co-administration (from 20 to 12 mg). o Rolapitant is not an inhibitor or inducer of CYP3A4 and therefore does not require a reduced dose of dexamethasone when co-administered. However, rolapitant is a moderate inhibitor of CYP2D6. o At present, no comparative studies have been carried out to identify differences in efficacy and toxicity between the three NK1 receptor antagonists. <u>Prevention of acute and delayed nausea and vomiting induced by moderately emetogenic chemotherapy (MEC)</u> • For the prevention of acute emesis in MEC-treated patients, a 5-HT_3 receptor antagonist plus dexamethasone is recommended. • There is no definitive evidence demonstrating an advantage of the use of palonosetron with respect to the other 5-HT_3 receptor antagonists, when both are combined with dexamethasone. • In patients receiving MEC with a known potential for delayed emesis (e.g. oxaliplatin, doxorubicin, cyclophosphamide), the use of dexamethasone for days two to three can be considered. • No routine prophylaxis for delayed emesis can be recommended for all other patients receiving MEC. • To prevent carboplatin-induced acute nausea and vomiting, a combination of an NK1 receptor antagonist, dexamethasone, and a 5-HT_3 receptor antagonist is recommended. If patients receive fosaprepitant, netupitant, or rolapitant on day one, no antiemetic prophylaxis for delayed emesis is required. If patients receive aprepitant on day one, aprepitant on days two and three is recommended. <u>Prevention of nausea and vomiting induced by multiple-day cisplatin chemotherapy</u> • Patients affected by metastatic germ cell tumors receiving multiple-day cisplatin should receive a 5-HT_3 receptor antagonist plus dexamethasone plus aprepitant for the prevention of acute nausea and vomiting and dexamethasone for delayed nausea and vomiting. <u>Prevention of acute and delayed nausea and vomiting induced by chemotherapy with low and minimal emetogenic potential</u> • A single antiemetic agent, such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, such as metoclopramide may be considered for

Clinical Guideline	Recommendation(s)
	prophylaxis in patients receiving chemotherapy of low emetic risk. • No antiemetic should be routinely administered before chemotherapy to patients without a history of nausea and vomiting receiving minimally emetogenic chemotherapy. • No antiemetic should be administered for prevention of delayed nausea and vomiting induced by low or minimally emetogenic chemotherapy. • If a patient experiences acute or delayed nausea or vomiting after low or minimally emetogenic chemotherapy, it is advised that, with subsequent chemotherapy treatments, the regimen for the next higher emetic level be given. <u>Breakthrough chemotherapy-induced emesis and refractory emesis</u> • Antiemetics are most effective when used prophylactically. Therefore, it is preferable to use maximally effective antiemetics as first-line therapy rather than withholding more effective antiemetics for later use at the time of antiemetic failure. • For the treatment of breakthrough nausea and vomiting, it is recommended to use an antiemetic with a different mechanism of action than that of the antiemetic(s) used for prophylaxis. The available evidence for breakthrough nausea and vomiting suggests the use of olanzapine 10 mg orally daily for three days. The mild to moderate sedation in this patient population, especially elderly patients, is a potential problem with olanzapine. <u>Prevention of nausea and vomiting induced by high-dose chemotherapy</u> • For patients receiving high-dose chemotherapy for stem cell transplant, a combination of a 5-HT_3 receptor antagonist with dexamethasone and aprepitant (125 mg orally on day one and 80 mg on days two to four) is recommended before chemotherapy. <u>Prevention of radiotherapy-induced nausea and vomiting</u> • High emetic risk: prophylaxis with a 5-HT_3 receptor antagonist and dexamethasone is recommended. • Moderate emetic risk: prophylaxis with 5-HT_3 receptor antagonist and dexamethasone (optional) is recommended. • Low emetic risk with cranium area of treatment: prophylaxis or rescue with dexamethasone is recommended. • Low emetic risk with head/neck, thorax, or pelvis as area of treatment: prophylaxis or rescue with dexamethasone, a dopamine receptor antagonist, or a 5-HT_3 receptor antagonist is recommended. • Minimal emetic risk: rescue with dexamethasone, dopamine receptor antagonist, or 5-HT_3 receptor antagonists. <u>Prevention of acute chemotherapy-induced nausea and vomiting in children</u> • In children receiving chemotherapy of high emetic risk, an antiemetic prophylaxis with a 5-HT_3 receptor antagonist (granisetron, ondansetron, tropisetron or palonosetron) plus dexamethasone plus aprepitant is recommended. • Children who cannot receive dexamethasone should receive a $5HT_3$ receptor antagonist plus aprepitant. • When aprepitant administration is not feasible or desirable, the guideline recommends a 5-HT_3 receptor antagonist plus dexamethasone be given to children receiving highly emetogenic chemotherapy. • Children receiving MEC should receive antiemetic prophylaxis with a 5-HT_3 receptor antagonist plus dexamethasone. Furthermore, children who cannot receive receptor antagonist should receive a 5-HT_3 receptor antagonist and aprepitant. • In children receiving chemotherapy of low emetogenicity, antiemetic prophylaxis with a 5-HT_3 receptor antagonist is recommended. • In children receiving chemotherapy of minimal emetogenicity, no antiemetic

Clinical Guideline	Recommendation(s)
	prophylaxis is recommended.
Society for Ambulatory Anesthesia: **Consensus Guidelines for the Management of Postoperative Nausea and Vomiting (2020)**[11]	Pediatric postoperative nausea and vomiting (PONV) management • Low risk prophylaxis: No treatment or 5-HT_3 receptor antagonist or dexamethasone. • Medium risk prophylaxis: 5-HT_3 receptor antagonist + dexamethasone. • High risk prophylaxis: 5-HT_3 receptor antagonist + dexamethasone + consider total intravenous anesthesia. • Rescue treatment: Use anti-emetic from different class than prophylactic drug-droperidol, promethazine, dimenhydrinate, metoclopramide; may also consider acupuncture/acupressure. Adult PONV management • One to two risk factors prophylaxis: Give two agents (5-HT_3 receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • More than two risk factors prophylaxis: Give three or four agents (5-HT_3 receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • Rescue treatment: Use anti-emetic from different class than prophylactic drug.
American Society of Clinical Oncology: **Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update (2020)**[12]	High-emetic-risk antineoplastic agents in adult patients • Adults treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of an NK_1 receptor antagonist, a serotonin (5-HT_3) receptor antagonist, dexamethasone, and olanzapine (day 1). Dexamethasone and olanzapine should be continued on days two to four. • Adults treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine (day 1). Olanzapine should be continued on days two to four. Moderate-emetic-risk antineoplastic agents in adult patients • Adults treated with carboplatin area under the curve (AUC) ≥ 4 mg/mL/min should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone (day 1). • Adults treated with moderate-emetic-risk antineoplastic agents (excluding carboplatin AUC ≥ 4 mg/mL/min) should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone (day 1). • Adults treated with cyclophosphamide, doxorubicin, oxaliplatin, and other moderate-emetic-risk antineoplastic agents known to cause delayed nausea and vomiting may be offered dexamethasone on days two to three. Low-emetic-risk antineoplastic agents in adult patients • Adults treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT_3 receptor antagonist or a single 8-mg dose of dexamethasone before antineoplastic treatment. Minimal-emetic-risk antineoplastic agents in adult patients • Adults treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis. Antineoplastic combinations in adult patients • Adults treated with antineoplastic combinations should be offered antiemetics appropriate for the component antineoplastic agent of greatest emetic risk. Adjunctive drugs in adult patients • Lorazepam is a useful adjunct to antiemetic drugs but is not recommended as a

Clinical Guideline	Recommendation(s)
	single-agent antiemetic. Cannabinoids in adult patients • Evidence remains insufficient for a recommendation regarding medical marijuana for the *prevention* of nausea and vomiting in patients with cancer receiving chemotherapy or radiation therapy. Evidence is also insufficient for a recommendation regarding the use of medical marijuana in place of the tested and US Food and Drug Administration–approved cannabinoids dronabinol and nabilone for the *treatment* of nausea and vomiting caused by chemotherapy or radiation therapy. Complementary and alternative therapies in adult patients • Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture/acupressure, and other complementary or alternative therapies for the *prevention* of nausea and vomiting in patients with cancer. High-dose chemotherapy with stem-cell or bone marrow transplantation in adult patients • Adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. • A four-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine may be offered to adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation. Multiday antineoplastic therapy in adult patients • Adults treated with multiday antineoplastic agents should be offered antiemetics before treatment that are appropriate for the emetic risk of the antineoplastic agent given on each day of the antineoplastic treatment and for two days after completion of the antineoplastic regimen. • Adults treated with four- or five-day cisplatin regimens should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. Breakthrough nausea and vomiting in adult patients • For patients with breakthrough nausea or vomiting, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; and ascertain that the best regimen is being administered for the emetic risk. • Adults who experience nausea or vomiting despite optimal prophylaxis and who did not receive olanzapine prophylactically should be offered olanzapine in addition to continuing the standard antiemetic regimen. • Adults who experience nausea or vomiting despite optimal prophylaxis and who have already received olanzapine may be offered a drug of a different class (e.g., an NK1 receptor antagonist, lorazepam or alprazolam, a dopamine receptor antagonist, dronabinol, or nabilone) in addition to continuing the standard antiemetic regimen. Anticipatory nausea and vomiting in adult patients • All patients should receive the most active antiemetic regimen appropriate for the antineoplastic agents being administered. Clinicians should use such regimens with initial antineoplastic treatment rather than assessing the patient's emetic response with less-effective antiemetic treatment. If a patient experiences anticipatory emesis, clinicians may offer behavioral therapy with systematic desensitization. High-emetic-risk radiation therapy in adult patients • Adults treated with high-emetic-risk radiation therapy should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone before each fraction and on the day after each fraction, if radiation therapy is not

Clinical Guideline	Recommendation(s)
	planned for that day. Moderate-emetic-risk radiation therapy in adult patients • Adults treated with moderate-emetic-risk radiation therapy should be offered a 5-HT_3 receptor antagonist before each fraction, with or without dexamethasone, before the first five fractions. Low-emetic-risk radiation therapy in adult patients • Adults treated with radiation therapy to the brain should be offered breakthrough dexamethasone therapy. Patients who are treated with radiation therapy to the head and neck, thorax, or pelvis should be offered breakthrough therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine-receptor antagonist. Minimal-emetic-risk radiation therapy in adult patients • Adults treated with minimal-emetic-risk radiation therapy should be offered breakthrough therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine-receptor antagonist. Concurrent radiation and antineoplastic agent therapy in adult patients • Adults treated with concurrent radiation and antineoplastic agents should receive antiemetic therapy appropriate for the emetic risk level of the antineoplastic agents, unless the risk level of the radiation therapy is higher. During periods when prophylactic antiemetic therapy for the antineoplastic agents has ended and ongoing radiation therapy would normally be managed with its own prophylactic therapy, patients should receive prophylactic therapy appropriate for the emetic risk of the radiation therapy until the next period of antineoplastic therapy, rather than receiving breakthrough therapy for the antineoplastic agents as needed. High-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with high-emetic-risk antineoplastic agents should be offered a three-drug combination of a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant or fosaprepitant. • Pediatric patients treated with high-emetic-risk antineoplastic agents who are unable to receive aprepitant or fosaprepitant should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. • Pediatric patients treated with high-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of palonosetron and aprepitant or fosaprepitant. Moderate-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with moderate-emetic-risk antineoplastic agents should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. • Pediatric patients treated with moderate-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of a 5-HT_3 receptor antagonist and aprepitant or fosaprepitant. Low-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with low-emetic-risk antineoplastic agents should be offered ondansetron or granisetron. Minimal-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis.

Clinical Guideline	Recommendation(s)
American College of Obstetricians and Gynecologists: **Practice Bulletin No. 189: Nausea and Vomiting of Pregnancy (2018)**[13]	General considerations • Treatment of nausea and vomiting of pregnancy with vitamin B6 (pyridoxine) alone or vitamin B6 plus doxylamine in combination is safe and effective and should be considered first-line pharmacotherapy. • The standard recommendation to take prenatal vitamins for one month before fertilization may reduce the incidence and severity of nausea and vomiting of pregnancy. • The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis, or hyperemesis gravidarum, or both, includes supportive therapy, and antithyroid drugs are not recommended. • Treatment of nausea and vomiting of pregnancy with ginger has shown some beneficial effects in reducing nausea symptoms and can be considered as a nonpharmacologic option. • Treatment of severe nausea and vomiting of pregnancy or hyperemesis gravidarum with methylprednisolone may be efficacious in refractory cases; however, the risk profile of methylprednisolone suggests it should be a last-resort treatment. • Early treatment of nausea and vomiting of pregnancy may be beneficial to prevent progression to hyperemesis gravidarum. • Intravenous hydration should be used for the patient who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present. Correction of ketosis and vitamin deficiency should be strongly considered. Dextrose and vitamins should be included in the therapy when prolonged vomiting is present, and thiamine should be administered before dextrose infusion to prevent Wernicke encephalopathy. • Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as the first-line treatment to provide nutritional support to the woman with hyperemesis gravidarum who is not responsive to medical therapy and cannot maintain her weight. • Peripherally inserted central catheters should not be used routinely in women with hyperemesis gravidarum given the significant complications associated with this intervention. Peripherally inserted central catheters should be utilized only as a last resort in the management of a woman with hyperemesis gravidarum because of the potential of severe maternal morbidity.
Society of Obstetricians and Gynaecologists of Canada: **Clinical Practice Guideline: Management of Nausea and Vomiting of Pregnancy (2016)**[14]	General considerations • Women experiencing nausea and vomiting of pregnancy may discontinue iron-containing prenatal vitamins during the first trimester and substitute them with folic acid or adult or children's vitamins low in iron. • Women should be counselled to eat whatever pregnancy-safe food appeals to them and lifestyle changes should be liberally encouraged. • Ginger may be beneficial in ameliorating the symptoms of nausea and vomiting of pregnancy. • Acupressure may help some women in the management of nausea and vomiting of pregnancy. • Mindfulness-based cognitive therapy as an adjunct to pyridoxine therapy may be beneficial. • Pyridoxine monotherapy or doxylamine/pyridoxine combination therapy is recommended as first line in treating nausea and vomiting of pregnancy due to their efficacy and safety. • Women with high risk for nausea and vomiting of pregnancy may benefit from preemptive doxylamine/pyridoxine treatment at the onset of pregnancy. • H1 receptor antagonists should be considered in the management of acute or chronic episodes of nausea and vomiting of pregnancy. • Metoclopramide can be safely used as an adjuvant therapy for the management of nausea and vomiting of pregnancy.

Clinical Guideline	Recommendation(s)
	• Phenothiazines are safe and effective as an adjunctive therapy for severe nausea and vomiting of pregnancy. • Despite potential safety concerns of ondansetron use in pregnancy, ondansetron can be used as an adjunctive therapy for the management of severe nausea and vomiting of pregnancy when other antiemetic combinations have failed. • Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. • When nausea and vomiting of pregnancy is refractory to initial pharmacotherapy, investigation of other potential causes should be undertaken.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the NK1 receptor antagonists are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Entity NK1 receptor antagonists[1-7]

Indication	Aprepitant	Fosaprepitant
Chemotherapy-Induced Nausea and Vomiting		
Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin	✔	✔
Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy	✔	✔
Postoperative Nausea and Vomiting		
Prevention of postoperative nausea and vomiting	✔ (generic capsules)	

Table 4. FDA-Approved Indications for the Combination NK1 receptor antagonists[6]

Indication	Netupitant and Palonosetron
Chemotherapy-Induced Nausea and Vomiting	
Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy*	✔

*Akynzeo® has not been studied for the prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide chemotherapy.

IV. Pharmacokinetics

The pharmacokinetic parameters of the NK1 receptor antagonists are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the NK1 receptor antagonists[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Aprepitant	60 to 65 (oral)	≥95	Liver (extensive)	Feces (extent unknown)	9 to 13
Fosaprepitant	100	≥95	Liver (extensive)	Renal (57) Feces (45)	9 to 13
Combination Products					

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Netupitant and Palonosetron	F: 100 N: not reported P: 97	F: 92 to 95 N >99.5 P: 62	N: Liver (extensive); P: Liver (partial)	N: Renal (4.7), Feces (86.5); P: Renal (85 to 93), Feces (5 to 8)	N: 80 P: 48

F= Fosnetupitant (injection formulation; prodrug of netupitant), N= Netupitant (oral formulation), P= Palonosetron

V. Drug Interactions

Major drug interactions with the NK1 receptor antagonists are listed in Table 6.

Table 6. Major Drug Interactions with the NK1 receptor antagonists[2-7]

Generic Name(s)	Interaction	Mechanism
Aprepitant, fosaprepitant	Pimozide	Aprepitant may inhibit the metabolism of pimozide, increasing the risk of life-threatening cardiac arrhythmias.
Aprepitant, fosaprepitant	Lomitapide	Concurrent use of strong or moderate CYP3A4 inhibitors, such as aprepitant, may elevate lomitapide plasma concentrations, increasing the risk of serious adverse reactions (e.g., hepatotoxicity). Lomitapide exposure has been reported to be increased 27-fold in the presence of a strong CYP3A4 inhibitor. Concomitant use of lomitapide with aprepitant is contraindicated.
Aprepitant	Corticosteroids	Aprepitant may inhibit the 3A4 isoenzyme and result in elevated plasma levels of dexamethasone, hydrocortisone, and methylprednisolone.
Aprepitant, fosaprepitant	Ranolazine	Aprepitant may inhibit the 3A4 isoenzyme, decreasing the metabolism of ranolazine. Ranolazine toxicity may occur, including QT-interval prolongation.
Aprepitant, fosaprepitant	Flibanserin	Concurrent use of flibanserin and aprepitant may result in increased flibanserin exposure and flibanserin adverse effects (hypotension, syncope, sedation) due to CYP3A4 inhibition.
Aprepitant, fosaprepitant	CYP3A4 inhibitors	Concurrent use of aprepitant and CYP3A4 inhibitors may result in increased plasma concentrations of aprepitant.
Aprepitant, fosaprepitant	CYP3A4 substrates	Aprepitant acts as a moderate inhibitor of CYP3A4 when administered as a 3-day regimen and can increase plasma concentrations of concomitant drugs that are substrates for CYP3A4.
Netupitant	CYP3A4 substrates	Netupitant is a moderate inhibitor of CYP3A4. Akynzeo should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when coadministered with Akynzeo. The inhibitory effect on CYP3A4 can last for multiple days.
Netupitant	CYP3A4 inducers/ inhibitors	Netupitant is mainly metabolized by CYP3A4. Avoid concomitant use of Akynzeo in patients who are chronically using a strong CYP3A4 inducer such as rifampin. A strong CYP3A inducer can decrease the efficacy of Akynzeo by substantially reducing plasma concentrations of netupitant. Concomitant use of Akynzeo with a strong CYP3A4 inhibitor (e.g., ketoconazole) can significantly increase the systemic exposure to netupitant. However, no dosage adjustment is necessary for single dose administration of Akynzeo.
5-HT_3 receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron)	Apomorphine	Significant adverse reactions, including profound hypotension and loss of consciousness, may occur when apomorphine is administered with 5-HT3 antagonists. The mechanism is unknown.

VI. Adverse Drug Events

The most common adverse drug events reported with the NK1 receptor antagonists are listed in Tables 7 and 8.

Table 7. Adverse Drug Events (%) Reported with the Single Entity NK1 receptor antagonists[1-7]

Adverse Events	Aprepitant	Fosaprepitant
Cardiovascular		
Bradycardia	≤4	<1
Chest discomfort/pain	-	<1
Hypertension	>0.5	-
Hypotension	≤6	<1
Myocardial infarction	>0.5	-
Palpitation	>0.5	<1
Tachycardia	>0.5	-
Central Nervous System		
Anxiety	>0.5	<1
Chills	-	<1
Cognitive disorder	-	<1
Confusion	>0.5	-
Depression	>0.5	-
Disorientation	>0.5	<1
Dizziness	≤7	<1
Dream abnormality	-	<1
Euphoria	-	<1
Fatigue	5 to 13	1 to 15
Gait disturbance	-	<1
Headache	-	2
Lethargy	-	<1
Malaise/fatigue	≤18	1 to 3
Peripheral neuropathy	>0.5	3
Somnolence	-	<1
Syncope	>0.5	-
Tremor	>0.5	-
Dermatological		
Acne	>0.5	<1
Angioedema	-	<1
Erythema	-	<1
Flushing	>0.5	<1
Hyperhidrosis	-	<1
Injection site induration	-	<1
Injection site pain	-	3
Oily skin	-	<1
Photosensitivity	-	<1
Pruritus	>0.5	<1
Rash	>0.5	<1
Skin lesion	-	<1
Stevens-Johnson Syndrome	>0.5	<1
Urticaria	>0.5	<1
Gastrointestinal		
Abdominal pain/discomfort	≤5	<1
Abdominal distention	-	<1
Acid reflux	>0.5	<1
Anorexia	-	2

Adverse Events	Aprepitant	Fosaprepitant
Appetite decreased	>0.5	-
Constipation	9 to 10	2
Diarrhea	≤10	13
Duodenal ulcer	>0.5	<1
Dyspepsia	≤6	2
Dysphagia	>0.5	-
Enterocolitis	>0.5	-
Epigastric discomfort	4	<1
Eructation	>0.5	-
Flatulence	>0.5	<1
Gastritis	4	-
Gastroesophageal reflux disease	-	<1
Hiccups	11	5
Nausea	6 to 13	<1
Neutropenic colitis	-	<1
Obstipation	>0.5	<1
Stomatitis	3	<1
Taste disturbance	>0.5	<1
Vomiting	-	<1
Xerostomia	>0.5	<1
Genitourinary		
Dysuria	>0.5	<1
Erythrocyturia	>0.5	-
Glucosuria	>0.5	-
Hematuria	-	<1
Leukocyturia	>0.5	-
Pelvic pain	>0.5	-
Pollakiuria	-	<1
Polyuria	-	<1
Proteinuria	7	-
Renal insufficiency	>0.5	-
Urinary tract infection	>0.5	-
Hematologic		
Anemia	>0.5	<1
Hemoglobin decreased	-	✔
Leukocytosis	>0.5	-
Neutropenia	3 to 13	<1
Thrombocytopenia	>0.5	-
Laboratory Test Abnormalities		
Alanine aminotransferase increased	≤6	1 to 3
Albumin decreased	>0.5	-
Alkaline phosphatase increased	>0.5	<1
Aspartate aminotransferase increased	3	1
Bilirubin increased	>0.5	-
Blood urea nitrogen increased	5	-
Hyperglycemia	>0.5	<1
Hypokalemia	>0.5	-
Hyponatremia	>0.5	<1
Musculoskeletal		
Arthralgia	>0.5	-
Back pain	>0.5	-
Dysarthria	>0.5	-
Muscle cramp	-	<1
Musculoskeletal pain	>0.5	-

Adverse Events	Aprepitant	Fosaprepitant
Myalgia	>0.5	<1
Weakness	≤18	3
Respiratory		
Cough	>0.5	<1
Dyspnea	>0.5	-
Hypoxia	>0.5	-
Pharyngitis	>0.5	<1
Pharyngolaryngeal pain	>0.5	-
Pneumonia	>0.5	-
Pneumonitis	>0.5	-
Postnasal drip	-	<1
Pulmonary embolism	>0.5	-
Respiratory infection	>0.5	-
Respiratory insufficiency	>0.5	-
Rigors	>0.5	-
Sneezing	-	<1
Throat irritation	-	<1
Wheezing	>0.5	-
Special Senses		
Conjunctivitis	>0.5	<1
Miosis	>0.5	-
Tinnitus	-	<1
Other		
Anaphylaxis	>0.5	<1
Angioedema	>0.5	-
Candidiasis	>0.5	<1
Deep vein thrombosis	>0.5	-
Dehydration	≤6	-
Diabetes mellitus	>0.5	-
Diaphoresis	>0.5	-
Edema	>0.5	<1
Epistaxis	-	-
Herpes simplex	>0.5	-
Hot flash	-	<1
Hypersensitivity	>0.5	<1
Hypoesthesia	>0.5	-
Hypothermia	>0.5	-
Hypovolemia	>0.5	-
Pain	>0.5	-
Polydipsia	-	<1
Septic shock	>0.5	-
Thrombophlebitis	-	<1
Vocal disturbance	>0.5	-
Weight gain	-	<1
Weight loss	>0.5	<1

✔ Percent not specified.
- Event not reported.

Table 8. Adverse Drug Events (%) Reported with the Combination NK1 receptor antagonists [1-7]

Adverse Events	Netupitant and Palonosetron
Central Nervous System	
Fatigue	4 to 7
Headache	9

Adverse Events	Netupitant and Palonosetron
Dermatologic	
Erythema	3
Gastrointestinal	
Constipation	3
Dyspepsia	4
Musculoskeletal	
Weakness	8

✓ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the NK1 receptor antagonists are listed in Table 9.

Table 9. Usual Dosing Regimens for the NK1 receptor antagonists[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Products			
Aprepitant	CINV: Capsule: given for three days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist, the recommended dose is 125 mg orally one hour prior to chemotherapy treatment (day one) and 80 mg once daily in the morning on days two and three Injectable emulsion: 100 to 130 mg administered intravenously on day one as an infusion or injection over a period of 30 minutes or two minutes initiated approximately 30 minutes prior to chemotherapy; administer as part of a regimen that includes dexamethasone and a 5-HT_3 antagonist as specified in the package labeling PONV: Capsule: 40 mg orally within three hours prior to induction of anesthesia	CINV in patients 12 years of age and older: Capsule: the pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults. CINV in patients 6 months to less than 12 years of age Powder packet: given for three days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist, the recommended dose is 3 mg/kg orally on day 1 (maximum dose of 125 mg) and 2 mg/kg on days 2 and 3 (maximum dose of 80 mg)	Capsule: 40 mg 80 mg 125 mg Capsule dose pack: 125-80 mg Injectable emulsion: 130 mg/18 mL Powder packet: 125 mg (25 mg/mL final concentration)
Fosaprepitant	CINV: Injection: 150 mg administered intravenously on day one only as an infusion over 20 to 30 minutes initiated approximately 30 minutes prior to chemotherapy; administer in conjunction with	CINV in patients ≥6 months of age: Injection: 12 to 17 years of age, 150 mg intravenously over 30 minutes; 2 to <12 years of age, 4 mg/kg (maximum dose 150 mg)	Injection: 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	a corticosteroid and a 5-HT3 antagonist as specified in the package labeling	intravenously over 60 minutes; 6 months to <2 years of age, 5 mg/kg (maximum dose 150 mg) intravenously over 60 minutes; administer in conjunction with a corticosteroid and a 5-HT_3 antagonist and adjust for multiday chemotherapy regimens as specified in the package labeling	
Combination Products			
Netupitant and palonosetron	CINV: Capsule: one capsule approximately one hour prior to initiation of chemotherapy on day one Injection: infuse one vial over 30 minutes starting 30 minutes before chemotherapy Should be administered in conjunction with dexamethasone as specified in the package labeling.	Safety and effectiveness have not been established in patients younger than 18 years of age.	Capsule: 300-0.5 mg Injection: 235-0.25 mg

CINV: chemotherapy-induced nausea and vomiting, PONV: postoperative nausea and vomiting

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the NK1 receptor antagonists are summarized in Table 10.

Table 10. Comparative Clinical Trials with the NK1 receptor antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting (CINV)				
Rapoport et al.[15] (2010) Aprepitant 125 mg one hour prior to chemotherapy followed by 80 mg on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to	DB, MC, PG, RCT Adult patients who were naïve to moderate or highly emetogenic chemotherapy and were scheduled to receive treatment with one or more moderately emetogenic agents	N=848 120 hours	Primary: Proportion of patients reporting no vomiting Secondary: Overall complete response (no emesis and no use of rescue therapy)	Primary: Significantly more patients in the aprepitant (triple therapy) group reported no vomiting (76.2%) compared to patients receiving dual therapy (62.1%) during the 120 hour study period (P<0.001). Secondary: Significantly more patients in the aprepitant (triple therapy) group reported complete response (68.7%) compared to patients receiving dual therapy (56.3%; P<0.001). There were no significant differences in adverse events between the two groups; however, the overall incidence of adverse events in the entire study population was 65%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chemotherapy				
Yeo et al.[16] (2009) Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy	DB, PC, RCT Breast cancer patients ≥18 years of age who were naïve to chemotherapy and were receiving a moderately emetogenic regimen (doxorubicin and cyclophosphamide)	N=127 120 hours	Primary: Complete response (no vomiting and no rescue therapy used) during the overall period (0 to 120 hours) Secondary: Proportion of patients with no vomiting, no nausea, no significant nausea, no rescue therapy, complete protection, and total control during the acute (0 to 24 hour), delayed (24 to 120 hours), and overall periods	Primary: There was no significant difference in the complete response rates for patients receiving aprepitant (triple therapy) compared to patients receiving dual therapy during the overall period (46.8 vs 41.9%, respectively; P=0.58). Secondary: During the overall period, there was no significant difference among the treatment groups in the proportion of patients reporting complete protection (P=0.71), total control (P=0.55), no vomiting (P=0.58), no significant nausea (P=0.71) and no nausea (P=0.57). Rescue medication use was lower in the aprepitant group than the control group (11 vs 20%; P=0.06). There was no significant difference between the two groups with respect to all the parameters of emesis control in the acute and delayed time frames. The median time to first vomiting after the initiation of chemotherapy was 64.4 hours for the aprepitant arm and 52.6 hours in the control arm (P=0.78).
Herrstedt et al.[17] (2005) Aprepitant 125 mg	DB, MC, PG, RCT Patients with breast carcinoma who	N=866 3 days of treatment	Primary: Proportion of patients with a complete response	Primary: Overall, the complete response was greater with the aprepitant regimen over the four cycles: 50.8 vs 42.5% for cycle one, 53.8 vs 39.4% for cycle two, 54.1 vs 39.3% for cycle three, and 55.0 vs 38.4% for cycle four. The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy	were naïve to emetogenic chemotherapy and treated with cyclophosphamide alone or in combination with doxorubicin or epirubicin	during cycles 1 to 4 of chemotherapy	(no emesis or use of rescue therapy) in cycle one, efficacy end points for the multiple-cycle extension were the probabilities of a complete response in cycles two to four and a sustained complete response rate across multiple cycles Secondary: Not reported	cumulative percentage of patients with a sustained complete response over all four cycles was greater with the aprepitant regimen (P=0.017). The aprepitant regimen was more effective than a control regimen for the prevention of nausea and emesis induced by moderately emetogenic chemotherapy over multiple chemotherapy cycles. Secondary: Not reported
Warr et al.[18] (2005) Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus	DB, PG, RCT Patients with breast cancer who were naïve to emetogenic chemotherapy and who were treated with a regimen of cyclophosphamide	N=857 120 hours	Primary: Proportion of patients with complete response (defined as no vomiting and no use of rescue therapy) 120 hours after initiation of	Primary: Overall complete response was greater with the aprepitant regimen than with the control regimen (50.8 vs 42.5%; P=0.015). Secondary: More patients in the aprepitant group reported minimal or no impact of CINV on daily life (63.5 vs 55.6%; P=0.019). Both treatments were generally well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy	alone, cyclophosphamide plus doxorubicin, or cyclophosphamide plus epirubicin		chemotherapy in cycle one Secondary: Proportion of patients with an average item score higher than 6 of 7 on the Functional Living Index-Emesis questionnaire	The aprepitant regimen was more effective than the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide.
Gralla et al.[19] (2005) Aprepitant 125 mg plus ondansetron 32 mg and dexamethasone 12 mg on day one; aprepitant 80 mg and dexamethasone 8 mg on days two to three; and dexamethasone 8	DB, PG, RCT (pooled analysis) Patients >18 years of age receiving their first cisplatin-based chemotherapy	N=1,043 120 hours	Primary: Complete response (defined as no vomiting and no rescue therapy) on days one to five Secondary: Not reported	Primary: In the total combined study population, regardless of treatment group or use of concomitant chemotherapy, complete response was achieved in 58% of patients. Analysis by treatment group showed a 20% greater efficacy with the aprepitant regimen (68 vs 48%; P<0.001). Among 13% of patients who received additional emetogenic chemotherapy (doxorubicin or cyclophosphamide), the aprepitant regimen provided a 33% improvement in the complete response rate compared to the control regimen (P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg on day four vs ondansetron 32 mg IV and dexamethasone 20 mg orally on day one; dexamethasone 8 mg twice daily on days two to four				
De Wit et al.[20] (2004) Aprepitant 125 mg, ondansetron 32 mg IV, dexamethasone 12 mg on day one, aprepitant 80 mg and dexamethasone 8 mg on days two to three, dexamethasone 8 mg on day four vs ondansetron 32 mg IV and dexamethasone 20 mg on day one, dexamethasone 8 mg twice daily on days two to four	DB, MC, RCT Patients with cancer who were receiving their first cycle of cisplatin-based chemotherapy	N=1,038 120 hours	Primary: No emesis and no significant nausea over the five days following cisplatin, for up to six cycles of chemotherapy Secondary: Not reported	Primary: In every cycle, the estimated probabilities (rates) of no emesis and no significant nausea were significantly higher (P<0.006) in the aprepitant group. In the first cycle, rates were 61% in the aprepitant group and 46% in the standard therapy group. Thereafter, rates for the aprepitant regimen remained higher throughout (59 vs 40% for the standard therapy by cycle six). Repeated dosing with aprepitant over multiple cycles was generally well tolerated. Those who received aprepitant in addition to standard therapy had consistently better antiemetic protection that was well maintained over multiple cycles of highly emetogenic chemotherapy. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Poli-Bigelli et al.[21] (2003) Aprepitant 125 mg, ondansetron 32 mg IV, and dexamethasone 12 mg orally on day one; aprepitant 80 mg and dexamethasone 8 mg orally on days two to three; and dexamethasone 8 mg orally on day four vs ondansetron 32 mg IV and dexamethasone 20 mg orally on day one, followed by dexamethasone 8 mg orally twice daily on days two to four	DB, MC, PG, RCT Patients with cancer who were scheduled to receive treatment with high-dose cisplatin chemotherapy	N=1,091 120 hours	Primary: Complete response (no emesis and no rescue therapy) during the five-day period post cisplatin therapy Secondary: Not reported	Primary: During the five days after chemotherapy, the percentages of patients who achieved a complete response were 62.7% in the aprepitant group compared to 43.3% in the standard therapy group (P<0.001). For day one, the complete response rates were 82.8% for the aprepitant group and 68.4% for the standard therapy group (P<0.001); for days two to five, the complete response rates were 67.7% in the aprepitant group and 46.8% in the standard therapy group (P<0.001). The overall incidence of adverse events was similar between the two treatment groups (72.8% in the aprepitant group and 72.6% in the standard therapy group) as were rates of serious adverse events, discontinuations due to adverse events, and deaths. In patients with cancer who were receiving high-dose cisplatin-based chemotherapy, therapy consisting of aprepitant (125 mg on day one and 80 mg on days two to three) plus a standard regimen of ondansetron and dexamethasone provided greater antiemetic protection compared to standard therapy alone and was generally well tolerated. Secondary: Not reported
Hesketh et al.[22] (2003) Aprepitant plus ondansetron and dexamethasone on day one; aprepitant and dexamethasone on	DB, MC, PG, RCT Patients with cancer who were receiving cisplatin for the first time	N=530 120 hours	Primary: Complete response (no emesis and no rescue therapy) on days one to five post cisplatin therapy Secondary:	Primary: The percentage of patients with complete response was significantly higher in the aprepitant group (72.7 vs 52.3% in the standard therapy group), as were the percentages on day one, and especially on days two to five (P<0.001 for all three comparisons). Compared to standard dual therapy, addition of aprepitant was generally well tolerated and provided consistent protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days two to three; dexamethasone on day four vs ondansetron and dexamethasone on day one; dexamethasone on days two to four			Not reported	Secondary: Not reported
Martin et al.[23] (2003) Aprepitant and dexamethasone plus ondansetron on day one, followed by aprepitant and dexamethasone on days two to five vs dexamethasone and ondansetron on day one, followed by dexamethasone on days two to five	DB, RCT Patients with cancer who were receiving cisplatin	N=381 5 days	Primary: Complete response, the Functional Living Index-Emesis Secondary: Not reported	Primary: Compared to standard therapy, significantly more patients treated with the high-dose aprepitant regimen achieved a complete response (71 vs 44%; P<0.001) and also reported no impact on daily life as indicated by the Functional Living Index-Emesis total score (84 vs 66%; P<0.01). Use of the Functional Living Index-Emesis demonstrated that improved control of emesis was highly effective in reducing the impact of CINV on patients' daily activities. Secondary: Not reported
Kang et al.[24] (2015) Aprepitant (125 mg for ages 12 to 17 years; 3.0	AC, DB, PG, RCT Patients 6 months to 17 years of age with documented malignancy	N=302 Up to 5 cycles	Primary: Complete response (defined as no vomiting, no retching, and no use of rescue	Primary: Seventy-seven (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase (P<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day one, followed by aprepitant (80 mg for ages 12 to 17 years; 2.0 mg/kg up to 80 mg for ages 6 months to <12 years) on days 2 and 3 vs placebo plus ondansetron on day one followed by placebo on days two and three (addition of dexamethasone was permitted)	scheduled to receive at least moderately emetic chemotherapy		medication) during the delayed phase Secondary: Complete response during the acute and overall phases, safety	Complete response during the acute and overall phases was also more common in patients in the aprepitant group than in those who were in the control group (P=0.0135 and P=0.0002). Median time to first vomiting episode was 96.3 hours (95% CI, 68.8 to not estimable) in the aprepitant group and 27.5 hours (95% CI, 19.3 to 35.6) in the control group (log-rank P<0.0001). Similarly, time to first rescue medication use was significantly longer for patients in the aprepitant group than in the control group (log-rank P=0.0024). Adverse events were reported by 120 (79%) of 152 patients in the aprepitant group and 116 (77%) of 150 in the control group. In addition to vomiting, the most commonly reported all-grade adverse events were anaemia, febrile neutropenia, and neutropenia.
Gore et al.[25] (2009) Aprepitant 125 mg one hour prior to chemotherapy followed by 80 mg on days two to three, plus ondansetron 0.15 mg/kg for three doses on days one	DB, MC, RCT Patients 11 to 19 years of age who were receiving emetogenic chemotherapy or who had experienced intolerable CINV with previous chemotherapy	N=46 120 hours	Primary: Complete response (no vomiting and no rescue therapy used), as well as the proportion of patients with no vomiting and/or no rescue therapy during the overall period (0 to 120 hours), acute	Primary: There was no significant difference among the treatment groups with regards to the complete response rates, proportion of patients reporting no vomiting, or the proportion of patients reporting no nausea during the overall period, acute period, or delayed period. There were no significant differences in adverse event rates between the two groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to two, plus dexamethasone 8 mg on day one followed by 4 mg on days two to four vs ondansetron 0.15 mg/kg for three doses on days one to two, plus dexamethasone 16 mg on day one followed by 8 mg on days two to four			period (0 to 24 hour), and delayed (24 to 120 hours) period Secondary: Not reported	
Kim et al.[26] (2017) Aprepitant 125 mg one hour prior to chemotherapy followed by 80 mg on days two to three, plus IV ondansetron 15 mg, plus dexamethasone 12 mg on day one vs placebo plus ondansetron IV 16 mg on day one	DB, MC, RCT Adult patients ≥20 years of age with a broad range of tumor types who were scheduled to receive a single dose of ≥1 moderately emetogenic chemotherapy agent	N=480 3 days	Primary: Proportion of patients who achieved no vomiting during the overall phase (0 to 120 h) Secondary: Proportion of patients with a complete response (defined as no vomiting and no use of rescue therapy) during the overall phase; safety	Primary: Analysis of the primary efficacy endpoint demonstrated a numerical, but not statistically significant, difference in proportion of patients with no vomiting during the overall phase between the aprepitant and control regimen groups (77.2 vs 72.0%; P=0.191). Secondary: The key secondary efficacy endpoint of complete response achievement during the overall phase was not statistically significant between the aprepitant and control regimen groups (73.4 vs 70.4%; P=0.458). Sequential testing of statistical significance for the additional secondary efficacy endpoints was not conducted because the key secondary hypothesis was not met. At least one adverse event was reported in 56.2 and 53.2% of participants in the aprepitant and control regimen groups, respectively. However, drug-related adverse events were rare, occurring in 3.7 and 3.6% of patients in the aprepitant and control regimen groups, respectively. The most commonly reported all-grade adverse events were gastrointestinal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 8 mg q12h on days 2 and 3, plus dexamethasone 20 mg on day one				disorders, including nausea (9.1 and 8.1%, respectively), diarrhea (6.6 and 7.3%), and constipation (0 and 8.9%).
Schmitt et al.[27] (2014) Aprepitant (125 mg orally on day one and 80 mg orally on days two to four), granisetron (2 mg orally on days one to four), and dexamethasone (4 mg orally on day one and 2 mg orally on days two to three) vs matching placebo, granisetron (2 mg orally on days one to four), and dexamethasone (8 mg orally on day one and 4 mg orally on days two to three)	DB, PC, PG, RCT Patients ≥18 years of age with multiple myeloma undergoing autologous transplantation after high-dose melphalan	N=362 7 days	Primary: Complete response (no emesis and no rescue therapy for 120 hours) Secondary: Complete response in acute (0 to 24 hours) or delayed phase (25 to 120 hours), rates of emesis, nausea and significant nausea, number of adverse events, and impact on quality of daily life, as assessed by FLIE score	Primary: Significantly more patients receiving aprepitant reported complete response within 120 hours of melphalan administration compared with placebo (58 vs 41%; OR, 1.92; 95% CI, 1.23 to 3.00; P=0.0042). Secondary: No emesis or additional antiemetic treatment in the acute phase was reported by 97 and 90% of patients receiving aprepitant and placebo, respectively (OR, 3.11; 95% CI, 1.23 to 8.92; P=0.022). During the delayed phase this was achieved in 60 and 46% of patients, respectively (OR, 1.80; 95% CI, 1.15 to 2.85; P=0.011), suggesting a lasting benefit after 24 hours. Major nausea was prevented in 94 and 88% of patients in the aprepitant and placebo arms, respectively (P=0.026). 74% of those receiving aprepitant, compared with 59% of patients receiving placebo, had an FLIE score indicating no impact on daily life (P=0.004). Rates of adverse events did not significantly differ between the two treatment arms.
Kusagaya et al.[28] (2015) Aprepitant (125	MC, OL, PRO, RCT Chemotherapy-	N=80 120 hours post-	Primary: Complete response rate in the overall phase (during the	Primary: The aprepitant add-on and double therapy groups showed overall complete response rates of 80.5% (95% CI, 68.4 to 92.6%) and 76.9% (95% CI, 63.7 to 90.1%; OR, 0.81; 95% CI, 0.27 to 2.36; P=0.788), respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg on day 1 and 80 mg on days 2 to 3) was administered in addition to control treatments (aprepitant group) vs palonosetron (0.75 mg) on day 1 and dexamethasone (8 mg) on days 1 to 3 (control group)	naïve patients ≥20 years of age with non-small-cell lung cancer receiving carboplatin-based chemotherapy	chemotherapy	120 h after chemotherapy administration) Secondary: Complete response rate in the acute (first 24 h after chemotherapy administration) and delayed phases (24 to 120 h after chemotherapy); nausea in the overall, acute, and delayed phases; and safety	Secondary: The proportion of patients with a complete response in the acute phase was 100% in both groups, indicating that no patients had vomiting or needed rescue antiemetic therapy. In the delayed phase, the complete response was similar between groups (80.5% in the aprepitant group versus 76.9% in the control group: OR, 0.81; 95% CI, 0.27 to 2.36; P=0.79). No significant differences were found in the complete control (no emesis, no use of rescue medication, and no nausea) rate between the aprepitant and control groups (overall phase: 78.1 and 69.2%, respectively; OR, 0.63; 95% CI, 0.23 to 1.73; P=0.45; delayed phase: 78.1 and 71.8%, respectively; OR, 0.72; 95% CI, 0.26 to 1.98; P=0.61; respectively). The incidences of patients with any adverse events were 95.1 and 94.9% in the aprepitant and control groups, respectively. The most common severe toxicities reaching grade three or four in both groups were leukopenia, neutropenia, and thrombocytopenia, which were deemed to be chemotherapy related. The prevalence of constipation was greater (but not significantly) in the aprepitant group (P=0.48).
Suzuki et al.[29] (2016) Aprepitant with dexamethasone and a 5-HT3 receptor antagonist (during chemotherapy cycle 2) vs dexamethasone and a 5-HT3 receptor antagonist	MC, OL Chemo-naïve patients ≥20 years of age with advanced non-small cell lung cancer (NSCLC) who received carboplatin-based chemotherapy	N=63 120 hours post-chemotherapy	Primary: Overall complete response rate, defined as no vomiting and no rescue therapy during the 120 h after administration of chemotherapy Secondary: Complete response rates in acute phase, rescue medication use	Primary: The overall complete response rate was significantly improved in the second cycle (aprepitant add-on cycle) (87.3%, 95% CI, 76.5 to 94.4%) compared with the first cycle (dexamethasone and 5-HT3 receptor antagonist treatment only) (65.1%, 95% CI, 52.0 to 76.7%; P<0.001). Secondary: There was no significant difference in complete response rates in the acute phase between each cycle (P=0.250). Rescue antiemetic therapy was required in 17 (27.0%) and seven patients (11.1%) in the first and second cycles, respectively (P=0.006). Among 22 patients who failed to demonstrate a complete response in the first cycle of chemotherapy with double antiemetic therapy, 15 (68.2%) patients achieved a complete response in the second cycle with triple antiemetic therapy including aprepitant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(during chemotherapy cycle 1)				
Nishimura et al.[30] (2015) SENRI Two-drug combination treatment (5-HT3 receptor antagonist plus dexamethasone) vs three-drug combination treatment (5-HT3 receptor antagonist plus dexamethasone plus aprepitant or fosaprepitant) All patients received the three drug treatment in the second course of chemotherapy	MC, OL, RCT Patients 20 years of age and older with colorectal cancer who underwent oxaliplatin-based chemotherapy	N=413 6 days	Primary: Proportion of patients with no emesis Secondary: Proportion of patients with no nausea, complete response and complete protection in the overall phase	Primary: The aprepitant group had significantly higher rates of no vomiting overall (95.7 vs 83.6%; RR, 1.1449; 95% CI, 1.07 to 1.23; P<0.0001), as well as in the separate analyses of both the acute phase (100 vs 96.7%; P=0.013) and the delayed phase (95.7 vs 84.7%; P=0.0003) compared with the control group. Secondary: The aprepitant group also had statistically significantly higher percentages of no significant nausea, complete response and complete protection than the control group overall.
Jordan et al.[31] (2009) Aprepitant 125 mg prior to chemotherapy, then 80 mg on	PRO Adult patients undergoing multiple-day chemotherapy of moderate or high	N=78 Variable duration	Primary: Complete response (no vomiting or use of rescue therapy) at the end of the treatment cycle	Primary: The percentage of patients with a complete response was 57.9% in those who were receiving highly emetogenic chemotherapy and 72.5% in those who were receiving moderately emetogenic chemotherapy. Secondary: During the acute and delayed phases, the complete response in patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days two to three, plus granisetron 1 mg on day one, plus dexamethasone 8 mg on days one to three	emetogenic potential		Secondary: Complete response in the acute and delayed phase of the treatment cycle	receiving highly emetogenic chemotherapy was 65.8 and 68.5%, respectively. During the acute and delayed phases, the complete response in patients receiving moderately emetogenic chemotherapy was 72.5 and 82.5%, respectively. The most common adverse events were related to chemotherapy, not antiemetic therapy.
Grunberg et al.[32] (2009) Aprepitant 285 mg plus dexamethasone 20 mg plus palonosetron 0.25 mg prior to chemotherapy (single dose therapy)	MC, PRO Adult patients with documented solid tumor who were naïve to chemotherapy and were receiving a moderately emetogenic regimen	N=41 120 hours	Primary: Complete response (no vomiting or use of rescue therapy) during the overall period (0 to 120 hours) during the first chemotherapy cycle Secondary: Proportion of patients with no vomiting, no nausea, and no significant nausea during the acute (0 to 24 hour), delayed (24 to 120 hours), and overall periods	Primary: Complete response was seen in 51% of patients during the overall period. A total of 76% of patients experienced a complete response during the acute period and 66% of patients experienced a complete response during the delayed period. Secondary: No emesis was seen in 95% of patients during the overall period. No emesis was reported for 100% of patients during the acute period and for 95% of patients during the delayed period. No nausea was seen in 32% of patients during the overall period and 56% of patients had no significant nausea. During the acute period, 59% of patients had no nausea and 79% of patients had no significant nausea. During the delayed period, 41% of patients had no nausea and 59% of patients had no significant nausea. There were no major adverse events seen during the study period that were attributed to the antiemetic regimen.
Gao et al.[33] (2013) Aprepitant 125 mg 1 hour before chemotherapy on day 1, and 80 mg once daily on the	OS, PRO Patients were consecutively included if they received 3-day cisplatin-based (25 mg/m^2/day)	N=41 8 days	Primary: Complete response in the overall phase of CINV Secondary: Complete response in the acute and	Primary and Secondary: Seven (17.1%) patients had no nausea, 22 (53.7%) experienced grade 1 nausea and 12 (29.2%) experienced grade 2 nausea. With regard to acute and delayed phase, 24.4 and 36.6% of patients were prevented from nausea. The complete response rate in the acute, delayed and overall phases was achieved in 63.4, 78.0 and 58.5% of patients respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
following 2 days, palonosetron 0.5 mg IV once daily on the days 1 and 3, and dexamethasone 5 mg IV once daily from day 1 to day 3	chemotherapy and had never treated with aprepitant before		delayed phases, safety and the severity of nausea	Regarding single days of the acute phase, the complete response rate decreased from 85.4% on day one to 65.8% on day three. In 23 patients (56.1%) who received the study treatment more than one cycle, the cumulative emetic protection rate after five cycles was 0.82. Regardless of cause, the most common side effects were hiccups (31.7%), fatigue (17.1%), headache (14.6%) and constipation (12.2%).
Hesketh et al.[34] (2012) All patients received the following antiemetics: day 1: aprepitant 125 mg 1 hours before chemotherapy; dexamethasone 8 to 10 mg IV or orally 30 minutes before chemotherapy; palonosetron 0.25 mg IV 30 minutes before chemotherapy; on days 2 to 3, dexamethasone 4 mg orally and aprepitant 80 mg orally each morning	OS, PRO Patients were required to have pathologically documented breast cancer and be ≥18 years of age, chemotherapy naïve, have a Karnofsky performance status of ≥60, and scheduled to receive their first course of chemotherapy with cyclophosphamide (≥500 mg/m^2) and doxorubicin (60 mg/m^2)	N=36 5 days	Primary: Proportion of patients achieving complete response during the 120-hour study period Secondary: Acute complete response (no emesis, no rescue antiemetics during the 24 hours following chemotherapy); acute complete control (no emesis, no nausea, no rescue antiemetics during the 24 hours following chemotherapy); delayed complete response (no emesis, no rescue antiemetics during hours 24–120 following	Primary: Complete response for the 120-hour study period was achieved in 18 (50%) patients. Secondary: Acute and delayed complete response rates were 81 (27/36) and 61% (22/36), respectively. No emesis rates for the acute, delayed, and overall study periods were 97 (35/36), 94 (34/36), and 92% (33/36), respectively. Complete control rates for the acute, delayed, and overall study periods were 53 (19/36), 36 (13/36), and 31% (11/36), respectively. No nausea rates for the acute, delayed, and overall study periods were 53 (19/36), 42 (15/36), and 36% (13/36), respectively. Overall 22 patients (61%) experienced some degree of nausea. Six patients (17%) noted moderate nausea. Antiemetic therapy was well tolerated overall. The most common treatment-related adverse events were headache in five patients (15%) and fatigue in four patients (10%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			chemotherapy); delayed complete control (no emesis, no nausea, no rescue antiemetics during hours 24–120 following chemotherapy); and safety	
Longo et al.[35] (2011) Palonosetron 0.25 mg IV, dexamethasone IV 20 mg, and aprepitant 125 mg 1 hour before chemotherapy on day 1; aprepitant 80 mg and dexamethasone on day 2; aprepitant 80 mg and dexamethasone 4 mg on day 3	MC, PRO Chemotherapy-naïve patients with histologically or cytologically proven solid or blood tumors	N=not reported 5 days	Primary: Proportion of patients who achieved a complete response (defined as no emetic episodes and no use of rescue therapy), during the overall phase Secondary: Complete control (defined as no emesis, no rescue therapy, and no more than mild nausea), complete response, and proportion of patients with no emesis, during the acute, delayed, and overall phases, proportion of patients with no nausea, nausea	Primary: 70.3% of patients had complete response during the overall phase. An analysis of each component of the primary end point showed that 92.8% of patients did not experience any vomiting, while 70.3% of patients did not use rescue medication throughout the entire observation period. Secondary: The majority of patients (59.9%) did not experience any nausea; 31.1% of patients experienced mild nausea, 8.1% moderate nausea, and 0.9% severe nausea. Nausea experience was the main reason for use of rescue medication: 53 patients (23.9%) due to nausea and 13 (5.9%) due to vomiting. None of the patients with complete response experienced more than mild nausea and then complete control rates coincided with the complete response rates. No major adverse events were recorded due to antiemetic therapy. The most commonly reported side effects were constipation (39% of patients) and headache (5%). Laxative therapy was allowed in patients who reported constipation. 41% of patients reported fatigue, 23% reported some grade of pain, and 33% reported a reduction in their social activity.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			severity, no use of rescue medication, and causes for the use of rescue therapy were assessed during the overall phase, quality of life during the whole study observation period, safety	
Herrington et al.[36] (2007) Aprepitant 125 mg orally on day 1, then 80 mg orally days 2 to 3 (Arm A) vs aprepitant 125 mg orally day 1, then placebo days 2 to 3 (Arm B) All patients received dexamethasone 12 mg orally and palonosetron 0.25 mg IV before chemotherapy.	DB, PC, RCT Patients ≥18 years of age with malignant disease and an Eastern Cooperative Oncology Group performance status of 0 to 2	N=75 5 days	Primary: Proportion of patients without emesis in the acute (day one) and delayed (days two to five) phases after chemotherapy Secondary: Assessment of prevention of acute and delayed nausea and the use of breakthrough antiemetics	Primary: The proportion of patients without emesis during the acute phase was similar between Arm A and Arm B (96.4 vs 100%, respectively; P=1.00). The proportion of patients without emesis during the delayed phase was similar between Arm A and Arm B (92.9 vs 92.6%, respectively; P=1.00). Secondary: The overall incidence of nausea and severity of nausea was not different among the treatment groups (P=NS). The frequency of rescue Antiemetics was similar among the treatment groups (P=NS).
Grunberg et al.[37] (2011)	AC, DB, RCT Male and female	N=2,322 Single dose or	Primary: Complete response in the overall	Primary: In the overall phase, 71.9% (95% CI, 69.1 to 74.5) of patients in the fosaprepitant group reported Complete response compared to 72.3% (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron and dexamethasone vs fosaprepitant 150 mg on day 1) plus ondansetron and dexamethasone	patients >18 years of age with histologically confirmed malignancies, Karnofsky scores 60, and predicted life expectancy 3 months, naive to cisplatin-containing chemotherapy and scheduled for a first course of cisplatin	3 day regimen	phase, defined as no vomiting or retching episodes with no use of rescue medication Secondary: Efficacy end points were the proportion of patients with complete response in the delayed phase and the proportion of patients with no vomiting in the overall phase	CI, 69.6 to 74.9) in the aprepitant group, a between-group difference of 0.4 percentage points (95% CI, 4.1 to 3.3). Secondary: In the delayed phase, 74.3% (95% CI, 71.6 to 76.9) of patients in the fosaprepitant group reported complete response compared to 74.2% (95% CI, 71.6 to 76.8) in the aprepitant group, a between-group difference of 0.1 percentage point (95% CI, 3.5 to 3.7). 72.9% (95% CI, 70.2 to 75.5) of patients in the fosaprepitant group reported no vomiting compared to 74.6% (95% CI, 71.9 to 77.1) in the aprepitant group, a between group difference of 1.7 percentage points (95% CI, 5.3 to 2.0).
Ando et al.[38] (2016) Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to five, plus a 5-HT3 receptor antagonist and dexamethasone (group A) vs fosaprepitant 150 mg on day 1) plus a 5-HT3 receptor	OL, RCT Japanese patients who started to receive chemotherapy including cisplatin (≥60 mg/m^2) for lung cancer, gastric cancer, esophageal cancer, or head and neck cancer	N=93 5 days	Primary: Nausea according to numeric rating scale, complete response (no vomiting or retching), complete control (no vomiting or retching and 'no symptom or mild' nausea) Secondary: Not reported	Primary: The complete response rates in group A and group B were, respectively, 97.9 and 97.8% for the acute phase (P=0.96), 87.5 and 84.4% for the first stage of the late phase (P=0.67) and 89.6 and 90.0% for the second stage of the late phase (P=0.91), showing no significant differences between the two groups in all phases. The complete response rate for the entire period was 85.4% in group A and 82.2% in group B, also showing no significant difference (P=0.90). The complete control rates in group A and group B were, respectively, 77.1 and 91.1% for the acute phase (P=0.066), 60.4 and 73.3% for the first stage of the late phase (P=0.19), and 66.7 and 71.1% for the second stage of the late phase (P=0.64). Although differences between the two groups were not of statistical significance in any phases, the complete control rate in group A tended to be slightly lower in the acute phase. The complete control rate for the entire period also did not differ significantly between group A (60.4%) and group B (64.4%) (P=0.85). For day-to-day changes in the nausea score, while a significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
antagonist and dexamethasone (group B)				consecutive increase was observed from day three to day seven in group A, the score increased only on days three and four in group B. However, no significant differences were detected by the two-way repeated measures analysis of variance. Secondary: Not reported
Jin et al.[39] (2012) Aprepitant vs placebo or no intervention	MA RCTs comparing the antiemetic efficacy of aprepitant with a placebo or no intervention for the prophylaxis of CINV	N=4,798 (15 trials) Duration varied	Primary: Complete response during the acute, delayed, and overall time intervals after initiation of qualifying chemotherapy, safety Secondary: Not reported	Primary: The cumulative incidence of emesis was significantly reduced in the aprepitant containing group on the first day (RR, 1.13; 95% CI, 1.10 to 1.16). Similar results were also obtained for delayed nausea and vomiting induced by highly or moderately emetogenic chemotherapy (from days two to five: RR, 1.35; 95% CI, 1.22 to 1.48; overall five days: RR, 1.30; 95% CI, 1.22 to 1.39). Aprepitant and ondansetron or granisetron was more efficacious than the non-aprepitant regimen, however, aprepitant and palonosetron was not more efficacious in the acute phase (RR, 1.19; 95% CI, 0.71 to 1.97) or in the delayed phase (RR, 2.02; 95% CI, 0.92 to 4.41) when compared to non-aprepitant regimen. There were no significant differences regarding the occurrence of adverse effects in aprepitant-containing groups and control groups in the pooled analysis. Secondary: Not reported
Roila et al.[40] (2014) Aprepitant 80 mg once per day on days two and three vs dexamethasone 4	DB, RCT Chemotherapy-naïve patients with breast cancer treated with anthracyclines plus cyclophosphamide	N=551 5 days	Primary: Rate of complete response (no vomiting or rescue treatment) on days two through five Secondary: Complete protection (no	Primary: Complete response was the same with both antiemetic prophylaxes (79.5%); therefore, dexamethasone was not superior to aprepitant. Secondary: Results related to all secondary end points were not significantly different between the two groups. On days two to five, day by day, the percentages of patients with no vomiting (from 92 to 97%) and no nausea (from 52 to 67%) were not significantly different between the two groups (data not shown).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg twice per day on days two and three All patients were treated with intravenous palonosetron 0.25 mg, dexamethasone 8 mg, and oral aprepitant 125 mg before chemotherapy.			vomiting, no rescue treatment, no significant nausea; visual analogue scale <25 mm), total control (no vomiting, no rescue treatment, no nausea; visual analogue scale <5 mm), no vomiting and no nausea (visual analogue scale <5 mm), no significant nausea, mean number of emetic episodes in patients who vomited, mean maximum severity of nausea, and mean duration of nausea	
Moon et al.[41] (2014) Aprepitant 40 mg by mouth vs palonosetron 0.075 mg IV	DB, RCT Patients 20 to 60 years of age who were scheduled to undergo laparoscopic gynecologic surgery under general anaesthesia	N=93 48 hours	Primary: Complete response (visual analogue scale nausea score <4 and no use of rescue therapy) 0 to 48 h after surgery Secondary: Effect of aprepitant quantified using a 10-point visual analogue scale for	Primary: Aprepitant was non-inferior to palonosetron in terms of complete response 0 to 48 hours after surgery (74 vs 77%). The nausea intensity in the recovery room and two hours after surgery assessed using the 10-point visual analogue scale was significantly lower in the aprepitant group (11.2 ± 2.1 and 9.7 ± 2.1, respectively) than in the palonosetron group (19.0 ± 2.2 and 19.4 ± 3.5, respectively; $P < 0.05$). However, the results at 6, 24, and 48 h after surgery did not differ significantly. Secondary: The pain intensity was also not significantly different throughout the study period. Fentanyl consumption via automated intravenous patient-controlled analgesia was significantly lower in the aprepitant group than in the palonosetron group at two and six hours after surgery. No significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			pain, consumption of intravenous patient-controlled analgesia, and use of rescue analgesics	differences were observed in the incidence and number of additional fentanyl administrations between the two groups.
Saito et al.[42] (2013) Granisetron 40 µg/kg IV and dexamethasone (20 mg) on day 1 and dexamethasone (8 mg) on days 2 and 3 vs fosaprepitant (150 mg), granisetron (40 µg/kg), and dexamethasone (10 mg) on day 1, dexamethasone (4 mg) on day 2, and dexamethasone (8 mg) on day 3	DB, MC, PC, RCT Patients ≥20 years of age who received cancer chemotherapy containing cisplatin (≥70 mg/m^2)	N=347 3 days	Primary: Percentage of patients who achieved a complete response (no emesis and no rescue therapy) in the overall phase Secondary: In the acute and delayed phases, the percentages of patients with a complete response, the percentages of patients with complete protection (no emesis, no rescue therapy, and no significant nausea) in the overall, acute, and delayed phases, with no emesis in the overall, acute, and delayed phases, and with no rescue therapy in the acute phase,	Primary: The percentage of patients who achieved a complete response (no emesis and no rescue therapy) in the overall phase (0–120 h) was significantly higher in the fosaprepitant group (64%; 95% CI, 16 to 46 vs 47%; 95% CI, 10 to 36; P=0.0015. Secondary: In the acute and delayed phases, the percentages of patients with a complete response were significantly higher in the fosaprepitant group (acute phase, 94 vs 81%; P=0.0006, delayed phase, 65 vs 49%; P=0.0025). Among the patients who had previously been treated with cisplatin and experienced vomiting, the complete response rates in the overall phase were higher in the fosaprepitant group (60.0 vs 30.3%). The percentages of patients with complete protection (no emesis, no rescue therapy, and no significant nausea) in the overall, acute, and delayed phases, with no emesis in the overall, acute, and delayed phases, and with no rescue therapy in the acute phase were significantly higher in the fosaprepitant group. The percentages of patients with no rescue therapy in the overall phase also did not differ significantly.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			percentages of patients with no rescue therapy in the overall phase	
Ruhlmann et al.[43] (2016) GAND-emesis Fosaprepitant 150 mg intravenously vs placebo Both groups were also treated with palonosetron 0.25 mg intravenously and dexamethasone 16 mg orally	DB, MC, RCT Women with cervical cancer scheduled to receive fractionated radiotherapy and weekly cisplatin 40 mg/m^2 for 5 weeks	N=234 5 weeks	Primary: Proportion of patients with sustained no emesis after 5 weeks of treatment Secondary: complete response (defined as no emesis and no use of rescue antiemetics); no nausea overall (defined as no nausea from day 1 of cycle 1 to day 7 of cycle 5); no significant nausea overall (defined as no or mild nausea from day 1 of cycle 1 to day 7 of cycle 5); no use of rescue medication overall (defined as no use of rescue medication from day 1 of cycle 1 to day 7 of cycle 5); and the mean time to first emetic episode	Primary: The proportion of patients with sustained no emesis at five weeks was 48.7% (95% CI, 25.2 to 72.2) for the placebo group compared with 65.7% (42.2 to 89.2) for the fosaprepitant group. There was a significantly lower cumulative risk of emesis in the fosaprepitant group compared with the placebo group (subhazard ratio, 0.58; 95% CI, 0.39 to 0.87; P=0.008). Secondary: The proportion of patients with overall complete response (days one to 35) was higher in the fosaprepitant group compared with the placebo group (24% of patients in the fosaprepitant group vs 14% in the placebo group; P=0.007). During cycle one no significant differences across treatment groups were recorded in complete response during the day one, days one to five, and days one to seven periods. The proportion of patients with no nausea overall (days one to 35) was also higher in the fosaprepitant group compared with placebo (15% of patients in the fosaprepitant group vs 8% in the placebo group; P=0.007). The difference in the proportion of patients with no significant nausea overall between treatments was not significant (26% of patients vs 22% of patients; P=0.078). The mean time to first emetic episode was 11.25 days (SD 9.00) in the fosaprepitant group and 14.89 days (11.67) in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Weinstein et al.[44] (2016) fosaprepitant 150 mg intravenously vs placebo Both groups were also treated with ondansetron and dexamethasone	DB, MC, RCT Patients ≥18 years of age with confirmed malignant disease, who were treatment naive to moderately and highly emetogenic chemotherapy, who were scheduled to receive ≥1 IV dose of moderately emetogenic chemotherapy	N=1015	Primary: Proportion of subjects achieving a complete response (no vomiting and no use of rescue medication) in the delayed phase (25 to 120 hours after chemotherapy) and safety Secondary: Complete response in the overall and acute phases (0 to 120 and 0 to 24 h, respectively) and no vomiting in the overall phase	Primary: Complete response in the delayed phase was achieved in more patients in the fosaprepitant (78.9%) versus the control regimen (68.5%) (treatment difference 10.4%; P<0.001). Secondary: Complete response during the overall phase was also achieved in more patients in the fosaprepitant regimen vs placebo (77.1 vs 66.9%; treatment difference, 10.2%; P<0.001). Both regimens had a high complete response in the acute phase (93.2 vs 91.0%; treatment difference, 2.3%; P=0.184). For no vomiting in the overall phase, the fosaprepitant regimen achieved a higher proportion than the control regimen for (82.7 vs 72.9%; treatment difference 9.8%; P<0.001).
Rapoport et al.[45] (2015) HEC-1 Day 1: Rolapitant 180 mg once plus granisetron 10 µg/kg IV plus dexamethasone 20 mg PO vs Day 1: placebo plus	AC, DB, MC, PG, RCT Patients ≥ 18 years of age with life expectancy ≥ 4 months, scheduled to receive a first course of cisplatin-based chemotherapy (≥ 60 mg/m^2)	N=532 One cycle	Primary: Complete response in the delayed phase of CINV Secondary: Complete response in the acute and overall phases, no emesis, no significant nausea, time to first emesis or to use of rescue medications	Primary: Complete response in the delayed phase of CINV was observed in 73% of the individuals who received rolapitant compared to 58% who received placebo (P=0.006). Secondary: Rolapitant significantly improved the outcome of complete response in the overall phase (P=0.001) and showed some improvement in complete response during the acute phase (P=0.0051). For the endpoint of no emesis, there was observed to be a significant response in the rolapitant group for the delayed and overall phase (P<0.001) and an improved response in this same group for the acute phase (P<0.002). No significant difference was observed between the groups when evaluating the endpoint of no significant nausea.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
granisetron 10 µg/kg IV plus dexamethasone 20 mg PO Both groups received dexamethasone 8 mg PO BID on days two to four				
Rapoport et al.[46] (2015) HEC -2 Day 1: Rolapitant 180 mg once plus granisetron 10 µg/kg IV plus dexamethasone 20 mg PO vs Day 1: placebo plus granisetron 10 µg/kg IV plus dexamethasone 20 mg PO Both groups received dexamethasone 8 mg PO BID on days two to four	AC, DB, MC, PG, RCT Patients ≥ 18 years of age with life expectancy ≥ 4 months, scheduled to receive a first course of cisplatin-based chemotherapy (≥ 60 mg/m^2)	N=555 One cycle	Primary: Complete response in the delayed phase of CINV Secondary: Complete response in the acute and overall phases, no emesis, no significant nausea, time to first emesis or to use of rescue medications	Primary: Complete response in the delayed phase of CINV was observed in 70% of the individuals who received rolapitant compared to 62% who received placebo (P=0.042). Secondary: No significant differences were observed for the secondary endpoints in the rolapitant group for the acute, overall and delayed phases.
Schwartzberg et	AC, DB, MC, PG,	N=1,369	Primary:	Primary:

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>al.[47]
(2015)

Day 1:
Rolapitant 180 mg once plus granisetron 2 mg PO plus dexamethasone 20 mg PO

vs

Day 1:
placebo plus granisetron 2 mg PO plus dexamethasone 20 mg PO

Both groups received granisetron 2 mg PO QD on days two and three</td><td>RCT

Patients ≥ 18 years of age, naïve to HEC/MEC, with life expectancy ≥ 4 months, scheduled to receive a first course of MEC including anthracycline</td><td>One cycle</td><td>Complete response in the delayed phase of CINV

Secondary:
Complete response in the acute and overall phases, no emesis, no significant nausea, time to first emesis or to use of rescue medications</td><td>Complete response in the delayed phase of CINV was observed in 71% of the individuals who received rolapitant compared to 62% who received placebo when evaluating the total population (P=0.0002). For the population that received an anthracycline, a complete response in the delayed phase of CINV was seen in 67% of the individuals who received rolapitant compared to 62% who received placebo (P=0.0465). When evaluating those that received a non-anthracycline MEC regimen, 76% of the rolapitant group had a complete response in the delayed phase of CINV compared to 64% in the placebo group (P=0.0008).

Secondary:
The rolapitant group had a significant improvement in complete response in the overall phase and in emesis rates in both the delayed and overall CINV phases. There were no significant differences in the other end points
<table>
<tr><td>Outcome, population</td><td>Phase</td><td>Rolapitant (%)</td><td>Placebo (%)</td><td>P-value</td></tr>
<tr><td>CR, total population</td><td>Acute</td><td>83</td><td>80</td><td>0.1425</td></tr>
<tr><td>CR, ANC</td><td>Acute</td><td>77</td><td>77</td><td>0.9659</td></tr>
<tr><td>CR, non-ANC MEC</td><td>Acute</td><td>91</td><td>84</td><td>0.0163</td></tr>
<tr><td>CR, total population</td><td>Overall</td><td>69</td><td>58</td><td><0.0001</td></tr>
<tr><td>CR, ANC</td><td>Overall</td><td>63</td><td>55</td><td>0.0332</td></tr>
<tr><td>CR, non-ANC, MEC</td><td>Overall</td><td>75</td><td>61</td><td>0.0003</td></tr>
<tr><td>No emesis</td><td>Delayed</td><td>80</td><td>70</td><td><0.001</td></tr>
<tr><td>No emesis</td><td>Acute</td><td>88</td><td>85</td><td>0.085</td></tr>
<tr><td>No emesis</td><td>Overall</td><td>79</td><td>65</td><td><0.001</td></tr>
<tr><td>No significant nausea</td><td>Delayed</td><td>73</td><td>69</td><td>0.194</td></tr>
<tr><td>No significant nausea</td><td>Acute</td><td>82</td><td>85</td><td>0.192</td></tr>
<tr><td>No significant nausea</td><td>Overall</td><td>71</td><td>67</td><td>0.118</td></tr>
</table>
ANC=anthracycline, CR=complete response, HEC=highly emetogenic chemotherapy,</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				MEC=moderately emetogenic chemotherapy
Meiri et al.[48] (2007) <u>Day two (fixed dose)</u> Dronabinol 2.5 mg by mouth four times daily vs ondansetron 8 mg by mouth twice daily vs dronabinol 2.5 mg by mouth four times daily plus ondansetron 8 mg by mouth twice daily vs placebo <u>Days three to five (flexible dose)</u> dronabinol 2.5-5 mg by mouth four times daily vs	DB, PC, PG, RCT Patients ≥18 years of age with malignancy that did not involve the bone marrow and be undergoing chemotherapy including a moderately to highly emetogenic regimen	N=64 5 days	Primary: Total response two to five days after moderately to highly emetogenic chemotherapy (no vomiting and/or retching, intensity of nausea <5 mm, and no use of rescue medication) Secondary: Complete response rate, nausea status, episodes of vomiting and/or retching, duration of nausea and vomiting and/or retching, intensity of nausea, Eastern Cooperative Oncology Group score, and quality of life	Primary: Total response during active treatment did not differ between treatment groups (P=NS) due to small sample size. Improvement (range 47 to 58%) in three active treatment groups compared to placebo (20%) implies clinically relevant improvement (days two to five). Secondary: Overall response to treatment: dronabinol (71%), ondansetron (64%), combination (53%), placebo (15%). Combination therapy did not provide benefit beyond that observed with either agent alone. Complete responder rate was 62% with dronabinol, 60% with combination therapy, 58% with ondansetron, and 20% with placebo (P<0.005 vs placebo). All active treatments reduced the intensity of nausea vs placebo (P<0.05). No significant difference was observed among groups for mean number of episodes of vomiting and/or retching. Active treatments reduced the number of episodes of vomiting to 0 by days four and five. Active treatment reduced the duration of vomiting/retching to 0 hours in all groups by days four and five. Duration of nausea was comparable among all groups. Changes from baseline in Eastern Cooperative Oncology Group score were significant in patients receiving dronabinol vs placebo (P=0.036, in favor of placebo) and in patients receiving dronabinol vs combination therapy (p=0.028). Improvement in quality of life was observed only in patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron 4 to 8 mg by mouth twice daily vs dronabinol 2.5 to 5 mg by mouth four times daily plus ondansetron 4 to 8 mg by mouth twice daily vs placebo Day one regimen consisted of dexamethasone 20 mg and ondansetron 16 mg administered to all study participants. Dronabinol 2.5 mg was also administered on day one in the three active treatment arms.				dronabinol vs combination therapy (3.6; P=0.033, in favor of dronabinol).
Aapro et al.[49] (2014) NEPA 08-18 Netupitant-palonosetron (300	DB, DD, MC, PG, RCT Patients ≥18 years of age who were chemotherapy naïve	N=1455 One cycle	Primary: Complete response (no emetic episode and no rescue medication) in preventing nausea	Primary: Complete response during the delayed phase was seen in 76.9% of the netupitant-palonosetron group compared to 69.5% of the palonosetron group (P=0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg-0.5 mg) plus dexamethasone 12 mg for one dose vs palonosetron 0.5 mg plus dexamethasone 20 mg for one dose	with an ECOG performance status of 0,1, or 2 and scheduled to receive an anthracycline/ cyclophosphamide regimen on Day 1 for treatment of a solid malignant tumor		and vomiting during the delayed phase Secondary: Complete response during the acute phase, the overall phase; Complete protection during the acute, delayed and overall phases; no emesis during the acute, delayed and overall phases; no significant nausea during the acute, delayed and overall phases; proportion of patients with scores reflecting "no impact on daily life" on daily life using the FLIE questionnaire	Complete response during the acute phase was seen in 88.4% of the netupitant-palonosetron group compared to 85.0% of the palonosetron group (P=0.047). Complete response during the overall phase was seen in 74.3% of the netupitant-palonosetron group compared to 66.6% of the palonosetron group (P=0.001). Significantly more patients in the netupitant-palonosetron group reported no emesis during the acute, delayed and overall phases compared with the palonosetron group (P=0.025, P=0.004, and P<0.001, respectively). Significantly more patients in the netupitant-palonosetron group reported no significant nausea during the delayed and overall phases, but not the acute phase, compared with the palonosetron group (delayed, P=0.014; overall, P=0.020; acute, P=0.747). Complete protection was achieved by more patients who received netupitant-palonosetron compared to palonosetron during the delayed (67.3 vs 60.3%; P=0.005) and overall phases (63.8 vs 57.9%; P=0.020). FLIE questionnaire results showed that a greater proportion of patients receiving netupitant-palonosetron vs patients receiving palonosetron reported no impact on daily living from CINV (nausea domain, P=0.015; vomiting domain, P=0.001; combined domain, P=0.005).
Hesketh et al.[50] (2014) NEPA 07-07 Netupitant-palonosetron 100 mg-0.5 mg for one dose vs	DB, DD, PG, MC, RCT Patients ≥18 years of age with histologically or cytologically confirmed malignant disease featuring solid tumor(s),	N=694 Multiple cycles	Primary: Complete response during the overall phase period Secondary: Complete response during the acute and delayed phases; complete protection during	Primary: During the overall phase, 87.4% of patients in the netupitant-palonosetron 100 mg-0.5 mg group achieved complete response (P=0.018); 87.6% in the netupitant-palonosetron 200 mg-0.5 mg group (P=0.017); 89.6%; in the netupitant-palonosetron 300 mg-0.5 mg group (P=0.004); 76.5% in the palonosetron alone group (P value not reported) and 86.6% in the aprepitant plus ondansetron group (P=0.027). Secondary: Complete response during the acute phase was seen in 98.5% of patients in the netupitant 300 mg-palonosetron 0.5mg group compared to 89.7% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
netupitant-palonosetron (200 mg-0.5 mg) for one dose vs netupitant-palonosetron (300 mg-0.5 mg) for one dose vs palonosetron 0.5 mg for one dose vs aprepitant 125 mg plus ondansetron 32 mg IV (exploratory arm) for one dose (All groups received dexamethasone therapy- varying doses based on study drug assigned)	chemotherapy naïve, Karnofsky index ≥ 70%; scheduled to receive HEC on Day 1 with a single dose of cisplatin ≥ 50 mg/m^2 either alone or in combination with other chemotherapy agents		the acute, delayed, and overall phases; no emesis during the acute, delayed, and overall phases; no significant nausea during the acute, delayed, and overall phases	the palonosetron alone group (P≤0.01). Complete response during the delayed phase was seen in 90.4% of patients in the netupitant 100 mg-palonosetron 0.5 mg group (P≤0.05), 91.2% in the netupitant 200 mg-palonosetron 0.5 mg group (P≤0.01) and 90.4 % of the netupitant 300 mg-palonosetron 0.5 mg group (P≤0.05) compared to 80.1% in the palonosetron group (no P value reported) and 88.8% in the aprepitant plus ondansetron group (P≤0.05). Complete protection was reported by more individuals in the netupitant-palonosetron 300 mg-0.5 mg group compared to palonosetron alone in the acute, delayed and overall phases (P≤0.01, P≤0.05, and P≤0.01, respectively). Significantly more patients in the netupitant-palonosetron 300 mg-0.5 mg group reported no emesis during the acute, delayed and overall phases compared to the palonosetron alone group (all P values ≤0.01). For the endpoint of no significant nausea, the netupitant-palonosetron 300 mg-0.5 mg group reported higher rates of 98.5% (P≤0.05) for the acute phase, 90.4% (P≤0.01) for the delayed phase, and 89.6% (P≤0.05) for overall phase compared to palonosetron alone (93.4, 80.9, and 79.4%, respectively; no P values reported). The exploratory arm of aprepitant plus ondansetron reported rates 94.0% for acute phase, 88.1% for delayed phase, and 85.8% for overall phase (P values not reported).
Gralla et al.[51] (2014) NEPA 10-29 Netupitant-	DB, DD, MC, PG, RCT Patients ≥18 years of age who were	N=413 Multiple cycles (total of 1961)	Primary: Safety (adverse events, vital sign measurements, laboratory tests	Primary: The most common treatment-emergent, drug-related adverse events reported in the treatment groups were constipation (netupitant-palonosetron, 3.6%; palonosetron-aprepitant, 1.0%) and headache (netupitant-palonosetron and palonosetron-aprepitant, both 1.0%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
palonosetron (300 mg-0.5 mg) plus dexamethasone for one dose (dose based on the emetogenic potential of the chemotherapy regimen) vs palonosetron 0.5 mg on Day one plus aprepitant (125 mg Day one and 80 mg Days two to three) plus dexamethasone (dose based on the emetogenic potential of the chemotherapy regimen)	chemotherapy naïve with an ECOG performance status of 0 to 2 and scheduled to receive repeated consecutive courses of chemotherapy with either highly or moderately emetogenic agents for treatment of a malignant tumor		including cardiac troponin I, physical examination ECG recordings including left ventricular ejection fraction) Secondary: Complete response during the acute, delayed and overall phases; no significant nausea during the acute, delayed and overall phases	Adverse events did not increase over multiple cycles, and the incidence, type and frequency of treatment-emergent adverse events was similar for both groups throughout the study. The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities. Secondary: Complete response rates during the overall phase were high in both treatment groups over all six cycles of chemotherapy, ranging from 81 to 92% in the netupitant-palonosetron group and from 76 to 88% in the palonosetron-aprepitant group. Complete response rates were numerically greater for patients receiving netupitant-palonosetron during the overall phase and the delayed phase. Complete response rates were similar for the treatment groups during the acute phase (P values not reported).
Aapro et al.[52] (2017) Netupitant-palonosetron 300-0.5 mg by mouth (Akynzeo®) vs palonosetron 0.5 mg by mouth	DB, ES, MC, RCT Patients ≥18 years, naïve to chemotherapy, and scheduled to receive their first course of an anthracycline/ cyclophosphamide regimen for treatment of a solid malignant tumor	N=1286 5969 chemotherapy cycles; 120 hours post-chemotherapy	Primary: Proportion of patients with an overall (0 to 120 h) complete response Secondary: Safety	Primary: The proportion of patients with an overall (0 to 120 h) complete response was significantly greater for netupitant-palonosetron compared with oral palonosetron during cycle one, and this was maintained in subsequent cycles. The incremental benefit of netupitant-palonosetron over oral palonosetron in cycles two through four was greater than that seen in cycle one (7.7% in cycle one, 13.6% in cycle two, 13.5% in cycle three, and 9.2% in cycle four). Complete response rates were similar for netupitant-palonosetron and oral palonosetron during the acute phase but higher for netupitant-palonosetron compared with oral palonosetron during the delayed phase.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Both treatment groups were also given dexamethasone				Secondary: There were no serious treatment-related adverse events during cycle one or during the multiple-cycle extension for either treatment group. There were also no treatment-related adverse events leading to discontinuation and no deaths for netupitant-palonosetron treated patients.
Schwartzberg et al.[53] (2018) Netupitant-palonosetron 235-0.25 mg intravenous vs netupitant-palonosetron 300-0.5 mg by mouth All patients received oral dexamethasone	DB, MC, RCT chemotherapy-naïve patients ≥18 years of age with solid tumors who were scheduled to receive their first course of highly emetogenic chemotherapy	N=404 5 days	Primary: Safety Secondary: Efficacy (emetic episodes and rescue medications intake per patient diary)	Primary: The overall incidence and intensity of treatment-emergent adverse events were similar between the two treatment groups in cycle 1 and throughout the study. The majority of patients experienced treatment-emergent adverse events of mild/moderate severity, with ~25% of patients in both groups experiencing severe treatment-emergent adverse events during cycle 1. The overall incidence of treatment-emergent adverse events decreased over repeated cycles in both groups (cycles 1 to 4 intravenous treatment: 59.1%, 53.1%, 52.1%, 26.2%; oral treatment: 67.2%, 52.5%, 49.3%, 24.8%). Secondary: Complete response rates in the overall phase for cycle 1 were 76.8% for intravenous treatment and 84.1% for oral treatment. No emesis rates were similar (84.2% intravenous treatment and 88.6% oral treatment).
Postoperative Nausea and Vomiting (PONV)				
Sinha et al.[54] (2014) Aprepitant 80 mg vs placebo All patients received intravenous ondansetron (4	DB, PC, RCT Morbidly obese adult patients undergoing laparoscopic bariatric surgery considered at high risk for PONV	N=124 3 days	Primary: Incidence of vomiting Secondary: Nausea verbal rating scale, complete response (no nausea or vomiting), rescue treatment use	Primary: The cumulative incidence of vomiting at 72 hours was 3.1% (2/64) the aprepitant group and 15.0% (9/60) in the placebo group (P=0.021). Secondary: Complete response to treatment was seen in 42.18 and 36.67% patients in the aprepitant and placebo groups, respectively (P=0.510). Verbal rating scale scores failed to show any statistically significant difference between the groups at all the recorded time points (P=0.675). There were no statistical differences with respect to rescue treatments for nausea and vomiting, as 42.18% in the aprepitant group vs 42.33% in the placebo group required additional antiemetics.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg) intraoperatively.				
Green et al.[55] (2012) Aprepitant 40 mg vs aprepitant 40 mg and scopolamine transdermal patch	DB, RCT Patients >18 years of age, ASA I–III, two or more Apfel four-point risk factors, undergoing an elective surgical procedure with a high risk of PONV expected to last at least 60 minutes	N=120 24 hours	Primary: Complete response Secondary: Incidences of nausea, vomiting, their composite, and the need for rescue medication	Primary: The aprepitant alone and aprepitant with scopolamine did not differ in complete responses (63 vs 57%; P=0.57). Secondary: Incidences of nausea, vomiting, their composite, and the need for rescue medication, all showed no statistical difference.
Hartrick et al.[56] (2010) Aprepitant 40 mg by mouth vs ondansetron 4 mg and dexamethasone (4 to 6 mg) plus either metoclopramide 10 mg, diphenhydramine 25 mg, or prochlorperazine 5 mg	OL, PRO Patients undergoing total knee arthroplasty receiving extended-release morphine for postoperative pain management	N=24 48 hours	Primary: Presence or absence of PONV during the postoperative period Secondary: Not reported	Primary: The percentage of patients experiencing PONV was significantly lower with aprepitant (25%) compared to the multimodal analgesia group (75%; P=0.039). There were no significant differences in pain scores, need for rescue therapy, or adverse events among the treatment groups. Secondary: Not reported
Diemunsch et al.[57] (2007) Aprepitant 40 mg	DB, MC, PC, RCT Patients ≥18 years of age (ASA I or III	N=922 48 hours	Primary: Complete response (no vomiting and no use of rescue	Primary: Complete response was achieved in 64% of patients in the aprepitant 40 mg group, 63% in the aprepitant 125 mg group, and 55% in the ondansetron group, indicating non-inferiority of the aprepitant treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
by mouth vs aprepitant 125 mg mouth vs ondansetron 4 mg IV	status) undergoing open abdominal surgery requiring at least one overnight hospital stay and receiving volatile-agent-based general anesthesia including nitrous oxide		therapy) over 0 to 24 hours after surgery; no vomiting over 0 to 24 hours after surgery Secondary: No vomiting in the first 48 hours after surgery	compared to ondansetron treatment. The percentage of patients with no vomiting over 0 to 24 hours was 84% with aprepitant 40 mg, 86% with aprepitant 125 mg, and 71% with ondansetron 4 mg (P<0.001 for both doses of aprepitant vs ondansetron). Secondary: The percentage of patients with no vomiting over 0 to 48 hours was 82% with aprepitant 40 mg, 85% with aprepitant 125 mg, and 66% with ondansetron 4 mg (P<0.001 for both doses of aprepitant vs ondansetron).
Atsuta et al.[58] (2017) Fosaprepitant 150 mg (group F) vs droperidol 1.25 mg (group D) dexamethasone (9.9 mg) was given to all patients	DB, PRO, RCT Patients 20 to 80 years of age scheduled to undergo elective craniotomy	N=186 72 hours post-op	Primary: Overall and cumulative incidence of vomiting during the first 72 h after surgery Secondary: Incidence of PONV, frequency of vomiting, nausea score, and use of rescue antiemetic during the first 72 h after surgery	Primary: The overall incidence of vomiting was significantly lower in group F patients (12.8%) than in group D patients (38%) (P<0.001, RR, 0.336; 95% CI, 0.186 to 0.605). The cumulative incidence of vomiting over the 72-h post-craniotomy observation period was significantly lower in group F patients than in group D patients (P<0.001). Secondary: With respect to PONV, there was no significant difference between the groups in either the overall incidence of PONV for 72 h [44.7% (group F) vs 54.3% (group D); P=0.24; RR, 0.822; 95% CI, 0.614 to 1.102] or the cumulative incidence of vomiting for 72 hours. The complete response (no PONV and no rescue) did not differ between the groups. The incidence and frequency of vomiting were significantly lower in group F at three time periods: zero to two, 24 to 48, and 48 to 72 hours. Lastly, there were no significant differences in nausea score or antiemetic use between the two groups, although the nausea score and nausea incidence were lower in group F at six to 24 hours.
Tsutsumi et al.[59] (2014) Fosaprepitant 150 mg IV vs	DB, PRO, RCT Patients between 20 and 80 years of age undergoing elective craniotomy under general anesthesia	N=64 48 hours	Primary: Incidence of nausea and vomiting, use of rescue antiemetics, and severity of pain	Primary: For the period from 0 to 24 hours, the percentage of patients who experienced vomiting (6 vs 50%, P<0.001; odds ratio=0.067, 95% CI, 0.014 to 0.327) and the complete response rate (66 vs 41%, P=0.045; OR, 2.790; 95% CI, 1.011 to 7.698) were significantly different in the fosaprepitant group compared to the ondansetron group. However, there were no statistically significant differences between the groups in the incidence of PONV or the need for rescue antiemetics during this time

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron 4 mg IV			Secondary: Not reported	period. The incidence of vomiting and complete response from 0 to 48 hours were similar to rates from 0 to 24 hours (P<0.05). Secondary: Not reported
Kakuta et al.[60] (2015) fosaprepitant 150 mg IV vs ondansetron 4 mg IV	DB, PRO, RCT Patients 20 to 80 years of age scheduled to undergo lower limb surgery (total hip arthroplasty, total knee arthroplasty, and rotational acetabular osteotomy) under general anesthesia	N=38 48 hours	Primary: Incidence of nausea and vomiting, use of rescue antiemetics, and severity of pain Secondary: Not reported	Primary: The incidence of PONV, complete response rate, rescue antiemetic use, nausea score, and visual analog scale score for pain were not significantly different between the two groups at all time points during the 48 hours after surgery. During the periods from 0 to 24 and 0 to 48 hours, the proportion of patients who experienced vomiting was significantly different between the groups (0 versus 26%; P=0.046). Secondary: Not reported
Gan et al.[61] (2007) Ondansetron 4 mg IV vs aprepitant 40 mg by mouth vs aprepitant 125 mg by mouth	DB, MC, PC, RCT Patients ≥18 years of age (ASA I or III status) who were scheduled to undergo open abdominal surgery requiring an overnight hospital stay and were scheduled to receive general anesthesia including nitrous oxide with volatile anesthetics	N=805 48 hours	Primary: Complete response (no vomiting and no use of rescue therapy in the 24 hours after surgery) Secondary: No rescue therapy 0 to 24 hours; no vomiting 0 to 48 hours	Primary: Complete response was achieved in 45% of patients in the aprepitant 40 mg group, 43% in the aprepitant 125 mg group, and 42% in the ondansetron group, indicating non inferiority of the aprepitant treatment compared to ondansetron treatment (P>0.5 for both doses of aprepitant vs ondansetron). Secondary: Over 0 to 24 hours, the treatments did not differ significantly in the use of rescue therapy (45, 44, and 46% for aprepitant 40 mg, 125 mg, and ondansetron, respectively). More patients in both aprepitant groups reported no vomiting for the 0 to 48 hour time interval compared to the ondansetron group (OR, 2.7 for aprepitant 40 mg vs ondansetron and 6.9 for aprepitant 125 mg vs ondansetron; P<0.001 for both ratios).

Drug regimen abbreviations: IV=intravenous
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, XO=crossover

Miscellaneous abbreviations: ASA=American Society of Anesthesiologists, CINV= chemotherapy-induced nausea and vomiting, ECG=electrocardiogram, ECOG= Eastern Cooperative Oncology Group performance status; FLIE= Functional Living Index-Emesis questionnaire; NNT=number needed to treat, PONV=postoperative nausea and vomiting

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 11. Relative Cost of the NK1 receptor antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Aprepitant	capsule*, capsule dose pack*, injectable emulsion, powder packet	Cinvanti®, Emend®*	$$$$-$$$$$	$$$$-$$$$$
Fosaprepitant	injection*	Emend®*	$$$$$	$$$$-$$$$$
Combination Products				
Netupitant and palonosetron	capsule, injection	Akynzeo®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

X. Conclusions

The neurokinin-1 (NK1) receptor antagonists are Food and Drug Administration (FDA)-approved for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), and aprepitant is also indicated for prevention of post-operative nausea and vomiting (PONV).[1-7] Aprepitant and fosaprepitant are available in a generic formulation.

The use of multiple antiemetic agents is generally required for the prevention of CINV. The selection of therapy depends on the emetogenic potential of the chemotherapy regimen. Guidelines recommend the use of an NK1

antagonist to prevent acute nausea and vomiting associated with moderately or highly emetogenic chemotherapy (in combination with a 5-HT_3 receptor antagonist and dexamethasone). Guidelines also recommend the use of NK1 antagonists to prevent delayed nausea and vomiting when administering highly emetogenic or anthracycline/cyclophosphamide chemotherapy regimens. Guidelines do not currently recommend one specific regimen over another.[9-12]

According to the Society for Ambulatory Anesthesia guidelines, not all surgical patients will benefit from prophylactic antiemetic therapy.[11] Prophylaxis is recommended for adult patients who have at least one risk factor for PONV. These patients should receive treatment with two or three antiemetic agents from different classes.[11] The guidelines also state that aprepitant 40 mg orally has the same PONV prevention effect as palonosetron 0.075 mg IV. Aprepitant 40 and 80 mg orally is more efficacious than ondansetron. Fosaprepitant (a prodrug of aprepitant) 150 mg IV is more efficacious than ondansetron. In a meta-analysis which compared aprepitant to various other antiemetics and placebo, aprepitant reduced the incidence of vomiting on both post-op days one and two; however, the quality of evidence was limited by the significant heterogeneity in the results.[11]

The safety and efficacy of the NK1 antagonists have been evaluated in several clinical trials for their FDA-approved indications.[15-61] There are currently no clinical trials that compare two different NK1 antagonist to each other. All agents are formulated as oral capsules or tablets, with the exception of fosaprepitant, which is an intravenous injection. An injectable formulation of Akynzeo® has also become available as fosnetupitant-palonosetron. Fosnetupitant is a prodrug of netupitant. For highly emetogenic chemotherapy, fosaprepitant and netupitant-palonosetron are given only on day one as a single dose, while aprepitant is given for three days. All NK1 antagonists are associated with drug interactions to some extent. Of particular concern are drug interactions with agents that are either substrates of CYP3A4 or inhibit/induce CYP3A4. Dose adjustments and contraindications may apply based on the concurrent agent.[1-7] Aprepitant/fosaprepitant is the only NK1 antagonist currently approved by the FDA for use in pediatric patients.[4-7] Due to its co-formulation, netupitant-palonosetron carries the associated warnings of palonosetron, including a risk for serotonin syndrome.[6]

There is insufficient evidence to support that one brand neurokinin-1 receptor antagonist is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand neurokinin-1 receptor antagonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand neurokinin-1 receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, Miscellaneous
AHFS Class 562292
November 9, 2022

I. Overview

The pathophysiology of nausea and vomiting is complex and involves multiple neurotransmitters and organ systems. Five neurotransmitter receptor sites play a key role in the vomiting reflex. These receptor sites include M1 (muscarinic), D2 (dopamine), H1 (histamine), 5-HT_3 (serotonin), and NK_1 (substance P). The available antiemetic drugs antagonize these receptors, leading to improvements in nausea and vomiting. Nausea and vomiting due to central or vestibular disorders respond well to anticholinergic agents and histamine H_1-receptor antagonists.[1-6]

The miscellaneous antiemetics are approved for the prevention and treatment of chemotherapy-induced nausea and vomiting, postoperative nausea and vomiting, motion sickness, and acquired immunodeficiency syndrome-related anorexia.[1-6] Amisulpride is a selective dopamine-2 (D2) and dopamine-3 (D3) receptor antagonist. D2 and D3 receptors in the central nervous system play a role in emesis.[3] Dronabinol is an orally active cannabinoid, which has complex effects on the central nervous system.[4] Scopolamine, an anticholinergic agent, exerts its effect by blocking the action of acetylcholine on autonomic receptors innervated by postganglionic cholinergic nerves and smooth muscles that lack cholinergic innervation.[5]

The miscellaneous antiemetics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Dronabinol and scopolamine are both available in a generic formulation. This class was last reviewed in August 2020.

Table 1. Miscellaneous Antiemetics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amisulpride	injection	Barhemsys®	none
Dronabinol	capsule	Marinol®*	dronabinol
Scopolamine	transdermal patch	Transderm-Scop®*	scopolamine

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antiemetics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Miscellaneous Antiemetics

Clinical Guideline	Recommendation(s)
National Comprehensive Cancer Network: **Clinical Practice Guidelines in Oncology: Antiemesis (2022)**[10]	Principles of emesis control for the cancer patient: • Prevention of nausea/vomiting is the goal. The risk of nausea/vomiting (acute ≤24 hours vs delayed >24 hours) for persons receiving anticancer agents of high and moderate emetic risk lasts for at least three days for high and two days for moderate after the last dose of anticancer agents. Patients need to be protected throughout the full period of risk. • Oral and parenteral serotonin receptor antagonists (5-HT_3 RAs) have equivalent efficacy when used at the appropriate doses and intervals. • Consider the toxicity of the specific antiemetic(s). • Choice of antiemetic(s) used should be based on the emetic risk of the therapy, prior experience with antiemetics, and patient factors. Continuous infusion may make an agent less emetogenic. The emetic risk is expected to be the same for biosimilars as for the parent compound unless otherwise noted.

Clinical Guideline	Recommendation(s)

	• Patient risk factors for anticancer agent-induced nausea/vomiting include:
	  ○ Younger age
	  ○ Female sex
	  ○ Previous history of anticancer agent-induced nausea/vomiting
	  ○ Little or no previous alcohol use
	  ○ Prone to motion sickness
	  ○ History of morning sickness during pregnancy
	  ○ Anxiety/high pretreatment expectation of nausea
	• There are other potential causes of emesis in patients with cancer (e.g., bowel obstruction, vestibular dysfunction, brain metastases, electrolyte imbalance, uremia, concomitant drugs, gastroparesis, cannabinoid hyperemesis syndrome, pancreatitis).
	
	For high emetic risk parenteral chemotherapy the following is recommended:
	• Preferred: combination of olanzapine, a neurokinin-1 receptor antagonist (NK1 RA), a 5-HT_3 RA, and dexamethasone.
	OR
	• Combination of olanzapine, palonosetron, and dexamethasone.
	OR
	• Combination of a NK1 RA, a 5-HT_3 RA, and dexamethasone.
	• The regimen and doses for each therapy are modified on days two to four after chemotherapy.
	
	For moderate emetic risk parenteral chemotherapy the following is recommended:
	• Combination of dexamethasone and a 5-HT_3 RA (palonosetron IV and granisetron SQ preferred).
	OR
	• Combination of olanzapine, palonosetron, and dexamethasone.
	OR
	• Combination of a NK1 RA, a 5-HT_3 RA, and dexamethasone.
	• The regimen and doses for each therapy are modified on days two and three after chemotherapy.
	
	For low emetic risk parenteral chemotherapy the following is recommended:
	• Dexamethasone; **OR**
	• Metoclopramide; **OR**
	• Prochlorperazine; **OR**
	• Dolasetron, granisetron or ondansetron (oral formulations).
	• Lorazepam PRN and H_2 blocker or PPI may be given with any regimen.
	
	For minimal emetic risk parenteral chemotherapy the following is recommended:
	• No routine prophylaxis
	
	For oral chemotherapy with moderate to high emetic risk the following is recommended:
	• A 5-HT_3 antagonist (dolasetron, granisetron, or ondansetron oral).
	• Lorazepam may be given.
	• An H_2 receptor blocker or PPI may be given.
	
	For oral chemotherapy with low to minimal emetic risk the following is recommended:
	• Metoclopramide PRN; **OR**
	• Prochlorperazine PRN (maximum 40 mg/day); **OR**
	• Dolasetron, granisetron or ondansetron.
	• Lorazepam PRN and H_2 blocker or PPI may be given with any regimen.

Clinical Guideline	Recommendation(s)
	Principles for managing multiday emetogenic chemotherapy regimens • Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea/vomiting based on their chemotherapy regimen. It is therefore difficult to recommend a specific antiemetic regimen for each day, especially since acute and delayed emesis may overlap after the initial day of chemotherapy until the last day. • After chemotherapy administration concludes, the period of risk for delayed emesis also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen. • Practical issues also need to be considered when designing the antiemetic regimen, taking into consideration the administration setting, preferred route of administration, duration of action of the 5-HT_3 receptor agonist and associated dosing intervals, tolerability of daily antiemetics (e.g., steroids), compliance issues, and individual risk factors. • Steroids: o Dexamethasone should be administered once daily (either orally or intravenously [IV]) for moderately or highly emetogenic chemotherapy and for two to three days after chemotherapy for regimens likely to cause delayed emesis. o Dexamethasone dose may be modified or omitted when the chemotherapy regimen already includes a corticosteroid. • Serotonin antagonists: o A serotonin antagonist should be administered prior to the first (and subsequent) doses of moderately or highly emetogenic chemotherapy. o The frequency or need for repeated administration depends on the agent chosen and its mode of administration (IV, oral, or transdermal). o When palonosetron or granisetron extended-release injection is used as part of an antiemetic regimen that does NOT contain an NK1 antagonist, palonosetron or granisetron extended-release injection are the preferred 5-HT_3 receptor antagonists. • NK1 receptor antagonists: o NK1 antagonists may be used for multiday chemotherapy regimens likely to be moderately or highly emetogenic associated with significant risk for delayed nausea and emesis. Principles for managing breakthrough emesis • The general principle of treatment for breakthrough nausea and vomiting is to add one agent from a different drug class to the current regimen. • No one drug class has been shown to be superior for the management of breakthrough emesis. • Consider around-the-clock administration rather than PRN. • The oral route is not likely to be feasible due to vomiting, therefore rectal or IV therapy is often required. • Ensure adequate hydration.
European Society of Medical Oncology/ Multinational Association of Supportive Care in Cancer: **Consensus Guidelines for the Prevention of Chemotherapy and**	Prevention of acute and delayed nausea and vomiting induced by highly emetogenic chemotherapy • For the prevention of cisplatin-containing highly emetogenic chemotherapy, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone, and an NK1 receptor antagonist (aprepitant, fosaprepitant, netupitant, or rolapitant), given before chemotherapy is recommended. • In patients receiving cisplatin-containing highly emetogenic chemotherapy treated with a combination of an NK1 receptor antagonist, a 5-HT_3 receptor antagonist and dexamethasone to prevent acute nausea and vomiting, dexamethasone on days two to four is suggested to prevent delayed nausea and vomiting.

Clinical Guideline	Recommendation(s)
Radiotherapy-Induced Nausea and Vomiting (2016)[8]	• In women with breast cancer receiving anthracycline/cyclophosphamide (AC) chemotherapy, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone, and an NK1 receptor antagonist (aprepitant, fosaprepitant, netupitant, or rolapitant), given before chemotherapy is recommended. • In women with breast cancer treated with a combination of a 5-HT_3 receptor antagonist, dexamethasone and an NK1 receptor antagonist to prevent acute nausea and vomiting, aprepitant or dexamethasone should be used on days two and three but not if fosaprepitant, netupitant, or rolapitant has been used on day one. If an NK1 receptor antagonist is not available for the prophylaxis of nausea and vomiting induced by AC chemotherapy, palonosetron is the preferred 5-HT_3 receptor antagonist. • For regimens including mechlorethamine, streptozocin, cyclophosphamide ≥1500 mg/m^2, carmustine, and dacarbazine, adding an NK1 receptor antagonist to the combination of a 5-HT_3 receptor antagonist and dexamethasone for all non-cisplatin and non-AC highly emetogenic chemotherapy is recommended. • Differences among the NK1 antagonists: o Aprepitant and netupitant are inhibitors of CYP3A4 and as a consequence, both significantly increase the exposure to oral dexamethasone; hence, reduction in oral dexamethasone doses is recommended during co-administration (from 20 to 12 mg). o Rolapitant is not an inhibitor or inducer of CYP3A4 and therefore does not require a reduced dose of dexamethasone when co-administered. However, rolapitant is a moderate inhibitor of CYP2D6. o At present, no comparative studies have been carried out to identify differences in efficacy and toxicity between the three NK1 receptor antagonists. <u>Prevention of acute and delayed nausea and vomiting induced by moderately emetogenic chemotherapy (MEC)</u> • For the prevention of acute emesis in MEC-treated patients, a 5-HT_3 receptor antagonist plus dexamethasone is recommended. • There is no definitive evidence demonstrating an advantage of the use of palonosetron with respect to the other 5-HT_3 receptor antagonists, when both are combined with dexamethasone. • In patients receiving MEC with a known potential for delayed emesis (e.g. oxaliplatin, doxorubicin, cyclophosphamide), the use of dexamethasone for days two to three can be considered. • No routine prophylaxis for delayed emesis can be recommended for all other patients receiving MEC. • To prevent carboplatin-induced acute nausea and vomiting, a combination of an NK1 receptor antagonist, dexamethasone, and a 5-HT_3 receptor antagonist is recommended. If patients receive fosaprepitant, netupitant, or rolapitant on day one, no antiemetic prophylaxis for delayed emesis is required. If patients receive aprepitant on day one, aprepitant on days two and three is recommended. <u>Prevention of nausea and vomiting induced by multiple-day cisplatin chemotherapy</u> • Patients affected by metastatic germ cell tumors receiving multiple-day cisplatin should receive a 5-HT_3 receptor antagonist plus dexamethasone plus aprepitant for the prevention of acute nausea and vomiting and dexamethasone for delayed nausea and vomiting. <u>Prevention of acute and delayed nausea and vomiting induced by chemotherapy with low and minimal emetogenic potential</u> • A single antiemetic agent, such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, such as metoclopramide may be considered for

Clinical Guideline	Recommendation(s)
	prophylaxis in patients receiving chemotherapy of low emetic risk. • No antiemetic should be routinely administered before chemotherapy to patients without a history of nausea and vomiting receiving minimally emetogenic chemotherapy. • No antiemetic should be administered for prevention of delayed nausea and vomiting induced by low or minimally emetogenic chemotherapy. • If a patient experiences acute or delayed nausea or vomiting after low or minimally emetogenic chemotherapy, it is advised that, with subsequent chemotherapy treatments, the regimen for the next higher emetic level be given. <u>Breakthrough chemotherapy-induced emesis and refractory emesis</u> • Antiemetics are most effective when used prophylactically. Therefore, it is preferable to use maximally effective antiemetics as first-line therapy rather than withholding more effective antiemetics for later use at the time of antiemetic failure. • For the treatment of breakthrough nausea and vomiting, it is recommended to use an antiemetic with a different mechanism of action than that of the antiemetic(s) used for prophylaxis. The available evidence for breakthrough nausea and vomiting suggests the use of olanzapine 10 mg orally daily for three days. The mild to moderate sedation in this patient population, especially elderly patients, is a potential problem with olanzapine. <u>Prevention of nausea and vomiting induced by high-dose chemotherapy</u> • For patients receiving high-dose chemotherapy for stem cell transplant, a combination of a 5-HT_3 receptor antagonist with dexamethasone and aprepitant (125 mg orally on day one and 80 mg on days two to four) is recommended before chemotherapy. <u>Prevention of radiotherapy-induced nausea and vomiting</u> • High emetic risk: prophylaxis with a 5-HT_3 receptor antagonist and dexamethasone is recommended. • Moderate emetic risk: prophylaxis with 5-HT_3 receptor antagonist and dexamethasone (optional) is recommended. • Low emetic risk with cranium area of treatment: prophylaxis or rescue with dexamethasone is recommended. • Low emetic risk with head/neck, thorax, or pelvis as area of treatment: prophylaxis or rescue with dexamethasone, a dopamine receptor antagonist, or a 5-HT_3 receptor antagonist is recommended. • Minimal emetic risk: rescue with dexamethasone, dopamine receptor antagonist, or 5-HT_3 receptor antagonists. <u>Prevention of acute chemotherapy-induced nausea and vomiting in children</u> • In children receiving chemotherapy of high emetic risk, an antiemetic prophylaxis with a 5-HT_3 receptor antagonist (granisetron, ondansetron, tropisetron or palonosetron) plus dexamethasone plus aprepitant is recommended. • Children who cannot receive dexamethasone should receive a $5HT_3$ receptor antagonist plus aprepitant. • When aprepitant administration is not feasible or desirable, the guideline recommends a 5-HT_3 receptor antagonist plus dexamethasone be given to children receiving highly emetogenic chemotherapy. • Children receiving MEC should receive antiemetic prophylaxis with a 5-HT_3 receptor antagonist plus dexamethasone. Furthermore, children who cannot receive receptor antagonist should receive a 5-HT_3 receptor antagonist and aprepitant. • In children receiving chemotherapy of low emetogenicity, antiemetic prophylaxis

Clinical Guideline	Recommendation(s)
	with a 5-HT_3 receptor antagonist is recommended. • In children receiving chemotherapy of minimal emetogenicity, no antiemetic prophylaxis is recommended.
Society for Ambulatory Anesthesia: **Consensus Guidelines for the Management of Postoperative Nausea and Vomiting (2020)[9]**	Pediatric postoperative nausea and vomiting (PONV) management • Low risk prophylaxis: No treatment or 5-HT_3 receptor antagonist or dexamethasone. • Medium risk prophylaxis: 5-HT_3 receptor antagonist + dexamethasone. • High risk prophylaxis: 5-HT_3 receptor antagonist + dexamethasone + consider total intravenous anesthesia. • Rescue treatment: Use anti-emetic from different class than prophylactic drug-droperidol, promethazine, dimenhydrinate, metoclopramide; may also consider acupuncture/acupressure. Adult PONV management • One to two risk factors prophylaxis: Give two agents (5-HT_3 receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • More than two risk factors prophylaxis: Give three or four agents (5-HT_3 receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • Rescue treatment: Use anti-emetic from different class than prophylactic drug.
American Society of Clinical Oncology: **Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update (2020)[10]**	High-emetic-risk antineoplastic agents in adult patients • Adults treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of an NK_1 receptor antagonist, a serotonin (5-HT_3) receptor antagonist, dexamethasone, and olanzapine (day 1). Dexamethasone and olanzapine should be continued on days two to four. • Adults treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine (day 1). Olanzapine should be continued on days two to four. Moderate-emetic-risk antineoplastic agents in adult patients • Adults treated with carboplatin area under the curve (AUC) ≥ 4 mg/mL/min should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone (day 1). • Adults treated with moderate-emetic-risk antineoplastic agents (excluding carboplatin AUC ≥ 4 mg/mL/min) should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone (day 1). • Adults treated with cyclophosphamide, doxorubicin, oxaliplatin, and other moderate-emetic-risk antineoplastic agents known to cause delayed nausea and vomiting may be offered dexamethasone on days two to three. Low-emetic-risk antineoplastic agents in adult patients • Adults treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT_3 receptor antagonist or a single 8-mg dose of dexamethasone before antineoplastic treatment. Minimal-emetic-risk antineoplastic agents in adult patients • Adults treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis. Antineoplastic combinations in adult patients • Adults treated with antineoplastic combinations should be offered antiemetics appropriate for the component antineoplastic agent of greatest emetic risk.

Clinical Guideline	Recommendation(s)
	Adjunctive drugs in adult patients • Lorazepam is a useful adjunct to antiemetic drugs but is not recommended as a single-agent antiemetic. Cannabinoids in adult patients • Evidence remains insufficient for a recommendation regarding medical marijuana for the *prevention* of nausea and vomiting in patients with cancer receiving chemotherapy or radiation therapy. Evidence is also insufficient for a recommendation regarding the use of medical marijuana in place of the tested and US Food and Drug Administration–approved cannabinoids dronabinol and nabilone for the *treatment* of nausea and vomiting caused by chemotherapy or radiation therapy. Complementary and alternative therapies in adult patients • Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture/acupressure, and other complementary or alternative therapies for the *prevention* of nausea and vomiting in patients with cancer. High-dose chemotherapy with stem-cell or bone marrow transplantation in adult patients • Adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. • A four-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine may be offered to adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation. Multiday antineoplastic therapy in adult patients • Adults treated with multiday antineoplastic agents should be offered antiemetics before treatment that are appropriate for the emetic risk of the antineoplastic agent given on each day of the antineoplastic treatment and for two days after completion of the antineoplastic regimen. • Adults treated with four- or five-day cisplatin regimens should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. Breakthrough nausea and vomiting in adult patients • For patients with breakthrough nausea or vomiting, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; and ascertain that the best regimen is being administered for the emetic risk. • Adults who experience nausea or vomiting despite optimal prophylaxis and who did not receive olanzapine prophylactically should be offered olanzapine in addition to continuing the standard antiemetic regimen. • Adults who experience nausea or vomiting despite optimal prophylaxis and who have already received olanzapine may be offered a drug of a different class (e.g., an NK1 receptor antagonist, lorazepam or alprazolam, a dopamine receptor antagonist, dronabinol, or nabilone) in addition to continuing the standard antiemetic regimen. Anticipatory nausea and vomiting in adult patients • All patients should receive the most active antiemetic regimen appropriate for the antineoplastic agents being administered. Clinicians should use such regimens with initial antineoplastic treatment rather than assessing the patient's emetic response with less-effective antiemetic treatment. If a patient experiences anticipatory emesis, clinicians may offer behavioral therapy with systematic

Clinical Guideline	Recommendation(s)
	desensitization. High-emetic-risk radiation therapy in adult patients • Adults treated with high-emetic-risk radiation therapy should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone before each fraction and on the day after each fraction, if radiation therapy is not planned for that day. Moderate-emetic-risk radiation therapy in adult patients • Adults treated with moderate-emetic-risk radiation therapy should be offered a 5-HT_3 receptor antagonist before each fraction, with or without dexamethasone, before the first five fractions. Low-emetic-risk radiation therapy in adult patients • Adults treated with radiation therapy to the brain should be offered breakthrough dexamethasone therapy. Patients who are treated with radiation therapy to the head and neck, thorax, or pelvis should be offered breakthrough therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine-receptor antagonist. Minimal-emetic-risk radiation therapy in adult patients • Adults treated with minimal-emetic-risk radiation therapy should be offered breakthrough therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine-receptor antagonist. Concurrent radiation and antineoplastic agent therapy in adult patients • Adults treated with concurrent radiation and antineoplastic agents should receive antiemetic therapy appropriate for the emetic risk level of the antineoplastic agents, unless the risk level of the radiation therapy is higher. During periods when prophylactic antiemetic therapy for the antineoplastic agents has ended and ongoing radiation therapy would normally be managed with its own prophylactic therapy, patients should receive prophylactic therapy appropriate for the emetic risk of the radiation therapy until the next period of antineoplastic therapy, rather than receiving breakthrough therapy for the antineoplastic agents as needed. High-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with high-emetic-risk antineoplastic agents should be offered a three-drug combination of a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant or fosaprepitant. • Pediatric patients treated with high-emetic-risk antineoplastic agents who are unable to receive aprepitant or fosaprepitant should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. • Pediatric patients treated with high-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of palonosetron and aprepitant or fosaprepitant. Moderate-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with moderate-emetic-risk antineoplastic agents should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. • Pediatric patients treated with moderate-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of a 5-HT_3 receptor antagonist and aprepitant or fosaprepitant. Low-emetic-risk antineoplastic agents in pediatric patients

Clinical Guideline	Recommendation(s)
	• Pediatric patients treated with low-emetic-risk antineoplastic agents should be offered ondansetron or granisetron. Minimal-emetic-risk antineoplastic agents in pediatric patients • Pediatric patients treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis.
American College of Obstetricians and Gynecologists: **Practice Bulletin No. 189: Nausea and Vomiting of Pregnancy (2018)**[11]	General considerations • Treatment of nausea and vomiting of pregnancy with vitamin B6 (pyridoxine) alone or vitamin B6 plus doxylamine in combination is safe and effective and should be considered first-line pharmacotherapy. • The standard recommendation to take prenatal vitamins for one month before fertilization may reduce the incidence and severity of nausea and vomiting of pregnancy. • The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis, or hyperemesis gravidarum, or both, includes supportive therapy, and antithyroid drugs are not recommended. • Treatment of nausea and vomiting of pregnancy with ginger has shown some beneficial effects in reducing nausea symptoms and can be considered as a nonpharmacologic option. • Treatment of severe nausea and vomiting of pregnancy or hyperemesis gravidarum with methylprednisolone may be efficacious in refractory cases; however, the risk profile of methylprednisolone suggests it should be a last-resort treatment. • Early treatment of nausea and vomiting of pregnancy may be beneficial to prevent progression to hyperemesis gravidarum. • Intravenous hydration should be used for the patient who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present. Correction of ketosis and vitamin deficiency should be strongly considered. Dextrose and vitamins should be included in the therapy when prolonged vomiting is present, and thiamine should be administered before dextrose infusion to prevent Wernicke encephalopathy. • Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as the first-line treatment to provide nutritional support to the woman with hyperemesis gravidarum who is not responsive to medical therapy and cannot maintain her weight. • Peripherally inserted central catheters should not be used routinely in women with hyperemesis gravidarum given the significant complications associated with this intervention. Peripherally inserted central catheters should be utilized only as a last resort in the management of a woman with hyperemesis gravidarum because of the potential of severe maternal morbidity.
Society of Obstetricians and Gynaecologists of Canada: **Clinical Practice Guideline: Management of Nausea and Vomiting of Pregnancy (2016)**[12]	General considerations • Women experiencing nausea and vomiting of pregnancy may discontinue iron-containing prenatal vitamins during the first trimester and substitute them with folic acid or adult or children's vitamins low in iron. • Women should be counselled to eat whatever pregnancy-safe food appeals to them and lifestyle changes should be liberally encouraged. • Ginger may be beneficial in ameliorating the symptoms of nausea and vomiting of pregnancy. • Acupressure may help some women in the management of nausea and vomiting of pregnancy. • Mindfulness-based cognitive therapy as an adjunct to pyridoxine therapy may be beneficial. • Pyridoxine monotherapy or doxylamine/pyridoxine combination therapy is recommended as first line in treating nausea and vomiting of pregnancy due to

Clinical Guideline	Recommendation(s)
	their efficacy and safety. • Women with high risk for nausea and vomiting of pregnancy may benefit from preemptive doxylamine/pyridoxine treatment at the onset of pregnancy. • H1 receptor antagonists should be considered in the management of acute or chronic episodes of nausea and vomiting of pregnancy. • Metoclopramide can be safely used as an adjuvant therapy for the management of nausea and vomiting of pregnancy. • Phenothiazines are safe and effective as an adjunctive therapy for severe nausea and vomiting of pregnancy. • Despite potential safety concerns of ondansetron use in pregnancy, ondansetron can be used as an adjunctive therapy for the management of severe nausea and vomiting of pregnancy when other antiemetic combinations have failed. • Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. • When nausea and vomiting of pregnancy is refractory to initial pharmacotherapy, investigation of other potential causes should be undertaken.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antiemetics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Miscellaneous Antiemetics[1-5]

Indication	Amisulpride	Dronabinol	Scopolamine
Anorexia			
Anorexia associated with weight loss in patients with acquired immunodeficiency syndrome		✔	
Chemotherapy-Induced Nausea and Vomiting			
Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments		✔	
Motion Sickness			
Prevention of nausea and vomiting associated with motion sickness			✔
Postoperative Nausea and Vomiting			
Prevention of postoperative nausea and vomiting associated with recovery from anesthesia and/or opiate analgesia and surgery			✔
Prevention of postoperative nausea and vomiting, either alone or in combination with an antiemetic of a different class	✔		
Treatment of postoperative nausea and vomiting in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis	✔		

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antiemetics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Miscellaneous Antiemetics[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amisulpride	Not reported	25 to 30	Not reported	Renal (74) Feces (23)	4 to 5
Dronabinol	10 to 20	97	Liver (extensive)	Renal (10 to 15) Feces (50)	19 to 36
Scopolamine	Not reported	Not reported	Liver	Renal (<10)	9.5

V. Drug Interactions

Major drug interactions with the miscellaneous antiemetics are listed in Table 5.

Table 5. Major Drug Interactions with the Miscellaneous Antiemetics[2]

Generic Name(s)	Interaction	Mechanism
Amisulpride	QT-interval prolonging drugs	Amisulpride causes dose- and concentration-dependent QT prolongation. To avoid potential additive effects, avoid use of amisulpride in patients taking droperidol. ECG monitoring is recommended in patients taking other drugs known to prolong the QT interval (e.g., ondansetron)
Amisulpride	Levodopa	Concurrent use of amisulpride and levodopa may result in decreased efficacy of both agents.
Dronabinol	Disulfiram	Concurrent use of disulfiram and dronabinol may result in disulfiram-like reaction.
Dronabinol	Metronidazole	Concurrent use of dronabinol and metronidazole may result in disulfiram-like reaction.
Scopolamine	Potassium chloride	Anticholinergics may slow GI motility, delaying potassium chloride tablet passage through the GI tract
Scopolamine	Anticholinergic agents	Concurrent use of scopolamine and anticholinergics may result in increased risk of CNS adverse reactions, intestinal obstruction, and urinary retention.
Scopolamine	CNS depressants	Concurrent use of scopolamine and CNS depressants may result in increased risk of drowsiness, dizziness, and disorientation.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antiemetics are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Single Entity Miscellaneous Antiemetics[1-4]

Adverse Events	Amisulpride	Dronabinol	Scopolamine
Cardiovascular			
Hypotension	3	✔	-
Palpitation	-	>1	-
Prolonged QT interval	✔	-	-
Tachycardia	-	>1	-
Central Nervous System			
Agitation	-	-	6
Amnesia	-	>1	-
Anxiety	-	>1	-
Ataxia	-	>1	-
Chills	4	-	-
Confusion	-	✔	4
Depersonalization	-	>1	-

Adverse Events	Amisulpride	Dronabinol	Scopolamine
Depression	-	✔	-
Dizziness	-	3 to 10	12
Drowsiness	-	3 to 10	8 to 17
Euphoria	-	8 to 24	-
Hallucinations	-	>1	-
Malaise/fatigue	-	✔	-
Nightmares	-	✔	-
Paranoia	-	3 to 10	-
Seizure	-	✔	-
Somnolence	-	3 to 10	-
Dermatological			
Contact dermatitis	-	-	✔
Flushing	-	>1	-
Gastrointestinal			
Abdominal distention	2	-	-
Abdominal pain/discomfort	-	3 to 10	-
Diarrhea	-	✔	-
Nausea	-	3 to 10	-
Vomiting	-	3 to 10	-
Xerostomia	-	-	29 to 67
Musculoskeletal			
Myalgia	-	✔	-
Weakness	-	>1	-
Special Senses			
Conjunctivitis	-	✔	-
Mydriasis	-	-	4
Tinnitus	-	✔	-
Visual disturbance	-	✔	5
Other			
Diaphoresis	-	<1	-
Hypokalemia	4	-	-
Increased serum prolactin	5	-	-
Infusion-site pain	6	-	-
Pharyngitis	-	-	3

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antiemetics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Miscellaneous Antiemetics[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amisulpride	Prevention of PONV: Injection: 5 mg as a single intravenous injection infused over one to two minutes at the time of induction of anesthesia Treatment of PONV: Injection: 10 mg as a single intravenous injection infused over one to two minutes in the event of nausea and/or vomiting after a surgical procedure	Safety and efficacy in children have not been established.	Injection: 5 mg/2 mL 10 mg/4 mL
Dronabinol	Anorexia:	Safety and efficacy in	Capsule:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule: initial, 2.5 mg twice daily, before lunch and supper; for patients unable to tolerate this dosage the dosage can be reduced to 2.5 mg/day administered as a single dose in the evening or at bedtime; if clinically indicated and in the absence of significant adverse effects, the dosage may be gradually increased to a maximum of 20 mg/day CINV: Capsule: initial, 5 mg/m^2, given one to three hours prior to the administration of chemotherapy, then every two to four hours after chemotherapy, for a total of 4 to 6 doses/day; should the 5 mg/m^2 dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose	children have not been established.	2.5 mg 5 mg 10 mg
Scopolamine	Prevention of motion sickness: Transdermal patch: apply one patch behind one ear at least four hours before antiemetic effect is required Prevention of PONV: Transdermal patch: apply patch the evening before scheduled surgery; maximum, one patch at any time	Safety and efficacy in children have not been established.	Transdermal patch: 1 mg/72 hours

CINV: chemotherapy-induced nausea and vomiting, PONV: postoperative nausea and vomiting

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antiemetics are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Miscellaneous Antiemetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Acquired Immunodeficiency Syndrome-Related Anorexia				
Beal et al.[13] (1995) Dronabinol 2.5 mg two times a day vs placebo	DB, MC, PC, PG Patients with AIDS-related anorexia and ≥2.3 kg weight loss	N=139 6 weeks	Primary: Patients rated appetite, mood, and nausea by using a 100-mm visual analogue scale three days weekly Secondary: Side effects	Primary: Dronabinol was associated with increased appetite above baseline (38 vs 8% for placebo; P=0.015), improvement in mood (10 vs -2%; P=0.06), and decreased nausea (20 vs 7%; P=0.05). Weight was stable in dronabinol patients, while placebo recipients had a mean loss of 0.4 kg (P=0.14). Of the dronabinol patients, 22% gained ≥2 kg, compared to 10.5% of placebo recipients (P=0.11). Secondary: Side effects were mostly mild to moderate in severity (euphoria, dizziness, thinking abnormalities); there was no difference in discontinuation of therapy between dronabinol (8.3%) and placebo (4.5%) recipients.
Struwe et al.[14] (1993) Dronabinol 5 mg two times a day for 5 weeks vs placebo	DB, PC, RCT HIV-infected patients who had ≥2.25 kg weight loss	N=12 7 weeks	Primary: Caloric intake, weight, percent body fat, serum prealbumin, and symptom distress Secondary: Not reported	Primary: During dronabinol treatment, patients experienced increased percent body fat (1%; P=0.04); decreased symptom distress (P=0.04); and a trends toward weight gain (0.5 kg; P=0.13), increased prealbumin (29.0 mg/L; P=0.11), and improved appetite score (P=0.14). Secondary: Not reported
Jatoi et al.[15] (2002) Dronabinol 2.5 mg two times a day vs megestrol acetate	DB, MC, RCT Patients >18 years of age with histologic evidence of an incurable malignancy other than brain, breast, ovarian, or	N=469 Variable duration	Primary: Appetite and change in weight Secondary: Not reported	Primary: A greater percentage of megestrol acetate-treated patients reported appetite improvement and weight gain compared to dronabinol-treated patients: 75 vs 49% (P=0.0001) for appetite and 11 vs 3% (P=0.02) for ≥10% baseline weight gain. Combination treatment resulted in no significant differences in appetite or weight compared to megestrol acetate alone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
800 mg/day liquid suspension vs dronabinol 2.5 mg two times a day and megestrol acetate 800 mg/day liquid suspension	endometrial cancer			Secondary: Not reported
Timpone et al.[16] (1997) Dronabinol 2.5 mg two times a day vs megestrol acetate 750 mg/day vs dronabinol 2.5 mg two times a day and megestrol acetate 750 mg/day vs dronabinol 2.5 mg two times a day and megestrol acetate 250 mg/day	MC, RCT Patients with HIV wasting syndrome	N=52 12 weeks	Primary: Occurrence of adverse events, drug discontinuation, new AIDS-defining conditions, CD4+ T lymphocyte, mean weight change, C_{max} and area under the curve, and visual analog scale for hunger score Secondary: Not reported	Primary: Occurrence of adverse events, drug discontinuation, new AIDS-defining conditions, or CD4+ T lymphocyte changes was not significantly different among the treatment arms. The mean weight change over 12 weeks was as follows: dronabinol (-2.0 kg), megestrol acetate 750 mg (6.5 kg), dronabinol + megestrol 750 mg (6.0 kg) and dronabinol + megestrol 250 mg (-0.3 kg; difference among treatment arms; P=0.0001). For megestrol acetate, but not dronabinol, there was a positive correlation at week two between both C_{max} and area under the curve with each of the following: (1) weight change, (2) breakfast visual analog scale for hunger score, and (3) dinner visual analog scale for hunger score. Serious adverse events assessed as related to dronabinol included central nervous system events and those assessed as related to megestrol acetate included dyspnea, liver enzyme changes, and hyperglycemia. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting (CINV)				
Meiri et al.[17] (2007) <u>Day two (fixed dose)</u> Dronabinol 2.5 mg by mouth four times daily vs ondansetron 8 mg by mouth twice daily vs dronabinol 2.5 mg by mouth four times daily plus ondansetron 8 mg by mouth twice daily vs placebo <u>Days three to five (flexible dose)</u> dronabinol 2.5-5 mg by mouth four times daily vs	DB, PC, PG, RCT Patients ≥18 years of age with malignancy that did not involve the bone marrow and be undergoing chemotherapy including a moderately to highly emetogenic regimen	N=64 5 days	Primary: Total response two to five days after moderately to highly emetogenic chemotherapy (no vomiting and/or retching, intensity of nausea <5 mm, and no use of rescue medication) Secondary: Complete response rate, nausea status, episodes of vomiting and/or retching, duration of nausea and vomiting and/or retching, intensity of nausea, Eastern Cooperative Oncology Group score, and quality of life	Primary: Total response during active treatment did not differ between treatment groups (P=NS) due to small sample size. Improvement (range 47 to 58%) in three active treatment groups compared to placebo (20%) implies clinically relevant improvement (days two to five). Secondary: Overall response to treatment: dronabinol (71%), ondansetron (64%), combination (53%), placebo (15%). Combination therapy did not provide benefit beyond that observed with either agent alone. Complete responder rate was 62% with dronabinol, 60% with combination therapy, 58% with ondansetron, and 20% with placebo (P<0.005 vs placebo). All active treatments reduced the intensity of nausea vs placebo (P<0.05). No significant difference was observed among groups for mean number of episodes of vomiting and/or retching. Active treatments reduced the number of episodes of vomiting to 0 by days four and five. Active treatment reduced the duration of vomiting/retching to 0 hours in all groups by days four and five. Duration of nausea was comparable among all groups. Changes from baseline in Eastern Cooperative Oncology Group score were significant in patients receiving dronabinol vs placebo (P=0.036, in favor of placebo) and in patients receiving dronabinol vs combination therapy (p=0.028). Improvement in quality of life was observed only in patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron 4 to 8 mg by mouth twice daily vs dronabinol 2.5 to 5 mg by mouth four times daily plus ondansetron 4 to 8 mg by mouth twice daily vs placebo Day one regimen consisted of dexamethasone 20 mg and ondansetron 16 mg administered to all study participants. Dronabinol 2.5 mg was also administered on day one in the three active treatment arms.				dronabinol vs combination therapy (3.6; P=0.033, in favor of dronabinol).
Lane et al.[18] (1991) Dronabinol 10 mg every 6 hours (group 1)	DB, MC, PG, RCT Patients 18 to 69 years of age with cancer who were receiving	N=62 Treatment began 24 hours prior to initiation of	Primary: Duration per episode of vomiting Secondary:	Primary: The median duration per episode of vomiting was 1 minute in group 3 vs 2 minutes in group 1 and 4 minutes in group 2 (P<0.001). Secondary: Side effects, primarily central nervous system, were more common in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs prochlorperazine 10 mg every 6 hours (group 2) vs dronabinol and prochlorperazine, each 10 mg every 6 hours (group 3)	chemotherapy	chemotherapy and continued for 24 hours after the last dose of chemotherapy	Side effects	group 1 than in group 2 (P<0.01); addition of prochlorperazine to dronabinol appeared to decrease the frequency of dysphoric effects seen with the latter agent. The combination was significantly more effective than either single agent in controlling CINV (P<0.001).
Machado et al.[19] (2008) Dronabinol or nabilone vs placebo or prochlorperazine	MA Patients with cancer who were receiving chemotherapy	N=1,719 (18 trials) Variable duration	Primary: Anti-emetic efficacy and patient preference Secondary: Not reported	Primary: The anti-emetic efficacy of dronabinol was not significantly different than placebo (RR, 0.47; 95% CI, 0.19 to 1.16; P=0.10). The anti-emetic efficacy of dronabinol was significantly greater than prochlorperazine (RR, 0.67; 95% CI, 0.47 to 0.96; P=0.03). The anti-emetic efficacy of nabilone was not significantly different than prochlorperazine (RR, 0.88; 95% CI, 0.72 to 1.08; P=0.21). Patients preferred dronabinol or nabilone over prochlorperazine (RR, 0.33; 95% CI, 0.24 to 0.44; P<0.00001). Secondary: Not reported
Niiranen et al.[20] (1985) Nabilone 2 mg every 12 hours vs prochlorperazine	DB, RCT, XO Lung cancer patients receiving chemotherapy with cisplatinum, vincristine, cyclophosphamide, adriamycin,	N=24 Two consecutive chemotherapy cycles	Primary: Reduction of vomiting episodes; adverse events; patient preference Secondary: Not reported	Primary: Nabilone was significantly more effective than prochlorperazine in the reduction of vomiting episodes. Adverse events (mainly vertigo) were seen in ~50% of nabilone-treated patients. Three patients were withdrawn from the study due to decreased coordination and hallucinations after nabilone. Adverse events were limited to mild drowsiness in one patient receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
15 mg every 12 hours	vindesine, and etoposide			prochlorperazine. Two-thirds of the patients preferred nabilone to prochlorperazine. Secondary: Not reported
Einhorn et al.[21] (1981) Nabilone vs prochlorperazine	DB, PRO, RCT Patients receiving chemotherapy	N=80 Two consecutive chemotherapy cycles	Primary: Relief of nausea and vomiting; adverse events Secondary: Not reported	Primary: Sixty patients (75%) reported nabilone to be more effective than prochlorperazine for relief of nausea and vomiting. Forty-six patients required further chemotherapy and continued taking nabilone as the antiemetic of choice. Adverse events consisted of hypotension and lethargy, which were more pronounced with nabilone. Secondary: Not reported
Côté et al.[22] (2016) Nabilone 0.5 mg titrated to a maximum of 4 pills a day vs placebo	DB, PC, RCT Patients 18 to 80 years of age with squamous cell carcinoma of the oral cavity, the oropharynx, the hypopharynx, and/or the larynx treated by radiotherapy alone, postoperative radiotherapy, radiochemotherapy alone, or postoperative radiochemotherapy	N=56 4 weeks	Primary: 15% deterioration of quality of life according to the European Organisation for Research and Treatment of Cancer Questionnaire Secondary: Three independent questionnaires assessing appetite, nausea, and toxicity; and a visual analog scale for pain	Primary: There was not any significant quality of life improvement in the nabilone group compared to placebo throughout the entire study period (P=0.4270), even when controlling for tumor sites, treatment modality, and stages of the disease. Secondary: Using the visual analog scale, there was no significant difference in pain between the two groups (P=0.6048). Consumption of analgic medication was not significantly different between the groups (P=0.6671), and nabilone did not lengthen the time required for a 20% increase of pain (P=0.4614). Patients' appetite was not significantly improved in the nabilone group compared to placebo (P=0.3295). There was no difference in nausea in the nabilone group (P=0.7105). Otherwise, consumption of antiemetic medication was similar in the two groups (P=0.6124). There was no difference in the occurrence of any of the adverse effects of nabilone, including drowsiness (P=0.3166), anxiety (P=0.9163), and xerostomia (P=0.8341).
Tramer et al.[23]	MA of RCT	N=1,366	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Cannabinoids (dronabinol 13 trials, levonantradol 1 trial and nabilone 16 trials) vs conventional anti-emetics (alizapride 1 trial, chlorpromazine 2 trials, domperidone 2 trials, haloperidol 1 trial, metoclopramide 4 trials, prochlorperazine 12 trials and thiethylperazine 1 trial) or placebo (12 trials) (trials may have >1 treatment arm)	published between 1975 and 1997 (literature search of databases including Medline, Embase and Cochrane library to August 2000) Patients receiving chemotherapy	(30 trials [average trial size N=46]) 24 hours	Anti-emetic efficacy (absence of nausea or vomiting in the first 24 hours of chemotherapy) Secondary: Number of patients who expressed preference for cannabis for control for future chemotherapy cycles and adverse effects	Cannabinoids were more effective anti-emetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone or alizapride for complete control of nausea (RR, 1.38; 95% CI, 1.18 to 1.62; NNT, 6) and for complete control of vomiting (RR, 1.28; 95% CI, 1.08 to 1.51; NNT, 8). Cannabinoids were not more effective in patients receiving very low or very high emetogenic chemotherapy. Secondary: In XO trials, patients preferred cannabinoids for future chemotherapy cycles (RR, 2.39; 95% CI, 2.05 to 2.78; NNT, 3). Side effects that were considered "potentially beneficial" that were observed more frequently in patients receiving cannabinoids were a "high", sedation, drowsiness and euphoria. Side effects that were considered harmful that were reported more often with cannabinoids were dizziness, dysphoria, depression, hallucinations, paranoia and arterial hypotension. Patients on given cannabinoids were more likely to withdraw due to side effects (RR, 4.67; 95% CI, 3.07 to 7.09; NNT, 11).
Motion Sickness				
Spinks et al.[24] (2011) Scopolamine transdermal patch, tablet, capsule, oral solution or IV	MA Patients with motion sickness	N=1,025 (14 trials) Duration varied	Primary: Prevention and treatment of clinically defined motion sickness Secondary: Task ability,	Primary: Scopolamine was more effective than placebo in the prevention of motion sickness symptoms (RR, 0.47; 95% CI, 0.31 to 0.71). Scopolamine transdermal patch was more effective than methscopolamine in preventing motion sickness (RR, 0.33; 95% CI, 0.09 to 1.19). Compared to meclizine, scopolamine showed a greater decrease in mean motion sickness score (89%) than meclizine (59%) (P value not reported),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo, antihistamines (cinnarizine, dimenhydrinate, meclizine, promethazine) and other drugs (calcium channel antagonists, lorazepam, methscopolamine) vs combination of scopolamine with cyclizine, ephedrine or placebo			psychological tests and adverse effects	and delayed the onset of symptoms for longer than meclizine (mean time and percentage increase from baseline, scopolamine 4.32 minutes [32.47%] vs meclizine 0.58 seconds [8.66%]; P value not reported). Scopolamine transdermal patch was equivalent to other antihistamines such as promethazine and dimenhydrinate in preventing motion sickness. Studies comparing the effectiveness of scopolamine with cinnarizine produced mixed results. When scopolamine alone or in combination with ephedrine was studied, the MA showed no statistically significant results, although; fewer participants treated with scopolamine alone reported symptoms (RR, 0.70; 95% CI, 0.39 to 1.26). Scopolamine was more effective at delaying the onset of motion sickness than lorazepam, which was found to hasten the onset of symptoms. The mean time and percentage change from baseline was 4.32 minutes (32.47%) with scopolamine compared to –1.35 minutes [–1.65%] with lorazepam (P values not reported). Secondary: There was no marked difference in performance (task ability and psychological tests) between scopolamine and placebo (P values not reported). Scopolamine was no more likely to induce drowsiness (RR, 1.42; 95% CI, 0.79 to 2.56; P value not reported), dizziness (10 to 27% vs 0 to 26%; P value not reported) or blurring of vision (RR, 2.73; 95% CI, 0.89 to 8.37; P=0.08) than placebo. Scopolamine (35 to 50%) was associated with more reports of dry mouth than placebo (5%), dimenhydrinate (0%) and methscopolamine (10%). No studies were available relating to the therapeutic effectiveness of scopolamine in the management of established symptoms of motion sickness.
Dahl et al.[25] (1984)	DB, DD, PC, RCT, XO	N=36 Each subject	Primary: Self reported nausea score, mean	Primary: Mean motion sickness scores were highest during the placebo period and decreased with the use of scopolamine and meclizine. There was a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Scopolamine transdermal patch (0.5 mg) vs meclizine 25 mg tablet vs placebo	Patients 20 to 39 years of age with no concomitant medication use that could influence trial outcome or recent travel by air or sea	went through 3 times with 70 hours between experiments	motion sickness score, adverse reactions Secondary: Not reported	significant difference between the scopolamine and placebo groups, the scopolamine and meclizine groups, but not the meclizine and placebo groups. However there was a statistical difference between meclizine and placebo for the last half of the trial period. The number of patients experiencing dry mouth was 21 for the scopolamine groups, eight for placebo, and six for meclizine. Secondary: Not reported
Postoperative Nausea and Vomiting (PONV)				
Kranke et al.[26] (2018) Amisulpride 5 mg intravenous vs placebo Administered at induction of general anesthesia, in addition to one standard, nondopaminergic antiemetic, most commonly ondansetron or dexamethasone	DB, MC, PC, RCT Adult surgical patients having three or four PONV risk factors	N=1,147 24 hours	Primary: Complete response, defined as no emesis or rescue medication use in the 24 hour postoperative period Secondary: Incidence of emesis, nausea, significant nausea, and use of rescue medication; safety	Primary: Complete response occurred in 330 of 572 (57.7%) of the amisulpride group and 268 of 575 (46.6%) of the control group (difference, 11.1 percentage points; 95% CI, 5.3 to 16.8; P<0.001). Secondary: The incidences of emesis (13.8 vs 20.0%, P=0.003), any nausea (50.0 vs 58.3%, P=0.002), significant nausea (37.1 vs 47.7%, P<0.001), and rescue medication use (40.9 vs 49.4%, P=0.002) were significantly lower in the amisulpride group. Adverse events and laboratory and electrocardiogram abnormalities occurred no more frequently with amisulpride than with placebo.
Gan et al.[27] (2017) Amisulpride 5 mg	2 identical DB, MC, PC, RCTs Adult inpatients	N=689 24 hours	Primary: Complete response, defined as no	Primary: In the U.S. study, 46.9% (95% CI, 39.0 to 54.9) of patients achieved complete response in the amisulpride group compared to 33.8% (95% CI, 26.2 to 42.0) in the placebo group (P=0.026). In the European study,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
intravenous vs placebo Administered at induction of general anesthesia	undergoing elective surgery during general anesthesia and having at least two of the four Apfel risk factors for PONV		vomiting/retching and no use of antiemetic rescue medication in the 24 hours postoperative period Secondary: Nausea incidence	complete response rates were 57.4% (95% CI, 49.2 to 65.3) for amisulpride and 46.6% (95% CI, 38.8 to 54.6) for placebo (P=0.070). Secondary: Nausea occurred less often in patients who received amisulpride than those who received placebo (U.S. study, P=0.070; European study, P=0.059).
Candiotti et al.[28] (2019) Amisulpride 5 mg intravenous vs amisulpride 10 mg intravenous vs placebo	DB, MC, PC, RCT Patients ≥18 years of age undergoing inhalational anesthesia, expected to last at least one hour, for an outpatient or inpatient surgical procedure who then experienced PONV	N=1,988 24 hours	Primary: Complete response, defined as no emesis in the period 30 minutes to 24 hours after study drug treatment and no use of rescue medication in the entire 24-hour period Secondary: Logistic modeling of the incidence of the primary efficacy variable to investigate the effects of adjustment for country, center, number and type of PONV risk factors, and type of operation	Primary: Complete response occurred in 39 of 181 patients (21.5%) in the placebo group compared to 60 of 191 patients (31.4%; P=0.016) and 59 of 188 patients (31.4%; P=0.016) in the amisulpride 5 and 10 mg groups, respectively. Secondary: A logistic regression model with treatment, number of baseline risk factors, type of operation (abdominal surgery versus other surgery), and center as factors showed a benefit for both 5 mg amisulpride (adjusted odds ratio, 1.76; 95% CI, 1.09 to 2.86; P=0.014) and 10 mg amisulpride (adjusted odds ratio, 1.72; 95% CI, 1.06 to 2.80; P=0.014) over placebo.
Habib et al.[29]	DB, MC, PC, RCT	N=702	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2019) Amisulpride 5 mg intravenous vs amisulpride 10 mg intravenous vs placebo	Patients ≥18 years of age undergoing inhalational anesthesia, expected to last at least one hour, for an outpatient or inpatient surgical procedure who then experienced PONV despite prophylaxis	24 hours	Complete response, defined as no emesis or rescue antiemetic use for 24 hours after study drug administration, excluding emesis in the first 30 min Secondary: Incidence of emesis and rescue medication use, nausea burden, time to treatment failure, and length of stay in postanesthesia care unit and hospital	Complete response occurred in more patients receiving 10 mg amisulpride (96 of 230, 41.7%) than placebo (67 of 235, 28.5%), a 13.2% difference (95% CI, 4.6 to 21.8; odds ratio, 1.80; P=0.006). A 5-mg dose of amisulpride did not show a significant benefit (80 of 237, 33.8%); the difference from placebo was 5.2% (95% CI, 3.1 to 13.6; odds ratio, 1.24; P=0.109). Secondary: The time to treatment failure was significantly longer for 10 mg amisulpride (median 443 min) than placebo (median 120 min), with a hazard ratio of 0.63 (95% CI, 0.50 to 0.80; P<0.001). Emesis occurred in significantly fewer patients after either 5 mg or 10 mg amisulpride than placebo. Most other secondary endpoints were significantly improved by 10 mg amisulpride but not 5 mg, including rescue medication use, incidence of significant nausea, maximal nausea severity, and nausea evolution. The mean length of stay in PACU after study drug dosing was 140.9 min with 10 mg amisulpride (SD, 174.2; median, 96.0 min; range, 0 to 1266) and 175.5 min with placebo (SD, 217.6; median, 116.0; range, 2 to 1353). Overall mean length of hospital stay after dosing was 50.3 hours (SD, 79.7; median, 24.4 h; range, 0.7 to 716.3) with 10 mg amisulpride and 56.3 hours (SD, 73.4; median, 29.2 h; range, 0.6 to 644.1) with placebo.
Green et al.[30] (2012) Aprepitant 40 mg vs aprepitant 40 mg and scopolamine transdermal patch	DB, RCT Patients >18 years of age, ASA I–III, two or more Apfel four-point risk factors, undergoing an elective surgical procedure with a high risk of PONV expected to last at least 60 minutes	N=120 24 hours	Primary: Complete response Secondary: Incidences of nausea, vomiting, their composite, and the need for rescue medication	Primary: The aprepitant alone and aprepitant with scopolamine did not differ in complete responses (63 vs 57%; P=0.57). Secondary: Incidences of nausea, vomiting, their composite, and the need for rescue medication, all showed no statistical difference.
Layeeque et al.[31] (2006)	RETRO	N=242	Primary: Rate and severity	Primary: The rate of nausea (59 vs 15%; P<0.001) and vomiting (29 vs 3%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dronabinol 5 mg as prophylaxis and prochlorperazine 25 mg rectal suppository after anesthesia vs standard preoperative care (which excludes prophylactic use of antiemetics)	Patients undergoing surgery	Variable duration	of PONV Secondary: Not reported	P<0.001) were significantly better in the patients treated prophylactically with dronabinol and prochlorperazine compared to those receiving standard preoperative care. Secondary: Not reported
Jones et al.[32] (2006) Scopolamine 1.5 mg transdermal patch vs placebo All patients received prophylactic IV ondansetron.	DB, PC, PRO, RCT Patients ≥18 years of age at high risk for PONV	N=56 72 hours following surgery	Primary: Incidence and severity of PONV, side effects, antiemetic requirements Secondary: Not reported	Primary: Patients in the scopolamine group had a lower incidence of PONV (P=0.043), longer time to first reported nausea (P=0.044), longer time to first episode of emesis (P=0.031), and decreased supplemental antiemetic requirements (P=0.016) compared to the placebo group. Secondary: Not reported
White et al.[33] (2007) Ondansetron 4 mg vs	DB, PC, RCT Patients 18 to 65 years of age scheduled to undergo major laparoscopic (e.g.,	N=77 72 hours	Primary: PONV or retching; need for rescue antiemetics, complete response rates (i.e., absence of protracted	Primary: There were no differences between the transdermal scopolamine and ondansetron treatment groups with respect to the incidence of PONV symptoms or need for rescue medications. Complete response rates did not differ significantly between the transdermal scopolamine and ondansetron treatment groups (51 and 47%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
scopolamine 1.5 mg transdermal patch	bariatric surgery) or plastic (e.g., abdominoplasty, reduction mammoplasty) surgery procedures		nausea or repeated episodes of emesis requiring antiemetic rescue medication) Secondary: Not reported	respectively). The requirement for rescue antiemetics was not significantly reduced in the transdermal scopolamine group compared to the ondansetron group during the 24 to 48 hour period (21 vs 40%; P=0.07). Secondary: Not reported
Gan et al.[34] (2009) Scopolamine 1.5 mg transdermal patch applied two hours prior to surgery and ondansetron 4 mg IV two to five minutes prior to induction of anesthesia vs ondansetron 4 mg IV two to five minutes prior to induction of anesthesia	DB, MC, RCT Adult female patients (ASA I or III status) at high risk for PONV who were undergoing outpatient gynecological laparoscopy, laparoscopic cholecystectomy, or breast augmentation surgery with an anticipated duration of one to three hours	N=620 24 hours	Primary: Complete antiemetic response through 24 hours postoperatively Secondary: Time elapsed between surgery and first episode of nausea or use of antiemetic medication, vomiting/retching or use of rescue medication, and vomiting/retching, nausea, or use of rescue medication	Primary: There was a significant increase in complete response rate in patients receiving combination therapy vs ondansetron alone (48 vs 39%; P=0.021). Secondary: The incidence of nausea, vomiting, or the use of rescue antiemetics was significantly less frequent in the post-anesthesia care unit and at 24 and 48 hours after surgery in the combination group compared to ondansetron monotherapy; however, there was no difference in these outcomes at hospital discharge. The time that elapsed before the first episode of nausea, vomiting, or the use of rescue antiemetic was significantly longer in the combination group compared to ondansetron monotherapy. The cumulative number of times rescue medication was given at 24 hours was less frequent with combination therapy compared to ondansetron monotherapy (P=0.047). The mean maximum severity of the nausea was significantly lower in the combination group than in the ondansetron group for those patients who experienced one or more nausea episodes at any time point during the 48 hours after surgery (P<0.05). The combination group had a significantly higher patient mean satisfaction score than the ondansetron monotherapy group (P=0.049). The overall incidence of adverse effects was significantly decreased in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				combination therapy group (36.7 vs 49%; P<0.01).
Sah et al.[35] (2009) Scopolamine 1.5 mg transdermal patch applied two hours prior to surgery and ondansetron 4 mg 30 minutes prior to the end of surgery vs ondansetron 4 mg 30 minutes prior to the end of surgery	DB, RCT Patients (ASA I or II status) at high risk for PONV who were undergoing outpatient plastic surgery	N=126 24 hours	Primary: Presence of vomiting, severity of nausea, rescue medications for nausea, and adverse events Secondary: Not reported	Primary: Transdermal scopolamine significantly decreased the frequency of postoperative nausea between eight and 24 hours; however, there was no significant reduction in the frequency of vomiting during any time period assessed. There was no significant difference in the use of rescue medications between the treatment groups (P=0.388). The most common adverse event was dry mouth (70%) for patients in the transdermal scopolamine group, but frequency of dry mouth was also high in the placebo group (63%). Sedation was seen in 40% of patients receiving transdermal scopolamine compared to 33% of patients in the placebo group. Secondary: Not reported
Tarkkila et al.[36] (1995) Scopolamine 1.5 mg transdermal patch and promethazine vs diazepam 5 to 15 mg vs promethazine 10 mg	DB, PRO Patients scheduled for arthroplasty surgery of the lower extremity who were anaesthetized with spinal anesthesia with a combination of isobaric bupivacaine 20 mg and morphine 0.3 mg	N=60 24 hours	Primary: Incidence of PONV Secondary: Not reported	Primary: A total of 60% of patients receiving promethazine and transdermal scopolamine were totally free from PONV symptoms compared to those premedicated with diazepam (40%) or promethazine alone (30%). Promethazine and transdermal scopolamine significantly reduced the number of patients with vomiting (25%). The combination was also more effective in reducing the incidence of nausea (25%) compared to promethazine alone (P<0.05). PONV occurred in the majority of patients during the first 12 hours following surgery. Secondary: Not reported
Vertigo				
Schmitt et al.[37]	DB, RCT, XO	N=12	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1986) Meclizine by mouth for one week vs scopolamine transdermal for one week vs placebo	Healthy subjects	7 days	Effect on vertigo symptoms Secondary: Side effects	Vertigo symptoms on day one of treatment were significantly less with transdermal scopolamine than oral meclizine or placebo and on day seven were significantly less with both scopolamine and meclizine compared to placebo. On day one, meclizine did not reduce vertigo symptoms significantly when compared to placebo. Secondary: Drowsiness was greater with use of oral meclizine than transdermal scopolamine.

Drug regimen abbreviations: IV=intravenous
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, XO=crossover
Miscellaneous abbreviations: AIDS= acquired immunodeficiency syndrome, ASA=American Society of Anesthesiologists, CINV= chemotherapy-induced nausea and vomiting, ECG=electrocardiogram, ECOG= Eastern Cooperative Oncology Group performance status; FLIE= Functional Living Index-Emesis questionnaire; HIV= Human immunodeficiency virus, NNT=number needed to treat, PONV=postoperative nausea and vomiting

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 11. Relative Cost of the Miscellaneous Antiemetics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amisulpride	injection	Barhemsys®	$	N/A
Dronabinol	capsule	Marinol®*	$$$$$	$$$$
Scopolamine	transdermal patch	Transderm-Scop®*	$$$$$	$$

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

X. Conclusions

The miscellaneous antiemetics are approved for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), motion sickness, and acquired immunodeficiency syndrome (AIDs)-related anorexia.[1-5] Dronabinol and scopolamine are available in a generic formulation.

The use of multiple antiemetic agents is generally required for the prevention of CINV. The selection of therapy depends on the emetogenic potential of the chemotherapy regimen. Guidelines recommend the use of an NK1 antagonist to prevent acute nausea and vomiting associated with moderately or highly emetogenic chemotherapy (in combination with a 5-HT_3 receptor antagonist and dexamethasone). Guidelines also recommend the use of NK1 antagonists to prevent delayed nausea and vomiting when administering highly emetogenic or anthracycline/cyclophosphamide chemotherapy regimens.[7,8,10]

Dronabinol is approved for the treatment of the nausea and vomiting associated with chemotherapy in patients who have failed to respond to conventional antiemetic treatments.[1,4] It is recommended as one of several options for the treatment of breakthrough nausea and vomiting.[10] Psychological and physiological dependence have occurred in patients receiving dronabinol, but addiction is uncommon and has only been seen after prolonged high dose administration.[4] Although chronic abuse of cannabis has been associated with decrements in motivation, cognition, judgment, and perception, no such decrements have been associated with the administration of dronabinol for therapeutic purposes.[4]

Scopolamine is the only miscellaneous antiemetic approved for the treatment of motion sickness. However, use for this indication has been largely replaced by the antihistamine antiemetics because of anticholinergic side effects. Both the oral and transdermal scopolamine products are effective in the treatment of motion sickness.[19-20]

Dronabinol is the only miscellaneous antiemetic approved for the treatment of AIDS-related anorexia. Clinical trials have demonstrated that dronabinol increases appetite in AIDS patients, but does not consistently produce weight gain.[13,16] Megestrol acetate, which is available in a generic formulation, was shown to be more effective than dronabinol for improving appetite and producing weight gain.[15-16] Adding dronabinol to megestrol acetate produced no additional clinical benefits.

Amisulpride is approved for the prevention of PONV either alone or in combination with an antiemetic of a different class and for the treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis.[3] For both indications, amisulpride has demonstrated a higher complete response after 24 hours compared to placebo.[26-29] It is given as a single intravenous injection infused over one to two minutes. Amisulpride carries a warning/precaution for QT prolongation, which occurs in a dose- and concentration-dependent manner. Avoid use in patients with congenital long QT syndrome and in patients taking droperidol. ECG monitoring is recommended in patients with pre-existing arrhythmias/cardiac conduction disorders; electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia); congestive heart failure; and in patients taking other medicinal products (e.g., ondansetron) or with other medical conditions known to prolong the QT interval.[3]

There is insufficient evidence to support that one brand miscellaneous antiemetic is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous antiemetics within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous antiemetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Proton-Pump Inhibitors
AHFS Class 562836
November 9, 2022

I. Overview

The proton-pump inhibitors (PPIs) are approved for the treatment of a variety of gastrointestinal disorders, including erosive esophagitis, gastric/duodenal ulcers, gastroesophageal reflux disease (GERD), hypersecretory conditions, as well as the eradication of *Helicobacter pylori* infections.[1-12] They suppress gastric acid secretion and are generally recognized as among the most potent acid suppressants available.[13] Parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to several stimuli. Within the parietal cell, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase (H^+K^+-exchanging ATPase) is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K+) for hydrogen ions (H+) resulting in a lower gastric pH.

The PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting ion exchange, causing an increase in gastric pH. They will only inhibit proton pumps that are actively secreting acid. It is estimated that only 70 to 80% of proton pumps are active following a meal.[13-14] Thus, single doses of a PPI will not completely inhibit acid secretion and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. Maximal acid suppression generally occurs within three to four days.[13-15]

In May 2010, the Food and Drug Administration (FDA) notified healthcare providers about a possible increased risk of fractures (hip, wrist, and spine) associated with the use of the PPIs.[16] This is based on the FDA's review of several epidemiologic studies, which used computerized claims data to evaluate the risk of fractures in patients treated with PPIs compared to patients who were not using PPIs. The greatest risk was seen in patients who received high doses or used PPIs for ≥1 year and was primarily observed in older patients. In March 2011, the FDA also notified healthcare providers that the PPIs may cause hypomagnesemia if taken for prolonged periods of time (generally ≥1 year).[17] Low serum magnesium levels can result in serious adverse events, including tetany, arrhythmias, and seizures. In ~25% of the cases reviewed, magnesium supplementation did not improve low serum magnesium levels and the PPI had to be discontinued. An additional safety announcement was made in February 2012, informing the public that the use of PPIs may be associated with an increased risk of *Clostridium difficile*–associated diarrhea.[18]

The proton-pump inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents with the exception of omeprazole/amoxicillin/rifabutin delayed-release capsule and omeprazole/clarithromycin/ amoxicillin combination package are available in a generic formulation. This class was last reviewed in August 2020.

Table 1. Proton-Pump Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Dexlansoprazole	delayed-release capsule	Dexilant®*	dexlansoprazole
Esomeprazole magnesium	delayed-release capsule, delayed-release powder for suspension	Nexium®*	esomeprazole
Esomeprazole sodium	injection^	Nexium I.V.®*	esomeprazole
Lansoprazole	delayed-release capsule, delayed-release orally disintegrating tablet	Prevacid®*	lansoprazole
Omeprazole	delayed-release capsule, delayed-release powder for suspension	Prilosec®*	omeprazole
Pantoprazole	delayed-release tablet,	Protonix®*, Protonix IV®*	pantoprazole

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	delayed-release granules for suspension, injection		
Rabeprazole	delayed-release tablet	Aciphex®*	rabeprazole
Combination Products			
Omeprazole, amoxicillin and rifabutin	delayed-release capsule	Talicia®	none
Omeprazole, clarithromycin, and amoxicillin	combination pack	Omeclamox-Pak®	none
Omeprazole and sodium bicarbonate	capsule§, powder packet	N/A	omeprazole and sodium bicarbonate
Lansoprazole, amoxicillin, and clarithromycin	combination pack	N/A	lansoprazole, amoxicillin, and clarithromycin

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
§Generic product requires prior authorization.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the proton-pump inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Proton-Pump Inhibitors

Clinical Guideline	Recommendation(s)
American College of Gastroenterology: **Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease (2021)**[19]	Gastroesophageal Reflux Disease (GERD) • Weight loss is recommended for GERD patients who are overweight/obese. • Avoid meals within two to three hours of bedtime. • Avoid tobacco products/smoking in patients with GERD symptoms. • Avoid "trigger foods" for GERD symptom control. • Elevate head of bed for nighttime GERD symptoms. • Treatment with proton pump inhibitors (PPIs) is recommended over treatment with histamine-2-receptor antagonists (H2RA) for healing and maintenance from erosive esophagitis. • PPI administration 30 to 60 minutes before a meal is recommended rather than at bedtime for GERD symptom control. • For patients with GERD who do not have erosive esophagitis or Barrett's esophagus, and whose symptoms have resolved with PPI therapy, an attempt should be made to discontinue PPIs or to switch to on-demand therapy in which PPIs are taken only when symptoms occur and discontinued when they are relieved. • For patients with GERD who require maintenance therapy with PPIs, the PPIs should be administered in the lowest dose that effectively controls GERD symptoms and maintains healing of reflux esophagitis. • Routine addition of medical therapies is not recommended in PPI nonresponders. • Maintenance PPI therapy indefinitely or antireflux surgery for patients with LA grade C or D esophagitis is recommended. • Baclofen is not recommended in the absence of objective evidence of GERD. • Treatment with a prokinetic agent of any kind is not recommended for GERD therapy unless there is objective evidence of gastroparesis. • Sucralfate is not recommended for GERD therapy except during pregnancy. • On-demand or intermittent PPI therapy is suggested for heartburn symptom control in patients with nonerosive reflux disease.

Clinical Guideline	Recommendation(s)
	• There is conceptual rationale for a trial of switching PPIs for patients who have not responded to one PPI. For patients who have not responded to one PPI, more than one switch to another PPI cannot be supported. • Use of the lowest effective PPI dose is recommended and logical but must be individualized. One area of controversy relates to abrupt PPI discontinuation and potential rebound acid hypersecretion, resulting in increased reflux symptoms. Although this has been demonstrated to occur in healthy controls, strong evidence for an increase in symptoms after abrupt PPI withdrawal is lacking. <u>Long-term PPI issues</u> • Regarding the safety of long-term PPI usage for GERD, patients should be advised as follows: "PPIs are the most effective medical treatment for GERD. Some medical studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. Those studies have flaws, are not considered definitive, and do not establish a cause-and-effect relationship between PPIs and the adverse conditions. High-quality studies have found that PPIs do not significantly increase the risk of any of these conditions except intestinal infections. Nevertheless, we cannot exclude the possibility that PPIs might confer a small increase in the risk of developing these adverse conditions. For the treatment of GERD, gastroenterologists generally agree that the well-established benefits of PPIs far outweigh their theoretical risks." • Switching PPIs can be considered for patients who experience minor PPI side effects including headache, abdominal pain, nausea, vomiting, diarrhea, constipation, and flatulence. • For patients with GERD on PPIs who have no other risk factors for bone disease, do not recommend that they raise their intake of calcium or vitamin D or that they have routine monitoring of bone mineral density. • For patients with GERD on PPIs who have no other risk factors for vitamin B12 deficiency, do not recommend that they raise their intake of vitamin B12 or that they have routine monitoring of serum B12 levels. • For patients with GERD on PPIs who have no other risk factors for kidney disease, do not recommend that they have routine monitoring of serum creatinine levels. • For patients with GERD on clopidogrel who have LA grade C or D esophagitis or whose GERD symptoms are not adequately controlled with alternative medical therapies, the highest quality data available suggest that the established benefits of PPI treatment outweigh their proposed but highly questionable cardiovascular risks. • PPIs can be used to treat GERD in patients with renal insufficiency with close monitoring of renal function or consultation with a nephrologist.
North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition/ European Society for Pediatric Gastroenterology, Hepatology, and Nutrition: **Pediatric Gastroesophageal Reflux Clinical**	<u>Non-pharmacological treatment</u> • Using thickened feedings is suggested for treating visible regurgitation/vomiting in infants with gastroesophageal reflux disease (GERD). • Modifying feeding volumes and frequency according to age and weight is suggested to avoid overfeeding in infants with GERD. • A two to four week trial of extensively hydrolyzed protein-based (or amino-acid based) formula is suggested in infants suspected of GERD after optimal non-pharmacological treatment has failed. • Use of positional therapy (i.e., head elevation, lateral and prone positioning) is not recommended to treat symptoms of GERD in sleeping infants. • Consider use of head elevation or left lateral positioning to treat symptoms of

Clinical Guideline	Recommendation(s)
Practice Guidelines (2018)[20]	GERD in children. • Do not use massage therapy to treat infant GERD. • Use of currently available lifestyle interventions or complementary treatments such as prebiotics, probiotics, or herbal medications is not suggested to treat GERD. • Inform caregivers and children that excessive body weight is associated with an increased prevalence of GERD. • Provide patient/parental education and support as part of the treatment of GERD. <u>Pharmacological treatment</u> • Antacids/alginates are not suggested for chronic treatment of infants and children with GERD. • Proton pump inhibitors (PPIs) are recommended as first-line treatment of reflux-related erosive esophagitis in infants and children with GERD. • Histamine-2 receptor antagonists (H_2RAs) are suggested in the treatment of reflux related erosive esophagitis in infants and children if PPIs are not available or contraindicated. • Do not use H_2RA or PPI for the treatment of crying/distress in otherwise healthy infants. • Do not use H_2RA or PPI for the treatment of visible regurgitation in otherwise healthy infants. • A four to eight week course of H_2RAs or PPIs is recommended for treatment of typical symptoms (i.e., heartburn, retrosternal or epigastric pain) in children with GERD. • Do not use H_2RAs or PPIs in patients with extraesophageal symptoms (i.e., cough, wheezing, asthma), except in the presence of typical GERD symptoms and/or diagnostic testing suggestive of GERD. • Evaluation of treatment efficacy and exclusion of alternative causes of symptoms is recommended in infants and children not responding to four to eight weeks of optimal medical therapy for GERD. • Regular assessment of the ongoing need of long-term acid suppression therapy is recommended in infants and children with GERD • Consider the use of baclofen prior to surgery in children in whom other pharmacological treatments have failed. • Do not use domperidone in the treatment of GERD in infants and children. • Do not use metoclopramide in the treatment of GERD in infants and children. • Do not use any other prokinetics (i.e., erythromycin, bethanechol) as a first-line treatment in infants and children with GERD.
American Gastroenterological Association: **Medical Position Statement on the Management of Gastroesophageal Reflux Disease (2008)[21]**	• Antisecretory drugs are recommended for the treatment of patients with esophageal GERD syndromes (healing esophagitis and symptomatic relief). PPIs are more effective than H_2RAs, which are more effective than placebo. • Twice-daily PPI therapy is recommended for patients with an esophageal syndrome with an inadequate symptom response to once-daily PPI therapy. • A short course or as-needed use of antisecretory drugs is recommended in patients with a symptomatic esophageal syndrome without esophagitis when symptom control is the primary objective. For a short course of therapy, PPIs are more effective than H_2RAs, which are more effective than placebo. • Long-term use of PPIs is recommended for the treatment of patients with esophagitis once they have proven clinically effective. Long-term therapy should be titrated down to the lowest effective dose based on symptom control. • The data suggest that on-demand therapy is a reasonable strategy in patients with an esophageal GERD syndrome without esophagitis, where symptom control is the primary objective.
European *Helicobacter pylori*	<u>Treatment</u> • *H pylori* resistance rates to antibiotics are increasing in most parts of the world.

Clinical Guideline	Recommendation(s)
Study Group: **Management of *Helicobacter pylori* Infection–The Maastricht V/ Florence Consensus Report (2016)[22]**	• Proton pump inhibitor (PPI)-clarithromycin-containing triple therapy without prior susceptibility testing should be abandoned when the clarithromycin resistance rate in the region is more than 15%. • For any regimen, the eradication rate can be predicted if the cure rates are known for susceptible and resistant strains and the prevalence of resistance in the population. • For an individual patient a history of any prior use of one of the key antibiotics proposed will identify likely antibiotic resistance despite low resistance rates in the population. Susceptibility based results simultaneously provide results that are both population- and individual-based. • In areas of high (>15%) clarithromycin resistance, bismuth quadruple or non-bismuth quadruple, concomitant (PPI, amoxicillin, clarithromycin and a nitroimidazole) therapies are recommended. • In areas of high dual clarithromycin and metronidazole resistance, bismuth quadruple therapy (BQT) is the recommended first-line treatment. • The treatment duration of bismuth quadruple therapy should be extended to 14 days, unless 10 day therapies are proven effective locally. • Clarithromycin resistance undermines the efficacy of triple and sequential therapy, metronidazole resistance undermines the efficacy of sequential therapy, and dual clarithromycin and metronidazole resistance undermines the efficacy of sequential, hybrid and concomitant therapy. • Currently, concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) should be the preferred non-bismuth quadruple therapy, as it has shown to be the most effective to overcome antibiotic resistance. • The recommended treatment duration of non-bismuth quadruple therapy (concomitant) is 14 days, unless 10 day therapies are proven effective locally. • In areas of low clarithromycin resistance, triple therapy is recommended as first-line empirical treatment. Bismuth-containing quadruple therapy is an alternative. • The use of high dose PPI twice daily increases the efficacy of triple therapy. Esomeprazole and rabeprazole may be preferred in Europe and North America where the prevalence of PPI extensive metabolizers is high. • The treatment duration of PPI-clarithromycin based triple therapy should be extended to 14 days, unless shorter therapies are proven effective locally. • After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing triple or quadruple therapy may be recommended. In cases of high quinolone resistance, the combination of bismuth with other antibiotics, or rifabutin, may be an option. • After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy are recommended as a second-line treatment. • After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy are recommended. • After failure of second-line treatment, culture with susceptibility testing or molecular determination of genotype resistance is recommended in order to guide treatment. • After failure of the first-line treatment (clarithromycin based) and second-line treatment (with bismuth-containing quadruple regimen), it is recommended to use the fluoroquinolone-containing regimen. In regions with a known high fluoroquinolones resistance, a combination of bismuth with different antibiotics or a rifabutin-containing rescue therapy should be considered. • After failure of the first-line treatment (triple or non-bismuth quadruple) and second-line treatment (fluoroquinolone-containing therapy), it is recommended to use the bismuth-based quadruple therapy.

Clinical Guideline	Recommendation(s)
	• After failure of first-line treatment with bismuth quadruple and second-line treatment (fluoroquinolone-containing therapy), it is recommended to use a clarithromycin-based triple or quadruple therapy. A combination of bismuth with different antibiotics may be another option. • In patients with penicillin allergy, in areas of low clarithromycin resistance, for a first-line treatment, a PPI-clarithromycin-metronidazole combination may be prescribed, and in areas of high clarithromycin resistance, BQT should be preferred. • Rescue regimen: A fluoroquinolone-containing regimen may represent an empirical second-line rescue option in the presence of penicillin allergy.
North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition/ European Society for Pediatric Gastroenterology, Hepatology, and Nutrition: **Joint Guidelines for the Management of *Helicobacter pylori* in Children and Adolescents (2016)[23]**	• The primary goal of clinical investigation of gastrointestinal symptoms is to determine the underlying cause of the symptoms and not solely the presence of *H pylori* infection. • During endoscopy, additional biopsies for rapid urease test and culture should only be taken if treatment is likely to be offered if infection is confirmed. • If *H pylori* infection is an incidental finding at endoscopy, treatment may be considered after careful discussion of the risks and benefits of *H pylori* treatment with the patient/parents. • A "test and treat" strategy is not recommended for *H pylori* infection in children. • Testing for *H pylori* is recommended in children with gastric or duodenal ulcers. If *H pylori* infection is identified then treatment should be advised and eradication be confirmed. • Diagnostic testing for *H pylori* infection is not recommended in children with functional abdominal pain or as part of the initial investigation in children with iron deficiency anemia. In children with refractory iron deficiency anemia in which other causes have been ruled out, testing for *H pylori* during upper endoscopy may be considered. • Noninvasive diagnostic testing for *H pylori* infection may be considered when investigating causes of chronic immune thrombocytopenic purpura. • Diagnostic testing for *H pylori* infection is not recommended when investigating causes of short stature. • It is recommended that clinicians wait at least two weeks after stopping PPI therapy and four weeks after stopping antibiotics before testing for *H pylori*. • The diagnosis of *H pylori* infection should be based on either (a) histopathology (*H pylori*–positive gastritis) plus at least one other positive biopsy-based test or positive culture. • Using antibody-based tests (IgG, IgA) for *H pylori* in serum, whole blood, urine, and saliva is not recommended in the clinical setting. • Antimicrobial sensitivity should be obtained for the infecting *H pylori* strain(s), and eradication therapy tailored accordingly. • The effectiveness of first-line therapy should be evaluated in national/regional centers. • The physician should explain to the patient/family the importance of adherence to the anti–*H pylori* therapy to enhance successful eradication. • First-line therapy for *H pylori* infection is as follows: o Susceptible to clarithromycin and metronidazole: Proton pump inhibitor (PPI) + amoxicillin + clarithromycin for 14 days with standard dose (or sequential therapy for 10 days) o Resistant to clarithromycin and susceptible to metronidazole: PPI + amoxicillin + metronidazole for 14 days, or bismuth-based o Resistant to metronidazole and susceptible to clarithromycin: PPI + amoxicillin + clarithromycin for 14 days, or bismuth-based o Resistant to clarithromycin and metronidazole: PPI + amoxicillin + metronidazole for 14 days with high dose for amoxicillin. Or bismuth-based

Clinical Guideline	Recommendation(s)
	○ Antimicrobial susceptibility unknown: high dose PPI + amoxicillin + metronidazole for 14 days, or bismuth-based • The outcome of anti–*H pylori* therapy should be assessed at least four weeks after completion of therapy using one of the following tests: (a) The 13C-urea breath (13C-UBT) test or (b) a 2-step monoclonal stool antigen test. • When *H pylori* treatment fails, rescue therapy should be individualized considering antibiotic susceptibility, the age of the child, and available antimicrobial options.
American College of Gastroenterology: **Treatment of *Helicobacter pylori* Infection (2017)**[24]	<u>Evidence-based first-line treatment strategies for providers in North America</u> • Patients should be asked about any previous antibiotic exposure(s) and this information should be taken into consideration when choosing an *H pylori* treatment regimen. • Clarithromycin triple therapy consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days remains a recommended treatment in regions where *H pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason. • Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option. Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin. • Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option. • Sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, clarithromycin, and a nitroimidazole for five to seven days is a suggested first-line treatment option. • Hybrid therapy consisting of a PPI and amoxicillin for seven days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for seven days is a suggested first-line treatment option. • Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10 to 14 days is a suggested first-line treatment option. • Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, fluoroquinolone, and nitroimidazole for five to seven days is a suggested first-line treatment option. <u>Options for salvage therapy when first-line therapy fails</u> • In patients with persistent *H pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient. • Bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options if a patient received a first-line treatment containing clarithromycin. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics. • Clarithromycin or levofloxacin-containing salvage regimens are the preferred treatment options, if a patient received first-line bismuth quadruple therapy. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics. • The following regimens can be considered for use as salvage treatment: ○ Bismuth quadruple therapy for 14 days. ○ Levofloxacin triple regimen for 14 days. ○ Concomitant therapy for 10 to 14 days. ○ Clarithromycin triple therapy should be avoided as a salvage regimen. ○ Rifabutin triple regimen consisting of a PPI, amoxicillin, and rifabutin for 10 days is a suggested salvage regimen. ○ High-dose dual therapy consisting of a PPI and amoxicillin for 14 days is a suggested salvage regimen.
American	• Patients with multiple risk factors associated with esophageal adenocarcinoma

Clinical Guideline	Recommendation(s)
Gastroenterological Association: **Medical Position Statement on the Management of Barrett's Esophagus (2011)**[25]	(age 50 years or older, male sex, white race, chronic GERD, hiatal hernia, elevated body mass index, and intra-abdominal distribution of body fat) should be screened for Barrett's esophagus. • Endoscopic surveillance should be performed in patients with Barrett's esophagus at the following intervals: no dysplasia: three to five years, low-grade dysplasia: six to 12 months, high-grade dysplasia in the absence of eradication therapy: three months. • For patients with Barrett's esophagus who are undergoing surveillance, an endoscopic evaluation should be performed using white light endoscopy and four-quadrant biopsy specimens be taken every 2 cm. Four-quadrant biopsy specimens should be obtained every 1 cm in patients with known or suspected dysplasia. • Specific biopsy specimens of any mucosal irregularities should be submitted separately to the pathologist. • Requiring chromoendoscopy or advanced imaging techniques for the routine surveillance of patients with Barrett's esophagus is not needed. • Attempts to eliminate esophageal acid exposure (PPIs in doses greater than once daily, esophageal pH monitoring to titrate PPI dosing, or antireflux surgery) for the prevention of esophageal adenocarcinoma is not recommended. • Patients should be screened to identify cardiovascular risk factors for which aspirin therapy is indicated. Aspirin solely to prevent esophageal adenocarcinoma in the absence of other indications is not recommended. • Endoscopic eradication therapy with radiofrequency ablation, photodynamic therapy or endoscopic mucosal resection is recommended in patients with confirmed high-grade dysplasia within Barrett's esophagus rather than surveillance. • Endoscopic mucosal resection is recommended for patients who have dysplasia in Barrett's esophagus associated with a visible mucosal irregularity to determine the T stage of the neoplasia.
American College of Gastroenterology: **Diagnosis and Management of Barrett's Esophagus (2022)**[26]	• At least once-a-day PPI therapy is suggested in patients with Barrett's esophagus without allergy or other contraindication to PPI use. • No recommendation could be made on combination therapy with ASA and PPI in patients with Barrett's esophagus to reduce the risk of progression to high-grade dysplasia/esophageal adenocarcinoma. • The use of antireflux surgery as an antineoplastic measure in patients with Barrett's esophagus is not suggested.
American College of Gastroenterology: **Guidelines for the Management of Dyspepsia (2017)**[27]	• Dyspepsia patients ≥60 years of age are suggested to have an endoscopy to exclude upper gastrointestinal neoplasia. • Endoscopy to investigate alarm features for dyspepsia is not suggested for patients under the age of 60 years to exclude upper GI neoplasia. • Dyspepsia patients <60 years of age should have a non-invasive test for *H pylori*, and therapy for *H pylori* infection if positive. • Dyspepsia patients <60 years of age should have empirical PPI therapy if they are *H pylori*-negative or who remain symptomatic after *H pylori* eradication therapy. • Dyspepsia patients <60 years of age not responding to PPI or *H pylori* eradication therapy should be offered prokinetic therapy. • Dyspepsia patients <60 years of age not responding to PPI or *H pylori* eradication therapy should be offered tricyclic antidepressant therapy. • Functional dyspepsia patients that are *H pylori* positive should be prescribed therapy to treat the infection. • Functional dyspepsia patients who are *H pylori*-negative or who remain symptomatic despite eradication of the infection should be treated with PPI therapy. • Functional dyspepsia patients not responding to PPI or *H pylori* eradication therapy (if appropriate) should be offered tricyclic antidepressant therapy.

Clinical Guideline	Recommendation(s)
	• Functional dyspepsia patients not responding to PPI, *H pylori* eradication therapy or tricyclic antidepressant therapy should be offered prokinetic therapy. • PPI, tricyclic antidepressant, and prokinetic therapy (in that order) is recommended in those that fail therapy or are *H pylori* negative • Functional dyspepsia patients not responding to drug therapy should be offered psychological therapies. • The routine use of complementary and alternative medicines for functional dyspepsia is not recommended. • Routine motility studies are not recommended for patients with functional dyspepsia. • Motility studies are suggested for selected patients with functional dyspepsia where gastroparesis is strongly suspected.
American Gastroenterological Association: **Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review (2022)**[28]	• All patients taking a PPI should have a regular review of the ongoing indications for use and documentation of that indication. This review should be the responsibility of the patient's primary care provider. • All patients without a definitive indication for chronic PPI should be considered for trial of de-prescribing. • Most patients with an indication for chronic PPI use who take twice-daily dosing should be considered for step down to once-daily PPI. • Patients with complicated gastroesophageal reflux disease, such as those with a history of severe erosive esophagitis, esophageal ulcer, or peptic stricture, should generally not be considered for PPI discontinuation. • Patients with known Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis should generally not be considered for a trial of de-prescribing. • PPI users should be assessed for upper gastrointestinal bleeding risk using an evidence-based strategy before de-prescribing. • Patients at high risk for upper gastrointestinal bleeding should not be considered for PPI de-prescribing. • Patients who discontinue long-term PPI therapy should be advised that they may develop transient upper gastrointestinal symptoms due to rebound acid hypersecretion. • When de-prescribing PPIs, either dose tapering or abrupt discontinuation can be considered. • The decision to discontinue PPIs should be based solely on the lack of an indication for PPI use, and not because of concern for PPI-associated adverse events (PAAEs). The presence of a PAAE or a history of a PAAE in a current PPI user is not an independent indication for PPI withdrawal. Similarly, the presence of underlying risk factors for the development of an adverse event associated with PPI use should also not be an independent indication for PPI withdrawal.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the proton-pump inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Proton-Pump Inhibitors[1-12]

Indication	Single Entity Agents						Combination Products			
	Dexlanso-prazole	Esome-prazole	Lanso-prazole	Ome-prazole	Panto-prazole	Rabe-prazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole and Sodium Bicarbonate	Lansoprazole and Amoxicillin and Clarithromycin	Omeprazole and Amoxicillin and Clarithromycin
Duodenal Ulcer										
Treatment of active duodenal ulcer			✔	✔		✔		✔		
Maintain healing of duodenal ulcers			✔							
Gastric Ulcer										
Reducing the risk of NSAID-associated gastric ulcers in patients with a history of a gastric ulcer who require the use of an NSAID		✔ §	✔							
Treatment of NSAID-associated gastric ulcer in patients who continue NSAID use			✔							
Treatment of active benign gastric ulcer			✔	✔				✔		
Gastroesophageal Reflux Disease										
Healing of erosive esophagitis	✔	✔	✔	✔	✔	✔		✔		
Maintenance of healed erosive esophagitis	✔	✔ §	✔	✔	✔ §	✔		✔		
Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease	✔	✔ §	✔	✔	✔ ‖	✔		✔		
***Helicobacter pylori* Infection**										
In combination with amoxicillin and clarithromycin for the treatment of patients with *H pylori* infection and duodenal ulcer disease to eradicate *H pylori*		✔ §	✔	✔		✔				
In combination with amoxicillin as dual therapy for the treatment of patients with *H pylori* infection and duodenal ulcer disease to eradicate *H*			✔							

Indication	Single Entity Agents						Combination Products			
	Dexlanso-prazole	Esome-prazole	Lanso-prazole	Ome-prazole	Panto-prazole	Rabe-prazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole and Sodium Bicarbonate	Lansoprazole and Amoxicillin and Clarithromycin	Omeprazole and Amoxicillin and Clarithromycin
pylori who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected										
In combination with clarithromycin for the treatment of patients with *H pylori* infection and duodenal ulcer disease to eradicate *H pylori*				✔						
Treatment of patients with *H pylori* infection and duodenal ulcer disease to eradicate *H pylori*									✔	✔
Treatment of *H pylori* infection in adults							✔			
Pathological Hypersecretory Conditions										
Long-term treatment of pathological hypersecretory conditions		✔ §	✔	✔	✔	✔				
Other										
Risk reduction of upper gastrointestinal bleeding in critically ill patients								✔		

NSAID=nonsteroidal anti-inflammatory drug
§Oral formulation only.
‖ Intravenous formulation only.

IV. Pharmacokinetics

The pharmacokinetic parameters of the proton-pump inhibitors (PPIs) are listed in Table 4. No relevant clinical information specific to the combination products for the treatment of *H Pylori* was identified. These products contain PPIs and are packaged with separate antibiotics. Pharmacokinetic properties of these products would be in line with the properties of their individuals components listed below. Reported pharmacokinetic properties of the fixed-dose combination of omeprazole and sodium bicarbonate are also expected to be similar to omeprazole as listed below.

Table 4. Pharmacokinetic Parameters of the Proton-Pump Inhibitors[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Dexlansoprazole	Not reported	96 to 98	Liver	Renal (50)	1 to 2
Esomeprazole	90	97	Liver	Renal (80)	1.0 to 1.5
Lansoprazole	80	97	Liver	Renal (14 to 33)	1.3 to 1.5
Omeprazole	30 to 40	95	Liver	Renal (77)	0.5 to 1.0
Pantoprazole	77	98	Liver	Renal (71 to 82)	1
Rabeprazole	52	95 to 98	Liver	Renal (90)	1 to 2

V. Drug Interactions

Major drug interactions with the proton-pump inhibitors are listed in Table 5. The drug interactions for the combination products should refer to the prescribing information of individual components.

Table 5. Major Drug Interactions with the Proton-Pump Inhibitors[2]

Generic Name(s)	Interaction	Mechanism
Proton-pump inhibitors (esomeprazole, lansoprazole, omeprazole, rabeprazole)	Clopidogrel	Use of proton-pump inhibitors may lead to reduced ability of clopidogrel to inhibit platelet aggregation and increase the risk of subsequent cardiovascular events. Inhibition of CYP2C19 isoenzymes by proton-pump inhibitors may decrease the activation of clopidogrel. Competitive inhibition CYP2C19 metabolism by proton-pump inhibitors and clopidogrel may be involved. Other mechanisms may exist.
Proton-pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)	Protease inhibitors	Plasma concentrations and pharmacologic effects of selected protease inhibitors may be decreased by proton-pump inhibitors. Reduction in therapeutic efficacy of these protease inhibitors may occur. In contrast, plasma concentrations of saquinavir may be increased by proton-pump inhibitors. Induction of cytochrome P450 isoenzymes 1A2 and 3A by proton-pump inhibitors may increase the metabolic elimination of selected protease inhibitors (atazanavir, nelfinavir, indinavir). Additionally, by increasing gastric pH, proton-pump inhibitors may decrease the solubility and serum concentrations of some protease inhibitors. The mechanism responsible for increased saquinavir concentrations when coadministered with proton-pump inhibitors is unknown, but may be related to inhibition of transport proteins.
Proton-pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)	Azole Antifungals	Proton-pump inhibitors may reduce the bioavailability of certain azole antifungals, reducing plasma levels and antifungal activity. Concurrent use should be avoided. If concurrent use is necessary, administer the oral azole antifungal with an acidic beverage.

Generic Name(s)	Interaction	Mechanism
Proton-pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)	Drugs dependent on gastric pH for absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate, ketoconazole/ itraconazole)	Proton pump inhibitors can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
Proton-pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)	Cilostazol	Plasma concentrations and pharmacologic effects of cilostazol may be increased by proton-pump inhibitors. Inhibition of cytochrome P450 2C19 isoenzymes by proton-pump inhibitors may decrease the metabolic elimination of cilostazol.
Proton pump inhibitors (esomeprazole, and omeprazole)	Tacrolimus	Concomitant administration of certain proton pump inhibitors and tacrolimus may increase tacrolimus levels in patients who are poor metabolizers of CYP 2C19.
Proton pump inhibitors (esomeprazole)	Thiopental	Concurrent use of esomeprazole and thiopental may result in increased volume of distribution and prolonged half life of thiopental.

VI. Adverse Drug Events

The most common adverse drug events reported with the proton-pump inhibitors (PPIs) are listed in Table 6. No relevant clinical information specific to the combination products for the treatment of *H Pylori* was identified. These products contain PPIs and are packaged with separate antibiotics. Therefore, adverse events of these products would be in line with the adverse events of their individual components. However, adverse events for omeprazole and sodium bicarbonate are listed as this agent is a fixed-dose product in which each unit contains both ingredients. Adverse events for omeprazole, amoxicillin and rifabutin are also listed as this agent is a fixed-dose product in which each unit contains the ingredients; however, the package insert notes that adverse reactions from the labeling of the individual components should also be considered.

Table 6. Adverse Drug Events (%) Reported with the Proton-Pump Inhibitors[1-12]

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
Cardiovascular								
Angina	<2	>1	<1	<1	<1	<1	-	<1
Arrhythmia	<2	-	<1	-	<1	<1	-	-
Atrial fibrillation	-	-	-	-	<1	-	-	6
Bradycardia	<2	-	<1	<1	-	<1	-	<1
Flushing	-	<1	-	-	-	-	-	-
Heart failure	-	-	-	-	<1	-	-	-
Hypertension	<2	3	<1	<1	<1	<1	-	8
Hypotension	-	-	<1	-	<1	-	-	10
Myocardial infarction	<2	-	<1	-	<1	<1	-	-
Palpitation	<2	-	<1	<1	<1	<1	-	<1
Sudden death	-	-	-	-	-	<1	-	-
Syncope	-	-	<1	-	<1	<1	-	-
Tachycardia	<2	<1	<1	<1	<1	<1	-	5
Central Nervous System								
Abnormal dreams	<2	-	<1	<1	<1	-	-	<1
Aggression	-	<1	-	<1	-	-	-	<1
Agitation	-	<1	<1	<1	-	<1	-	<1
Amnesia	-	-	<1	-	-	-	-	-
Anxiety	<2	2	<1	<1	≥1	-	-	3
Apathy	-	<1	-	<1	-	-	-	<1
Asthenia	-	<1	-	1.1	-	-	-	-
Cerebrovascular accident	-	-	<1	-	-	-	-	-
Cerebral hemorrhage	-	-	-	-	-	<1	-	-
Cerebral infarction	-	-	<1	-	-	-	-	-

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
Chills	-	-	<1	-	<1	-	-	-
Confusion	-	<1	<1	<1	<1	-	-	<1
Dementia	-	-	<1	-	-	-	-	-
Depersonalization	-	-	<1	-	-	-	-	-
Depression	<2	<1	<1	<1	<1	<1	-	<1
Dizziness	<2	<1	3	<2	≥1	<1	-	-
Fatigue	-	<1	-	<1	-	-	-	<1
Hallucinations	<2	<1	<1	<1	<1	-	-	<1
Headache	<2	5.5	3 to 7	7	2 to 9	2 to 5	8 to 16	-
Hypertonia	-	<1	-	-	-	-	-	-
Insomnia	<2	2	<1	<1	<1	<1	-	<1
Malaise	-	<1	<1	<1	-	<1	-	<1
Memory impairment	<2	-	-	-	-	-	-	-
Migraine	<2	<1	<1	-	≥1	<1	-	-
Nervousness	-	<1	<1	<1	<1	<1	-	<1
Paresthesia	<2	<1	<1	<1	<1	<1	-	<1
Psychomotor hyperactivity	<2	-	-	-	-	-	-	-
Pyrexia	-	2	-	-	-	-	-	20
Seizure	<2	-	<1	-	<1	<1	-	-
Shock	-	-	<1	-	-	-	-	-
Somnolence	-	<1	<1	<1	<1	<1	-	<1
Speech disorder	-	-	<1	-	-	-	-	-
Stevens-Johnson syndrome	-	-	-	<1	<1	<1	-	<1
Tremor	<2	<1	<1	<1	<1	<1	-	<1
Vertigo	<2	<1	<1	<1	<1	<1	-	<1
Dermatological								
Acne	<2	<1	-	-	<1	-	-	-
Alopecia	-	<1	<1	<1	<1	<1	-	<1
Angioedema	-	<1	-	-	-	-	-	-
Cellulitis	-	-	-	-	-	<1	-	-
Dermatitis	<2	<1	-	-	-	<1	-	-
Diaphoresis	-	-	<1	-	<1	<1	-	-
Dry skin	-	-	<1	<1	-	-	-	<1

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
Eczema	-	-	-	-	<1	-	-	-
Erythema	<2	-	-	-	-	-	-	-
Erythema multiforme	-	<1	<1	<1	<1	<1	-	<1
Hyperhidrosis	-	<1	-	<1	-	-	-	<1
Photosensitivity	-	<1	<1	<1	<1	<1	-	<1
Pruritus	<2	<1	<1	<1	<1	<1	-	<1
Rash	<2	<1	<1	1.5	<2	<1	3 to 5	6
Skin carcinoma	-	-	<1	-	-	-	-	-
Skin lesion	<2	-	-	-	-	-	-	-
Stevens-Johnson syndrome	<2	<1	<1	-	✔	-	-	✔
Sunburn	<2	-	-	-	-	-	-	-
Sweating	-	<1	-	-	-	-	-	-
Toxic epidermal necrolysis	<2	<1	<1	<1	<1	<1	-	<1
Urticaria	<2	<1	<1	<1	<1	<1	-	<1
Endocrine and Metabolic								
Breast enlargement	-	-	<1	-	-	<1	-	-
Breast pain	-	-	<1	-	-	-	-	-
Breast tenderness	-	-	<1	-	-	-	-	-
Diabetes mellitus	<2	-	<1	-	<1	<1	-	-
Dysmenorrhea	<2	<1	<1	-	<1	<1	-	-
Goiter	<2	<1	<1	-	<1	-	-	-
Gout	-	-	<1	-	<1	<1	-	-
Gynecomastia	-	<1	<1	<1	-	<1	-	<1
Hot flashes	<2	-	-	-	-	-	-	-
Hyperparathyroidism	-	<1	-	-	-	-	-	-
Hypothyroidism	<2	-	<1	-	-	<1	-	-
Hyperthyroidism	-	-	-	-	-	<1	-	-
Impotence	-	-	-	-	<1	<1	-	-
Libido decreased	-	-	-	-	<1	-	-	-
Menorrhagia	<2	-	<1	-	-	<1	-	-
Metrorrhagia	-	-	-	-	-	<1	-	-
Testicular pain	-	-	-	<1	-	-	-	<1

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
Weight decrease	-	<1	<1	-	<1	<1	-	✔
Weight increase	<2	<1	<1	<1	<1	<1	-	<1
Gastrointestinal								
Abdomen enlarged	-	<1	<1	<1	-	<1	-	<1
Abdominal pain	4	6	2.8	5	1 to 4	<1	4	-
Abnormal taste	<2	<1	<1	<1	<1	<1	-	<1
Anorexia	-	<1	<1	<1	<1	<1	-	<1
Appetite increased	-	-	<1	-	<1	-	-	-
Barrett's esophagus	<2	-	-	-	-	-	-	-
Breath odor	<2	-	<1	-	-	-	-	-
Cholecystitis	<2	-	-	-	<1	<1	-	-
Cholelithiasis	<2	-	<1	-	<1	<1	-	-
Colitis	<2	-	<1	-	<1	<1	-	-
Colonic polyp	<2	-	-	-	-	-	-	-
Constipation	<2	2	1	1	≥1	2	-	5
Diarrhea	5	4	4	3	2 to 6	3	10 to 14	4
Duodenitis	<2	-	-	-	<1	<1	-	-
Dyspepsia	<2	<1	<1	-	≥1	<1	1 to 2	-
Dysphagia	<2	<1	<1	-	<1	<1	-	-
Dysphonia	<2	-	-	-	-	-	-	-
Enteritis	<2	-	<1	-	-	-	-	-
Epigastric pain	-	<1	-	-	-	-	-	-
Eructation	<2	-	<1	-	-	-	-	-
Esophageal stenosis	-	-	<1	-	-	-	-	-
Esophageal ulcer	-	-	<1	-	-	-	-	-
Esophageal varices	-	<1	-	-	-	-	-	-
Esophagitis	<2	-	<1	-	<1	<1	-	-
Flatulence	1 to 3	7	<1	3	2 to 4	3	-	-
Gastric polyp	<2	-	-	<1	-	-	-	<1
Gastric retention	-	<1	-	-	-	-	-	-
Gastritis	<2	-	<1	<1	<1	<1	-	<1
Gastroenteritis	<2	-	<1	-	-	<1	-	-
Gastrointestinal carcinoma	-	-	-	-	<1	-	-	-
Gastrointestinal dysplasia	-	<1	-	-	-	-	-	-

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
Gastrointestinal hemorrhage	-	-	<1	-	<1	<1	-	-
Gastrointestinal hypermotility	<2	-	-	-	-	-	-	-
Gastrointestinal perforation	<2	-	-	-	-	-	-	-
Gastrointestinal ulceration	<2	-	-	-	-	-	-	-
Hematemesis	<2	-	<1	-	<1	-	-	-
Hematochezia	<2	-	-	-	-	-	-	-
Hemorrhoids	<2	-	-	-	-	-	-	-
Hiccups	<2	-	-	-	<1	-	-	-
Impaired gastric emptying	<2	-	-	-	-	-	-	-
Irritable bowel syndrome	<2	-	-	-	-	-	-	-
Melena	-	-	<1	-	<1	<1	-	-
Nausea	3	6	1.3	4	2	2	4 to 5	✔
Pancreatitis	<1	<1	<1	<1	<1	<1	-	<1
Rectal bleeding	<2	-	<1	-	<1	<1	-	-
Stomatitis	-	<1	<1	<1	<1	<1	-	<1
Ulcerative colitis	-	-	<1	-	-	<1	-	-
Vomiting	1 to 2	<3	<1	3	2	<1	2	-
Xerostomia	<2	<1	<1	<1	<1	<1	-	<1
Genitourinary								
Albuminuria	-	<1	<1	-	<1	<1	-	-
Dyspareunia	<2	-	-	-	-	-	-	-
Dysuria	<2	<1	<1	-	<1	<1	-	-
Glycosuria	-	<1	<1	<1	<1	-	-	<1
Epididymitis	-	-	-	-	<1	-	-	-
Hematuria	-	<1	<1	<1	<1	<1	-	<1
Impotence	-	<1	<1	-	-	-	-	-
Interstitial nephritis	-	<1	<1	<1	<1	<1	-	<1
Kidney calculus	-	-	<1	-	<1	<1	-	-
Libido changes	<2	-	<1	-	-	-	-	-
Polyuria	-	<1	<1	-	-	<1	-	-

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
Proteinuria	-	<1	-	<1	-	-	-	<1
Pyelonephritis	-	-	-	-	<1	-	-	-
Pyuria	-	-	-	<1	-	-	-	<1
Urethral pain	-	-	<1	-	<1	-	-	-
Urinary frequency/urgency	-	-	<1	<1	-	-	-	<1
Urinary retention	-	-	<1	-	-	-	-	-
Urinary tract infection	-	4	<1	<1	≥1	-	-	2
Urine discoloration	-	-	-	-	-	-	13	-
Vaginitis	-	<1	<1	-	<1	-	-	-
Vulvovaginal candidiasis	-	-	-	-	-	-	2	-
Hematologic								
Agranulocytosis	-	<1	<1	<1	-	<1	-	<1
Anemia	<2	>1	<1	<1	-	<1	-	8
Eosinophilia	-	-	<1	-	<1	-	-	-
Leukocytosis	-	<1	-	<1	<1	<1	-	<1
Leukopenia	-	<1	<1	<1	<1	<1	-	<1
Neutropenia	<2	-	<1	<1	-	<1	-	<1
Pancytopenia	-	<1	<1	<1	<1	<1	-	<1
Thrombocythemia	<2	-	-	-	-	-	-	-
Thrombocytopenia	<2	<1	<1	<1	<1	<1	-	10
Hepatic								
Cirrhosis	-	-	-	-	-	<1	-	-
Hepatic encephalopathy	-	<1	-	<1	<1	<1	-	<1
Hepatic failure	-	<1	-	<1	<1	-	-	<1
Hepatic necrosis	-	-	-	<1	-	-	-	<1
Hepatitis	-	<1	-	<1	<1	<1	-	<1
Hepatomegaly	<2	-	-	-	-	-	-	-
Hepatotoxicity	-	-	<1	-	-	-	-	-
Jaundice	-	<1	-	<1	<1	<1	-	<1
Laboratory Test Abnormalities								
Alanine aminotransferase increased	<2	<1	<1	<1	≥1	<1	-	<1
Alkaline phosphatase	<2	<1	<1	<1	<1	<1	-	<1

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
increased								
An aspartate aminotransferase increased	<2	<1	<1	<1	<1	<1	-	2
Bilirubin increased/decreased	<2	<1	<1	<1	<1	<1	-	<1
Creatine phosphokinase increased	-	-	-	-	<1	<1	-	-
Creatinine increased	<2	<1	<1	<1	<1	-	-	<1
Hyperglycemia	<2	-	<1	-	-	-		11
Hyperkalemia	<2	-	-	-	-	-	-	-
Hyperlipidemia	<2	-	<1	-	-	<1	-	-
Hyperuricemia	-	<1	-	-	<1	-	-	-
Hypocalcemia	<2	-	-	-	-	-	-	6
Hypoglycemia	-	-	<1	<1	-	<1	-	<1
Hypokalemia	<2	<1	-	-	-	<1	-	12
Hypomagnesemia	✔	✔	✔	✔	✔	✔	-	✔
Hyponatremia	-	<1	-	<1	<1	<1	-	4
Liver function test abnormalities	-	<1	-	-	2	-	-	-
Thyroid stimulating hormone increased	-	<1	-	-	-	-	-	-
Vitamin B_{12} deficiency	-	<1	-	-	-	-	-	-
Musculoskeletal								
Arthralgia	-	3	<1	-	≥1	<1	-	-
Arthritis	<2	<1	<1	-	-	<1	-	-
Asthenia	-	-	-	-	≥1	-	-	-
Back pain	-	>1	-	1	≥1	-	-	-
Dysarthria	-	-	-	-	<1	-	-	-
Fibromyalgia	-	<1	-	-	-	-	-	-
Hypertonia	-	<1	-	-	-	-	-	-
Muscular weakness	-	<1	-	<1	-	-	-	<1
Myalgia	<2	-	<1	<1	<1	<1	-	<1
Myositis	-	-	<1	-	-	-	-	-
Rhabdomyolysis	-	-	-	-	<1	<1	-	-

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
Respiratory								
Asthma	<2	<1	<1	-	<1	<1	-	-
Bronchitis	<2	4	<1	-	≥1	-	-	-
Bronchospasm	-	<1	-	<1	-	-	-	<1
Cough	<2	>1	<1	1	≥1	-	-	-
Dyspnea	<2	<1	<1	-	≥1	<1	-	-
Hemoptysis	-	-	<1	-	-	-	-	-
Hyperventilation	<2	-	-	-	-	-	-	-
Hypoxia	-	-	-	-	-	<1	-	-
Lung fibrosis	-	-	<1	-	-	-	-	-
Nasopharyngitis	<2	-	-	-	-	-	-	-
Pharyngeal pain	-	-	-	<1	-	-	-	<1
Pharyngitis	<2	<1	<1	-	>1	3	-	-
Pharyngolaryngeal pain	-	<1	-	-	-	-	≤4	-
Pneumonia	-	-	<1	-	<1	-	-	11
Rhinitis	-	>1	<1	-	-	-	-	-
Rhinorrhea	-	<1	-	-	-	-	-	-
Sinusitis	<2	4	<1	-	≥1	-	-	-
Upper respiratory tract infection	2 to 3	-	<1	2	≥1	-	-	-
Special Senses								
Amblyopia	-	-	<1	-	-	<1	-	-
Blepharitis	-	-	<1	-	-	-	-	-
Blurred vision	<2	<1	<1	<1	<1	-	-	<1
Cataract	-	-	<1	-	<1	<1	-	-
Conjunctivitis	-	<1	<1	-	-	-	-	-
Deafness	-	-	<1	-	<1	<1	-	-
Diplopia	-	-	<1	<1	<1	<1	-	<1
Dry eyes	-	-	<1	-	-	-	-	-
Ear pain	<2	-	-	-	-	-	-	-
Eye irritation	<2	-	-	-	-	-	-	-
Eye swelling	<2	-	-	-	-	-	-	-
Glaucoma	-	-	<1	-	<1	<1	-	-
Ocular irritation	-	-	-	<1	-	-	-	<1
Ocular pain	-	<1	-	-	-	-	-	4

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
Optic atrophy	-	-	-	<1	-	-	-	<1
Optic neuropathy	-	-	-	<1	<1	-	-	<1
Parosmia	-	-	<1	-	-	-	-	-
Ptosis	-	-	<1	-	-	-	-	-
Retinal degeneration	-	-	<1	-	-	-	-	-
Tinnitus	<2	<1	<1	<1	<1	-	-	<1
Vision changes	-	-	<1	-	<1	<1	-	-
Other								
Allergic reaction	-	-	<1	<1	<1	<1	-	<1
Anaphylaxis	<2	<1	<1	<1	<1	<1	-	<1
Angioedema	-	<1	-	<1	<1	<1	-	<1
Bursitis	-	-	-	-	<1	-	-	-
Candidiasis	-	<1	<1	<1	-	-	-	<1
Carcinoid tumor of the stomach	-	<1	-	-	-	-	-	-
Carcinoma	-	-	<1	-	-	-	-	-
Cervical lymphadenopathy	-	<1	-	-	-	-	-	-
Dehydration	-	<1	<1	-	<1	-	-	-
Edema	<2	<1	<1	<1	<1	<1	-	<1
Epistaxis	-	<1	<1	<1	<1	<1	-	<1
Fever	<2	-	<1	<1	<1	<1	-	<1
Flu-like syndrome	-	1	<1	-	≥1	-	-	-
Fracture	✔	✔	✔	✔	✔	✔	-	✔
Hypersensitivity	<2	-	-	<1	-	-	-	<1
Hypoesthesia	-	<1	<1	-	-	-	-	-
Infection	<2	-	<1	-	>1	2	-	-
Inflammation	<2	-	-	-	-	-	-	-
Joint sprains/pain	<2	-	<1	<1	-	-	-	<1
Leukocytoclastic vasculitis	<2	-	-	-	-	-	-	-
Lymphadenopathy	<2	-	<1	-	-	-	-	-
Otitis externa	-	-	-	-	<1	-	-	-
Otitis media	-	<1	-	-	-	-	-	-
Pain	<2	<1	<1	<1	<1	<1	-	<1

Adverse Events	Single Entity Agents						Combination Products	
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole, Amoxicillin and Rifabutin	Omeprazole/ Sodium Bicarbonate
Sepsis	-	-	-	-	-	-	-	5
Weakness	<2	-	<1	-	-	-	-	-

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the proton-pump inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Proton-Pump Inhibitors[1-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Dexlansoprazole	Erosive esophagitis: Capsule (DR): treatment, 60 mg once daily for up to eight weeks; maintenance, 30 mg once daily (controlled studies did not extend beyond six months in adults and 16 weeks in patients 12 to 17 years of age) Gastroesophageal reflux disease: Capsule (DR): 30 mg once daily for four weeks	Safety and efficacy in children <12 years of age have not been established.	Capsule (DR): 30 mg 60 mg
Esomeprazole	Erosive esophagitis: Capsule, powder for suspension: treatment, 20 to 40 mg once daily for four to eight weeks; maintenance, 20 mg once daily Injection: treatment, 20 to 40 mg once daily for up to 10 days; maintenance, 20 mg once daily Gastroesophageal reflux disease: Capsule, powder for suspension: 20 mg once daily for four weeks; an additional four weeks may be considered if symptoms do not completely resolve Injection: 20 to 40 mg once daily for four weeks; an additional four weeks may be considered if symptoms do not completely resolve *H pylori* eradication: Capsule, powder for suspension: triple therapy: 40 mg once daily for 10 days (with amoxicillin 1,000 mg and clarithromycin 500 mg twice daily) NSAID-associated gastric ulcer: Capsule, powder for suspension: 20 mg or 40 mg once daily for up to six months Pathological hypersecretory conditions: Capsule, powder for suspension: 40 mg twice daily (individual dose; doses up to 240 mg have been administered)	Erosive esophagitis: Capsule (DR), powder for suspension (DR): >1 month to one year of age, 3 to 5 kg, 2.5 mg once daily for six weeks; 5 to 7.5 kg, 5 mg once daily for six weeks; 7.5 to 12 kg, 10 mg once daily for six weeks; one to 11 years of age, <20 kg: 10 mg once daily for eight weeks; ≥20 kg, 10 or 20 mg once daily for eight weeks Gastroesophageal reflux disease: Capsule (DR), powder for suspension (DR): one to 11 years of age, 10 mg once daily for up to eight weeks; 12 to 17 years of age, 20 or 40 mg once daily for up to eight weeks Injection: >1 month to one year of age, 0.5 mg/kg daily; one to 17 years of age, <55 kg, 10 mg once daily; ≥55 kg: 20 mg once daily	Capsule (DR): 20 mg 40 mg Injection: 20 mg 40 mg Powder for suspension (DR): 2.5 mg 5 mg 10 mg 20 mg 40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Lansoprazole	Duodenal ulcer: Capsule (DR), orally disintegrating tablet (DR): treatment, 15 mg once daily for four weeks; maintenance, 15 mg once daily Erosive esophagitis: Capsule (DR), orally disintegrating tablet (DR): treatment, 30 mg once daily for eight to 16 weeks, maintenance, 15 mg once daily Gastric ulcer treatment: Capsule (DR), orally disintegrating tablet (DR): 30 mg once daily up to eight weeks Gastroesophageal reflux disease: Capsule (DR), orally disintegrating tablet (DR): 15 mg once daily for up to eight weeks Heartburn: Capsule (DR), orally disintegrating tablet (DR): 15 mg once daily for 14 days *H pylori* eradication: Capsule (DR), orally disintegrating tablet (DR): triple therapy: 30 mg twice daily for 10 or 14 days (with amoxicillin 1,000 mg and clarithromycin 500 mg twice daily) Dual therapy: 30 mg three times daily for 14 days (with amoxicillin one g three times daily) NSAID-associated gastric ulcer: Capsule (DR), orally disintegrating tablet (DR): treatment, 30 mg once daily up to eight weeks; risk reduction, 15 mg once daily up to 12 weeks Pathological hypersecretory conditions: Capsule (DR), orally disintegrating tablet (DR): 60 mg once daily	Erosive esophagitis: Capsule (DR), orally disintegrating tablet (DR): Treatment, one to 11 years of age, ≤30 kg, 15 mg once daily for up to 12 weeks; >30 kg, 30 mg once daily for up to 12 weeks; 12 to 17 years of age: 30 mg once daily up to 12 weeks Gastroesophageal reflux disease: Capsule (DR), orally disintegrating tablet (DR): one to 11 years of age, ≤30 kg, 15 mg once daily for up to 12 weeks; >30 kg, 30 mg once daily for up to 12 weeks; 12 to 17 years of age: 15 mg once daily for up to eight weeks	Capsule (DR): 15 mg 30 mg Orally disintegrating tablet (DR): 15 mg 30 mg
Omeprazole	Duodenal ulcer: Capsule, powder for suspension: treatment, 20 mg once daily for four to eight weeks Erosive esophagitis:	Erosive esophagitis: Capsule, powder for suspension: one to 16 years of age, 5 to 10 kg, 5 mg daily; 10 to 20 kg, 10 mg daily; ≥20 kg: 20 mg	Capsule (DR): 10 mg 20 mg 40 mg Powder for

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule, powder for suspension: treatment, 20 mg once daily for four to eight weeks; maintenance, 20 mg once daily Gastric ulcer: Capsule, powder for suspension: treatment, 40 mg once daily for four to eight weeks Gastroesophageal reflux disease: Capsule, powder for suspension: 20 mg once daily for four weeks *H pylori* eradication: Capsule, powder for suspension: triple therapy, 20 mg twice daily for 10 days (with amoxicillin 1,000 mg and clarithromycin 500 mg twice daily); dual therapy, 40 mg once daily for 14 to 28 days (with clarithromycin 500 mg three times a day) Pathological hypersecretory conditions: Capsule, powder for suspension: 60 mg once daily up to 120 mg three times daily	daily; one month to <1 year of age, 3 to <5 kg, 2.5 mg daily; 5 to <10 kg, 5 kg daily; ≥10 kg, 10 mg daily Gastroesophageal reflux disease: Capsule, powder for suspension: one to 16 years of age, 5 to 10 kg, 5 mg daily; 10 to 20 kg, 10 mg daily; ≥20 kg, 20 mg daily	suspension (DR): 2.5 mg 10 mg
Pantoprazole	Erosive esophagitis: Granules for suspension (DR), tablet (DR): treatment, 40 mg once daily for eight to 16 weeks; maintenance, 40 mg once daily Injection: treatment, 40 mg once daily for seven to 10 days Gastroesophageal reflux disease: Injection: 40 mg once daily for seven to 10 days Pathological hypersecretory conditions: Granules for suspension (DR), tablet (DR): 40 mg twice daily up to 240 mg daily Injection: 80 mg twice daily up to 240 mg daily for up to six days	Erosive esophagitis: Granules for suspension (DR), tablet (DR): ≥5 years of age, 15 to 40 kg, 20 mg daily for eight weeks; >40 kg, 40 mg daily for eight weeks	Granules for suspension (DR): 40 mg Injection: 40 mg Tablet (DR): 20 mg 40 mg
Rabeprazole	Duodenal ulcer: Tablet (DR): treatment, 20 mg once daily for four weeks Erosive esophagitis: Tablet (DR): treatment, 20 mg once daily for four to eight weeks;	Gastroesophageal reflux disease: ≥12 years of age: Tablet (DR): 20 mg once daily for up to eight weeks	Capsule (DR; sprinkle): 5 mg 10 mg Tablet (DR): 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maintenance, 20 mg once daily Gastroesophageal reflux disease: Tablet (DR): 20 mg once daily for four to eight weeks *H pylori* eradication: Tablet (DR): triple therapy, 20 mg twice daily for seven days (with amoxicillin 1,000 mg and clarithromycin 500 mg twice daily) Pathological hypersecretory conditions: Tablet (DR): 60 mg once daily up to 100 mg once daily or 60 mg twice daily	One to 11 years of age: Capsule (DR; sprinkle): <15 kg, 5 mg once daily for up to 12 weeks with the option to increase to 10 mg if inadequate response; ≥15 kg, 10 mg once daily for up to 12 weeks	
Combination Products			
Omeprazole, amoxicillin and rifabutin	Treatment of *H pylori* infection: Tablet (DR): Four capsules every eight hours for 14 days with food	Safety and efficacy in children have not been established.	DR capsule: 10-250-12.5 mg
Omeprazole, clarithromycin, and amoxicillin	*H pylori* eradication: Combination package: omeprazole 20 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg administered twice daily for 10 days	Safety and efficacy in children have not been established.	Combination package: 20-500-500 mg
Omeprazole and sodium bicarbonate	Duodenal ulcer: Capsule, powder: treatment, 20 mg once daily for four to eight weeks Erosive esophagitis: Capsule, powder: treatment, 20 mg once daily for four to eight weeks; maintenance, 20 mg once daily Gastric ulcer: Capsule, powder: treatment, 40 mg once daily for four to eight weeks Gastroesophageal reflux disease: Capsule, powder: 20 mg once daily for four weeks Upper gastrointestinal bleeding: Capsule, powder: 40 mg; followed by 40 mg six to eight hours later and 40 mg once daily thereafter for 14 days	Safety and efficacy in children have not been established.	Capsule: 20 mg-1.1 gram 40 mg-1.1 gram Powder packet: 20-1,680 mg 40-1,680 mg
Lansoprazole, amoxicillin, and clarithromycin	*H pylori* eradication: Combination package: lansoprazole 30 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg administered twice daily for 10 to 14 days	Safety and efficacy in children have not been established.	Combination package: 30-500-500 mg

DR=delayed-release, NSAID=nonsteroidal antiinflammatory drug

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the proton-pump inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Proton-Pump Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gastroesophageal Reflux Disease				
Sharma et al.[29] (2009) Dexlansoprazole 60 mg QD vs dexlansoprazole 90 mg QD vs lansoprazole 30 mg QD	AC, DB, MC, RCT (2 trials) Patients ≥18 years of age with endoscopically confirmed erosive esophagitis	N=4,092 8 weeks	Primary: Complete healing of erosive esophagitis as assessed by endoscopy Secondary: Percentage of patients with complete healing of erosive esophagitis over four weeks as assessed by endoscopy, percentage of patients with baseline esophagitis grade C or D who had complete healing over eight weeks as assessed by endoscopy at week four	Primary: Dexlansoprazole 60 and 90 mg was found to be non-inferior to lansoprazole for healing erosive esophagitis. Dexlansoprazole healed 92 to 95% of patients compared to 86 to 92% of patients receiving lansoprazole (P>0.025). Secondary: Week four healing was >64% in all groups and there were no significant differences between the treatment groups. In a post-hoc analysis of combined data from study one and study two, dexlansoprazole 90 mg was more effective than lansoprazole in the healing of moderate-to-severe erosive esophagitis at week eight. The median percentage of 24-hour heartburn-free days was 82.1% for dexlansoprazole 60 mg, 84.2% for dexlansoprazole 90 mg and 80.0% for lansoprazole 30 mg in study 1 and 83.0, 80.8 and 78.3% respectively, in study two. All three treatment groups were highly effective at relieving nighttime symptoms. The percentage of patients who achieved sustained resolution of heartburn was >80% in all treatment groups (P=not significant). The median percentage of days without rescue medication usage was also similar among treatment groups (P>0.05).
Peura et al.[30] (2009) Dexlansoprazole 30 to 90 mg QD	MA Patients with GERD-related disorders	N=4270 (7 trials) Variable duration	Primary: Adverse events Secondary: Not reported	Primary: Treatment-emergent adverse events occurred less frequently in patients receiving dexlansoprazole (15.64 to 18.75) than in patients receiving placebo (24.49) or lansoprazole (21.06) per 100 patient-months.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs lansoprazole 30 mg QD vs placebo				The most frequent treatment-emergent adverse events reported among all patients taking dexlansoprazole were diarrhea, upper respiratory tract infections, gastrointestinal and abdominal pains, nausea and vomiting, headaches, and flatulence, bloating and distention (P=not significant vs placebo and lansoprazole). The relative risks for nausea, headache, dyspepsia, abdominal tenderness and esophagitis were lower in the dexlansoprazole group compared to the placebo group. Abdominal distension, hiatal hernia, nasopharyngitis and Barrett's oesophagus were lower for the dexlansoprazole group compared to the lansoprazole group. Secondary: Not reported
Tsai et al.[31] (2004) Esomeprazole 20 mg on-demand therapy vs lansoprazole 15 mg QD All patients received esomeprazole 20 mg QD for 2 to4 weeks for acute treatment of GERD, then proceeded into the maintenance phase and were randomized into	MC, PG, SB, RCT Patients 18 to80 years of age with >6 month history of GERD without esophageal mucosal breaks and reported symptoms in >4 out of the previous seven days	N=622 6 months	Primary: Time to discontinuation from maintenance phase due to unwillingness to continue Secondary: Time to discontinuation due to insufficient heartburn control, patient satisfaction, and symptom assessment	Primary: Time to discontinuation from maintenance phase due to unwillingness to continue was significantly longer for patients taking esomeprazole on demand therapy compared to lansoprazole QD (P=0.001). At six months, significantly more patients on lansoprazole were unwilling to continue therapy compared to esomeprazole (13 vs 6%; P=0.001). Secondary: Of the patients that discontinued therapy, 4.8% taking lansoprazole and 2.9% taking esomeprazole reported heartburn as the reason for unwillingness to continue. The time to discontinuation due to insufficient heartburn control was not reported. Significantly more patients cited adverse events with lansoprazole as the reason for unwillingness to continue treatment (P=0.0028). Patient satisfaction was significantly higher with esomeprazole after one month of treatment (P=0.02). At three and six months, patient satisfaction was similar for both groups. The frequency of heartburn symptoms recorded at clinic visits were higher with esomeprazole compared to lansoprazole at one, three, and six months.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
the above treatment groups.				
Castell et al.[32] (2002) Esomeprazole 40 mg QD in the morning vs lansoprazole 30 mg QD in the morning	DB, MC, PG, RCT Adult patients with endoscopically documented erosive esophagitis	N=5,241 8 weeks	Primary: Healing rates at eight weeks Secondary: Healing rates at week four, resolution of investigator-recorded heartburn at week four, time to first and time to sustained relief of heartburn and proportion of heartburn-free days and nights	Primary: Esomeprazole demonstrated significantly higher healing rates at eight weeks compared to lansoprazole (92.6 vs 88.8%; P=0.0001). Secondary: Esomeprazole demonstrated higher healing rates at four weeks compared to lansoprazole (79.4 vs 75.1%). Resolution of heartburn at week four was significantly higher with esomeprazole compared to lansoprazole (62.9 vs 60.2%; P≤0.05). No significant difference was observed in time to first resolution of heartburn (median of two days for both treatment groups); however RCT, time to sustained relief was significantly less with esomeprazole (7 vs 8 days; P≤0.01). There was no significant difference in the proportion of heartburn-free days between treatment groups; however RCT, heartburn-free nights were significantly higher with esomeprazole (87.1 vs 85.8%; P≤0.05).
Howden et al.[33] (2002) Esomeprazole 40 mg QD vs lansoprazole 30 mg QD	DB, MC, RCT Adult patients with endoscopically documented erosive esophagitis	N=284 8 weeks	Primary: Healing rates at eight weeks Secondary: Healing rates at week four, proportion of patients reporting heartburn-free days and nights, and rate of healing or improvement of esophagitis by two grades	Primary: Comparable healing rates at week eight were observed between esomeprazole compared to lansoprazole (89.1 vs 91.4%, respectively). Secondary: Healing rates at week four were comparable between the two treatment groups (77.0% for lansoprazole and 78.3% for esomeprazole). The percentage of patients reporting heartburn-free days and nights were comparable between treatment groups. Healing or improvement of esophagitis by two grades was observed in 90% of patients taking lansoprazole and 81% taking esomeprazole.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chey et al.[34] (2003) Esomeprazole 40 mg QD vs lansoprazole 30 mg QD	DB, MC, RCT Adult patients with symptomatic GERD	N=3,034 2 weeks	Primary: Average symptom severity after day three Secondary: Percentage of patients without daytime and nighttime heartburn after day one, symptom relief after day one, and symptom severity after day one, day seven and day 14	Primary: No statistically significant differences were noted between the two treatment groups in symptom severity after day three. Secondary: No statistically significant differences were noted for any of the secondary endpoints.
Devault et al.[35] (2006) Esomeprazole 20 mg QD vs lansoprazole 15 mg QD	DB, MC, PG, RCT Patients 18 to 75 years of age with erosive esophagitis (Los Angeles Grade A, B, C or D) who were treated and healed	N=1,026 6 months	Primary: Remission rates Secondary: Observed remission rate at three months and six months	Primary: Estimated endoscopic/symptomatic remission rate during a period of six months was significantly higher (P=0.0007) for patients on esomeprazole (84.8%) compared to lansoprazole (75.9%). Secondary: Observed endoscopic/symptomatic remission rates at three months (92.8 vs 86.8%; P<0.0001) and six months (86.2 vs 77.6%; P<0.0001) were significantly higher in the esomeprazole group compared to the lansoprazole group. There was no significant difference between esomeprazole and lansoprazole at six months with regards to patients reporting no heartburn (82.9 and 79.2%), acid regurgitation (86.8 and 85.8%), dysphagia (97.6% and 96.4%) or epigastric pain (91.6 and 89.5%). Both treatments were well tolerated.
Fennerty et al.[36] (2005)	DB, MC, RCT Patients with	N=999 8 weeks	Primary: Healing rates at week eight	Primary: Healing rates at week eight were significantly greater in patients taking esomeprazole compared to lansoprazole (82.4 vs 77.5%; P=0.007).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Esomeprazole 40 mg QD vs lansoprazole 30 mg QD	moderate-severe erosive esophagitis (Los Angeles Grade C or D)		Secondary: Resolution of heartburn symptoms at week four	Secondary: Significantly more patients taking esomeprazole had resolution of heartburn symptoms at week 4 than lansoprazole (72.0 vs 63.6%; P=0.005).
Lauritsen et al.[37] (2003) Esomeprazole 20 mg QD vs lansoprazole 15 mg QD	DB, MC, RCT Patients with healed esophagitis	N=1,391 6 months	Primary: Remission rates at six months Secondary: Not reported	Primary: Remission rates at six months were significantly higher with esomeprazole compared to lansoprazole (83 vs 74%; P<0.0001). Secondary: Not reported
Richter et al.[38] (2001) Esomeprazole 40 mg QD vs omeprazole 20 mg QD	DB, MC, PG, RCT Adult patients with erosive esophagitis	N=2,425 8 weeks	Primary: Healing rates at eight weeks Secondary: Healing rates at four weeks, and resolution of heartburn symptoms at week four, time to first resolution and sustained resolution of heartburn, and proportion of heartburn-free days and nights	Primary: Significantly more patients taking esomeprazole were healed at eight weeks compared to those taking omeprazole (93.7 vs 84.2%; P<0.001). Secondary: Significantly more patients taking esomeprazole were healed at four weeks compared to those taking omeprazole (81.7 vs 68.7%; P<0.001). Significantly more patients taking esomeprazole had complete resolution of heartburn compared to those taking omeprazole (68.3 vs 58.1%; P<0.001). Time to first resolution was significantly greater with esomeprazole at day one (45.3 vs 32.0%; P≤0.0005) and day seven (85.6 vs 81.6%; P≤0.0005) compared to omeprazole. Time to sustained resolution with esomeprazole was significantly greater at day one, 14, and 28 compared to omeprazole (P≤0.0005). Esomeprazole resulted in greater heartburn-free days (74.9 vs 69.7%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P<0.001) and nights (90.8 vs 87.9%; P<0.001).
Armstrong et al.[39] (2004) Esomeprazole 40 mg QD vs esomeprazole 20 mg QD vs omeprazole 20 mg QD	DB, MC, PG, RCT (three studies) Patients with heartburn for >6 months with a normal endoscopy	N=2,645 4 weeks	Primary: Complete resolution of heartburn at four weeks Secondary: Complete resolution of heartburn at 14 days, adequate control of heartburn, relief of other reflux and gastrointestinal symptoms, and relief of heartburn (assessed by patient diary)	Primary: Complete resolution of heartburn at four weeks was comparable for all treatment arms throughout the three studies. Secondary: Complete resolution of heartburn at two weeks was comparable for all treatment arms throughout the three studies. For adequate control of heartburn in study A, 60.5% taking esomeprazole 40 mg, 66.0% on esomeprazole 20 mg, and 63.1% on omeprazole 20 mg reported adequate control. In study B, 73.5% taking esomeprazole 40 mg, and 72.8% on omeprazole 20 mg reported adequate heartburn control. In study C, 67.9% taking esomeprazole 20 mg, and 65.3% on omeprazole 20 mg reported adequate heartburn control. After four weeks, relief of other reflux and gastrointestinal symptoms was comparable in all treatment arms throughout the three studies. In study A, relief of heartburn reported by patients was higher with esomeprazole 20 mg. No differences were detected throughout the other two studies.
Kahrilas et al.[40] (2000) Esomeprazole 40 mg QD vs esomeprazole 20 mg QD vs	DB, MC, PG, RCT Patients with endoscopically documented reflux esophagitis	N=1,960 8 weeks	Primary: Healing rates after eight weeks Secondary: Resolution of heartburn symptoms at week four, time to first and time to sustained relief of heartburn, and	Primary: Healing rates for both esomeprazole 40 mg QD (94.1%; P<0.001 vs omeprazole) and 20 mg QD (89.9%; P<0.05 vs omeprazole) were statistically higher than omeprazole 20 mg QD (86.9%). Secondary: Resolution of heartburn symptoms was significantly higher for patients taking esomeprazole 40 mg compared to those taking omeprazole 20 mg (64.7 vs 57.2%; P=0.005). There were no significant differences between omeprazole 20 mg and esomeprazole 20 mg (61.0%). Time to first resolution of heartburn symptoms was significantly higher

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
omeprazole 20 mg QD			proportion of heartburn-free days and nights	for patients taking esomeprazole 40 mg compared to omeprazole (P=0.013). There were no significant differences between omeprazole 20 mg and esomeprazole 20 mg. Time to sustained resolution of heartburn symptoms was significantly higher for patients taking esomeprazole 40 mg (five days) compared to omeprazole (nine days; P=0.0006). There were no significant differences between omeprazole 20 mg and esomeprazole 20 mg (eight days). Proportion of heartburn-free days was significantly higher for patients taking esomeprazole 40 mg (72.7%) compared to omeprazole (67.1%; P=0.002). There were no significant differences between omeprazole 20 mg and esomeprazole 20 mg (69.3%). Proportion of heartburn-free nights was significantly higher for patients taking esomeprazole 40 mg (84.7%; P=0.001) and 20 mg (83.6%; P=0.013) compared to omeprazole (80.1%).
Schmitt et al.[41] (2006) Esomeprazole 40 mg QD vs omeprazole 20 mg QD	DB, MC, PG, RCT Patients 18 to 75 years of age with erosive esophagitis confirmed by endoscopy; patients were excluded if positive for *H pylori*, any bleeding disorder, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal strictures or Barrett's esophagus	N=1,148 8 weeks	Primary: Proportion of patients with healed erosive esophagitis at week eight Secondary: Diary and investigator assessments of heartburn symptoms and safety	Primary: The proportion of patients with healed erosive esophagitis at week eight was 92.2% for esomeprazole and 89.9% for omeprazole (P=0.189). The proportion of patients with healed erosive esophagitis at week four was 71.5% for esomeprazole and 68.6% for omeprazole (no P value reported). Treatment with esomeprazole was associated with significantly higher healing rates compared to omeprazole at weeks eight (88.4 vs 77.5%; P=0.007) and four (60.8 vs 47.9%; P=0.02) in patients with moderate-to-severe (Los Angeles grade C or D) erosive esophagitis at baseline but were not significantly different for patients with mild disease (grade A or B). Secondary: After four weeks of treatment, there were no significant differences between esomeprazole and omeprazole in the proportions of patients with investigator-assessed resolution of heartburn (65.0 vs 63.1%; P=0.48), the percentage of heartburn-free days (74.5 vs 73.0%; P=0.39) or the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				percentage of heartburn-free nights (86.2 vs 84.5%; P=0.21). Both treatments had similar tolerability.
Lightdale et al.[42] (2006) Esomeprazole 20 mg QD vs omeprazole 20 mg QD	DB, MC, PG, RCT Patients 18 to 75 years of age with erosive esophagitis confirmed by endoscopy; patients excluded if positive for *H pylori*, any bleeding disorder, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal strictures or Barrett's esophagus	N=1,176 8 weeks	Primary: Proportion of patients with healed erosive esophagitis at weeks eight Secondary: Diary and investigator assessments of heartburn symptoms and safety	Primary: The proportion of patients with healed erosive esophagitis at week eight was 90.6% for esomeprazole and 88.3% for omeprazole (P=0.621). Similar healing rates were achieved at weeks four and eight with esomeprazole and omeprazole in the entire study population and when patients were classified according to baseline erosive esophagitis severity. Secondary: Patients in both treatment groups had similar control of heartburn at week four. Adverse events were reported with similar frequencies among the esomeprazole and omeprazole patients.
Glatzel et al.[43] (2006) Esomeprazole 40 mg QD vs pantoprazole 40 mg QD	DB, MC, PG, RCT Patients >18 years of age with endoscopically-confirmed GERD grades A-D (Los Angeles Classification)	N=585 42 days	Primary: GERD symptoms using the Request-gastrointestinal patient-oriented self-assessment subscale during the pretreatment phase (seven days), treatment phase (28 days), and post-treatment phase (seven days) Secondary: Not reported	Primary: <u>Pretreatment Phase:</u> The median values of the mean ReQuest-gastrointestinal scores were similar for both the pantoprazole (4.20) and esomeprazole (4.56) treatment groups (P=0.455). The mean number of episodes and the mean number of days with GERD-related symptoms were similar for both groups. <u>Treatment Phase:</u> The median of the mean ReQuest-gastrointestinal score of the last three days of treatment were 0.22 in the pantoprazole and 0.30 in the esomeprazole group, demonstrating non-inferiority of pantoprazole. The mean number of episodes decreased from 1.2 (week one) to 0.7 (week four) and the maximum ReQuest-gastrointestinal scores from 3.2 and 3.7 (pantoprazole and esomeprazole, respectively, week one) to 1.0 and 1.1 (pantoprazole and esomeprazole, respectively, week four).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Post-treatment Phase: The mean number of symptom episodes was significantly lower in the pantoprazole group than in the esomeprazole group (P=0.0265). Patients in the pantoprazole group had 2.1 days of GERD symptoms and patients in the esomeprazole group had 2.3 days of GERD symptoms. The ReQuest-gastrointestinal scores were significantly lower for the pantoprazole group than for the esomeprazole group (1.44 vs 2.18, respectively; P=0.0313). The relapse rates were 46.3% in the pantoprazole group vs 56.9% in the esomeprazole group (P=0.0221). The time to relapse was 5.7 days in the pantoprazole group and 4.8 days in the esomeprazole group. The median of the mean ReQuest-GI score was lower in the pantoprazole group than in the esomeprazole group (0.56 vs 1.01; P=0.084). Secondary: Not reported
Labenz et al.[44] (2005) Esomeprazole 40 mg QD vs pantoprazole 40 mg QD	DB, MC, RCT Adult patients with reflux esophagitis with history of GERD symptoms for at least 6 months	N=3,170 8 weeks	Primary: Healing rates at eight weeks Secondary: Healing rates at four and eight weeks by baseline esophagitis severity, time to sustained symptom relief, and proportion of heartburn-free days	Primary: At eight weeks, healing rates for esomeprazole 40 mg QD (95.5%) were statistically higher than for pantoprazole 40 mg QD (92.0%; P<0.001). Secondary: At four and eight weeks, healing rates for esomeprazole 40 mg QD was statistically higher than for pantoprazole 40 mg QD for erosive esophagitis grades B to D (Los Angeles grading; P<0.05). No significant difference was noted for grade A esophagitis. Time to sustained resolution of heartburn symptoms were significantly shorter with esomeprazole 40 mg (six days) compared to pantoprazole (eight days; P<0.001). Proportion of heartburn-free days was significantly higher with esomeprazole 40 mg (70.7%) compared to omeprazole (67.3%; P<0.01).
Labenz et al.[45] (2009)	DB, MC, RCT Adult patients with	N=3,151 4 weeks	Primary: Factors associated with heartburn	Primary: At week four, heartburn had resolved in 72.5% of patients treated with esomeprazole and in 66.9% of patients treated with pantoprazole.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Esomeprazole 40 mg QD vs pantoprazole 40 mg QD	reflux esophagitis with history of GERD symptoms for at least six months		resolution Secondary: Not reported	The use of esomeprazole rather than pantoprazole (OR, 1.31; 95% CI, 1.12 to 1.54; P=0.0008), positive *H pylori* status (OR, 1.44; 95% CI, 1.19 to 1.74; P=0.0001) and greater age (OR, 1.013; 95% CI, 1.14 to 1.59; P=0.0005) were associated with increased likelihood of heartburn resolution. Secondary: Not reported
Labenz et al.[46] (2009) Esomeprazole 20 mg QD vs pantoprazole 20 mg QD	DB, MC, RCT (Post-hoc analysis) Adult patients with reflux esophagitis with history of GERD symptoms for at least six months	N=2,766 6 months	Primary: Factors associated with heartburn relapse Secondary: Not reported	Primary: Heartburn relapse were lower with esomeprazole (OR, 2.08; 95% CI, 1.67 to 2.63; P<0.0001) compared to pantoprazole. Esomeprazole treatment was the factor most strongly associated with freedom from heartburn relapse (OR, 2.08; P<0.0001). Other factors significantly associated with freedom from heartburn relapse were *H pylori* infection, greater age, non-obesity, absence of epigastric pain at baseline, pre-treatment nonsevere heartburn and GERD symptom duration ≤5 years. Secondary: Not reported
Scholten et al.[47] (2003) Esomeprazole 40 mg QD vs pantoprazole 40 mg QD	DB, MC, PG, RCT Adult patients with GERD grade B and C (Los Angeles classification system)	N=217 4 weeks	Primary: GERD-related symptoms reported Secondary: Relief rates of GERD-related symptoms, gastrointestinal symptom rating scale score, and time to first symptom relief	Primary: Both treatment groups reported similar relief of gastrointestinal symptoms (P>0.05). Secondary: At four weeks, the proportion of patients reporting no or mild heartburn was 99% with pantoprazole and 98% with esomeprazole. There were no significant differences in gastrointestinal symptom rating scale scores between the two treatment groups (P>0.05). Patients taking pantoprazole reported time to first symptom relief after a mean of 3.7 days compared to 5.9 days with esomeprazole (P=0.034).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Klok et al.[48] (2003) Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	MA Patients receiving a PPI for the treatment of GERD, PUD, or *H pylori*	41 trials Variable duration	Primary: Success rates (defined as endoscopically determined cure for GERD and PUD or absence of *H pylori*) Secondary: Not reported	Primary: For GERD treatment, esomeprazole 40 mg per day was found to have significantly greater healing rates compared to omeprazole 20 mg per day (RR, 1.18; 95% CI, 1.14 to 1.23). For all other comparisons in GERD, no significant difference was found. For PUD treatment, pantoprazole 40 mg/day was found to have significantly greater healing rates compared to omeprazole 20 mg per day (RR, 1.07; 95% CI, 1.02 to 1.13). For all other comparisons, no significant difference was found. No significant differences were found in *H pylori* eradication rates between PPIs. Secondary: Not reported
Gralnek et al.[49] (2006) Esomeprazole vs omeprazole, lansoprazole, or pantoprazole	MA Patients with erosive esophagitis	N=15,316 (10 trials) 4 to 8 weeks	Primary: Relative risk of erosive esophagitis healing, symptom relief, and adverse events Secondary: Not reported	Primary: At four and eight weeks, there was 10% (RR, 1.10; 95% CI, 1.05 to 1.15) and 5% (RR, 1.05; 95% CI, 1.02 to 1.08) relative increase in the probability of healing, respectively, with esomeprazole vs alternative PPIs. At eight weeks, there was an absolute risk reduction of 4% with a NNT of 25. The effectiveness of esomeprazole was inversely proportional to the baseline erosive esophagitis severity. The calculated NNTs by Los Angeles grade of erosive esophagitis (grades A to D) were 50, 33, 14, and 8, respectively. At four weeks, esomeprazole was associated with an 8% relative increase in the probability of GERD symptom relief (RR, 1.08; 95% CI, 1.05 to 1.11) compared to alternative PPIs. There was an absolute risk reduction of 4% with a NNT of 25. There was a significantly higher incidence of headaches reported with esomeprazole (22%) compared to alternative PPIs. There were no differences in reported rates of diarrhea, abdominal pain, nausea, or total adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Hoogendoorn et al.[50] (2009) Esomeprazole	MC, OS Patients being treated for GERD with a PPI other than esomeprazole and whose physician had decided to switch them to esomeprazole regardless of whether the patients were satisfied with their previous PPI therapy	N=4,929 28 days	Primary: Proportion of patients achieving greater satisfaction with esomeprazole compared to previous PPI therapy Secondary: Satisfaction with esomeprazole therapy and symptoms	Primary: The proportion of patients who were satisfied with therapy increased following the switch to esomeprazole. The proportion of patients who were more satisfied with esomeprazole than with previous PPI therapy was 71.3%. There was an increase in the proportion of patients who became free of GERD symptoms after switching to esomeprazole, with only 26.9% of patients continuing to experience symptoms (vs 84.0% at baseline). There was a reduction in the incidence of all common GERD symptoms. Overall, the level of satisfaction was highest for 72.4% of patients who were symptom-free following the switch to esomeprazole therapy. Among those patients who experienced symptoms despite non-esomeprazole PPI therapy at study entry, 69.4% were symptom-free after switching to esomeprazole, and of those patients who had been using concomitant therapy to control GERD symptoms at baseline, 62.0% were no longer using any such medication during the esomeprazole treatment period. Secondary: Of the 1,069 patients who had been satisfied with their PPI therapy at baseline, 39.4% were even more satisfied with esomeprazole therapy.
Richter et al.[51] (2001) Lansoprazole 30 mg QD vs omeprazole 20 mg QD	DB, MC, RCT Adult patients with endoscopically documented erosive esophagitis	N=3,510 8 weeks	Primary: Percentage of heartburn-free days and nights following one to three days and one week of treatment; and the frequency and severity of day- and nighttime heartburn Secondary:	Primary: The percentage of heartburn-free days was significantly higher with lansoprazole compared to omeprazole after one to three days of treatment and after one week of treatment (P<0.0001). The percentage of heartburn-free nights was significantly higher with lansoprazole compared to omeprazole after one to three days of treatment and after one week of treatment (P<0.0001). Average severity of heartburn symptoms was significantly less in patients taking lansoprazole compared to omeprazole. Significantly higher number of patients taking lansoprazole had recorded

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	no heartburn compared to omeprazole at any time during the first 14 days (P<0.001). At eight weeks, patients reporting no heartburn throughout the entire study was also significantly higher for lansoprazole (P<0.05). Secondary: Not reported
Sharma et al.[52] (2001) Lansoprazole 30 mg QD vs omeprazole 20 mg QD	MA Patients with endoscopically diagnosed erosive esophagitis where healing rates had to be reported after four and/or eight weeks	N=2,040 (6 trials) 4 to 8 weeks	Primary: Differences in pooled healing rates at four and eight weeks PP and ITT data Secondary: Not reported	Primary: Pooled healing rates after four weeks were 77.7% for lansoprazole and 74.7% for omeprazole (absolute benefit increase, 3.1%; 95% CI, -1.1 to 7.3) in the PP analysis. After four weeks, pooled healing rates were 72.7% for lansoprazole and 70.8% for omeprazole (absolute benefit increase, 2.0%; 95% CI, -2.0 to 6.0) for the ITT analysis. After eight weeks, pooled healing rates were 88.7% for lansoprazole and 87.0% for omeprazole (absolute benefit increase, 1.7%; 95% CI, -1.5 to 5.0) in the PP analysis. After eight weeks, pooled healing rates were 83.3% for lansoprazole and 81.8% for omeprazole (absolute benefit increase, 1.5%; 95% CI, -1.9 to 4.9) in the ITT analysis. Lansoprazole and omeprazole healing rates were not statistically different. Secondary: Not reported
Caro et al.[53] (2001) Lansoprazole, pantoprazole, or rabeprazole vs omeprazole,	MA Patients receiving acute and maintenance therapy for GERD	41 trials Variable duration	Primary: Healing and relapse rates Secondary: Not reported	Primary: Compared to omeprazole 20 mg daily, the healing RRs after eight weeks were as follows: lansoprazole 30 mg daily RRs, 1.02 (95% CI, 0.98 to 1.06); rabeprazole 20 mg daily, RRs, 0.93 (95% CI, 0.87 to 1.00); and pantoprazole 40 mg daily, RRs, 0.98 (95% CI, 0.90 to 1.07). Relapse rates after 6 months were as follows: lansoprazole 30 mg daily 6 to 29%; rabeprazole 20 mg daily 9%; and omeprazole 20 mg daily 7 to 42%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ranitidine or placebo				Secondary: Not reported
Miner et al.[54] (2010) Omeprazole 20.6 mg QD vs lansoprazole 15 mg QD	DB, RCT, SC, XO Healthy volunteers who were 18 to 65 years of age	N=40 5 days	Primary: Percentage time that gastric pH was >4.0 during 24-hour monitoring Secondary: Not reported	Primary: The mean percentage time that gastric pH was >4.0 over 24-hours during day 5 was greater for omeprazole (mean, 45.7%) than for lansoprazole (mean, 36.8%; P<0.0001). The mean percentage time that gastric pH was >4.0 from 10 pm to 6 am was 24.3% with omeprazole and 21.8% with lansoprazole (P=0.28). The mean median gastric pH was 3.685 with omeprazole and 3.058 with lansoprazole (P<0.0001). There were no serious adverse events in the study. Secondary: Not reported
Pilotto et al.[55] (2007) Omeprazole 20 mg QD vs lansoprazole 30 mg QD vs pantoprazole 40 mg QD vs rabeprazole 20 mg QD	OL, RCT, SC Patients ≥65 years of age with a diagnosis of esophagitis grade I-IV according to the Savary-Miller classification	N=320 8 weeks	Primary: Healing of acute esophagitis, symptoms, and adverse events Secondary: Not reported	Primary: According to the PP and ITT analyses, healing rates of esophagitis were: omeprazole, 81.0 and 75.0%, lansoprazole, 90.7% (P=0.143 vs omeprazole) and 85% (P=0.167 vs omeprazole), pantoprazole, 93.5% (P=0.04 vs omeprazole) and 90.0% (P=0.02 vs omeprazole), rabeprazole, 94.6% (P=0.02 vs omeprazole) and 88.8% (P=0.04 vs omeprazole), respectively. The rates of symptom disappearance in the four treatment groups (omeprazole, lansoprazole, pantoprazole, rabeprazole) were 86.9, 82.4, 100, and 100% for heartburn, 100, 75.0, 92.9, and 90.1% for acid regurgitation, and 95.0, 82.6, 95.2, and 100% for epigastric pain, respectively. Comparisons between the four PPIs demonstrated that pantoprazole and rabeprazole were more effective than omeprazole (100 vs 86.9%, and 100 vs 86.9%, respectively; P<0.05) and more effective than lansoprazole (100 vs 82.4%; P=0.0001 and 100 vs 82.4%; P=0.005, respectively) in decreasing heartburn. Lansoprazole was less effective in improving acid regurgitation and epigastric pain than omeprazole (P=0.0001, P=0.033, respectively), pantoprazole (P=0.005, P=0.028, respectively), and rabeprazole (P=0.026, P=0.0001, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				All four PPIs were well tolerated. Adverse events were reported only by four patients (1.3%). Secondary: Not reported
Katz et al.[56] (2007) Omeprazole suspension 40 mg for seven days vs esomeprazole 40 mg for seven days vs lansoprazole 30 mg for seven days Following a 10 to 14 day washout between treatment periods, patients were XO to one of the alternative treatments.	OL, RCT, XO Non-Asian patients ≥18 years of age with a history of GERD at least partially responsive to antacids or acid suppressants and had recurrent night-time symptoms for the previous three months, baseline gastric pH ≤2.5 prior to randomization; patients were excluded for concurrent gastrointestinal diseases other than GERD, a significant history of gastrointestinal diseases in the past five years and any history of gastric surgery or any other significant unstable illness	N=54 21 days (XO at 7 days)	Primary: Occurrence of nocturnal acid breakthrough (gastric pH <4 for more than one hour during the night-time from 22:00 to 06:00 hours) Secondary: Percentage of time gastric pH>4 and median gastric pH in cumulative two-hour increments during the nighttime period and over 24 hours	Primary: After seven days of bedtime dosing, omeprazole significantly reduced nocturnal acid breakthrough compared to esomeprazole and lansoprazole (61 vs 92 and 92%; P<0.001 for both comparisons). Secondary: During the first half of the night, percentage of time with gastric pH >4 and median gastric pH were significantly higher after omeprazole (52% and 4.34, respectively) compared to esomeprazole (30% and 2.37, respectively) or lansoprazole (12% and 1.51, respectively; P<0.001 for both comparisons). Over the eight hour nighttime period, the percentage of time with gastric pH >4 and median gastric pH were significantly higher after omeprazole (53% and 4.04, respectively) than lansoprazole (34% and 2.09, respectively; P<0.001 for both comparisons) but comparable to esomeprazole (55% and 4.85, respectively). The percentage of time with gastric pH >4 for the 24-hour period was 44% with omeprazole compared to 59% with esomeprazole (P<0.001) and 28% with lansoprazole (P<0.001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bardhan et al.[57] (2001) Omeprazole 20 QD vs pantoprazole 20 mg QD	OL, PG, RCT Adult patients with grade I GERD	N=327 8 weeks	Primary: Rate of symptom relief at weeks two and four and healing rates at week four and eight Secondary: Not reported	Primary: At two and four weeks, the rate of symptom relief was similar for pantoprazole (70 and 77%) and omeprazole (79 and 84%). Healing rates at 4 weeks were comparable between pantoprazole (84%) and omeprazole (89%). Healing rates at 8 weeks were comparable between pantoprazole (90%) and omeprazole (95%). Secondary: Not reported
Zheng et al.[58] (2009) Omeprazole 20 mg QD vs pantoprazole 40 mg QD vs lansoprazole 30 mg QD vs esomeprazole 40 mg QD	RCT Patients 36 to 85 years of age with endoscopically proven reflux esophagitis	N=274 8 weeks	Primary: Relief of heartburn during in the first week of drug administration Secondary: Not reported	Primary: For all patients, heartburn scores were significantly lower with esomeprazole after the first and second days of therapy than with omeprazole (P=0.0031 and P=0.0092, respectively), lansoprazole (P=0.0039 and P=0.0088, respectively), and pantoprazole (P=0.0009 and P=0.0036, respectively). The difference between tended to disappear after five days of therapy. There was no significant difference in acid reflux between the groups. For patients who initially reported heartburn or acid reflux symptoms, complete disappearance of heartburn symptoms occurred more rapidly in patients receiving esomeprazole for five days than in those receiving omeprazole (P=0.0018, P=0.0098, P=0.0027, P=0.0137, P=0.0069, respectively), pantoprazole (P=0.0006, P=0.0005, P=0.0009, P=0.0031, P=0.0119, respectively), and lansoprazole (P=0.0020, P=0.0046, P=0.0037, P=0.0016, P=0.0076, respectively). The difference between tended to disappear after five days of therapy. There was no significant difference in acid reflux scores between the groups. There were no significant differences between the four groups in the rate of endoscopic healing of reflux esophagitis at week eight. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Delcher et al.[59] (2000) Omeprazole 20 mg QD vs rabeprazole 20 mg QD vs rabeprazole 10 mg BID	DB, PG, RCT Adult patients with ulcerative or erosive GERD	N=310 8 weeks	Primary: Healing rates Secondary: Improvement of gastrointestinal symptoms, number of hours missed from normal daily activity, the use of antacids, and physical well-being	Primary: At four weeks, the rates of healing were comparable among rabeprazole 20 mg QD (94%), rabeprazole 10 mg BID (93%), and omeprazole (98%). At four weeks, the rates of healing were comparable among rabeprazole 20 mg QD (97%), rabeprazole 10 mg BID (98%), and omeprazole (100%). Secondary: At four and eight weeks, improvements in gastrointestinal symptoms were comparable among all treatment groups. Use of antacid tablets was comparable between all treatment groups. There were no significant differences between treatment groups in the General Well-Being Schedule (a quality-of-life measurement) or in a rating of overall physical well being.
Pace et al.[60] (2005) Omeprazole 20 mg QD vs rabeprazole 20 mg QD	DB, RCT Patients with grade I to III GERD	N=560 8 weeks	Primary: Healing rates Secondary: Time to first day with satisfactory relief	Primary: After eight weeks, rates of healing for rabeprazole (97.9%) were equivalent to omeprazole (97.5%). Secondary: Rabeprazole had a statistically faster time to satisfactory relief (2.8 days) compared to omeprazole (4.7 days; P=0.0045).
Edwards et al.[61] (2001) Omeprazole 20 mg daily vs esomeprazole 20-40 mg daily, lansoprazole 30	MA Patients receiving acute treatment for GERD	12 trials 4 to 8 weeks	Primary: Healing rates Secondary: Not reported	Primary; Compared to omeprazole 20 mg daily, esomeprazole 40 mg daily had significantly greater healing rates at week 4 (RR, 1.14; 95% CI, 1.10 to 1.18) and at week 8 (RR, 1.08; 95% CI, 1.05 to 1.10). Compared to omeprazole 20 mg daily, there was no significant difference in healing rates at four or eight weeks with lansoprazole 30 mg daily, pantoprazole 40 mg daily, and rabeprazole 20 mg daily. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily, pantoprazole 40 mg daily, or rabeprazole 20 mg daily				
Edwards et al.[62] (2009) Omeprazole 20 to 40 mg QD vs esomeprazole 40 mg QD vs lansoprazole 30 mg QD vs pantoprazole 40 mg QD	MA Patients with severe erosive esophagitis (grades C and D in the Los Angeles classification system)	12 trials 4 to 8 weeks	Primary: Endoscopic healing rate after the initiation of PPI treatment in patients with severe erosive esophagitis Secondary: Not reported	Primary: Among the four PPIs compared to omeprazole 20 mg as the baseline treatment, esomeprazole 40 mg was the only one to demonstrate significantly higher healing rates at 4 weeks (OR, 1.84; 95% CI, 1.50 to 2.22). Results for the other PPIs compared to omeprazole 20 mg were: omeprazole 40 mg (OR, 1.65; 95% CI, 0.80 to 3.03), lansoprazole 30 mg (OR, 1.21; 95% CI; 0.96 to 1.51) and pantoprazole 40 mg (OR, 1.02; 95% CI, 0.71 to 1.43). The estimated probabilities of which PPI is the most effective at healing patients with severe esophagitis at four weeks were: 68% esomeprazole 40 mg, followed by 32% omeprazole 40 mg, with there being 0% probability of lansoprazole 30 mg, omeprazole 20 mg, or pantoprazole 40 mg being the most effective. Among the four PPIs compared to omeprazole 20 mg as the baseline treatment, esomeprazole 40 mg was the only one to demonstrate significantly higher healing rates at eight weeks (OR, 1.91; 95% CI, 1.13 to 2.88). Results for the other PPIs compared to omeprazole 20 mg were: omeprazole 40 mg (OR, 1.44; 95% CI, 0.63 to 2.84), lansoprazole 30 mg (OR, 1.23; 95% CI, 0.72 to 1.99) and pantoprazole 40 mg (OR, 1.39; 95% CI, 0.43 to 3.26). The estimated probabilities of which PPI is the most effective at healing patients with severe esophagitis at eight weeks were: 68% esomeprazole 40 mg, 18% omeprazole 40 mg, 12% pantoprazole 40 mg, 2% lansoprazole 30 mg and 0% omeprazole 20 mg. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Goh et al.[63] (2007) Pantoprazole 20 mg QD vs esomeprazole 20 mg QD	DB, MC, PG, RCT Patients ≥18 years of age with endoscopically confirmed GERD (Los Angeles grades A-D) who were healed (defined as absence of esophagitis, and 'no' or 'mild' heartburn and acid regurgitation)	N=1,303 6 months	Primary: Combined symptomatic and endoscopic remission (absence of endoscopic findings and 'no' or 'mild' heartburn and acid regurgitation. Secondary: Not reported	Primary: Pantoprazole and esomeprazole were equally effective at maintaining patients in remission; 84% of pantoprazole and 85% of esomeprazole patients remained in combined endoscopic and symptomatic remission at six months. Combined endoscopic and symptomatic remission was independent of Helicobacter pylori status. Both treatments were well tolerated and no safety concerns arose over the six-month maintenance phase. Adverse events occurred in 22% of pantoprazole-treated patients and 23% of esomeprazole-treated patients. Secondary: Not reported
Bardhan et al.[64] (2007) Pantoprazole 40 mg QD vs esomeprazole 40 mg QD	DB, MC, PG, RCT Patients ≥18 years of age with endoscopically confirmed erosive esophagitis (Los Angeles classification A-D)	N=582 12 weeks	Primary: Complete remission rates at 12 weeks Secondary: Complete remission rates at four- and eight-weeks; endoscopically confirmed healing rates at four-, eight- and 12-weeks; symptom relief rates at four-, eight- and 12-weeks; endoscopically confirmed healing rates, symptom relief rates and	Primary: Complete remission rates at 12 weeks were similar with pantoprazole and esomeprazole (93 and 90%, respectively). Secondary: The complete remission rates after four and eight weeks were similar with pantoprazole and esomeprazole (59 and 62% at four weeks, and 86 and 84% at eight weeks, respectively). All complete remission rates were similar at four, eight and 12 weeks. Endoscopically confirmed healing rates were similar at four-eight weeks, and more effective with pantoprazole at 12 weeks (95% CI, 0.02 to 7.27): four weeks: 75% for both pantoprazole and esomeprazole. eight weeks: 90 and 94% (pantoprazole and esomeprazole, respectively). 12 weeks: 93 and 97% (pantoprazole and esomeprazole, respectively). Symptoms were relieved in similar proportions on both treatments. There was no statistically significant difference at any time point. The *H pylori* status had no influence on endoscopically confirmed healing rates, symptom relief rates or complete remission rates.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			complete remission rates at four-, eight- and 12-weeks for *H pylori* positive and negative patients	
Eggleston et al.[65] (2009) Rabeprazole 20 mg QD vs esomeprazole 20 to 40 mg QD	AC, DB, MC, RCT Patients ≥18 years of age having episodes of heartburn, with or without regurgitation, for three months or longer and for ≥3 days in the seven days prior to randomization	N=1,392 4 weeks	Primary: Proportion of patients with complete heartburn relief, satisfactory heartburn relief, complete regurgitation relief and satisfactory regurgitation relief Secondary: Change in primary symptom scores, change in Patient Assessment of Upper Gastrointestinal Symptom dimension scores, median times to achieve complete and satisfactory relief of heartburn and regurgitation, proportions of 24-h periods heartburn free and regurgitation free,	Primary: Rabeprazole 20 mg was non-inferior to esomeprazole 40 mg for satisfactory heartburn relief (P=0.991), complete regurgitation relief (P=0.483), satisfactory regurgitation (P=0.363). Non-inferiority of rabeprazole 20 mg was not proven compared esomeprazole 40 mg for complete heartburn relief, but the difference between the two treatments was not statistically significant (95% CI, -12.0 to 0.5). Rabeprazole 20 mg was non-inferior and not different from esomeprazole 20 mg for all primary endpoints. Esomeprazole 20 mg was non-inferior to esomeprazole 40 mg for satisfactory heartburn relief, complete regurgitation relief, and satisfactory regurgitation relief. Non-inferiority of esomeprazole 20 mg vs esomeprazole 40 mg for complete heartburn relief was not proven, but the difference between the two treatments was not statistically significant (95% CI, -10.0 to 2.4). Secondary: There were no significant differences between the treatments groups with regards to the mean improvements in Patient Assessment of Upper Gastrointestinal Symptom scores over time for heartburn symptoms and regurgitation symptoms and for individual Patient Assessment of Upper Gastrointestinal Symptom dimensions. Satisfactory relief of both heartburn symptoms and regurgitation symptoms was rapid for all treatments (median ≤1 day) but not significantly different. The mean percentage of 24-hour periods free of heartburn symptoms were significantly different among treatment groups: 56.3% (95% CI, 53.1 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			change in Short Form-36 domain scores and the proportions of patients and investigators rating overall satisfaction of treatment as satisfied or very satisfied	59.5) for rabeprazole 20 mg, 63.4% (95% CI, 60.2 to 66.6) for esomeprazole 40 mg and 56.1% (95% CI, 52.9 to 59.3) for esomeprazole 20 mg (P=0.0014). The difference between rabeprazole 20 mg and esomeprazole 40 mg was statistically significant (P=0.002). No differences among treatment groups were observed in the mean number of 24-hour periods free of regurgitation symptoms (P=0.229). Quality of life, as measured by Short Form-36, improved significantly from baseline for all domains for all treatment groups with no significant differences observed among treatment groups. Investigators were satisfied or very satisfied for 77.1% of rabeprazole 20 mg treated patients, 81.0% of esomeprazole 40 mg treated patients and 75.8% of esomeprazole 20 mg treated patients (P=0.138). Satisfaction rates obtained from patients were similar (satisfied or very satisfied) with 77.6, 81.7 and 77.6% respectively (P=0.209).
Laine et al.[66] (2011) Rabeprazole extended-release 50 mg QD vs esomeprazole 40 mg QD	2 AC, DB, MC, RCT Patients 18 to 75 years of age with a history of GERD symptoms for ≥3 months before screening, heartburn at least two days/week for ≥1 month before screening endoscopy and moderate-to-severe erosive GERD (Los Angeles grade C or D) at screening endoscopy; patients were excluded if they tested positive	N=2,130 8 weeks	Primary: Proportion of patients with endoscopically confirmed healing by week four and week eight Secondary: Proportion of patients who achieved a sustained resolution of heartburn (seven or more consecutive days) at week four, and safety; exploratory endpoints included the time to first	Primary: In study I, 80% of patients treated with rabeprazole experienced endoscopically confirmed healing by week eight compared to 75% in the esomeprazole group (95% CI, 0.0 to 10.0). In study II, there was no difference healing rates between patients treated with rabeprazole (77.5%) or esomeprazole (78.4%) by week eight of treatment (difference, 0.9; 95% CI, -5.9% to 4.0%). At week four, 54.8% of patients randomized to rabeprazole achieved healing compared to 50.3% of patients receiving esomeprazole in study I (P=0.162). In study II, the four-week healing rates were not significantly different between patients treated with rabeprazole or esomeprazole (50.9 vs 50.7%, respectively; P=0.828). Secondary: In study I, the proportion of patients with sustained heartburn resolution at four weeks was not significantly different between patients randomized to receive rabeprazole compared to esomeprazole (48.3 vs 48.2%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	for *H pylori* in the month before screening endoscopy; current or history of esophageal motility disorders, Barrett's esophagus, esophageal strictures or esophagitis due to an etiology other than GERD, Zollinger-Ellison syndrome or other acid hypersecretory conditions or current gastric or duodenal ulcer		heartburn-free day, time to first resolution of heartburn, percentage of heartburn-free days and nights, investigator-recorded sustained resolution and other GERD symptoms at week four and week eight	respectively; P=0.991). Similarly, no statistically significant difference in sustained resolution was apparent between the treatment groups at week four in study II (53.2 vs 52.5%; P=0.757). Treatment-emergent adverse events occurred in 289 (28%) patients treated with rabeprazole and 282 (27%) patients in the esomeprazole group. One percent of patients in each group discontinued treatment due to an adverse event. Diarrhea was the most frequently reported adverse event in both treatment groups. Two deaths were reported in the rabeprazole group (one each for acute coronary syndrome and head injury). In the ITT population, results for all the exploratory endpoints were comparable between the rabeprazole and esomeprazole treatment groups with no statistically significant differences reported.
Haddad et al.[67] (2013) Rabeprazole 0.5 or 1.0 mg/kg (granule formulation) Dose was further standardized by weight range-children 6 to 14.9 kg (low-weight cohort) received 5 or 10 mg and children ≥15 kg (high-weight cohort) received 10 or 20 mg.	DB, MC, PG, RCT Patients age 1 to 11 years of age with endoscopically/ histologically-proven GERD	N=127 12 weeks	Primary: Endoscopic/ histologic healing at week 12 (defined as grade 0 on the Hetzel-Dent classification scale and/or grade 0 on the Histological Features of Reflux Esophagitis scale) Secondary: Changes in Total GERD Symptoms and Severity score and frequency of symptoms	Primary: Treatment with rabeprazole was associated with 81% of patients achieving endoscopic/histologic healing at week 12. Higher healing was observed in the low-weight cohort (82% [5 mg dose], 94% [10 mg dose]) compared to high-weight cohort (76% [10 mg dose], 78% [20 mg dose]). Histological changes demonstrated a statistically significant increase in Grimelius stain at week 104 compared to baseline (P<0.01). There were no significant fluctuations in CgA immunostained positive cells throughout the treatment period. Secondary: Mean Total GERD Symptoms and Severity score decreased from 19.7 points at baseline to 8.6 points at week 12 (P<0.001). Average frequency of symptoms per child decreased from 7.7 at week 1 to 4.7 at week 12 (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most common (>10%) treatment-emergent adverse events included cough and vomiting (14% each), abdominal pain (12%) and diarrhea (11%).
Peptic Ulcer Disease				
Subei et al.[68] (2007) Esomeprazole 20 mg BID, amoxicillin 1 g BID, and clarithromycin 500 mg BID for one week, followed by three weeks of placebo (EAC) vs omeprazole 20 mg BID, amoxicillin 1 g BID, and clarithromycin 500 mg BID for one week, followed by three weeks of omeprazole 20 mg QD monotherapy (OAC)	DB, MC, PC, RCT Patients >18 years of age, active duodenal ulcer of at least five mm, and positive for *H pylori*, assessed by a *Helicobacter* urease test	N=382 8 weeks	Primary: Four- and eight-week duodenal ulcer healing rates Secondary: Eight-week *H pylori* eradication rates	Primary: At the end of the four-week follow-up period, duodenal ulcer healing rates were similar with EAC compared to OAC (73.7 and 76.1%, respectively; 95% CI, −11.2 to 6.4). At the end of the eight-week follow-up period, duodenal ulcer healing rates were similar with esomeprazole, amoxicillin, and clarithromycin compared to omeprazole, amoxicillin, and clarithromycin (86% in both groups; 95% CI, −8.46 to 5.0). Secondary: *H pylori* eradication rates were similar at the end of the eight-week follow-up period for the esomeprazole, amoxicillin, and clarithromycin and omeprazole, amoxicillin, and clarithromycin treatment groups (74.7 and 78.7%, respectively; 95% CI, −12.6 to 4.6).
Gisbert et al.[69] (2004) Esomeprazole based *H pylori* therapies	MA Randomized trials investigating the use of esomeprazole based *H pylori* therapies and other	Number of trials analyzed was not reported	Primary: *H pylori* eradication rates for esomeprazole therapies Secondary:	Primary: Dual therapy with esomeprazole and clarithromycin therapy resulted in an eradication rate of 51 to 54%. Mean eradication rates following triple therapy with esomeprazole, clarithromycin, and either amoxicillin or metronidazole was 82 to 86%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs omeprazole based *H pylori* therapies	PPI based *H pylori* therapies were included in the analysis		Comparison of eradication rates for esomeprazole vs omeprazole therapy	Secondary: Mean eradication rates for esomeprazole-based therapies (85%) were comparable to omeprazole-based therapies (82%; OR, 1.19; 95% CI, 0.8 to 1.74).
Wu et al.[70] (2007) Esomeprazole 40 mg QD vs rabeprazole 20 mg BID All patients also received amoxicillin 1 g BID and clarithromycin 500 mg BID for one week.	RCT Patients diagnosed with gastritis or peptic ulcer with *H pylori* infection	N=420 12 to 16 weeks	Primary: *H pylori* eradication rates, compliance and adverse events Secondary: Not reported	Primary: *H pylori* eradication rates were similar in the esomeprazole and rabeprazole treatment groups (89.4 and 90.5%, respectively; P=0.72). Compliance rates were similar between the treatment groups (100 and 99.5% in the esomeprazole and rabeprazole groups, respectively; P=0.32). Adverse events were similar between the treatment groups (3.83 and 6.16% in the esomeprazole and rabeprazole groups, respectively; P=0.27). Secondary: Not reported
Veldhuyzen van Zanten et al.[71] (2003) Lansoprazole 30 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg BID for seven days vs placebo	DB, RCT Adult patients positive with *H pylori* and who had functional dyspepsia	N=157 12 months	Primary: Severity of dyspepsia Secondary: *H pylori* eradication rates and patients requiring additional health care use	Primary: Severity of dyspepsia was not significantly different between treatment groups after 12 months (P>0.05). Both treatment groups demonstrated improvement of symptoms throughout the study. Secondary: Lansoprazole-clarithromycin-amoxicillin therapy achieved an eradication rate of 82 vs 6% with placebo. The proportion of patients requiring additional medication after the seven-day treatment was similar between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Schwartz et al.[72] (1998) Lansoprazole 30 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg BID for 14 days vs lansoprazole 30 mg TID for 14 days vs lansoprazole 30 mg BID and clarithromycin 500 mg BID or TID for 14 days vs lansoprazole 30 mg BID or TID and amoxicillin 1,000 mg TID for 14 days	DB, RCT Adult patients positive with *H pylori* and duodenal ulcers	N=352 4 to 6 weeks	Primary: *H pylori* eradication rates Secondary: Recurrence of ulcers at six months	Primary: The eradication rates of triple therapy (lansoprazole-clarithromycin-amoxicillin; 94%) were significantly greater (P<0.05) compared to dual therapy (lansoprazole and clarithromycin or amoxicillin; 53 to 77%) and lansoprazole monotherapy (2%). Secondary: Recurrence of ulcers at six months was lower with triple therapy (7%) compared to dual therapies (13 to 23%) and lansoprazole monotherapy (69%).
Bazzoli et al.[73] (1998) Lansoprazole based *H pylori* therapies	MA Randomized trials investigating the use of lansoprazole based *H pylori*	N=1,354 (16 trials) Variable duration	Primary: *H pylori* eradication rates for lansoprazole therapies	Primary: Eradication rates for lansoprazole monotherapy (six-to eight-week duration) were comparable to dual therapy with lansoprazole (six-to eight-week duration) and amoxicillin (two- to four-week duration; OR, 0.8, 95% CI, 0.3 to 1.9 for gastric ulcers; OR, 1.5; 95% CI, 0.4 to 5.7 for duodenal ulcers).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs omeprazole based *H pylori* therapies	therapies and other PPI based *H pylori* therapies were included in the analysis		Secondary: Comparison of eradication rates for lansoprazole vs omeprazole therapy	Mean eradication rates for triple therapy with lansoprazole was significantly higher than observed with dual lansoprazole therapy (91.8 vs 57.1%; OR, 8.5; 95% CI, 2.9 to 24.5). Secondary: Mean eradication rates for lansoprazole-based therapies (80.6%) were comparable to omeprazole-based therapies (69.6%, OR, 0.9; 95% CI, 0.6 to 1.3).
Choi et al.[74] (2007) Omeprazole 20 mg BID vs pantoprazole 40 mg BID vs rabeprazole 20 mg BID vs esomeprazole 40 mg BID All patients also received clarithromycin 500 mg BID and amoxicillin 1 g BID for 1 week.	PRO, RCT Patients who underwent upper endoscopy for various gastrointestinal symptoms and were found to have *H pylori* infections by histologic exams	N=576 1 week	Primary: *H Pylori* eradication rates by PPI type and adverse events Secondary: Not reported	Primary: There was no significant difference between the eradication rates in the four groups (64.9, 69.3, 69.3, and 70.3% for omeprazole, pantoprazole, rabeprazole, and esomeprazole, respectively; P=0.517). When eradication rates were compared in all study subjects according to the presence of an ulcer or not, no significant difference was found. Adverse events were most common in the esomeprazole group (P<0.05), but the frequencies of individual symptoms were not significantly different among the four groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gisbert et al.[75] (2004) Pantoprazole based *H pylori* therapies vs lansoprazole or omeprazole based *H pylori* therapies	MA Randomized trials investigating the use of pantoprazole-based *H pylori* therapies and lansoprazole- or omeprazole-based *H pylori* therapies were included in the analysis; therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized were included	Number of trials analyzed was not reported	Primary: *H pylori* eradication rates for pantoprazole therapies Secondary: Comparison of eradication rates for pantoprazole vs other similar (same antibiotics and duration of use) PPI therapies, comparison of pantoprazole therapies to similar omeprazole and lansoprazole therapies	Primary: Fourteen-day therapy with pantoprazole 40 mg BID and clarithromycin 500 mg TID therapy resulted in a mean eradication rate of 60%. Mean eradication rates following seven-day therapies were as follows: pantoprazole-amoxicillin-clarithromycin 78%, pantoprazole-clarithromycin-nitroimidazole 84%, and pantoprazole-amoxicillin-nitroimidazole 74%. Secondary: Mean eradication rates for pantoprazole-based therapies (83%) with antibiotics was comparable to other PPI based therapies (81%; OR, 1.0; 95% CI, 0.61 to 1.64). Mean eradication rates for pantoprazole-based therapies (83%) were comparable to omeprazole-based therapies (82%; OR, 0.91; 95% CI, 0.49 to 1.69). Mean eradication rates for pantoprazole-based therapies (78%) were comparable to those with lansoprazole-based therapies (75%; OR, 1.22; 95% CI, 0.68 to 2.17).
Gisbert et al.[76] (2003) Rabeprazole based *H pylori* therapies vs lansoprazole or omeprazole based *H pylori* therapies	MA Randomized trials investigating the use of rabeprazole based *H pylori* therapies and lansoprazole or omeprazole based *H pylori* therapies were included in the analysis	Number of trials analyzed was not reported	Primary: *H pylori* eradication rates for rabeprazole therapies Secondary: Comparison of eradication rates for rabeprazole vs other similar (same antibiotics and duration of use) PPI therapies, comparison of rabeprazole	Primary: Rabeprazole dual therapy with amoxicillin for 14 days resulted in a mean eradication rate of 73%. Mean eradication rates for low-dose rabeprazole (20 mg/day) triple therapy with amoxicillin and clarithromycin for seven days was 81 and 75% with high-dose rabeprazole (40 mg/day). Mean eradication rate for rabeprazole triple therapy with a nitroimidazole and clarithromycin for seven days was 85%. Secondary: Mean eradication rate for rabeprazole-based therapies (79%) with antibiotics was comparable to other PPI-based therapies (77%; OR, 1.15; 95% CI, 0.93 to 1.42).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			therapies to similar omeprazole and lansoprazole therapies	Mean eradication rates for rabeprazole-based therapies (77%) were comparable to omeprazole-based therapies (77%; OR, 1.03; 95% CI, 0.81 to 1.32). Mean eradication rates for rabeprazole-based therapies (82%) were comparable to lansoprazole-based therapies (79%; OR, 1.17; 95% CI, 0.79 to 1.74).
Ji et al.[77] (2006) Rabeprazole 10 mg QD vs omeprazole 20 mg QD	PRO, RCT Patients ≥18 years of age with at least one, but no more than three, active gastric antral or duodenal ulcers with a diameter ≥5 to ≤30 mm, when measured by open biopsy forceps	N=112 6 weeks	Primary: The remaining ratios of the ulcer at one week of treatment Secondary: Healing rates of the ulcer at 6 weeks of treatment; effects of CYP2C19 genotypes on ulcer healing rapidity; symptom improvement or resolution	Primary: The remaining ratios of peptic ulcers observed after one week of treatment were equivalent in the two groups. The remaining ratios of ulcer were 45.5% in the rabeprazole group and 50.3% in the omeprazole group (P=0.475). Secondary: The healing rates of peptic ulcers observed after six weeks of treatment were similar in the two groups (80.6% in the rabeprazole group and 87.0% in the omeprazole group; P=0.423). CYP2C19 genotypes had no effects on the remaining ratio or peptic ulcers after one week or the healing rates of peptic ulcers after six weeks in both groups. The proportions of patients with improvement or resolution of daytime and night-time ulcer pain were comparable for both groups at one week and six weeks.
Liu et al.[78] (2013) Rabeprazole 20 mg BID vs lansoprazole 30 mg BID Both groups	AC, RCT Patients with a diagnosis of nonulcer dyspepsia (gastritis) or peptic ulcer with *H pylori* infection including both duodenal and/or gastric ulcers	N=426 7 days	Primary: Efficacy and safety of regimen for *H pylori* infection Secondary: Not reported	Primary: In an intention-to-treat analysis, 87.84% (195/222) and 85.96% (196/228) of patients in rabeprazole and lansoprazole groups, respectively, were free of *H pylori* infection after eradication therapy (P=0.56). In per protocol analysis, the *H pylori* eradication rate was 91.98% in the rabeprazole group and 91.59% in the lansoprazole group (P=0.88). There was no difference in eradication rate in the two groups. Adherence was 99.5% and 100% in the rabeprazole and lansoprazole groups respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
received amoxicillin 1 gram BID and clarithromycin 500 mg BID for seven days.				Among the 16 (7.2%) cases in the rabeprazole group who reported adverse events, taste perversion (10 cases) and dizziness (5 cases) were the most common. A total of 13 (5.70%) patients in the lansoprazole group reported adverse events and the most common complaints were taste perversion (6 cases) and dizziness (6 cases). There were no statistically significant differences in eradication rates, compliance rates, or the presence of adverse events. Secondary: Not Reported
Murakami et al.[79] (2008) Rabeprazole 10 mg BID vs lansoprazole 30 mg BID vs omeprazole 20 mg BID All patients also received amoxicillin 750 mg BID and metronidazole 250 mg BID for one week.	RCT Patients with gastric ulcers, duodenal ulcers, and gastritis, active *H pylori* infection, and failed eradication therapy with a PPI, amoxicillin and clarithromycin	N=169 4 weeks	Primary: *H pylori* eradication rates after one week of treatment and four weeks of follow-up Secondary: Not reported	Primary: *H pylori* eradication rates were not significantly different between the different PPI treatment groups (91.4% with the rabeprazole-based group, 91.1% with lansoprazole-based group, and 90.9% with omeprazole-based group). Secondary: Not reported
Kalfus et al.[80] (2020) ERADICATE Hp	DB, MC, RCT Treatment-naïve	N=118 35 days	Primary: Modified intent-to-treat (mITT) *H.*	Primary: The mITT *H. pylori* eradication rate with Talicia® of 89.4% (95% CI, 82.0 to 96.8%) was greater than both the literature-derived comparator rate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All-in-one combination of omeprazole 40 mg, amoxicillin 1000 mg, and rifabutin 50 mg (Talicia®) every 8 hours for 14 days vs placebo	adults with *H. pylori* infection and dyspepsia Forty-three treatment failures (7 and 36 subjects in the Talicia® and placebo groups, respectively) were eligible to be treated in the standard-of-care phase		*pylori* eradication rate Secondary: Safety	(P<0.001) and the standard-of-care rate of 63.0% (95% CI, 44.8 to 81.1%; P=0.006). Secondary: Adverse events with an incidence ≥5% for Talicia® were diarrhea (12.7%), headache (11.9%), chromaturia (9.3%), abdominal tenderness (6.8%), and dizziness (5.1%). No leukopenia was noted.
Graham et al.[81] (2020) ERADICATE Hp2 All-in-one combination of omeprazole 40 mg, amoxicillin 1000 mg, and rifabutin 50 mg (Talicia®) every 8 hours for 14 days vs active comparator (amoxicillin, 3 g, and omeprazole, 120 mg) every 8 hours for 14 days	DB, MC, RCT Treatment-naive adults with epigastric discomfort and confirmed *H pylori* infection	N=455 4 weeks	Primary: Between-group difference for *H pylori* eradication rate, demonstrated by ^{13}C urea breath test 4 weeks after treatment Secondary: Safety	Primary: In the intention-to-treat population, the eradication rate was higher with Talicia® than with the active comparator (228 vs 227 patients, respectively; 83.8% [95% CI, 78.4% to 88.0%] vs 57.7% [95% CI, 51.2% to 64.0%]; P<0.001). Secondary: Eradication rates were unaffected by resistance to clarithromycin or metronidazole. No rifabutin resistance was detected. The most commonly reported adverse events (incidence ≥5%) were diarrhea (10.1% Talicia® vs 7.9% with active comparator), headache (7.5% vs 7.0%), and nausea (4.8% vs 5.3%).
Lamouliatte et al.[82] (1998) Triple therapy with	PRO, RCT Adult patients positive with *H*	N=50 14 days	Primary: *H pylori* eradication rates	Primary: *H pylori* eradication rates with dual therapy (37.5%) were significantly lower than with triple therapy (95.2%; P<0.0002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lansoprazole 30 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg BID for 14 days vs dual therapy with lansoprazole 30 mg, amoxicillin 1,000 mg BID for 14 days	*pylori* and dyspepsia		Secondary: Not reported	Secondary: Not reported
Ulmer et al.[83] (2003) Triple therapy with lansoprazole, omeprazole, or pantoprazole with two other antibiotics for seven days	MA Clinical trials using PPI-based triple therapy for seven days in *H pylori* infections	N=8,383 (79 trials) 7 days	Primary: Eradication rates Secondary: Not reported	Primary: Eradication rates for all therapies were 71.9 to 83.9% in the ITT population and 78.5 to 91.2% for the per-protocol analysis. Pooled data analysis indicated that lansoprazole, omeprazole, or pantoprazole based therapies are comparable in *H pylori* eradication. Secondary: Not reported
Vergara et al.[84] (2003) Triple therapy with esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole	MA Randomized trials investigating *H pylori* triple therapy with a PPI with comparable antibiotic regimens differing only in the PPI utilized	14 trials 7 to 14 days	Primary: Direct comparison of eradication rates in the ITT population between PPIs Secondary: Not reported	Primary: Pooled eradication rates with omeprazole (74.7%) were comparable to rates observed with lansoprazole (76%; OR, 0.91; 95% CI, 0.69 to 1.21). Pooled eradication rates with omeprazole (77.9%) were comparable to rates observed with rabeprazole (81.2%; OR, 0.81; 95% CI, 0.58 to 1.15). Pooled eradication rates with omeprazole (87.7%) were comparable to rates observed with esomeprazole (89%; OR, 0.89; 95% CI, 0.58 to 1.35). Pooled eradication rates with lansoprazole (81%) were comparable to rates observed with rabeprazole (85.7%; OR, 0.77; 95% CI, 0.48 to 1.22).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Wang et al.[85] (2006) Esomeprazole-based *H pylori* therapies vs omeprazole- and pantoprazole-based *H pylori* therapies	MA RCTs investigating the use of esomeprazole-based *H pylori* therapies and other PPI-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	11 trials 1 week (*H pylori* eradication)	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: The mean *H pylori* eradication rates with esomeprazole-based therapies were comparable to that for other PPI-based regimens (86 vs 81%; OR, 1.38; 95% CI, 1.09 to 1.75). Subanalysis that included only studies comparing different doses of esomeprazole with omeprazole or pantoprazole did not reveal any statistically significant differences between the treatments. No serious adverse events were reported. Secondary: Not reported
Hsu et al.[86] (2005) Esomeprazole 40 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for one week vs pantoprazole 40 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for one week	PRO, RCT Patients ≥18 years old, infected with *H pylori*, with endoscopically proven PUD or gastritis	N=200 8 weeks (follow-up endoscopy)	Primary: *H pylori* eradication rates, adverse events and compliance Secondary: Ulcer healing	Primary: The ITT analysis demonstrated a significantly higher eradication rate for patients in the esomeprazole group compared to for the pantoprazole group (94 vs 82%; P=0.009). Both groups had a similar frequency of adverse events (15 vs 24%) and drug compliance (97 vs 96%). Secondary: Patients who had peptic ulcers diagnosed by initial endoscopy showed similar ulcer healing rates with esomeprazole (36/40) and pantoprazole (38/42) therapy.
Felga et al.[87] (2010)	OL	N=493	Primary: Eradication rates	Primary: In the ITT population, the eradication rate was 88.8% (95% CI, 86 to 92)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Omeprazole or other PPI (dose not specified) BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for one week	Patients with current or previous PUD and documented *H pylori* infection through a positive urea breath test, serology, rapid urease test, or histological examination of gastric mucosa; patients were excluded if they were <18 years of age, presented with a severe comorbidity, pregnancy, infants, patients who had previously undergone gastrectomy, allergy to study medications, and patients who used NSAIDs, antibiotic therapy, or bismuth salts up to four weeks before study inclusion.	7 days	12 weeks following completion of therapy and adverse events Secondary: Not reported	at 12 weeks and 82.7% (95% CI, 79 to 86) in the per-protocol population. Adverse events were reported in 35.5% of treated patients; however only six (7%) of these patients discontinued treatment due to adverse events. Tobacco use and NSAID use were associated with an increase in frequency of adverse events. The most commonly reported adverse events were abdominal pain, nausea, vomiting, diarrhea and taste perversion. Secondary: Not reported
McNicholl et al.[88] (2012) Rabeprazole- or esomeprazole based *H pylori*	MA RCTs investigating the use of rabeprazole- or esomeprazole-based	N=35 trials Treatment duration not reported	Primary: *H pylori* eradication rates based Secondary:	Primary: Compared to first-generation PPIs, rabeprazole demonstrated a higher eradication rate in patients with *H pylori* (80.5 vs 76.2%). The OR was 1.21 (95% CI, 1.02 to 1.42) and the NNT was 23. Esomeprazole treatment was associated with a higher *H pyl*ori eradication

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapies vs lansoprazole-, omeprazole- or pantoprazole based *H pylori* therapies	*H pylori* therapies compared to first-generation PPIs (omeprazole-lansoprazole-pantoprazole) or with one another		Not reported	compared to the first generation PPIs (82.3 vs 77.6%, respectively). The OR for eradication was 1.32 (95% CI, 1.01 to 1.73) and the NNT was 21. Subanalyses by dose indicated that only treatment with esomeprazole 40 mg BID significantly improved eradication rates compared to esomeprazole therapy with either dose (OR, 2.27; 95% CI, 1.07 to 4.82; NNT, 9). There was no statistically significant difference in *H pylori* eradication rates between rabeprazole-and esomeprazole-based treatment regimens (OR, 0.90, 95% CI, 0.70 to 1.17). The NNT was 50. There was no statistically significant difference in eradication rates with rabeprazole- or esomeprazole-based therapies in CYP2C19 poor metabolizers compared to extensive metabolizers (OR, 1.19; 95% CI, 0.73 to 1.95). Similarly, no differences in eradication rates occurred between CYP2C19 poor metabolizers and extensive metabolizers (OR, 1.76; 95% CI, 0.99 to 3.12). There was no statistically significant difference in eradication rates between rabeprazole- and esomeprazole based therapies compared to first generation PPIs with on the basis of poor CYP2C19 metabolism (OR, 0.91; 95% CI, 0.41 to 1.98). There was a statistically significant increase in *H pylori* eradication rate with rabeprazole- and esomeprazole-based regimens compared to first generation PPIs in patients who were extensive CYP2C19 metabolizers (OR, 1.37, 95% CI, 1.02 to 1.84).
Miscellaneous				
Ramdani et al.[89] (2002) Lansoprazole 30 to 120 mg/day or omeprazole 20 to	OL, PRO Adult patients with Zollinger-Ellison syndrome maintained on	N=11 7 to 10 days	Primary: Median 24-hour intragastric pH and percentage of time at or below pH 3, 4, 5, and 6	Primary: Median 24-hour intragastric pH for pantoprazole (5.3) was comparable to the median pH for lansoprazole and omeprazole (4.6 for both agents; P=0.90). There were no significant differences in percentage of time at or below pH

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 mg/day vs pantoprazole 40 to 200 mg/day All patients previously maintained on lansoprazole or omeprazole received pantoprazole for 7 to 10 days.	omeprazole or lansoprazole		Secondary: Basal acid output	3, 4, 5, and 6 between pantoprazole and lansoprazole or omeprazole (P>0.05). Secondary: Median basal acid output was similar between pantoprazole and lansoprazole or omeprazole.
Conrad et al.[90] (2005) Immediate-release omeprazole suspension (two 40 mg dose on day one then 40 mg daily thereafter) vs cimetidine intravenous (300 mg bolus then 50 mg/hour thereafter)	DB, RCT Hospitalized patients >16 years of age in intensive care units with an anticipated stay ≥72 hours with >1 additional risk for upper gastrointestinal bleed	N=359 14 days	Primary: Clinically significant upper gastrointestinal bleed Secondary: Median gastric pH, percentage of patients with median gastric pH >4, and the percentage of patients with inadequate gastric pH control	Primary: Clinically significant upper gastrointestinal bleeding was observed in seven (3.9%) of the patients taking immediate-release omeprazole compared to ten (5.5%) of the patients taking cimetidine. The upper bound of the one-sided 97.5% CI for the difference in bleeding rates was 2.8%, less than the 5% prespecified "non-inferiority" margin. Secondary: Median gastric pH was significantly higher in patients taking immediate-release omeprazole compared to cimetidine (median pH values not reported; P<0.001). A significantly higher percentage of patients on immediate-release omeprazole had median daily gastric pH>4 compared to patients on cimetidine (P≤0.01 on days 1 to 13, P=0.2 on day 14). A significantly higher percentage of patients on cimetidine had inadequate gastric pH control (58%) compared to immediate-release omeprazole (18.0%; P<0.001).
Castell et al.[91] (2005)	OL, RCT, XO Adult patients 18 to	N=36 16 days	Primary: Control of nocturnal gastric	Primary: Median percentage of time with gastric pH>4 was significantly higher with immediate-release omeprazole (54.7%) compared to pantoprazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Immediate-release omeprazole suspension dosed 40 mg daily for one week, then 20 or 40 mg BID for one day vs pantoprazole 40 mg daily for one week, then 40 mg BID for one day Study participants underwent eight days of treatment followed by a 10 to 14 day washout period. Afterwards participants underwent an additional eight days treatment on the other agent.	65 years of age with GERD with recurrent nighttime symptoms for the previous three months		acidity measured by the following: percentage of time with gastric pH>4, median gastric pH, and nocturnal acid breakthrough Secondary: Not reported	(26.5%; P<0.001). Median gastric pH was significantly higher with immediate-release omeprazole (4.7) compared to pantoprazole (2.0; P<0.001). Significantly less nocturnal acid breakthrough was observed with immediate-release omeprazole (53.1%) compared to pantoprazole (78.1%; P=0.005). Secondary: Not reported
Regula et al.[92] (2006) Omeprazole 20 mg QD vs pantoprazole 20 mg QD	DB, MC, PG, RCT Rheumatic patients >55 years of age on continual NSAIDs and with ≥1 recognized risk factor that contributes to the development of gastrointestinal	N=595 6 months	Primary: Therapeutic failure (peptic ulcer, >10 erosions or petechiae in the stomach or duodenum, reflux esophagitis, or discontinuation due to gastrointestinal	Primary: After six months, the probabilities of remaining in remission were 90% with pantoprazole 20 mg, 93% with pantoprazole 40 mg and 89% with omeprazole for lack of therapeutic failure (P values not reported). After six months, the probabilities of remaining in remission were 91% with pantoprazole 20 mg, 95% with pantoprazole 40 mg and 93% with omeprazole for lack of endoscopic failure (P values not reported). During the study, a similar proportion of patients reported adverse events in each treatment group (29% of patients receiving pantoprazole 20 mg;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pantoprazole 40 mg QD	injury; patients were excluded if they had Zollinger-Ellison syndrome, esophageal structures, previous surgery of the gastrointestinal tract, current peptic ulcer or peptic ulcer complication		symptoms or an adverse event) and lack of endoscopic failure at six months and adverse events Secondary: Primary end points at three months	37% of patients receiving pantoprazole 40 mg and 33% of patients receiving omeprazole; P values not reported). Secondary: After three months, the probabilities of remaining in remission were 94% with pantoprazole 20 mg, 97% with pantoprazole 40 mg and 94% with omeprazole for lack of therapeutic failure (P values not reported). After three months, the probabilities of remaining in remission were 96% with pantoprazole 20 mg, 99% with pantoprazole 40 mg and 96% with omeprazole for lack of endoscopic failure (P values not reported).
Chan et al.[93] (2017) Rabeprazole 20 mg vs famotidine 40 mg All patients received aspirin 80 mg QD	DB, RCT Users of low-dose aspirin (≤325 mg/day) with a history of endoscopically confirmed ulcer bleeding with negative results from tests for *H pylori* after healing of ulcers	N=270 12 months	Primary: Composite of recurrent upper GI bleeding or recurrent endoscopic ulcers at month 12 Secondary: Lower GI bleed incidence	Primary: Nine patients (7.9%; 95% CI, 4.2 to 14.7%) receiving rabeprazole and 13 patients (12.4%; 95% CI, 7.4 to 20.4%) receiving famotidine had recurrent upper GI bleeding or endoscopic ulcers at month 12 (P=0.26). The cumulative incidence of upper GI bleeding during the 12-month study was 0.7% (95% CI, 0.1 to 5.1% in the rabeprazole group and 3.1% (95% CI, 1.2 to 8.1%) in the famotidine group (P=0.16). Secondary: The cumulative incidence of lower GI bleeding was 1.5% in the rabeprazole group and 1.6% in the famotidine group (P=0.96).

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ITT=intent-to-treat, MA=meta-analysis, MC=multicenter, NNT=number needed to treat, OL=open-label, OR, odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PP=Per Protocol, PRO=prospective, RCT=randomized controlled trial, RR=rate ratio, SB=single-blind, SC=single center, XO=crossover
Miscellaneous abbreviations: GERD=gastroesophageal reflux disease, NSAID=nonsteroidal antiinflammatory drug, PPI=proton pump inhibitor, PUD=peptic ulcer disease

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
Nelson et al. conducted an analysis of the impact of converting patients with gastroesophageal reflux disease (GERD) from omeprazole to lansoprazole through a managed care plan policy.[94] Patients converted were surveyed by telephone prior to the interchange and 30 days after the interchange. Survey questions focused on heartburn symptoms while awake, at night, the use of over the counter (OTC) heartburn preparations, diet changes due to heartburn, and patient satisfaction. After the interchange, an increased frequency of heartburn was reported in 35% of the patients while awake, 9% reported an increased frequency of heartburn that kept them from falling asleep, 33% reported an increased frequency in the use of OTC heartburn preparations, and 13% reported an increased frequency in diet modifications due to heartburn symptoms. Mean patient satisfaction scores based on a 10-point scale decreased significantly from baseline (9.00 vs 7.29; P<0.001).

Impact on Physician Visits
Meineche-Schmidt evaluated health care resource utilization following the use of double doses of omeprazole.[95] Patients with dyspepsia received omeprazole 40 mg once daily, omeprazole 20 mg once daily, or placebo for two weeks. Complete symptom relief was comparable between omeprazole 40 mg (66.4%) and omeprazole 20 mg (63.0%; 95% confidence interval, -4.5 to 11.4). Relapse rates after 12 months were comparable between the groups (67.7% for omeprazole 40 mg, 34.7% for omeprazole 20 mg, and 63.3% for placebo). There was no difference in the number of contacts with the general practitioner, referrals to specialists, hospitals, or use of dyspepsia medications.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the Proton-Pump Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Dexlansoprazole	delayed-release capsule	Dexilant®*	$$$$$	$$$$$
Esomeprazole magnesium	delayed-release capsule, delayed-release powder for suspension, injection	Nexium®*	$$$$$	$$
Esomeprazole	injection^	Nexium I.V.®*	$$$$$	$$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
sodium				
Lansoprazole	delayed-release capsule, delayed-release orally disintegrating tablet	Prevacid®*	$$$$$	$$$
Omeprazole	delayed-release capsule, delayed-release powder for suspension	Prilosec®*	$$$$$	$
Pantoprazole	delayed-release tablet, delayed-release granules for suspension, injection	Protonix®*, Protonix IV®*	$$$$$	$
Rabeprazole	delayed-release tablet	Aciphex®*	$$$$$	$
Combination Products				
Omeprazole, amoxicillin and rifabutin	delayed-release capsule	Talicia®	$$$$$	N/A
Omeprazole, clarithromycin, and amoxicillin	combination pack	Omeclamox-Pak®	$	N/A
Omeprazole and sodium bicarbonate	capsule§, powder packet	N/A	N/A	$$
Lansoprazole, amoxicillin, and clarithromycin	combination pack	N/A	N/A	$$$$$

*Generic is available in at least one dosage form or strength.
§Generic product requires prior authorization.

X. Conclusions

The proton-pump inhibitors (PPIs) are potent inhibitors of gastric acid secretion and have been shown to be effective for the treatment of a variety of acid-related disorders. All agents with the exception of omeprazole/amoxicillin/rifabutin delayed-release capsule and omeprazole/clarithromycin/amoxicillin combination package are available in a generic formulation.

PPIs are currently marketed in a variety of dosage formulations. All PPIs are available in delayed-release oral formulations, with the exception of esomeprazole, and can be dosed once daily. In addition, esomeprazole, omeprazole, and pantoprazole are available in a delayed-release oral suspension. Esomeprazole and pantoprazole are also available in intravenous formulations for short-term use in patients unable to take medications by mouth.

Guidelines recognize that the PPIs are more effective than histamine H_2-receptor antagonists for the treatment of erosive esophagitis and symptomatic gastroesophageal reflux disease (GERD).[19-21,25-26] Clinical trials have demonstrated similar efficacy among the PPIs for these indications.[29,33-34,39,41-43,47,52-53,57,59-61,63-66] While some studies have demonstrated greater efficacy with one PPI over another, the overall differences are small (often ranging from 3 to 9%).[32,35,36-38,40,44,48,51,56,61] Although the results are statistically significant, the clinical significance of these differences is not clear. It should be noted that most of the comparative trials of the PPIs evaluated Food and Drug Administration (FDA)-approved doses. However, therapeutically equivalent doses of the PPIs have not been well established. Guidelines do not give preference to one PPI over another for the treatment of erosive esophagitis or symptomatic GERD.[19-21,25-26]

Guidelines recommend the use of a PPI in combination with antibiotics as first-line therapy for the treatment of patients with *H pylori* infection and duodenal ulcer disease to eradicate *H pylori*.[22-24] Clinical trials have generally demonstrated similar efficacy among the PPIs for this indication.[68-70,73-79,83-85] Some studies have shown a significantly greater decrease in *H Pylori* eradication rate with one PPI compared to another; however, the clinical significance of these results are not clear.[86,88] Guidelines do not give preference to one PPI over another for the eradication of *H pylori*.[22-24]

In August 2010, the prescribing information was updated to include information on the risk of osteoporosis-related fractures of the hip, wrist, or spine.[1-12] The risk was increased in patients who received high-dose (i.e., multiple daily doses) and long-term therapy (≥1 year). It is recommended that patients use the lowest dose and shortest duration of therapy appropriate to the condition being treated. In March 2011, the FDA notified healthcare providers that the PPIs may cause hypomagnesemia if taken for prolonged periods of time (≥1 year).[17] The FDA recommends obtaining serum magnesium levels prior to the initiation of therapy, as well as periodically thereafter, in patients expected to be on PPIs for long periods of time. It is also recommended that magnesium levels be obtained in patients who are taking digoxin, diuretics, or other drugs that may cause hypomagnesemia. Additionally, in November 2014 the prescribing information was updated to include information on the risk of acute interstitial nephritis and vitamin B12 deficiency. Acute interstitial nephritis is generally attributed to an idiopathic hypersensitivity reaction, and vitamin B12 deficiency occurs rarely in patients taking acid-suppressing medications longer than three years. [1-12] In July 2017 a warning for reports of cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) patients taking PPIs was added to the package insert. [1-12] These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving a PPI, discontinue the drug and refer the patient to the appropriate specialist for evaluation. An additional warning for fundic gland polyps was added in June 2018. PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Use the shortest duration of PPI therapy appropriate to the condition being treated.[1-12] Warnings were also added for acute tubulointerstitial nephritis, severe cutaneous adverse reactions, and hypomagnesemia and mineral metabolism since the last review.[1-12]

There is insufficient evidence to support that one brand proton-pump inhibitor is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand proton-pump inhibitors within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand proton-pump inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Calcitonin Gene-Related Peptide (CGRP) Antagonists
AHFS Class 283212
November 9, 2022

I. Overview

Migraine is a brain condition marked by attacks of moderate to severe throbbing headache with associated symptoms that may include nausea, vomiting, photophobia, and phonophobia.[1-3] Migraines may present with or without aura. Migraine with aura is primarily characterized by the focal neurological symptoms that usually precede or accompany the headache.[2] Patients with migraine can be diagnosed with chronic migraine, which is characterized by 15 or more headache days per month for at least three months, with migraine features present on at least eight days per month.[2] Migraine not subclassified as chronic migraine has been called episodic migraine.

Calcitonin gene-related peptide (CGRP) is a 37-amino acid peptide which functions as a neurotransmitter in the central and peripheral nervous system and as a vasodilator. There have been several approaches in the development of agents that target this pathway including the investigation of small molecule CGRP receptor antagonists for the treatment of acute migraine attacks as well as monoclonal antibodies, such as erenumab-aooe, for use in migraine prevention.[4] CGRP has been thought to play a causal role in pain modulation as well as migraine pathophysiology.[4] Atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, and rimegepant are all indicated for the preventive treatment of migraine in adults. Galcanezumab is also indicated for the treatment of episodic cluster headache in adults. Rimegepant and ubrogepant are indicated for the acute treatment of migraine with or without aura in adults.[5-13]

The calcitonin gene-related peptide (CGRP) antagonists included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. No agents are available in a generic formulation. This class was last reviewed in August 2020.

Table 1. CGRP Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Atogepant	tablet	Qulipta®	none
Eptinezumab-jjmr	injection	Vyepti®	none
Erenumab-aooe	injection	Aimovig®	Aimovig®CC
Fremanezumab-vfrm	injection	Ajovy®	Ajovy®CC
Galcanezumab-gnlm	injection	Emgality®	none
Rimegepant	sublingual tablet	Nurtec ODT®	none
Ubrogepant	tablet	Ubrelvy®	none

PDL=Preferred Drug List
[cc]Denotes agent is preferred with clinical criteria in place.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the CGRP antagonists are summarized in Table 2.

Table 2. Treatment Guidelines using the CGRP Antagonists

Clinical Guideline	Recommendation(s)
American Academy of Neurology and the American Headache Society: **Pharmacological Treatment for Pediatric Migraine Prevention**	Pediatric migraine prevention • Clinicians should inform patients and caregivers that in clinical trials of preventive treatments for pediatric migraine, many children and adolescents who received placebo improved and most preventive medications were not superior to placebo. • Clinicians should engage in shared decision-making regarding the use of short-term treatment trials (a minimum of two months) for those who could benefit from preventive treatment.

Clinical Guideline	Recommendation(s)
(2019) and **Acute Treatment of Migraine in Children and Adolescents (2018)**[14,15]	• Clinicians should discuss the evidence for amitriptyline combined with cognitive behavioral treatment (CBT) for migraine prevention, inform patients of the potential side effects of amitriptyline including risk of suicide, and work with families to identify providers who can offer this type of treatment. • Clinicians should discuss the evidence for topiramate and propranolol for migraine prevention in children and adolescents and their side effects in this population. • There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents. • Clinicians must consider the teratogenic effects of topiramate and valproate in their choice of migraine prevention therapy recommendations to patients of childbearing potential. • Clinicians must recommend daily folic acid supplementation to patients of childbearing potential who take topiramate or valproate. <u>Pediatric migraine treatment</u> • Clinicians should prescribe ibuprofen oral solution (10 mg/kg) as an initial treatment option to reduce pain in children and adolescents with migraine. • For adolescents with migraine, clinicians should prescribe sumatriptan/naproxen tablet, zolmitriptan nasal spray (NS), sumatriptan NS, rizatriptan orally disintegrating tablet, or almotriptan tablet to reduce headache pain. • Clinicians should counsel patients and families that a series of medications may need to be used to find treatments that most benefit the patient. • Clinicians should offer an alternate triptan, if one triptan fails to provide pain relief, to find the most effective agent to reduce migraine symptoms. • Clinicians may prescribe a nonoral route when headache peaks in severity quickly, is accompanied by nausea or vomiting, or oral formulations fail to provide relief. • Clinicians should counsel patients and families that if their headache is successfully treated by their acute migraine medication, but headache recurs within 24 hours of their initial treatment, taking a second dose of acute migraine medication can treat the recurrent headache. • In adolescents whose migraine is incompletely responsive to a triptan, clinicians should offer ibuprofen or naproxen in addition to a triptan to improve migraine relief. • Clinicians must not prescribe triptans to those with a history of ischemic vascular disease or accessory conduction pathway disorders to avoid the morbidity and mortality associated with aggravating these conditions. • Clinicians may consider referral of children and adolescents with hemiplegic migraine or migraine with brainstem aura who do not respond to other treatments to a headache specialist to find effective treatment.
American Academy of Family Physicians: **Migraine Headache Prophylaxis (2019)** and **Acute Migraine Headache: Treatment Strategies (2019)**[16,17]	<u>Migraine headache prophylaxis</u> • First-line agents for prophylactic treatment include: divalproex, metoprolol, propranolol, timolol, and topiramate. • Second-line agent for prophylactic treatment include: amitriptyline, atenolol, nadolol, and venlafaxine. • Frovatriptan is a first-line treatment for the prevention of menstrual-associated migraines. Naratriptan and zolmitriptan are second-line treatments for the same indication. • Amitriptyline is considered an option for patients with depression or insomnia and is the only tricyclic antidepressant that has substantial data that supports its effectiveness. <u>Acute treatment</u> • First-line treatment options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan,

Clinical Guideline	Recommendation(s)
	rizatriptan, sumatriptan, and zolmitriptan), and combined regimens (e.g., acetaminophen/aspirin/caffeine and sumatriptan/naproxen). ▪ Eletriptan has the least cardiovascular risk. ▪ Frovatriptan is recommended for menstrual migraine. • Second-line treatment options include antiemetics, intranasal dihydroergotamine, and ketorolac. • Options for refractory migraine include intravenous dexamethasone, parenteral dihydroergotamine, intravenous magnesium sulfate, opioids, and intravenous valproate.
American Academy of Neurology and the American Headache Society: **Evidence-based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults (2012)**[18] (Reaffirmed July 2015)	• The following medications are established as effective and should be offered for migraine prevention: o Antiepileptic drugs: divalproex sodium, sodium valproate, topiramate. o β-blockers: metoprolol, propranolol, timolol o Triptans: frovatriptan for short-term menstrually associated migraine prevention. • The following medications are probably effective and should be considered for migraine prevention: o Antidepressants: amitriptyline, venlafaxine. o β-blockers: atenolol, nadolol. o Triptans: naratriptan, zolmitriptan for short-term menstrually associated migraine prevention. • The following medications are possibly effective and may be considered for migraine prevention: o Angiotensin converting enzyme inhibitors: lisinopril. o Angiotensin receptor blockers: candesartan. o α 1 agonists: clonidine, guanfacine. o Antiepileptic drugs: carbamazepine. o β-blockers: nebivolol, pindolol. • Evidence is conflicting or inadequate to support or refute the use of the following medications for migraine prevention: o Antiepileptic drugs: gabapentin. o Antidepressants: ▪ Selective serotonin reuptake inhibitor/selective/serotonin-norepinephrine reuptake inhibitors: fluoxetine, fluvoxamine. ▪ Tricyclics: protriptyline. o Antithrombotics: acenocoumarol, Coumadin, picotamide. o β-blockers: bisoprolol. o Calcium-channel blockers: nicardipine, nifedipine, nimodipine, verapamil. o Acetazolamide. o Cyclandelate. • The following medication is established as ineffective and should not be offered for migraine prevention: o Lamotrigine. • The following medication is probably ineffective and should not be considered for migraine prevention: o Clomipramine. • The following medications are possibly ineffective and may not be considered for migraine prevention: o Acebutolol. o Clonazepam. o Nabumetone. o Oxcarbazepine. o Telmisartan.
American Headache Society Consensus Statement:	Prophylactic treatment • Established Efficacy o Oral: Candesartan, divalproex, metoprolol, propranolol, timolol, topiramate,

Clinical Guideline	Recommendation(s)
Update on integrating new migraine treatments into clinical practice (2021)[19]	valproate sodium ○ Parenteral: Eptinezumab, erenumab, fremanezumaab, calcanezumab, onabotulinumtoxin A • Probably Effective ○ Oral: Amitriptyline, atenolol, lisinopril, memantine, nadolol, venlafaxine ○ Parenteral: Onabotulinumtoxin A + CGRP mAb Acute treatment • Established Efficacy ○ Migraine Specific: Triptans, ergotamine derivatives, CGRPs, lasmiditan ○ Nonspecific: ▪ NSAIDs (ASA, celecoxib oral solution, diclofenac, ibuprofen, naproxen) ▪ Combination analgesic (APAP + ASA + caffeine) • Probably Effective ○ Migraine Specific: Ergotamine, other forms of dihydroergotamine ○ Nonspecific ▪ NSAIDs (flurbiprofen, ketoprofen, IV/IM ketorolac) ▪ IV magnesium ▪ Isometheptene-containing compounds ▪ Antiemetics (chlorpromazine, metoclopramide, promethazine)

ACEI=angiotensin converting enzyme inhibitors, AEDs=antiepileptic drugs, ARBs=angiotensin receptor blockers, MAMs=menstrual-associated migraines, NSAIDs= non-steroidal antiinflammatory drugs

III. Indications

The Food and Drug Administration (FDA)-approved indications for the CGRP antagonists are noted in Table 3.

Table 3. FDA-Approved Indications for the CGRP Antagonists[7-13]

Indication	Atogepant	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab	Rimegepant	Ubrogepant
The acute treatment of migraine with or without aura in adults						✔	✔
The preventive treatment of migraine in adults		✔	✔	✔	✔		
The preventive treatment of episodic migraine in adults	✔					✔	
The treatment of episodic cluster headache in adults					✔		

IV. Pharmacokinetics

The pharmacokinetic parameters of the CGRP antagonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the CGRP Antagonists[6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Atogepant	Not reported	Not reported	Hepatic (% not reported)	Feces (42); Renal (5)	11 hours
Eptinezumab	Not reported	Not reported	Not reported	Not reported	27 days

Erenumab	82	Not reported	Not reported	Not reported	28 days
Fremanezumab	Not reported	Not reported	Not reported	Not reported	31 days
Galcanezumab	Not reported	Not reported	Not reported	Not reported	27 days
Rimegepant	64	95	Not reported	Feces (78); Renal (24)	11 hours
Ubrogepant	Not reported	87	Hepatic (% not reported)	Feces (42); Renal (6)	5 to 7 hours

V. Drug Interactions

Major drug interactions with the CGRP antagonists are listed in Table 5.

Table 5. Major Drug Interactions with the CGRP Antagonists[5,6]

Generic Name(s)	Interaction	Mechanism
Atogepant, rimegepant, ubrogepant	CYP3A4 inhibitors	Concomitant administration with inhibitors of CYP3A4 may result in increased exposure.
Atogepant, rimegepant	CYP3A inducers	Concomitant administration with strong or moderate inducers of CYP3A can result in a significant reduction in exposure, which may lead to loss of efficacy of the CGRP antagonist.
Atogepant	Rifampin	Concurrent use of atogepant and rifampin may result in reduced and/or increased atogepant exposure.
Atogepant	OATP inhibitors	Concurrent use of atogepant and OATP inhibitors (e.g., gemfibrozil, cyclosporine, eltrombopag) may result in increased exposure to atogepant.
Rimegepant, ubrogepant	P-gp and BCRP inhibitors	Rimegepant and ubrogepant are substrates of P-gp and BCRP efflux transporters. Concomitant administration with inhibitors of P-gp or BCRP may result in a significant increase in rimegepant/ ubrogepant exposure.
Ubrogepant	CYP3A4 inducers	Concomitant administration of ubrogepant with inducers of CYP3A can result in a reduction in ubrogepant exposure, which may lead to loss of efficacy of ubrogepant.

VI. Adverse Drug Events

The most common adverse drug events reported with the CGRP antagonists are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the CGRP Antagonists[5]

Adverse Events	Atogepant	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab	Rimegepant	Ubrogepant
Gastrointestinal							
Constipation	6	-	3	-	-	-	-
Decreased appetite	1 to 2	-	-	-	-	-	-
Dry mouth	-	-	-	-	-	-	<1 to 2
Nausea	5 to 9	2	-	-	-	✔	2 to 4
Weight loss	4 to 5	-	-	-	-	-	-
Musculoskeletal							
Muscle cramps	-	-	≤2	-	-	-	-
Muscle spasm	-	-	≤2	-	-	-	-
Other							
Antibody development	-	18 to 21	3 to 6	≤2	5 to 13	-	-
Drowsiness	≤6	-	-	-	-	-	-
Fatigue	≤6	2	-	-	-	-	-
Hypersensitivity reaction	-	1 to 2	✔	✔	✔	✔	-
Injection site reaction	-	-	5 to 6	43 to 45	18	-	-

Adverse Events	Atogepant	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab	Rimegepant	Ubrogepant
Nasopharyngitis		8	-	-	-	-	-
Somnolence	-	-	-	-	-	-	2 to 3

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the CGRP antagonists are listed in Table 7.

Table 7. Usual Dosing Regimens for the CGRP Antagonists[5-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Atogepant	Preventive treatment of episodic migraine: Tablet: 10 mg, 30 mg, or 60 mg taken orally once daily with or without food	Safety and effectiveness in pediatric patients have not been established.	Tablet: 10 mg 30 mg 60 mg
Eptinezumab-jjmr	Preventive treatment of migraine: Injection: 100 mg administered by intravenous infusion every three months; some patients may benefit from a dosage of 300 mg administered by intravenous infusion every three months	Safety and effectiveness in pediatric patients have not been established.	Injection: 100 mg/mL
Erenumab	Preventive treatment of migraine: Injection: 70 mg injected subcutaneously once monthly; some patients may benefit from a dosage of 140 mg injected subcutaneously once monthly	Safety and effectiveness in pediatric patients have not been established.	Injection: 70 mg/mL 140 mg/mL
Fremanezumab	Preventive treatment of migraine: Injection: 225 mg injected subcutaneously once monthly; or 675 mg every three months, which is administered as three consecutive subcutaneous injections of 225 mg each	Safety and effectiveness in pediatric patients have not been established.	Injection: 225 mg/1.5 mL
Galcanezumab	Preventive treatment of migraine: Injection: 240 mg (two consecutive subcutaneous injections of 120 mg each) once as a loading dose, followed by 120 mg injected subcutaneously once monthly Treatment of episodic cluster headache in adults: Injection: 300 mg (three consecutive subcutaneous injections of 100 mg each) at the onset of the cluster period, and then monthly until the end of the cluster period	Safety and effectiveness in pediatric patients have not been established.	Injection: 100 mg/mL 120 mg/mL
Rimegepant	Acute treatment of migraine: Sublingual tablet: 75 mg taken orally. The maximum dose in a 24-hour period is 75 mg	Safety and effectiveness in pediatric patients have not been established.	Sublingual tablet: 75 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Preventive treatment of episodic migraine: Sublingual tablet: 75 mg taken orally every other day		
Ubrogepant	Acute treatment of migraine: Tablet: 50 mg or 100 mg taken orally; if needed, a second dose may be taken at least two hours after the initial dose. The maximum dose in a 24-hour period is 200 mg	Safety and effectiveness in pediatric patients have not been established.	Tablet: 50 mg 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the CGRP antagonists are summarized in Table 8.

Table 8. Comparative Clinical Trials with the CGRP Antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ailani et al.[20] (2021) ADVANCE Atogepant 10 mg orally once daily vs atogepant 30 mg orally once daily vs atogepant 60 mg orally once daily vs placebo	DB, MC, PC, RCT Adults 18 to 80 years of age with four to 14 migraine days per month	N=910 12 weeks	Primary: Change from baseline in the mean number of migraine days per month across the 12 weeks Secondary: Headache days per month, a reduction from baseline of at least 50% in the 3-month average of migraine days per month, quality of life, and scores on the Activity Impairment in Migraine-Diary	Primary: The mean change from baseline in the mean number of migraine days per month across the 12-week treatment period was −3.7 with 10 mg atogepant, −3.9 with 30 mg atogepant, −4.2 with 60 mg atogepant, and −2.5 with placebo. The mean difference from placebo was −1.2 days with 10 mg atogepant (95% CI, −1.8 to −0.6), −1.4 days with 30 mg atogepant (95% CI, −1.9 to −0.8), and −1.7 days with 60 mg atogepant (95% CI, −2.3 to −1.2) (P<0.001 for all comparisons with placebo). Secondary: The mean change from baseline in the mean number of headache days per month across the 12-week treatment period was −3.9 for 10 mg atogepant, −4.0 for 30 mg atogepant, −4.2 for 60 mg atogepant, and −2.5 for placebo (P<0.001 for all comparisons with placebo). The mean change from baseline in the mean number of days of use of medication for the treatment of migraine attacks per month across the 12-week treatment period was −3.7 for 10 mg atogepant, −3.7 for 30 mg atogepant, −3.9 for 60 mg atogepant, and −2.4 for placebo (P<0.001 for all comparisons with placebo). A reduction of 50% or more in the 3-month average of migraine days per month occurred in 55.6% of the participants in the 10 mg atogepant group, 58.7% of those in the 30 mg atogepant group, 60.8% of those in the 60 mg atogepant group, and 29.0% of those in the placebo group (P<0.001 for all comparisons with placebo). Significant differences between all three atogepant doses and placebo were observed for the secondary end points, with the exception of the score on the Performance of Daily Activities domain of the AIM-D (difference, −1.2; 95% CI, −2.6 to 0.2) and the score on the Physical Impairment domain of the AIM-D (difference, −1.1; 95% CI, −2.3 to 0.1) for 10-mg atogepant.
Ashina et al.[21] (2020) PROMISE-1	DB, MC, PC, RCT Adults 18 to 75 years of age with a	N=888 56 weeks	Primary: Change from baseline in monthly migraine days over	Primary: Eptinezumab 100 mg and 300 mg demonstrated statistically significant reduction from baseline in the frequency of migraine days during weeks one to 12 compared to placebo (eptinezumab 30 mg, −0.82; 95% CI, −1.39

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Eptinezumab 30 mg IV every 12 weeks vs eptinezumab 100 mg IV every 12 weeks vs eptinezumab 300 mg IV every 12 weeks vs placebo	diagnosis of migraine per the International Classification of Headache Disorders criteria at or before the age of 50 years with four to 14 migraine days per month		weeks one to 12 Secondary: Migraine responder rates	to −0.25; P=0.0046 vs placebo [unadjusted]; eptinezumab 100 mg, −0.69; 95% CI, −1.25 to −0.12; P=0.0182 vs placebo; eptinezumab 300 mg, −1.11; 95% CI, −1.68 to −0.54; P=0.0001 vs placebo). Eptinezumab 30 mg did not reach statistical significance per the testing hierarchy. Secondary: For weeks one to 12, corresponding ≥75% responder rates were 24.7%, 22.2%, 29.7%, and 16.2%, for 30 mg, 100 mg, 300 mg, and placebo, respectively. The ≥50% migraine responder rates for weeks one to 12 were 50.2% for eptinezumab 30 mg, 49.8% for eptinezumab 100 mg, 56.3% for eptinezumab 300 mg, and 37.4% for placebo. Data from the eptinezumab 300 mg treatment group demonstrated that monthly ≥75% migraine responder rates were sustained throughout the 12-week interval (31.5% during weeks one to four and 29.7% during weeks one to 12).
Lipton et al.[22] (2020) PROMISE-2 Eptinezumab 100 mg IV every 12 weeks vs eptinezumab 300 mg IV every 12 weeks vs placebo	DB, MC, PC, RCT Adults 18 to 65 years of age with a diagnosis of migraine per the International Classification of Headache Disorders criteria at or before the age of 50 years	N=1,072 12 weeks	Primary: Change from baseline in mean monthly migraine days over weeks one to 12 Secondary: Migraine responder rates	Primary: Both 100 and 300 mg of eptinezumab demonstrated statistically significant reductions in monthly migraine days during weeks 1 to 12 (P<0.0001). Monthly migraine days decreased from 16.1 to 8.5 days in the eptinezumab 100 mg group, from 16.1 to 7.9 days in the eptinezumab 300 mg group, and from 16.2 to 10.5 days in the placebo group. Secondary: Patients in both eptinezumab dose groups were more likely to achieve ≥75% migraine response during weeks one to four than were patients in the placebo group (common odds ratios, 2.4; 95% CI, 1.7 to 3.5 for eptinezumab 100 mg and 3.2; 95% CI 2.2 to 4.6 for eptinezumab 300 mg). They also were more likely to achieve ≥75% migraine response during weeks one to 12 (common odds ratios, 2.0; 95% CI, 1.4 to 3.0 for eptinezumab 100 mg and 2.8; 95% CI, 1.9 to 4.0 for eptinezumab 300 mg) and ≥50% migraine response during weeks one to 12 (common odds ratios, 2.1; 95% CI, 1.6 to 2.8 for eptinezumab 100 mg and 2.4; 95% CI, 1.8 to 3.3 for eptinezumab 300 mg).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ashina et al.[23] (2022) DELIVER Eptinezumab 100 mg IV every 12 weeks vs eptinezumab 300 mg IV every 12 weeks vs placebo	DB, MC, RCT Adults with episodic or chronic migraine with at least four monthly migraine days (as per International Headache Society guidelines) and documented evidence of two-to-four previous preventive treatment failures within the past 10 years	N=891 24 weeks	Primary: Change from baseline in mean monthly migraine days over weeks one to 12 Secondary: Migraine responder rates	Primary: The change from baseline to weeks one to 12 in mean monthly migraine days was –4.8 with eptinezumab 100 mg, –5.3 with eptinezumab 300 mg, and –2.1 with placebo. The difference from placebo in change in mean monthly migraine days from baseline was significant with eptinezumab 100 mg (–2.7; 95% CI, –3.4 to –2.0; P<0.0001) and eptinezumab 300 mg (–3.2; 95% CI, –3.9 to –2.5; P<0.0001). Secondary: Patients treated with eptinezumab were significantly more likely than those treated with placebo to have a reduction of at least 50% and at least 75% from baseline in monthly migraine days following the first infusion (P<0.001 for all comparisons).
Goadsby et al.[24] (2017) STRIVE Erenumab 70 mg SC monthly vs erenumab 140 mg SC monthly vs placebo	DB, MC, PC, PG, RCT Adults 18 to 65 years of age with a history of episodic migraine with or without aura for at least 12 months before screening. Patients had to have at least four and fewer than 15 migraine days per month and fewer than 15 migraine days per month on average during the three-month period before screening	N=955 6 months	Primary: Change from baseline to months four through six in the mean number of migraine days per month Secondary: Reduction from baseline of 50% or greater in mean migraine days over months four to six, change from baseline in the number of days of use of acute migraine-specific medication over	Primary: The mean number of migraine days per month at baseline was reduced by 3.2 in the 70 mg erenumab group and by 3.7 in the 140 mg erenumab group, as compared to 1.8 days in the placebo group (P<0.001 for each dose vs placebo). Secondary: A 50% or greater reduction in the mean number of migraine days per month was achieved for 43.3% of patients in the 70 mg erenumab group and 50.0% of patients in the 140 mg erenumab group, as compared with 26.6% in the placebo group (P<0.001 for each dose vs placebo). The change from baseline in the monthly acute migraine-specific medication days was reduced by 1.1 in the 70 mg erenumab group and by 1.6 in the 140 mg erenumab group, as compared to 0.2 days in the placebo group (P<0.001 for each dose vs placebo). Physical-impairment scores improved by 4.2 and 4.8 in the 70 mg and 140 mg erenumab groups, respectively, as compared with 2.4 points in the placebo group (P<0.001 for each dose vs placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	and had to demonstrate at least 80% adherence to reporting with an electronic diary during the four-week baseline phase Individuals with prior treatment failures were allowed in the study except when there was no therapeutic response to > two classes of migraine prevention treatment. Protocol amendment during enrollment phase allowed individuals to have concomitant use of one migraine-preventative medication (if no changes to dose within two months of baseline phase or any time during the trial)		months four to six, change from baseline in scores on the physical-impairment and everyday-activities domains of the MPFID over months four to six (scale 0 to 100, with higher scores representing greater migraine burden on functioning)	Every day-activities scores improved by 5.5 and 5.9 points in the 70 mg and 140 mg erenumab groups, respectively, as compared with 3.3 points in the placebo group (P<0.001 for each dose vs placebo). The rates of adverse events were similar between erenumab and placebo. A total of 35 of the 628 patients (5.6%) for whom postbaseline antibody data were available tested positive for anti-erenumab binding antibodies (8.0% in the 70 mg group and 3.0% in the 140 mg group). One patient in the 70 mg group tested positive for neutralizing antibodies (0.2%).
Dodick et al.[25] (2018) ARISE Erenumab 70 mg	DB, MC, PC, RCT Adults 18 to 65 years of age with a history of episodic	N=577 3 months	Primary: Change from baseline in monthly migraine days at month three	Primary: Individuals receiving erenumab experienced a reduction of 2.9 monthly migraine days from baseline compared with a reduction of 1.8 days for placebo (LS mean treatment difference, -1.0; 95% CI, -1.6 to -0.5; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SC monthly vs placebo	migraine (≥4 to <15 migraine days/month and <15 headache days/month) with or without aura for at least 12 months before screening Individuals with prior treatment failures were allowed in the study except when there was no therapeutic response to > two classes of migraine prevention treatment. Protocol amendment during enrollment phase allowed individuals to have concomitant use of one migraine-preventative medication (if no changes to dose within two months of baseline phase or any time during the trial).		Secondary: Change from baseline at month three for the following: reduction of 50% or greater in monthly migraine days per month, change in acute migraine-specific medication treatment days, and ≥ five-point score reduction in Physical Impairment and Impact on Everyday Activities domain scores measured by the MPFID	Secondary: A ≥ 50% reduction in monthly migraine days was achieved by 39.7% in the erenumab group and 29.5% in the placebo group (OR, 1.59; 95% CI, 1.12 to 2.27; P=0.010). Migraine-specific medication treatment days were reduced by 1.2 for the erenumab group and 0.6 for the placebo group, given a treatment difference of -0.6 (95% CI, -1.0 to -0.2; P=0.002). The ≥ 5-point reduction rates in MPFID-Physical Impairment were 33.0% and 27.1% (OR, 1.33; 95% CI, 0.92 to 1.90, P=0.13). The ≥ 5-point reduction rates in MPFID-Everyday Activities were 40.4% and 35.8% (OR, 1.22; 95% CI, 0.87 to 1.71, P=0.26). Most frequent adverse events were upper respiratory tract infection, injection site pain and nasopharyngitis. These were similar to placebo. Twelve erenumab-treated patients (4.3%) developed anti-erenumab-binding antibodies through week 12.
Tepper et al.[26] (2017) Erenumab 70 mg	DB, MC, PC, RCT Patients from 18 to 65 years of age with	N=667 3 months	Primary: Change from baseline in monthly migraine days at	Primary: The mean number of migraine days per month at baseline was reduced by 6.6 days for both erenumab groups, as compared to 4.2 days in the placebo group (OR, -2.5; 95% CI, -3.5 to -1.4; P<0.001 for each dose vs placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SC monthly vs erenumab 140 mg SC monthly vs placebo	a documented diagnosis of chronic migraine with or without aura Individuals were allowed to use acute headache treatments including migraine-specific medication and NSAIDS during the study.		month three Secondary: Achievement of a ≥50% reduction from baseline in monthly migraine days and change from baseline in monthly acute migraine-specific medication days at month three.	Secondary: A 50% or greater reduction in the mean number of migraine days per month was achieved for 39.9% of patients in the 70 mg erenumab group and 41.2% of patients in the 140 mg erenumab group, as compared with 23.5% in the placebo group (P<0.001 for each dose vs placebo). The change from baseline in the monthly acute migraine-specific medication days was reduced by 3.5 in the 70 mg erenumab group and by 4.1 in the 140 mg erenumab group, as compared to 1.6 days in the placebo group (P<0.001 for each dose vs placebo).
Reuter et al.[27] (2018) LIBERTY Erenumab 140 mg SC monthly vs placebo	DB, MC, PC, RCT Patients from 18 to 65 years of age with a history of episodic migraine with or without aura for at least 12 months, had migraine for an average of 4 to 14 days per month during the three months before screening, and had been treated unsuccessfully (in terms of either efficacy or tolerability, or both) with between two and four preventive treatments	N=246 12 weeks	Primary: Proportion of patients achieving a ≥50% reduction in the mean number of monthly migraine days during weeks nine to 12 Secondary: Safety and tolerability	Primary: At 12 weeks, 36 (30%) of 119 patients in the erenumab group had a ≥50% reduction in the monthly number of migraine days, compared with 17 (14%) of 124 in the placebo group (OR, 2.7; 95% CI, 1.4 to 5.2; P=0.002). Secondary: The tolerability and safety profiles of erenumab and placebo were similar. The most frequent treatment-emergent adverse event was injection site pain, which occurred in seven (6%) participants in both groups.
Ashina et al.[28] (2021)	OL	N=383	Primary: Change in monthly	Primary: Mean (standard error) change in MMDs from baseline of 8.7 (0.2) days

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Erenumab 70 mg SC monthly, increasing to 140 mg following a protocol amendment	Patients 18 to 60 years of age who had successfully completed the DB treatment phase (4 to 14 migraine days per month for ≥12 months prior to screening)	5 years	migraine days (MMDs), change in monthly acute migraine-specific medication (AMSM) days in patients with baseline AMSM use, and change in health-related quality of life as measured by patient-reported outcomes Secondary: Safety	was -5.3 (0.3) days; an average reduction of 62.3% at year five. Among patients using AMSM at baseline (6.3 [2.8] treatment days), mean change in monthly AMSM days was -4.4 (0.3) days at the end of five years. Patient-reported outcomes indicated stable improvements in disability, headache impact, and migraine-specific quality of life. Secondary: Exposure-adjusted patient incidence rates of adverse events were 123.0/100 patient-years; adverse events were most frequently nasopharyngitis, upper respiratory tract infection, and influenza. Serious adverse events reported by 49 patients (3.8/100 patient-years) were mostly single occurrence. Two fatal adverse events were reported. There were no increases in incidence of adverse events, serious adverse events, or adverse events leading to treatment discontinuation over five years of exposure.
Reuter et al.[29] (2022) HER-MES Erenumab 70 or 140 mg SC monthly vs topiramate 50 to 100 mg/day	DB, DD, RCT Adults with ≥4 migraine days per month and naïve to study drugs	N=767 24 weeks	Primary: Medication discontinuation due to an adverse event Secondary: Proportion of patients that achieved ≥50% reduction from baseline in monthly migraine days	Primary: In the erenumab group, 10.6% discontinued medication due to adverse events compared to 38.9% in the topiramate group (odds ratio, 0.19; 95% CI, 0.13 to 0.27; P<0.001). Secondary: Significantly more patients achieved a ≥50% reduction in monthly migraine days from baseline with erenumab (55.4% vs. 31.2%; odds ratio 2.76; 95% CI, 2.06 to 3.71; P<0.001).
Dodick et al.[30] (2018) Fremanezumab 225 mg SC monthly vs	DB, MC, PC, RCT Patients from 18 to 70 years of age with episodic migraine (six to 14 headache days, with at least four migraine days,	N=875 12 weeks	Primary: Mean change in mean number of monthly migraine days during the 12-week period after the first dose	Primary: During the 12-week period after the first dose, the mean numbers of migraine days per month were 4.9 days for the monthly fremanezumab dosing group (LSM change from baseline, –3.7 days) and 5.3 days for the fremanezumab single-higher-dose group (LSM change from baseline, –3.4 days) compared with 6.5 days for the placebo group (LSM change from baseline, –2.2 days). There was a statistically significant difference with monthly dosing vs placebo of –1.5 days (95% CI, –2.01 to –0.93 days;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fremanezumab 675 mg SC once (to support a quarterly dosing regimen) vs placebo	during 28-day pre-treatment period) in whom multiple medication classes had not previously failed		Secondary: Proportion of patients achieving ≥50% reduction in the mean number of monthly migraine days from baseline to week 12, the mean change from baseline to week 12 in the monthly mean number of monthly days with use of any acute headache medications, the mean change from baseline to week four in the number of migraine days, the mean change from baseline to week 12 in mean number of monthly migraine days in patients not receiving concomitant migraine preventive medication, and the mean change in the MIDAS score	P<0.001) and with the single higher dose vs placebo of –1.3 days (95% CI, –1.79 to –0.72 days; P<0.001). Secondary: The proportion of patients with response rates of at least a 50% reduction in mean number of monthly migraine days during the 12-week treatment period were 47.7% for the fremanezumab monthly dosing group (difference vs placebo, 19.8%; 95% CI, 12.0 to 27.6%; P<0.001) and 44.4% for the fremanezumab single-higher-dose group (difference vs placebo, 16.5%; 95% CI, 8.9 to 24.1%; P<0.001) compared with 27.9% for the placebo group. The mean numbers of monthly days with any acute headache medication use during the 12-week treatment period were 4.4 days for the fremanezumab monthly dosing group (LSM change from baseline, –3.0 days; LSM difference from placebo, –1.4 days; 95% CI, –1.84 to –0.89 days; P<0.001) and 4.6 days for the single-higher-dose group (LSM change from baseline, –2.9 days; LSM difference from placebo, –1.3 days; 95% CI, –1.76 to –0.82 days; P<0.001) compared with 5.8 days for the placebo group (LSM change from baseline, –1.6 days). During the four-week period after the first dose, monthly migraine days were 5.3 days for the fremanezumab monthly dosing group (LSM change from baseline, –3.5 days; LSM difference from placebo, –1.8 days; 95% CI, –2.43 to –1.18 days; P<0.001) and 5.7 days for the fremanezumab single-higher-dose group (LSM change from baseline, –3.3 days; LSM difference from placebo, –1.6 days; 95% CI, –2.22 to –0.97 days; P<0.001) compared with 7.2 days for the placebo group (LSM change from baseline, –1.7 days). Among patients not receiving concomitant preventive migraine medications, the monthly mean numbers of migraine days were 4.8 days for the fremanezumab monthly dosing group (LSM change from baseline, –3.7 days; LSM difference from placebo, –1.3 days; 95% CI, –1.92 to –0.70 days; P<0.001) and 5.3 days for the fremanezumab single-higher-dose group (LSM change from baseline, –3.5 days; LSM difference from placebo, –1.1 days; 95% CI, –1.75 to –0.54 days; P<0.001) compared with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				6.4 days for the placebo group (LSM change from baseline, –2.4 days). At four weeks after administration of the last dose of the study drug, mean MIDAS scores were 12.6 points for the fremanezumab monthly dosing group (LSM change from baseline, –24.6 points; LSM difference from placebo, –7.0 points; 95% CI, –10.51 to –3.53 points; P<0.001) and 14.6 points for the single-higher-dose group (LSM change from baseline, –23.0 points; LSM difference from placebo, –5.4 points; 95% CI, –8.90 to –1.93 points; P=0.002) compared with 19.4 points for the placebo group (LSM change from baseline, –17.5 points).
Silberstein et al.[31] (2017) Fremanezumab 675 mg SC at baseline then 225 mg SC monthly vs fremanezumab 675 mg SC once (to support a quarterly dosing regimen) vs placebo	DB, PC, RCT Patients 18 to 70 years of age with chronic migraine (defined as headache of any duration or severity on ≥15 days per month and migraine on ≥8 days per month)	N=1130 12 weeks	Primary: Mean change in the average number of headache days (days in which headache pain lasted ≥4 consecutive hours and had a peak severity of at least a moderate level or days in which acute migraine–specific medication [triptans or ergots] was used to treat a headache of any severity or duration) per month from pre-intervention period Secondary: Mean change from baseline in the average number of migraine days per month, the	Primary: There was a larger reduction in the average number of migraine days per month with fremanezumab quarterly (by 4.9±0.4 days) and fremanezumab monthly (by 5.0±0.4 days) than with placebo (by 3.2±0.4 days) (P<0.001 for both comparisons with placebo). Secondary: More patients who received fremanezumab had a reduction of ≥50% in the average number of headache days per month (quarterly regimen, 38%; monthly regimen, 41%) than did patients who received placebo (18%) (P<0.001 for both comparisons with placebo). There was a larger reduction in the average number of days per month in which acute headache medication was used in the fremanezumab groups (by 3.7±0.3 days with the quarterly regimen and by 4.2±0.3 days with the monthly regimen) than in the placebo group (by 1.9±0.3 days) (P<0.001 for both comparisons with placebo). Adverse events were reported for 64% of the patients receiving placebo, 70% of those receiving fremanezumab quarterly (P=0.06 vs placebo), and 71% of those receiving fremanezumab monthly (P=0.03 vs placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			percentage of patients with a reduction of ≥50% in the average number of headache days per month, and the mean change from baseline in the average number of days per month in which acute headache medication was used	
Ferrari et al.[32] (2019) FOCUS Fremanezumab 675 mg SC at baseline then 225 mg SC monthly vs fremanezumab 675 mg SC once (to support a quarterly dosing regimen) vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with episodic or chronic migraine who had documented failure to two to four classes of migraine preventive medications in the past 10 years	N=838 12 weeks	Primary: Mean change from baseline in the monthly average number of migraine days during the entire 12 weeks Secondary: Change from baseline in the monthly average number of migraine days during the 4-week period after the first dose of study drug and the proportions of participants with a ≥50% response (i.e., participants achieving a ≥50% reduction in the	Primary: Reductions from baseline in monthly average migraine days over 12 weeks were greater versus placebo (least-squares mean change, -0.6) with quarterly fremanezumab (LSM change, -3.7; LSM difference vs placebo -3.1; 95% CI, -3.8 to -2.4; P<0.0001) and with monthly fremanezumab (LSM change, -4.1; LSM difference vs placebo, -3.5; 95% CI, -4.2 to -2.8; P<0.0001). The mean percentage change from baseline in the monthly average number of migraine days during the 12-week treatment period was −8.5% in the placebo group, −34.9% in the fremanezumab quarterly group, and −36.8% in the fremanezumab monthly group. Secondary: Reductions from baseline in the monthly average number of migraine days were greater with quarterly fremanezumab versus placebo as early as four weeks after starting study treatment (−3.6; 95% CI, −4.3 to −2.8; P<0.0001) and monthly fremanezumab (−3.5; 95% CI, −4.2 to −2.8; P<0.0001). The proportions of participants with a ≥50% response were higher versus placebo (9%) over 12 weeks with quarterly fremanezumab (34%; OR, 5.8; 95% CI, 3.6 to 9.6; P<0.0001) and with monthly fremanezumab (34%; 5.8; 95% CI, 3.6 to 9.5; P<0.0001). The proportions of participants with a ≥50% response were higher versus placebo (10%) at four weeks for quarterly fremanezumab (38%; OR, 5.8; 95% CI, 3.6 to 9.3; P<0.0001) and monthly fremanezumab (36%; 5.3; 95% CI, 3.3 to 8.4;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			monthly average number of migraine days during the 4-week and 12-week periods after the first dose of study drug)	P<0.0001).
Goadsby et al.[33] (2020) Fremanezumab 225 or 675 mg SC at baseline then 225 mg SC monthly (monthly dosing) vs fremanezumab 675 mg SC every 3 months (quarterly dosing)	DB, MC, RCT (extension of HALO studies) Patients 18 to 70 years of age with migraine	N=1,890 52 weeks	Primary: Safety Secondary: Efficacy	Primary: The most commonly reported adverse events were injection-site reactions (induration 33%, pain 31%, and erythema 26%). Secondary: Fremanezumab reduced monthly migraine days (chronic migraine quarterly -7.2 days, chronic migraine monthly -8.0 days, episodic migraine quarterly -5.2 days, episodic migraine monthly -5.1 days) and headache days of at least moderate severity (chronic migraine quarterly -6.4 days, chronic migraine monthly -6.8 days, episodic migraine quarterly -4.4, episodic migraine monthly -4.2 days) from baseline to 12 months. Reductions in any acute headache medication use and headache-related disability were also maintained over 12 months.
Detke et al.[34] (2018) REGAIN Galcanezumab 120 mg SC monthly (with a 240 mg loading dose) vs galcanezumab 240 mg SC monthly	DB, MC, PC, RCT Patients 18 to 65 years of age with chronic migraine	N=1,113 3-month DB, PC, treatment phase and a 9-month OL extension	Primary: Overall mean change from baseline in the number of monthly migraine headache days during the three-month DB treatment phase Secondary: Response rates (proportion of patients with ≥50%,	Primary: Mean number of monthly migraine headache days at baseline was 19.4 for the total sample. Both galcanezumab dose groups demonstrated greater overall mean reduction in the number of monthly migraine headache days compared to placebo (placebo, −2.7; galcanezumab 120 mg, −4.8; galcanezumab 240 mg, −4.6; P<0.001 for each dose compared to placebo). Secondary: Over the three months of treatment, the mean percentages of patients with ≥50% and ≥75% reduction from baseline in migraine headache days were higher for both galcanezumab doses than for placebo (≥50% response rate: both doses P<0.001; ≥75% response rate: 120 mg, P<0.05; 240 mg, P<0.001). After adjustment for multiplicity, galcanezumab 240 mg demonstrated statistical improvement vs placebo on the primary and all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			≥75%, and 100% reduction from baseline in monthly migraine headache days across months one to three), mean change in functioning at month three measured by the Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive score, overall mean reduction in monthly migraine headache days with acute headache medication use across months one to three, and additional headache parameters	key secondary endpoints except for 100% response rate, while galcanezumab 120 mg had statistical improvement vs placebo on the primary endpoint and the ≥50% response rate. There were no statistical differences between doses on any other (non-key) efficacy measure. There were no clinically meaningful differences between galcanezumab doses and placebo on any safety or tolerability outcome except for a higher incidence of treatment-emergent injection-site reaction (P<0.01), injection-site erythema (P<0.001), injection-site pruritus (P<0.01), and sinusitis (P<0.05) in the galcanezumab 240-mg group relative to placebo.
Camporeale et al.[35] (2018) Galcanezumab 120 mg SC monthly (with a 240 mg loading dose) vs galcanezumab 240 mg SC monthly	MC, OL, RCT Patients 18 to 65 years of age with episodic or chronic migraine	N=270 12 months	Primary: Safety and tolerability Secondary: Overall change from baseline in the number of monthly migraine headache days, headache days, responder analysis of ≥30%,	Primary: There was no between-dose group difference in the percentage of patients who discontinued due to an adverse event (4.7 vs 5.0% for galcanezumab 120 mg vs 240 mg, respectively). There were no significant differences between dose groups in the frequency of any of adverse events that occurred with ≥5% frequency; however, there was a higher percentage of upper respiratory tract infection events in the galcanezumab 240 mg dose group (14.9%) compared with 120 mg group (7.0%). Most of the treatment-emergent adverse events were reported as mild-to-moderate in severity and there were no deaths. Across both dose groups, the most common (≥10% frequency) events were injection site pain, nasopharyngitis, upper respiratory tract infection, injection site reaction,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			≥50%, ≥75, and 100% reduction in migraine headache days, the percentage of patients who maintained a monthly migraine headache days response, and change from baseline in the number of days acute treatment is taken for migraine or headache	back pain, and sinusitis. In addition, injection site bruising, injection site hematoma, injection site pruritus, and injection site induration were reported in > 2% in both galcanezumab dose groups combined. Laboratory values, vital signs, or electrocardiograms did not show any clinically meaningful differences between galcanezumab doses. Secondary: Compared to baseline, the overall reduction in the number of monthly migraine headache days was 5.6 (95% CI, -6.3 to -5.0) and 6.5 (95% CI, -7.1 to -5.8) for patients treated with galcanezumab 120 mg and 240 mg, respectively. Reduction in the mean monthly migraine headache days was apparent as early as the first month and was sustained throughout the treatment period. The overall mean reduction from baseline in the number of monthly non-migraine headache days averaged over 12 months was 2.2 and 2.1 in the galcanezumab 120 mg and 240 mg dose groups, respectively. In both galcanezumab dose groups, there were statistically significant within-group reductions from baseline in the number of monthly migraine headache days or headaches with acute medication use at each month (P<0.001). The overall mean reduction from baseline in number of monthly days with acute medication use for migraines or headaches was 5.1 in both dose groups.
Stauffer et al.[36] (2018) EVOLVE-1 Galcanezumab 120 mg or 240 mg SC monthly vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with at least a one-year history of migraine, four to 14 migraine headache days per month and a mean of ≥2 migraine attacks per month within the past three months, and were diagnosed prior to 50 years of age	N=858 6 months treatment and additional 5 months follow-up	Primary: Overall mean change from baseline in the number of monthly migraine headache days during the treatment period Secondary: ≥50%, ≥75%, and 100% reduction in MMDs, migraine headache days with acute medication use, scores from the	Primary: After multiplicity adjustment, monthly galcanezumab doses of 120 mg and 240 mg resulted in statistically significantly greater LS mean change from baseline of monthly MHDs compared with placebo. The LS mean change difference from placebo was −1.9 days for galcanezumab 120 mg, and −1.8 days for galcanezumab 240 mg (both P<0.001). Secondary: After multiplicity adjustment, galcanezumab 120 mg and 240 mg statistically significantly reduced the number of monthly MHDs with acute medication use compared with placebo by −1.8 and −1.6 days (P<0.001), respectively. The mean percentage of patients with ≥50%, ≥75%, and 100% reduction from baseline in monthly MHD during treatment was statistically significantly greater in both galcanezumab dose groups compared with placebo (P<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Migraine-Specific Quality of Life questionnaire, Patient Global Impression of Severity, and MIDAS, and adverse events	After multiplicity adjustment, galcanezumab treatment statistically significantly improved Migraine-Specific Quality of Life questionnaire Role-Function Restrictive scores compared with placebo during treatment (P<0.001). Both galcanezumab doses also demonstrated superiority in other domains of the Migraine-Specific Quality of Life questionnaire scale (LS mean change difference compared with placebo; mean of month four to six, all P<0.001): role function-preventive (120 mg, 5.6 and 240 mg, 4.7); emotional function (120 mg, 8.3 and 240 mg, 7.2); and total (120 mg, 7.3 and 240 mg, 6.7). After multiplicity adjustment, there was a statistically significantly greater mean improvement from baseline in Patient Global Impression of Severity rating in both the galcanezumab 120-mg (−0.3; P=0.002) and 240-mg (−0.3; P=0.008) dose groups compared with placebo for month four to six. For the MIDAS total score, the LS mean change at month six was statistically significantly improved in both the galcanezumab 120-mg (−21.2; P<0.001) and 240-mg (−20.1; P<0.002) treatment groups compared with placebo (−14.9). Although not part of the multiplicity adjustment, there were no statistically significant differences between galcanezumab dose groups for any of the efficacy measures. The percentage of patients who reported at least one treatment-emergent adverse event was greater in the galcanezumab dose groups; none was statistically significant. Injection-site pain was the most frequently reported treatment-emergent adverse events among all treatment groups, but there were no statistically significant differences. Treatment-emergent adverse events related to injection site other than injection-site pain that were reported at a greater rate in one or both galcanezumab dose groups (>2%) compared with placebo were injection-site erythema, injection-site pruritus, and injection-site reaction.
Skljarevski et al.[37] (2018) EVOLVE-2 Galcanezumab 120 mg or 240 mg SC monthly	DB, MC, RCT Patients 18 to 65 years of age with a diagnosis of migraine with or without aura who	N=915 Study period I= medical examinations and washout of migraine	Primary: Overall mean change from baseline in the number of monthly migraine headache days	Primary: The LS mean change from baseline in monthly migraine headache days over the six-month study period for galcanezumab 120 and 240 mg were significantly (P<0.001) reduced by 2.02 (±0.27) and 1.90 (±0.27) monthly migraine headache days, respectively, relative to placebo. Secondary:

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vs placebo	had migraine for at least one year prior to enrollment, migraine onset prior to age 50 years, four to 14 migraine headache days, at least two migraine attacks during the baseline period, and an 80% compliance rate in using the electronic diary	preventive medications for ≥30 days (4 months for botulinum toxin A) Study period II= establish the baseline number of migraine headache days (30 to 40 days) Study period III= 6-month DB treatment phase	Secondary: ≥50%, ≥75%, and 100% reduction in MMDs, migraine headache days with acute medication use, scores from the Migraine-Specific Quality of Life questionnaire, Patient Global Impression of Severity, and MIDAS	Both doses were superior to placebo for all key secondary endpoints (P<0.001 for all outcomes except for Patient Global Impression of Severity, which was P=0.002 for the 120 mg dose and P=0.012 for the 240 mg dose). Injection site pain was the most common treatment-emergent adverse event, reported at similar rates in all treatment groups. Both galcanezumab doses had significantly more injection site reactions and injection site pruritus, and the 240 mg group had significantly more injection site erythema versus placebo.
Goadsby et al.[38] (2019) Galcanezumab 300 mg SC monthly vs placebo	DB, MC, RCT Patients 18 to 65 years of age with a history of episodic cluster headaches who had a cluster headache attack frequency of ≥1 attack every other day, ≥4 total attacks, and no more than 8 attacks per day during 7 consecutive days of the prospective baseline period	N=106 (Recruitment was halted before the trial reached the planned sample size of 162 because too few volunteers met the eligibility criteria) 8 weeks	Primary: Mean change from baseline in the weekly frequency of cluster headache attacks across weeks 1 through 3 after receipt of the first dose Secondary: Percentage of patients who had a reduction from baseline of at least 50% in the weekly frequency of cluster	Primary: The mean reduction in the weekly frequency of cluster headache attacks across weeks one through three was 8.7 in the galcanezumab group, as compared with 5.2 in the placebo group (between-group difference in mean change, 3.5 attacks per week; 95% CI, 0.2 to 6.7; P=0.04). The mean percentage reduction from baseline in the weekly frequency of cluster headache attacks across weeks one through three was 52% in the galcanezumab group, as compared with 27% in the placebo group. Secondary: The key secondary end point of the percentage of patients having a reduction of at least 50% in the weekly frequency of cluster headache attacks at week three was 71% in the galcanezumab group, as compared with 53% in the placebo group (P=0.046). There was a higher frequency of adverse events in the galcanezumab group than in the placebo group (43% vs 33%), with a majority of the

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			headache attacks at week 3; safety	events being rated mild to moderate in severity. Adverse events leading to discontinuation occurred in 4% of the patients in the galcanezumab group and 2% of those in the placebo group. Injection-site pain occurred in 8% of the patients in the galcanezumab group, as compared with none in the placebo group (P=0.04).
Mulleners et al.[39] (2020) CONQUER Galcanezumab 120 mg SC monthly (with a 240 mg loading dose) vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age, with episodic or chronic migraine, with migraine onset before the age of 50 years, who had a documented failure of preventive medications from two to four drug categories in the past 10 years owing to lack of efficacy or tolerability, or both	N=462 3 months	Primary: Overall mean change from baseline in number of monthly migraine headache days during the three-month treatment period Secondary: Response rates	Primary: Galcanezumab-treated patients in the total population had a greater reduction in the number of monthly migraine headache days compared with placebo (least-squares mean change difference from placebo, −3.1; 95% CI, −3.9 to −2.3]; P<0.0001; effect size, 0.72). Secondary: Regarding the key secondary endpoints, mean percentage of patients with at least 50%, at least 75%, and 100% reduction from baseline in monthly migraine headache days was greater in the galcanezumab group compared with placebo in the total population (all P<0.0001) and episodic migraine subgroup (all P≤0.0001). The mean percentage of patients with chronic migraine who had at least 30% reduction from baseline in monthly migraine headache days was 54% for galcanezumab-treated patients and 24% for patients receiving placebo (OR, 3.8; 95% CI, 2.2 to 6.3; P<0.0001). In the chronic migraine subgroup, there was also a greater mean percentage of patients in the galcanezumab group than the placebo group with at least 50% reduction (P<0.0001) and at least a 75% reduction from baseline in monthly migraine headache days (P=0.019).
Croop et al.[40] (2019) Rimegepant 75 mg vs placebo If needed, patients took rescue medication for rescue or	DB, MC, PC, RCT Patients ≥18 years of age with diagnosis of migraine with or without aura and a history of two to eight migraine attacks per month	N=1,466 Single dose	Primary: Proportion of patients who were pain free (defined as a reduction of moderate or severe headache pain to no pain) at two hours following initial dose and proportion of patients who were most bothersome	Primary: The percentage of patients who experienced freedom from headache pain at two hours post first dose was 21.2% in the rimegepant group compared to 10.9% in the placebo group (risk difference, 10.4; 95% CI, 6.5 to 14.2; P=0.001). The percentage of patients who were most bothersome symptom-free at 2 hours post first dose was 35.1% in the rimegepant group compared to 26.8% in the placebo group (risk difference, 8.3; 95% CI, 3.4 to 13.2; P=0.001). Secondary: The percentage of patients who experienced pain relief at two hours post

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recurrence of migraine after 2 hours post initial dose.			symptom-free (defined as the absence of the self-identified most bothersome symptom [photophobia, phonophobia, or nausea]) at two hours following initial dose Secondary: Pain relief at two hours, sustained pain freedom from 2 to 48 hours, use of rescue medication within 24 hours and percentage of patients reporting normal function at two hours	first dose was 59.3% in the rimegepant group compared to 43.3% in the placebo group (risk difference, 16.1; 95% CI, 10.8 to 21.3; P=0.001). The percentage of patients who experienced sustained pain relief from 2 to 48 hours was 47.8% in the rimegepant group compared to 27.7% in the placebo group (risk difference, 20.1; 95% CI, 15.1 to 25.2; P=0.001). The percentage of patients who did not use rescue medication within the first 24 hours was 85.8% in the rimegepant group compared to 70.8% in the placebo group (risk difference, 15.0; 95% CI, 10.7 to 19.3; P=0.001). The percentage of patients reporting normal function at two hours was 38.1% in the rimegepant group compared to 25.8% in the placebo group (risk difference, 12.3; 95% CI, 7.4 to 17.2; P=0.001).
Lipton et al.[41] (2019) Rimegepant 75 mg vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with diagnosis of migraine with or without aura and a history of two to eight migraine attacks per month	N=1,186 Single migraine attack	Primary: Freedom from pain (which was defined by the presence of no pain in a person who had had pain of moderate or severe intensity immediately before administration of the dose) and freedom from the patient's most bothersome	Primary: Two hours after the dose of rimegepant or placebo, 19.6% of the patients in the rimegepant group, as compared with 12.0% in the placebo group, were free from pain (absolute difference, 7.6 percentage points; 95% CI, 3.3 to 11.9; P<0.001). The percentage of patients who had freedom from their most bothersome symptom two hours after the dose was 37.6% in the rimegepant group as compared with 25.2% in the placebo group (absolute difference, 12.4 percentage points; 95% CI, 6.9 to 17.9; P<0.001). Secondary: Freedom from photophobia at two hours after the dose was administered was reported in 37.4% in the rimegepant group and in 22.3% in the placebo group (P<0.001), and freedom from phonophobia was reported in 36.7% and 26.8%, respectively (P=0.004). The percentage of patients who

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			symptom associated with migraine (i.e., phonophobia, photophobia, or nausea), two hours after the dose Secondary: Freedom from photophobia and from phonophobia, pain relief (which was defined by the presence of mild pain or no pain in a patient who had had pain of moderate or severe intensity immediately before administration of the dose), and freedom from nausea	had pain relief two hours after the dose was 58.1% in the rimegepant group as compared with 42.8% in the placebo group (P<0.001). The percentage of patients who had freedom from nausea two hours after the dose did not differ significantly between the treatment groups (48.1% in the rimegepant group and 43.3% in the placebo group, P=0.21). (All percentages are Cochran–Mantel–Haenszel estimates.) As a result of this nonsignificant difference, and in accordance with the hierarchical analysis, no statistical inferences can be drawn from the remainder of the secondary end points.
Croop et al.[42] (2021) Rimegepant 75 mg every other day vs placebo	DB, MC, PC, RCT Adults with at least a one-year history of migraine	N=747 12 weeks	Primary: Change from the four-week observation period in the mean number of migraine days per month in the last four weeks of the double-blind treatment phase (weeks 9 to 12) Secondary: Safety	Primary: The change from the observation period in mean number of migraine days per month during weeks nine to 12 was -4.3 days (95% CI, -4.8 to -3.9) with rimegepant and -3.5 days (95% CI, -4.0 to -3.0) with placebo (least squares mean difference, -0.8 days; 95% CI, -1.46 to -0.20; P=0.0099). Secondary: Participants who received rimegepant and placebo were equally likely to have an adverse event, with 133 (36%) individuals in each treatment group reporting an adverse event. Adverse events occurring in at least 2% of rimegepant-treated participants were nasopharyngitis, nausea, urinary tract infection, and upper respiratory tract infection. Nearly all adverse events were mild or moderate in severity. Seven (2%) participants who received rimegepant and four (1%) who received placebo discontinued the study

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				due to an adverse event; no patients died.
Dodick et al.[43] (2019) ACHIEVE I Ubrogepant 50 mg vs ubrogepant 100 mg vs placebo If needed, patients took a randomly assigned either a second dose (active or placebo) or rescue medication for rescue or recurrence of migraine within 2 to 48 hours post initial dose.	DB, MC, PC, RCT Patients 18 to 75 years of age with diagnosis of migraine with or without aura and a history of two to eight migraine attacks per month	N=1,672 Single dose with optional second dose	Primary: Proportion of patients who were pain free (defined as a reduction of moderate or severe headache pain to no pain) at two hours following initial dose and proportion of patients who were most bothersome symptom-free (defined as the absence of the self-identified most bothersome symptom [photophobia, phonophobia, or nausea]) at two hours following initial dose Secondary: Pain relief at two hours, sustained pain freedom from 2 to 24 hours	Primary: The percentage of patients who experienced freedom from headache pain at two hours post first dose was 19.2% in the ubrogepant 50 mg group compared to 11.8% in the placebo group (OR, 1.83; 95% CI, 1.25 to 2.66; P=0.002). The percentage of patients who experienced freedom from headache pain at two hours post first dose was 21.2% in the ubrogepant 100 mg group compared to 11.8% in the placebo group (OR, 2.04; 95% CI, 1.41 to 2.95; P<0.001). The percentage of patients who were most bothersome symptom-free at 2 hours post first dose was 38.6% in the ubrogepant 50 mg group compared to 27.8% in the placebo group (OR, 1.7; 95% CI, 1.27 to 2.28; P=0.002). The percentage of patients who were most bothersome symptom-free at two hours post first dose was 37.7% in the ubrogepant 100 mg group compared to 27.8% in the placebo group (OR, 1.63; 95% CI, 1.22 to 2.17; P=0.002). Secondary: Pain relief at two hours was achieved in 49.1% of the placebo group, 60.7% of the 50-mg ubrogepant group (P=0.002), and 61.4% of the 100-mg ubrogepant group (P=0.002). At two hours, 29.8% in the placebo group had no disability and were able to function normally, as compared with 40.6% in the 50-mg ubrogepant group (OR vs placebo, 1.67; 95% CI, 1.22 to 2.27) and 42.9% in the 100-mg ubrogepant group (OR vs placebo, 1.93; 95% CI, 1.42 to 2.61). No statistical difference between groups was shown for the comparison between the 50-mg dose and placebo at the level of sustained freedom from pain during the period from two to 24 hours or for the comparison between the 100-mg dose and placebo at the level of absence of phonophobia at two hours; therefore, according to the hierarchical design, no inferences can be made about differences between the ubrogepant groups and placebo for subsequent outcomes.
Lipton, et al.[44] (2019)	DB, MC, PC, RCT	N=1,686	Primary: Proportion of	Primary: The percentage of patients who experienced freedom from headache pain

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ACHIEVE II Ubrogepant 25 mg vs ubrogepant 50 mg vs placebo If needed, patients took a randomly assigned either a second dose (active or placebo) or rescue medication for rescue or recurrence of migraine within 2 to 48 hours post initial dose.	Patients 18 to 75 years of age with diagnosis of migraine with or without aura and a history of two to eight migraine attacks per month	Single migraine attack	patients who were pain free (defined as a reduction of moderate or severe headache pain to no pain) at two hours following initial dose and proportion of patients who were most bothersome symptom-free (defined as the absence of the self-identified most bothersome symptom [photophobia, phonophobia, or nausea]) at two hours following initial dose Secondary: Pain relief at two hours, sustained pain relief from two to 24 hours, sustained pain freedom from two to 24 hours, and absence of each migraine-associated symptom (photophobia, phonophobia, nausea) at two	at two hours post first dose was 20.7% in the ubrogepant 25 mg group compared to 14.3% in the placebo group (OR, 1.56; 95% CI, 1.09 to 2.22; P=0.03). The percentage of patients who experienced freedom from headache pain at two hours post first dose was 21.8% in the ubrogepant 50 mg group compared to 14.3% in the placebo group (OR, 1.62; 95% CI, 1.14 to 2.29; P=0.01). The percentage of patients who were most bothersome symptom-free at 2 hours post first dose was 34.1% in the ubrogepant 25 mg group compared to 27.4% in the placebo group (OR, 1.37; 95% CI, 1.02 to 1.83; P=0.07). The percentage of patients who were most bothersome symptom-free at two hours post first dose was 38.9% in the ubrogepant 100 mg group compared to 27.4% in the placebo group (OR, 1.65; 95% CI, 1.25 to 2.20; P=0.01). Secondary: For the secondary outcomes of pain relief from two to 24 hours, the responder rates in the 50-mg group were greater than in the placebo group (OR, 1.77; 95% CI, 1.35 to 2.32; adjusted P=0.01) as they were for sustained pain relief from two to 24 hours (OR, 2.16; 95% CI, 1.59 to 2.92; adjusted P=0.01) and for sustained pain freedom from two to 24 hours (OR, 1.85; 95% CI, 1.20 to 2.83; adjusted P=0.01). Although the trend held at the two-hour mark for the absence of photophobia (OR, 1.52; 95% CI, 1.14 to 2.02; adjusted P=0.02) and the absence of phonophobia (OR, 1.39; 95% CI, 1.05 to 1.84; adjusted P=0.04), responder rates were not significantly greater for the secondary outcome of absence of nausea (OR, 1.12; 95% CI, 0.83 to 1.51).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hours	

Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MC=multicenter, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
LS=least squares, MIDAS=Migraine Disability Assessment, MMDs=monthly migraine days, MPFID=migraine physical function impact diary, SC=subcutaneous

Additional Evidence

Dose Simplification:
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy:
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits:
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the CGRP Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Atogepant	tablet	Qulipta®	$$$$$	N/A
Eptinezumab-jjmr	injection	Vyepti®	$$$$$	N/A
Erenumab-aooe	injection	Aimovig®	$$$$$	N/A
Fremanezumab-vfrm	injection	Ajovy®	$$$$$	N/A
Galcanezumab-gnlm	injection	Emgality®	$$$$$	N/A
Rimegepant	sublingual tablet	Nurtec ODT®	$$$$$	N/A
Ubrogepant	tablet	Ubrelvy®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.

X. Conclusions

Atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, and rimegepant are all indicated for the preventive treatment of migraine in adults. Galcanezumab is also indicated for the treatment of episodic cluster headache in adults. Rimegepant and ubrogepant are indicated for the acute treatment of migraine with or without aura in adults.[5-13] CGRP antagonists are available in oral and injectable formulations with variable dosing regimens. No agents are available in a generic formulation.

In general, the recommended treatment of mild-to-moderate acute migraine attacks without vomiting or severe nausea is non-steroidal antiinflammatory drugs (NSAIDs) or acetaminophen. For moderate to severe cases, triptans have been shown to be an effective option.[14-19] Prophylactic drug treatment for migraines may be considered in patients who experience four or more migraines per month, in patients whose migraines do not respond to acute drug treatment, or in patients who experience frequent, very long, or uncomfortable auras.[16] It may also be appropriate when quality of life, business duties, or school attendance is severely impaired. A migraine prophylaxis regimen is regarded as successful if the migraine attacks per month are decreased by at least 50% within three months.[16]

The American Academy of Neurology/American Headache Society and the American Academy of Family Physicians guidelines recommend prophylactic agents such as antiepileptic drugs (e.g., divalproex, sodium valproate, topiramate), β-blockers (e.g., metoprolol, propranolol, timolol), and antidepressants (e.g., amitriptyline, venlafaxine). Various triptans (e.g., frovatriptan, zolmitriptan, naratriptan) can also be used for the short-term menstrual-associated migraine prevention.[16,18] The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice lists the CGRP inhibitors as treatment options with established efficacy for prophylactic and acute treatment.[19]

Currently, the injectable CGRP inhibitors have not been compared in head-to-head trials; however, data comparing these agents with placebo injections have shown reductions of approximately three to four migraine days per month in patients with episodic attacks and approximately four to six migraine days per month in those with chronic migraines. In these trials, the mean change difference from placebo was ranged from -1.1 to -2.4 days, which was found to be statistically significant. All four agents were well tolerated in clinical trials with the most common adverse reaction reported being injection site reactions.[21-39]

Currently, the oral CGRP inhibitors also have not been compared in head-to-head trials. Data comparing these agents with placebo have shown proportion of patients who were pain free at two hours following initial dose to range from 19.2 to 21.8% in the experimental groups and 10.9 to 14.3% in the placebo groups, which demonstrated statistical significance in all trials.[20,40-44] These agents were well tolerated in clinical trials with the most common adverse reaction reported being nausea.[5]

There is insufficient evidence to support that one brand CGRP antagonist is safer or more efficacious than another. The drugs in this AHFS class are used in a specific patient population. Because these agents have not been written into the guidelines and very specific criteria must be met prior to initiating therapy, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand CGRP antagonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand CGRP antagonist agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics – Barbiturates
AHFS Class 282404
November 9, 2022

I. Overview

The barbiturates are approved for the treatment of insomnia and for the induction of sedation. Some of the agents are also approved for use as an adjunct to anesthesia, as well as for the treatment of seizure disorders. The barbiturates affect the gamma-aminobutyric acid system and cause reversible depression of all excitable tissues, especially the central nervous system. They depress the sensory cortex, decrease motor activity, and alter cerebellar function. Depression of the central nervous system may range from sedation to general anesthesia.[1-5]

The use of barbiturates is associated with abuse and psychological/physical dependence.[1-5] Individuals who have psychological dependence may increase the dosage or decrease the dosing interval. This behavior may result in a fatal overdose. Tolerance to the sedative-hypnotic effects occurs rapidly, and these agents lose their effectiveness for sleep induction/maintenance after two weeks.[1-6] Complex behaviors such as "sleep driving", as well as other behaviors, have been reported in patients who are not fully awake after taking a sedative-hypnotic.[1,2,5] Despite their extensive use in the past, the use of barbiturates has largely been replaced by benzodiazepines.

The barbiturates that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Phenobarbital is available in a generic formulation. This class was last reviewed in November 2020.

Table 1. Barbiturates Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amobarbital	injection	Amytal Sodium®	none
Pentobarbital	injection	N/A	pentobarbital
Phenobarbital	elixir, injection, tablet	N/A	phenobarbital
Secobarbital	capsule	Seconal Sodium®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the barbiturates are summarized in Table 2.

Table 2. Treatment Guidelines Using the Barbiturates

Clinical Guideline	Recommendation(s)
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)**[7]	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments. • Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible. • When pharmacotherapy is utilized, the choice of a specific pharmacological agent should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects. • For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is: o Short-intermediate acting benzodiazepine receptor agonists or ramelteon. o Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful. o Sedating antidepressants, especially when used in conjunction with

Clinical Guideline	Recommendation(s)
	treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. o Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressant. o Other sedating agents. Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect. • Over-the-counter antihistamine or antihistamine/analgesic type drugs (over-the-counter "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data. • Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia. • Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments), potential for dosage escalation, and rebound insomnia. • Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication. • Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia. • Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. • Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders. • Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.
American Academy of Sleep Medicine: **Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults (2017)**[8]	<u>Recommendations for treating sleep onset insomnia</u> • Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Recommendations are listed alphabetically. • Eszopiclone is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 14 minutes greater, compared to placebo (95% CI, 3 to 24 minute reduction). o Quality of Sleep: moderate-to-large improvement in quality of sleep, compared to placebo. • Ramelteon is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was nine minutes greater, compared to placebo (95% CI, 6 to 12 minute reduction). o Quality of Sleep: No improvement in quality of sleep, compared to placebo. • Temazepam is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 37 minutes greater, compared to placebo (95% CI, 21 to 53 minute reduction). o Quality of Sleep: Small improvement in quality of sleep, compared to placebo.

Clinical Guideline	Recommendation(s)
	• Triazolam is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was nine minutes greater, compared to placebo (95% CI, 4 to 22 minute reduction). o Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. • Zaleplon is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 10 minutes greater, compared to placebo (95% CI, 0 to 19 minute reduction). o Quality of Sleep: No improvement in quality of sleep, compared to placebo. • Zolpidem is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was five to 12 minutes greater, compared to placebo (95% CI, 0 to 19 minute reduction). o Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. <u>Recommendations for treating sleep maintenance insomnia</u> • Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Recommendations are listed alphabetically. • Doxepin is recommended as a treatment for sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 26 to 32 minutes longer, compared to placebo (95% CI, 18 to 40 minute improvement). o Wake After Sleep Onset: Mean reduction was 22 to 23 minutes greater, compared to placebo (95% CI, 14 to 30 minute reduction). o Quality of Sleep: Small-to-Moderate improvement in quality of sleep, compared to placebo. • Eszopiclone is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 28 to 57 minutes longer, compared to placebo (95% CI, 18 to 76 minute improvement). o Wake After Sleep Onset: Mean reduction was 10 to 14 minutes greater, compared to placebo (95% CI, 2 to 18 minute reduction). o Quality of Sleep: moderate-to-large improvement in quality of sleep, compared to placebo. • Temazepam is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 99 minutes longer, compared to placebo (95% CI, 63 to 135 minute improvement). o Wake After Sleep Onset: Not reported. o Quality of Sleep: Small improvement in quality of sleep, compared to placebo. • Suvorexant is recommended as a treatment for sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 10 minutes longer, compared to placebo (95% CI, 2 to 19 minute improvement). o Wake After Sleep Onset: Mean reduction was 16 to 28 minutes greater, compared to placebo (95% CI, 7 to 43 minute reduction). o Quality of Sleep: Not reported. • Zolpidem is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 29 minutes longer, compared to placebo (95% CI, 11 to 47 minute improvement).

Clinical Guideline	Recommendation(s)
	○ Wake After Sleep Onset: Mean reduction was 25 minutes greater, compared to placebo (95% CI, 18 to 33 minute reduction). ○ Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. Not recommended for treating insomnia • The following drugs are not recommended for the treatment of sleep onset or sleep maintenance insomnia (versus no treatment) in adults: Diphenhydramine, Melatonin, Tiagabine, Trazodone, L-tryptophan, Valerian.
Department of Veterans Affairs and Department of Defense: **The Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea (2019)**[9]	Treatment and management of chronic insomnia disorder – behavioral and psychological treatments • It is recommended that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. • Offer brief behavioral therapy for insomnia (BBT-I). • There is insufficient evidence to recommend for or against group versus individual CBT-I for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against internet-based CBT-I as an alternative to face-to-face based CBT-I for the treatment of chronic insomnia disorder. • CBT-I is suggested over pharmacotherapy as first-line treatment. • Offer CBT-I for the treatment of chronic insomnia disorder that is comorbid with another psychiatric disorder. • There is insufficient evidence to recommend for or against mindfulness meditation for the treatment of chronic insomnia disorder. • Sleep hygiene education is not suggested as a standalone treatment. Treatment and management of chronic insomnia disorder – complementary and integrative health treatments • Offer auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against acupuncture other than auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against aerobic exercise, resistive exercise, tai chi, yoga, and qigong for the treatment of chronic insomnia disorder. • Cranial electrical stimulation is not suggested. Treatment and management of chronic insomnia disorder – over-the-counter treatments • Diphenhydramine is not suggested. • Melatonin is not suggested. • Valerian and chamomile are not suggested. • Kava is not recommended. Treatment and management of chronic insomnia disorder – pharmacotherapy • In patients who are offered a short-course of pharmacotherapy for the treatment of chronic insomnia disorder, use of low-dose (i.e., 3 mg or 6 mg) doxepin or a non-benzodiazepine benzodiazepine receptor agonist is suggested. • There is insufficient evidence to recommend for or against the use of ramelteon for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against the use of suvorexant for the treatment of chronic insomnia disorder. • the use of antipsychotic drugs is not suggested for the treatment of chronic insomnia disorder.

Clinical Guideline	Recommendation(s)
	• The use of benzodiazepines is not suggested for the treatment of chronic insomnia disorder. • The use of trazodone is not suggested for the treatment of chronic insomnia disorder.
International League Against Epilepsy: **Updated International League Against Epilepsy Evidence Review of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes (2013)**[10]	Adults with partial onset seizures • Carbamazepine, levetiracetam, phenytoin, and zonisamide are established treatments as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures. Valproic acid is probably effective and gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin are possibly effective for partial onset seizures. Clonazepam and primidone are potentially efficacious/effective. Children with partial-onset seizures • Oxcarbazepine is established as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures. Carbamazepine, phenobarbital, phenytoin, topiramate, valproic acid and vigabatrin may be effective and clobazam, clonazepam, lamotrigine and zonisamide are potentially efficacious/ effective. Elderly adults with partial-onset seizures • Gabapentin and lamotrigine are effective as initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures. Carbamazepine may be effective and topiramate and valproic acid are potentially efficacious/effective. Adults with generalized-onset tonic-clonic seizures • Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective as initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures. Gabapentin, levetiracetam and vigabatrin are potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures. Children with generalized-onset tonic-clonic seizures • Carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective for children with newly diagnosed or untreated generalized onset tonic-clonic seizures. Oxcarbazepine is potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures. Children with absence seizures • Ethosuximide and valproic acid are established treatments for children with newly diagnosed or untreated absence seizures. Lamotrigine is possibly efficacious/ effective as initial monotherapy. Gabapentin is inefficacious/ineffective for children with absence seizures. • Based on scattered reports, the following antiepileptic drugs may precipitate or aggravate absence seizures: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine and vigabatrin. No conclusion can be made about levetiracetam efficacy/effectiveness for absence seizures since the failed class III placebo-controlled trial was uninformative. Children with benign childhood epilepsy with centrotemporal spikes • Carbamazepine and valproic acid are possibly effective as initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes. Gabapentin, levetiracetam, oxcarbazepine, and sulthiame* are potentially efficacious/effective.

Clinical Guideline	Recommendation(s)
	Juvenile myoclonic epilepsy • Topiramate and valproic acid are potentially efficacious/effective for patients with newly diagnosed juvenile myoclonic epilepsy. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine and vigabatrin may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic-clonic seizures. There has been a report that lamotrigine may exacerbate seizures in juvenile myoclonic epilepsy.
National Institute for Clinical Excellence: **Epilepsies in children, young people and adults (2022)**[11]	Treatment with antiseizure medications • Develop an individualized antiseizure medication treatment strategy with the person, and their family and carers if appropriate. • Take into account any particular issues for older people starting an antiseizure medication, especially those with comorbidities. • Use a single antiseizure medication (monotherapy) to treat epilepsy whenever possible. • Review the diagnosis of epilepsy if seizures continue despite an optimal dose of a first-line antiseizure medication. • If first-line monotherapy is unsuccessful and epilepsy diagnosis remains confirmed, try monotherapy with another antiseizure medication, using caution during the changeover period: o Increase the dose of the second medicine slowly while maintaining the dose of the first medicine. o If the second medicine is successful, slowly taper off the dose of the first medicine. o If the second medicine is unsuccessful, slowly taper off the dose of the second medicine and consider an alternative. • If monotherapy is unsuccessful, consider trying an add-on treatment. • When starting an add-on treatment, carefully titrate the additional medicine and review treatment frequently, including monitoring for adverse effects such as sedation. • If trials of add-on treatment do not result in a reduction in seizures, use the regimen that provides the best balance between effectiveness and tolerability of side effects. • Discuss with the person, and their family and carers as appropriate, the benefits of taking as few medicines as possible to maintain seizure freedom or control. When to start antiseizure medication • Start treatment with an antiseizure medication once the diagnosis of epilepsy is confirmed. • Consider starting treatment after a first unprovoked seizure if any of the following apply: o an examination identifies signs of neurological deficit o the electroencephalogram (EEG) shows unequivocal epileptic activity o after a discussion of the risk of further seizures, the person or their family or carers consider the risk unacceptable brain imaging shows a structural abnormality. Safety considerations • Follow Medicines and Healthcare products Regulatory Agency (MHRA) safety advice on switching between different manufacturers' products of a particular antiseizure medication. • Be aware that phenytoin is associated with an increased risk of serious skin reactions in people of Han Chinese or Thai family background. • Be aware that carbamazepine and potentially medicines with a similar chemical structure (such as oxcarbazepine and eslicarbazepine acetate) are associated with

Clinical Guideline	Recommendation(s)
	an increased risk of serious skin reactions in people of Han Chinese, Thai, European or Japanese family background. • Be aware that long-term treatment with some antiseizure medications (such as carbamazepine, phenytoin, primidone and sodium valproate) is associated with decreased bone mineral density and increased risk of osteomalacia. Follow the MHRA safety advice on antiepileptics: adverse effects on bone and consider vitamin D and calcium supplementation for people at risk. Antiseizure medications for women and girls • Give women and girls with epilepsy information and support that is tailored to their age-specific and developmental needs. Review regularly information provided about contraception, folic acid supplementation, conception, pregnancy, breastfeeding, caring for children, and menopause. • Discuss with women and girls with epilepsy who are able to have children (including young girls who are likely to need treatment when they are able to have children), and their families or carers if appropriate, the risks to an unborn child of taking antiseizure medications during pregnancy, such as congenital malformations, neurodevelopmental impairments and fetal growth restriction. • Assess the risks and benefits of treatment with individual antiseizure medications when prescribing antiseizure medications for women and girls who are able to have children, now or in the future. Take into account the latest data on the risks to the unborn child and be aware that there are important uncertainties about the risks, particularly with newer drugs. Follow the MHRA safety advice on antiepileptic drugs in pregnancy. • Specifically, discuss the risks to the unborn child of using sodium valproate during pregnancy, including the increased risk with higher doses and polytherapy. Follow the MHRA safety advice on valproate use by women and girls. • Be aware that some antiseizure medications, for example, carbamazepine, oxcarbazepine, phenytoin and topiramate, can impair the effectiveness of hormonal contraceptives. • Be aware that oestrogen-containing hormonal contraceptives and hormone replacement therapy can impair the effectiveness of lamotrigine. • Explain that breastfeeding for most women and girls taking antiseizure medications is generally safe and should be encouraged. Support each mother to choose a feeding method that bests suits her and her family. • Decisions about antiseizure therapy and breastfeeding should be made between the woman or girl and the prescriber, and take into account the benefits of breastfeeding alongside the potential risks of the medication affecting the child. Monitoring and review • Arrange regular (at least annual) monitoring reviews for adults with epilepsy and any of the following: o a learning disability o drug-resistant epilepsy o a high risk of sudden unexpected death in epilepsy (SUDEP; see the section on reducing the risk of epilepsy-related death) o a serious comorbidity, such as complex psychosocial, cognitive or mental health problems o who are taking antiseizure medications associated with long-term side effects or drug interactions o who are able to get pregnant and are taking valproate or any other high-risk teratogenic antiseizure medication (see also the MHRA safety advice on antiepileptic drugs in pregnancy). • Discuss monitoring reviews with children and young people with epilepsy and their families and carers if appropriate, and agree a frequency for regular reviews

Clinical Guideline	Recommendation(s)
	that is: ○ individually tailored to the child or young person's needs, preferences and the nature of their epilepsy and ○ at least every 12 months. • Consider monitoring antiseizure medication levels in people with epilepsy and any of the following: ○ uncontrolled seizures ○ side effects from their medication ○ a specific clinical condition needing closer supervision (such as pregnancy or renal failure) ○ poor adherence to medication. • Explain to people with epilepsy and, if appropriate, their families and carers, that they can ask for a review of their care if they have concerns, need support or their care needs change, for example, to support medicines withdrawal, pregnancy planning or to review treatment if seizures recur. Provide contact details and information on how to access epilepsy services.
American Academy of Neurology: **Evidence-Based Guideline Update: Medical Treatment of Infantile Spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (2012)**[12] Reaffirmed 2021	• To date, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone, and vigabatrin. • Low-dose adrenocorticotropic hormone should be considered as an alternative to high-dose adrenocorticotropic hormone for treatment of infantile spasms. • Adrenocorticotropic hormone or vigabatrin may be offered for short-term treatment of infantile spasms. Evidence suggests that adrenocorticotropic hormone may be offered over vigabatrin. • There is insufficient evidence to recommend the use of dexamethasone, prednisolone and methylprednisolone as being as effective as adrenocorticotropic hormone for short-term treatment of infantile spasms. • The data is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam, levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for the treatment of infantile spasms. • Hormonal therapy (adrenocorticotropic hormone or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. • A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
Infantile Spasms Working Group: **Infantile Spasms: A U.S. Consensus Report (2010)**[13]	• To improve outcomes in infantile spasms, the goals include early recognition and diagnosis, short-term treatment with a first-line therapy, timely electroencephalography evaluation to assess treatment effectiveness and prompt treatment modification if indicated. • Effective treatment should produce both cessation of spasms and resolution of hypsarrhythmia on electroencephalography. • The dose of the chosen first-line agent should be adjusted to achieve the maximum effective dose in as short amount of time as clinically indicated. • There is insufficient evidence to recommend the best approach in events of relapse. Possible treatment options include using the previously effective agent and dose, using the previously effective agent at the maximum dose or using a new agent. • Adrenocorticotropic hormone is considered first-line therapy for infantile spasms. There is insufficient evidence to recommend the optimal dose and duration of treatment, although short duration is preferable to avoid adverse events. Treatment with the maximum dose of adrenocorticotropic hormone should be continued for two weeks followed by taper and evaluation of treatment response. • Vigabatrin is considered first-line therapy for infantile spasms, especially in patients with comorbid tuberous sclerosis complex. Vigabatrin should be initiated at 50 mg/kg/day and increased up to 100 to 150 mg/kg/day if indicated. Efficacy

Clinical Guideline	Recommendation(s)
	should be assessed within two weeks following dose titration. Responders to treatment may continue therapy for six to nine months, with continued ophthalmic evaluation. • No recommendations can be given with regard to oral corticosteroids in the treatment of infantile spasms. • Ketogenic diet may be considered as second-line therapy when first-line therapies fail or are inappropriate. • Patients with refractory spasms, concomitant partial seizures or focal abnormalities on the electroencephalography may be evaluated for surgery.
European Federation of Neurological Societies: **Guideline on the Management of Status Epilepticus (2010)**[14]	<u>Initial pharmacological treatment for generalized convulsive status epilepticus and non-convulsive status epilepticus</u> • The preferred treatment is intravenous administration of lorazepam 0.1 mg/kg; however, depending on the patients' general medical condition, treatment can be started at a lower dose of 4 mg, to be repeated if seizures continue for >10 minutes after first injection. • If lorazepam is not available, diazepam 10 mg (route of administration not specified) directly followed by phenytoin (15 to 18 mg/kg) or equivalent fosphenytoin. • General management of refractory status epilepticus includes treatment in an intensive care unit. <u>Pharmacological treatment for refractory generalized convulsive status epilepticus and subtle status epilepticus</u> • Immediate infusions of anesthetic doses of midazolam, propofol or barbiturates are recommended due to the progressive risk of brain and systemic damage. • If midazolam is given, seizure suppression is recommended. This goal should be maintained for at least 24 hours. Simultaneous initiation of the chronic medication the patient with be treated with in the future should be initiated. • For elderly patients in whom intubation and artificial ventilation would not be justified, further non-anesthetizing anticonvulsants may be tried. <u>Pharmacological treatment for refractory non-convulsive status epilepticus</u> • Due to poor evidence and lack of any head-to-head trials, no recommendations can be made regarding which of the non-anaesthetizing anticonvulsants should be the drug of choice. • Recommendations include phenobarbital, valproic acid and levetiracetam. • If treatment regimen includes the administration of anesthetics, use the same protocol as refractory generalized convulsive status epilepticus.
American Epilepsy Society/ American Academy of Neurology: **Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults (2016)**[15]	<u>Initial therapy phase (five to 20 minutes)</u> • A benzodiazepine (specifically intramuscular (IM) midazolam, intravenous (IV) lorazepam, or IV diazepam) is recommended as the initial therapy of choice, given their demonstrated efficacy, safety, and tolerability. • Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration, compared with the three recommended benzodiazepines above, positions it as an alternative initial therapy rather than a drug of first choice. • For pre-hospital settings or where the three first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives. <u>Second therapy phase (begins when the seizure duration reaches 20 minutes and should conclude by the 40-minute mark when response or lack of response to the second therapy should be apparent)</u> • Reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any one of these options is better than the others.

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td><u>Third therapy phase (begins when seizure duration reaches 40 minutes)</u>
• There is no clear evidence to guide therapy in this phase.
• If second therapy fails to stop the seizures, treatment considerations should include repeating second-line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).</td></tr>
<tr><td>American Academy of Neurology/ American Epilepsy Society: Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment of New Onset Epilepsy (2018)[16]</td><td>• Lamotrigine use should be considered to decrease seizure frequency.
• Lamotrigine use should be considered, and gabapentin use may be considered to decrease seizure frequency in patients aged ≥60 years.
• Levetiracetam use may be considered to decrease seizure frequency.
• Zonisamide use may be considered to decrease seizure frequency.
• Vigabatrin use appears to be less efficacious than immediate-release carbamazepine use and may not be offered; furthermore, toxicity profile precludes vigabatrin use as first-line therapy.
• Pregabalin use at 150 mg/day is possibly less efficacious than lamotrigine use at 100 mg/day.
• Evidence is insufficient to consider gabapentin, oxcarbazepine, or topiramate instead of carbamazepine.
• Evidence is insufficient to consider topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
• Data are lacking to support or refute use of third-generation antiepileptic drugs, clobazam, felbamate, or vigabatrin in treating new-onset epilepsy.
• Data are lacking to support or refute use of newer antiepileptic drugs in treating unclassified generalized tonic-clonic seizures.</td></tr>
<tr><td>American Academy of Neurology/ American Epilepsy Society: Efficacy and Tolerability of the New Antiepileptic Drugs II: Treatment of Refractory Epilepsy (2018)[17]</td><td><u>Summary of guidelines on the use of antiepileptic drugs (AEDs) in treatment-resistant epilepsy, based on Level A and B recommendations</u>
<table>
<tr><th>AED</th><th>Adjunctive focal adult</th><th>Focal mono-therapy</th><th>Idiopathic generalized epilepsy</th><th>Lennox-Gastaut syndrome</th><th>Adjunctive focal pediatric</th></tr>
<tr><td>Gabapentin</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>Yes</td></tr>
<tr><td>Lamotrigine</td><td>Yes</td><td>Yes</td><td>Yes (only in childhood absence epilepsy</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Levetiracetam</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td>Oxcarbazepine</td><td>Yes</td><td>Yes</td><td>No</td><td>No</td><td>Yes</td></tr>
<tr><td>Tiagabine</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td>Topiramate</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Zonisamide</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
</table>
• For treatment-resistant adult focal epilepsy (TRAFE), immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency. Lacosamide, eslicarbazepine, and extended-release topiramate use should also be considered to decrease seizure frequency in this population. Vigabatrin and rufinamide should be considered established as effective for decreasing seizure frequency in TRAFE but are not first-line agents (retinopathy risk with vigabatrin and modest benefit with rufinamide). Ezogabine use should be considered to decrease seizure frequency in this population but carries a serious risk of skin and retinal discoloration. Clobazam and extended-release oxcarbazepine use may be considered to decrease seizure frequency in TRAFE.
• Eslicarbazepine use may be considered to decrease seizure frequency as monotherapy for TRAFE. Data are insufficient to recommend the use of second- and the other third-generation AEDs as monotherapy in TRAFE.</td></tr>
</table>

Clinical Guideline	Recommendation(s)
	• For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine use should be considered as add-on therapy to decrease seizure frequency in treating adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy. • For Lennox-Gastaut syndrome, rufinamide use should be considered established as effective to decrease seizure frequency as add-on therapy, and clobazam use should be considered. • For add-on therapy for treatment-resistant focal epilepsy, levetiracetam use should be considered to decrease seizure frequency (for ages one month to 16 years), zonisamide use should be considered to decrease seizure frequency (for ages six to 17 years), and oxcarbazepine use should be considered to decrease seizure frequency (for ages one month to four years). Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, pregabalin, rufinamide, tiagabine, or vigabatrin as add-on therapy for the treatment of these children or adolescents.

*Agent not available in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the barbiturates are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Barbiturates[1-5]

Indication	Amobarbital	Pentobarbital	Phenobarbital	Seco-barbital
Anesthesia				
Preanesthetic	✔	✔	✔ *	✔
Anticonvulsant				
Anticonvulsant in the emergency control of certain acute convulsive episodes		✔	✔ *	
Long-term anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures			✔ *	
Treatment of generalized and partial seizures			✔ *†	
Sedative-Hypnotic				
Short-term treatment of insomnia	✔	✔	✔ *	✔
Sedation	✔	✔	✔ *†	

*Parenteral formulation.
†Oral formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the barbiturates are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Barbiturates[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Amobarbital	Not reported	Not reported	Liver	Renal Feces (4 to 5)	8 to 42 hours
Pentobarbital	Not reported	Not reported	Liver	Renal Feces (less common)	15 to 50 hours
Phenobarbital	>95	20 to 60	Liver	Renal (21)	1.5 to 4.9 days
Secobarbital	90	52 to 57	Liver	Renal	19 to 34 hours

V. Drug Interactions

Major drug interactions with the barbiturates are listed in Table 5.

Table 5. Major Drug Interactions with the Barbiturates[2]

Generic Name(s)	Interaction	Mechanism
Barbiturates (amobarbital, pentobarbital, phenobarbital, secobarbital)	Anticoagulants	Barbiturates reduce the effects of anticoagulants through increased metabolic clearance of anticoagulants, probably caused by induction of hepatic microsomal enzymes.
Barbiturates (amobarbital, pentobarbital, phenobarbital, secobarbital)	Benzodiazepines	Concurrent use of barbiturates and benzodiazepines may result in additive respiratory depression.
Barbiturates (amobarbital, pentobarbital, phenobarbital, secobarbital)	Butalbital	Concurrent use of barbiturates and butalbital may result in additive respiratory depression.
Barbiturates (amobarbital, pentobarbital, phenobarbital, secobarbital)	Centrally acting muscle relaxants	Concurrent use of barbiturates and centrally acting muscle relaxants may result in additive respiratory depression.
Barbiturates (amobarbital, pentobarbital, phenobarbital, secobarbital)	Chloral hydrate	Concurrent use of barbiturates and chloral hydrate may result in additive respiratory depression.
Barbiturates (amobarbital, pentobarbital, phenobarbital, secobarbital)	Sodium oxybate	Concurrent use of sodium oxybate and barbiturates may result in an increase in sleep duration and central nervous system depression.
Barbiturates (phenobarbital)	Hepatitis C virus protease inhibitors	Plasma concentrations and pharmacologic effects of hepatitis C virus protease inhibitors may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of hepatitis C virus protease inhibitors.
Barbiturates (phenobarbital)	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of lurasidone.
Barbiturates (phenobarbital)	Praziquantel	Praziquantel plasma concentrations may be decreased by phenobarbital. The antiparasitic effect of praziquantel may be decreased. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of praziquantel.
Barbiturates (phenobarbital)	Ranolazine	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of ranolazine.

Generic Name(s)	Interaction	Mechanism
Barbiturates (phenobarbital)	Rilpivirine	Plasma concentrations and pharmacologic effects of rilpivirine may be reduced by phenobarbital possibly resulting in loss of virologic response or resistance. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of rilpivirine.
Barbiturates (phenobarbital)	Voriconazole	Plasma concentrations and pharmacologic effects of Voriconazole may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of voriconazole.
Barbiturates (amobarbital, phenobarbital, secobarbital)	Clozapine	Clozapine plasma concentrations may be reduced, possibly through induction of hepatic metabolism of clozapine, decreasing the pharmacologic effects.
Barbiturates (amobarbital, phenobarbital, secobarbital)	Methoxyflurane	Barbiturates appear to stimulate degradation of methoxyflurane, perhaps to nephrotoxic metabolites. Enhanced renal toxicity may occur.
Barbiturates (amobarbital, phenobarbital, secobarbital)	Tacrolimus	Plasma concentrations and pharmacologic effects of tacrolimus may be decreased, due to increased hepatic metabolism of tacrolimus via CYP3A4.
Barbiturates (amobarbital, phenobarbital, secobarbital)	Ulipristal	Plasma concentrations and pharmacologic effects of ulipristal may be decreased by barbiturates. Coadministration of butabarbital with ulipristal may reduce the efficacy of ulipristal.
Barbiturates (pentobarbital)	Tolvaptan	Plasma concentrations of tolvaptan may be decreased by pentobarbital.
Barbiturates (phenobarbital)	Epothilones	The pharmacologic effects of epothilones may be decreased by strong CYP3A4 inducers, such as phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of epothilones.
Barbiturates (phenobarbital)	Human immunodeficiency virus protease inhibitors	Plasma concentrations and pharmacologic effects of human immunodeficiency virus protease inhibitors may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of human immunodeficiency virus protease inhibitors.
Barbiturates (phenobarbital)	Mammalian target of rapamycin inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination and decrease pharmacological of mammalian target of rapamycin inhibitors.
Barbiturates (phenobarbital)	Non-nucleoside reverse transcriptase inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination and decrease pharmacological of non-nucleoside reverse transcriptase inhibitors.
Barbiturates (phenobarbital)	Tyrosine kinase receptor inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination of tyrosine kinase receptor inhibitors. Concomitant use is not recommended.
Barbiturates (amobarbital, phenobarbital, secobarbital)	Vasopressin receptor antagonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be decreased by barbiturates. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of vasopressin receptor antagonists.
Barbiturates (phenobarbital)	Deferasirox	Plasma concentrations and pharmacologic effects of deferasirox may be decreased by phenobarbital.

Generic Name(s)	Interaction	Mechanism
		Induction of UDP-glucuronosyltransferase by phenobarbital may increase the metabolic elimination of deferasirox.
Barbiturates (phenobarbital)	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of dronedarone.
Barbiturates (phenobarbital)	Maraviroc	Induction of CYP3A4 isoenzymes by long-acting barbiturates may increase the metabolic elimination of maraviroc and decrease its pharmacologic effects.
Barbiturates (phenobarbital)	Mifepristone	Plasma concentrations and pharmacologic effects of mifepristone may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of mifepristone.
Barbiturates (phenobarbital)	Roflumilast	Plasma concentrations and pharmacologic effects of roflumilast may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of roflumilast.
Barbiturates (phenobarbital)	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of ticagrelor.
Barbiturates (phenobarbital)	Vandetanib	Plasma concentrations and pharmacologic effects of vandetanib may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of vandetanib.

VI. Adverse Drug Events

The most common adverse drug events reported with the barbiturates are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Barbiturates[1-5]

Adverse Events	Amobarbital	Pentobarbital	Phenobarbital	Secobarbital
Cardiovascular				
Bradycardia	✔	-	✔	-
Hypotension	✔	-	✔	✔
Syncope	✔	-	✔	-
Central Nervous System				
Abnormal thinking	✔	-	-	-
Agitation	✔	-	✔	-
Anxiety	✔	-	✔	-
Ataxia	✔	-	✔	-
Confusion	✔	-	✔	✔
Central nervous system depression	✔	-	✔	✔
Central nervous system excitation	-	-	✔	-
Complex sleep-related activities	-	-	-	✔
Depression	-	-	-	✔
Dizziness	✔	-	✔	✔
Drowsiness	-	-	✔	✔
Excitement	-	-	-	✔
Faint feeling	-	-	-	✔
Fever	✔	-	-	✔
Hallucinations	✔	-	✔	✔

Adverse Events	Amobarbital	Pentobarbital	Phenobarbital	Secobarbital
Hangover effect	-	-	✔	✔
Headache	✔	-	✔	✔
Hyperkinesia	✔	-	✔	-
Impaired judgment	-	-	✔	-
Insomnia	✔	-	✔	✔
Lethargy	-	-	✔	-
Lightheadedness	-	-	-	✔
Nervousness	✔	-	✔	✔
Nightmares	✔	-	✔	✔
Psychiatric disturbances	✔	-	-	-
Somnolence	✔	✔	✔	-
Dermatological				
Exfoliative dermatitis	-	-	✔	✔
Injection site reaction	✔	-	-	-
Rash	-	-	✔	✔
Stevens-Johnson syndrome	-	-	✔	✔
Urticaria	-	-	-	✔
Gastrointestinal				
Constipation	✔	-	✔	✔
Nausea	✔	-	✔	✔
Vomiting	✔	-	✔	✔
Hematologic				
Agranulocytosis	-	-	✔	✔
Megaloblastic anemia	✔	-	✔	✔
Thrombocytopenia	-	-	✔	✔
Thrombophlebitis	-	-	✔	✔
Respiratory				
Apnea	✔	-	✔	✔
Atelectasis	✔	-	-	-
Hypoventilation	✔	-	✔	-
Laryngospasm	-	-	✔	✔
Respiratory depression	-	-	✔	✔
Other				
Anaphylaxis	-	-	-	✔
Angioedema	✔	-	-	✔
Dependence	-	-	-	-
Gangrene	-	-	✔	-
Hypersensitivity reaction	✔	-	-	-
Liver damage	✔	-	-	-
Oliguria	-	-	✔	-
Pain at injection site	-	-	✔	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the barbiturates are listed in Table 7.

Table 7. Usual Dosing Regimens for the Barbiturates[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amobarbital	Preanesthetic: Injection: 65 to 500 mg administered intramuscularly or intravenously two to	Preanesthetic: Injection: 65 to 500 mg administered intravenously	Injection: 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	three times daily Hypnotic (short-term treatment of insomnia): Injection: 65 to 200 mg administered intramuscularly or intravenously at bedtime Sedative (sedation): Injection: 30 to 50 mg administered intramuscularly or intravenously two to three times daily	Hypnotic (short-term treatment of insomnia): Injection: six to 12 years of age, 65 to 500 mg administered intravenously Sedative (sedation): Injection: six years of age and older, 30 to 50 mg administered intramuscularly or intravenously two to three times daily	
Pentobarbital	Anesthesia, short-term treatment of insomnia, sedation, and seizure in the emergency control of certain acute convulsive episodes: Injection: 150 to 200 mg administered intramuscularly as a single injection; There is no average intravenous dosage; a commonly used dosage for a 70 kg adult is 100 mg intravenously initially, maximum rate of 50 mg/min; after 1 minute may give additional small doses at 1 minute intervals if necessary up to total of 200 to 500 mg.	Anesthesia, short-term treatment of insomnia, sedation, and seizure in the emergency control of certain acute convulsive episodes: Injection: 2 to 6 mg/kg administered intramuscularly; maximum 100 mg per dose.	Injection: 50 mg/mL
Phenobarbital	Acute convulsions: Injection: 20 to 320 mg intramuscularly or intravenously, repeated in six hours as necessary, maximum 600 mg/24 hours Anticonvulsant: Elixir: 60 to 200 mg/day Tablet: 50 to 100 mg two or three times daily Hypnotic (short-term treatment of insomnia): Elixir: 100 to 200 mg/day at bedtime, up to maximum 400 mg in 24 hours Injection, tablet: 100 to 320 mg at bedtime, up to maximum 600 mg in 24 hours for injection and 400 mg in 24 hours for tablet Preanesthetic: Injection: 100 to 200 mg intramuscularly 60 to 90 minutes before surgery Sedative (sedation): Elixir, tablet: 30 to120 mg/day in two to three divided doses, up to maximum 400 mg in 24 hours	Anticonvulsant: Elixir: 3 to 6 mg/kg/day Injection: 4 to 6 mg/kg/day for seven to 10 days to blood level of 10 to 15 µg/mL or 10 to 15 mg/kg/day intramuscularly or intravenously Tablet: 15 to 50 mg two or three times daily Preanesthetic: Injection: 1 to 3 mg/kg intramuscularly or intravenously 60 to 90 minutes prior to procedure Sedative (sedation): Tablet: 6 mg/kg/day in three divided doses Status epilepticus: Injection: 15 to 20 mg/kg intravenously over 10 to 15 minutes	Elixir: 20 mg/5 mL Injection: 50 mg/mL 65 mg/mL 130 mg/mL Tablet: 15 mg 16.2 mg 30 mg 32.4 mg 60 mg 64.8 mg 97.2 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: 30 to 120 mg/day in two to three divided doses intramuscularly or intravenously		
Secobarbital	Hypnotic (short-term treatment of insomnia): Capsule: 100 mg at bedtime Preanesthetic: Capsule: 200 to 300 mg one to two hours before surgery	Preanesthetic: Capsule: 2 to 6 mg/kg one to two hours before surgery, maximum dose of 100 mg	Capsule: 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the barbiturates are summarized in Table 8. Although the barbiturates have been available for decades, there are few clinical trials available that directly compare the various agents.

Table 8. Comparative Clinical Trials with the Barbiturates

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Alcohol Detoxification				
Mariani et al.[18] (2006) Phenobarbital 60 mg QID for one day, 60 mg TID for one day, 60 mg BID for one day then 60 mg QD for one day vs gabapentin 2,400 mg on day one (titrated), 600 mg TID for one day, 600 mg BID for one day, then 600 mg QD for one day	OL, RCT Patients 18 to 60 years of age who were admitted for inpatient alcohol detoxification	N=27 4 days	Primary: Treatment failure and severity of withdrawal symptoms Secondary: Not reported	Primary: There was no significant difference in the number of patients completing treatment among the phenobarbital treatment group compared to the gabapentin group (62 vs 71%; P<0.70). Rescue medication was required in 38% of the phenobarbital group and this proportion did not differ significantly from the gabapentin group (57%; P<0.45). The results of each withdrawal-symptom rating scale and the number of hours of sleep per night did not differ significantly between treatment groups. No withdrawal seizures or symptoms of alcohol withdrawal delirium were demonstrated in either treatment group. Secondary: Not reported
Insomnia				
Okawa et al.[19] (1978) Secobarbital 100 mg vs	DB, RCT, XO (two trials) Patients 18 to 60 years of age with a history of insomnia and two of the following: onset of	N=76 2 nights	Primary: Patient preference questionnaire, success (defined as sleep onset in 30 minutes or less and sleep duration of six hours or more),	Primary: One trial compared triazolam to placebo and involved 19 patients. Sixteen patients preferred triazolam over placebo and three expressed no preference (P<0.001). Triazolam demonstrated greater efficacy over placebo in overall sleep (P<0.001), onset (P<0.001), duration (P<0.002) and number of awakenings (P<0.002). Triazolam was determined to be significantly more successful in 15 of 19 patients (P<0.004). No difference in next-morning alertness was noted between the two study groups. Seven

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triazolam 0.5 mg vs placebo	sleep longer than 30 minutes, duration of sleep six hours or less, or experiencing three or more awakenings		adverse effects Secondary: Not reported	patients receiving active treatment experienced mild-to-moderate adverse effects, with dizziness, drowsiness and headache as the most frequently reported. In comparison, three of the patients in the placebo group experienced mild-to-moderate side effects. The second trial was a combined study of 57 patients comparing triazolam and secobarbital. The results of the patient preference questionnaire were analyzed and showed a significant preference for triazolam (41 patients) over secobarbital (10 patients), with six having no preference for either agent (P<0.001). Significant improvement was seen with triazolam compared to secobarbital (P<0.001) in sleep onset, duration of sleep and number of awakenings. Feelings of alertness the next morning did not differ between treatment groups. Success was established in 73% of triazolam treated patients whereas only 30% of the secobarbital treated patients were determined successful (P<0.001). Thirteen patients in the secobarbital group reported adverse effects ranging from drowsiness and restlessness to dry mouth. More patients on triazolam reported side effects. Secondary: Not reported
Seizures				
Arya et al.[20] (2013) Antiepileptic drugs as monotherapy and adjunctive therapy	SR RCTs, SRs and MAs for pediatric population with partial onset or focal seizures classified based on monotherapy and add-on therapy criteria modified from updated International League Against Epilepsy guidelines and American	46 trials Variable duration	Primary: Complete seizure freedom during the observed unit time using 50% responder rate (the proportion of patients experiencing a reduction of ≥50% in seizure frequency during the treatment phase compared to the baseline phase), retention of	Primary: The only antiepileptic drug with Class I evidence for efficacy as initial monotherapy for partial-onset seizures in children is oxcarbazepine. Carbamazepine, clobazam, lamotrigine, phenobarbital, phenytoin, topiramate, valproate, vigabatrin and zonisamide have Class III evidence of efficacy for monotherapy of partial-onset seizures in children. Gabapentin, lamotrigine, levetiracetam, oxcarbazepine and topiramate have Class I evidence of efficacy for treatment of partial-onset seizures in children. The efficacy of phenobarbital monotherapy in children with partial-onset seizures was from open-label trials and as a result, the status of phenobarbital as monotherapy remains undefined. There is no systematic evidence for the efficacy or tolerability of phenobarbital as adjunctive

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	Academy of Neurology/ American Epilepsy Society report		patients on study medication Secondary: Not reported	therapy in children with refractory partial-onset seizures. Secondary: Not reported
Nolan SJ et al.[21] (2013) Phenobarbitone vs phenytoin	SR Adults and children with partial onset seizures or generalized tonic-clonic seizures with or without other generalized seizure types	N=599 (4 trials) Variable duration	Primary: Time to treatment withdrawal (a HR>1 indicates a clinical advantage for phenytoin) Secondary: Time to 12-month seizure-free period (remission), six-month remission and first seizure post randomization; for all outcomes, a HR>1 indicates a clinical advantage for phenytoin	Primary: Phenobarbitone was more likely to be withdrawn than phenytoin based on the overall pooled HR that was calculated using fixed effects and adjusted for seizure type (HR, 1.62; 95% CI, 1.23 to 2.14; P=0.0007). Substantial heterogeneity was present between the trials and when this was accounted for with random effects, the test for interaction between treatment effect and epilepsy type was not significant (Chi^2=1.92; P=0.17). Secondary: The pooled HR for time to 12-month remission was 0.90 (95% CI, 0.69 to 1.18). The pooled HR for time to six-month remission was 0.92 (95% CI, 0.73 to 1.16). The pooled HR for time to first seizure was 0.85 (95% CI, 0.68 to 1.05).
Malamiri et al.[22] (2012) Phenobarbital 20 mg/kg (loading dose) followed by 5 mg/kg divided in two doses and given 12 hours and 24 hours after the loading dose (maintenance dose)	RCT Children two years of age and older (range three to 16 years) with convulsive status epilepticus and acute prolonged seizures who had experienced convulsions while attending	N=60 24 hours	Primary: Termination of all convulsive activity within 20 minutes of starting anticonvulsant infusion, without respiratory depression or hypotension and without another convulsion within one hour	Primary: Twenty-seven out of thirty patients (90%) in the valproate group had their seizures controlled in less than 20 minutes after beginning infusion. Twenty-three out of thirty patients (77%) in the phenobarbital group had their seizures controlled in less than 20 minutes after beginning infusion. There was no statistically significant difference found between the two groups (Fischer Exact Test; P=0.189). Secondary: Termination of seizures within 20 minutes and no seizure recurrence within 24 hours after termination of seizure was 77% in the valproate group (23 out of 30 participants). Termination of seizures within 20 minutes and no seizure recurrence within 24 hours after termination of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sodium valproate 20 mg/kg diluted in 20 mL saline (loading dose) followed by continuous infusion of 1 mg/kg per hour, given 60 minutes after the bolus dose (maintenance dose)	emergency rooms and whose seizures were not controlled by a bolus of intravenous diazepam 0.2 mg/kg within five minutes		Secondary: Freedom from seizures for 24 hours after seizure termination, adverse effects	seizure was 37% in the phenobarbital group (11 out of 30 participants); (Fisher Exact Test; P=0.004). The overall occurrence of clinical adverse effects was 74% in the phenobarbital group and 24% in the valproate group (Fisher Exact Test; P<0.001). Seven patients in the valproate group had adverse effects: three reported lethargy, three reported vomiting, and one developed significant hypotension requiring vasopressor infusion. Seventeen patients in the phenobarbital group had adverse effects: 17 reported lethargy, four had vomiting, and one developed respiratory depression requiring bag and mask ventilation.
Su et al.[23] (2016) Phenobarbital 20 mg/kg (loading dose) followed by IV dose of 100 mg every 6 hours vs valproate 30 mg/kg (loading dose) followed by a continuous infusion at a rate of 1 to 2 mg/kg per hour	PRO, RCT Adults ≥18 years of age with generalized convulsive status epilepticus who initially received treatment with diazepam (0.2 mg/kg IV, twice) and did not respond to diazepam treatment	N=73 Variable duration	Primary: Number of patients with effective seizure control, defined as a cessation of clinical and electroencephalo-graphic seizure activity within 10 to 20 min of loading dose administration Secondary: Relapse rates, adverse events	Primary: Intravenous phenobarbital was successful in 81.1% (30/37) of patients with generalized convulsive status epilepticus, and intravenous valproate was successful in 44.4% (16/36) of patients (P<0.05). Secondary: Relapse of status epilepticus within 24 h occurred in 6.7 and 31.3% of patients in the phenobarbital and valproate groups, respectively (P<0.05). Relapse of nonconvulsive status epilepticus within 24 h did not reach statistical significance (20.0 vs 31.3%). More severe adverse events were seen in the phenobarbital group (13.5 vs 0%; P=0.04), in which six patients had transient depressed respiration and two (5.4%) needed ventilation; five patients developed hypotension and two (5.4%) required vasopressor support. Moreover, two patients developed gastric motility insufficiency, two showed a transient transaminase increase, and one developed bone marrow suppression. After phenobarbital withdrawal, the patients returned to normal levels within one month. In contrast, in the valproate group, no patients showed hypotension or hypoventilation, and six showed transient hyperammonemia without hepatic injury or hyperammonemia encephalopathy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Painter et al.[24] (1999) Phenobarbital 25 µg/mL vs phenytoin 3 µg/mL	RCT, SB Neonates with seizures	N=59 5 years	Primary: Complete seizure control determined by electro-encephalography Secondary: Not reported	Primary: Phenobarbital controlled seizures completely in 43% of patients, while phenytoin controlled seizures in 45% of patients (P=1.00). Secondary: Not reported
Smith et al.[25] (2003) Phenobarbital vs carbamazepine	MA Children or adults with partial-onset seizures or generalized-onset tonic-clonic seizures	N=684 (4 trials) Variable duration	Primary: Time to withdrawal, time to 12-month remission, time to first seizure Secondary: Not reported	Primary: Time to withdrawal was significantly improved with carbamazepine over phenobarbital (HR, 1.63; 95% CI, 1.23 to 2.15). There was no significant difference between treatment groups for the time to 12-month remission and time to first seizure (HR, 0.87; 95% CI, 0.65 to 1.17 and HR, 0.85; 95% CI, 0.68 to 1.05 respectively). Further analysis of each type of seizure indicated that phenobarbital provided statistical benefit over carbamazepine for time to first partial-onset seizure, whereas carbamazepine demonstrated benefit over phenobarbital in patients for time to first generalized-onset tonic-clonic seizures. Secondary: Not reported
Nolan et al.[26] (2015) Phenobarbital vs carbamazepine	MA Children or adults with newly onset partial or generalized epilepsy	N=836 (6 trials) Variable duration	Primary: Time to withdrawal Secondary: Time to 12-month remission, time to first seizure	Primary: Time to withdrawal was significantly improved with carbamazepine over phenobarbital (HR, 1.49; 95% CI, 1.15 to 1.94). Secondary: There was no significant difference between treatment groups for the time to 12-month remission and time to first seizure (HR, 0.93; 95% CI, 0.72 to 1.19 and HR, 0.86; 95% CI, 0.71 to 1.04 respectively).
Treiman et al.[27] (1998) Phenobarbital 15	DB, MC, RCT Adults with overt or subtle generalized	N=518 5 years	Primary: Success (defined as cessation of all motor and	Primary: For treatment success in overt status epilepticus, a significant difference overall in the frequency of success was found, reported as: lorazepam, 64.9%; phenobarbital, 58.2%; diazepam/phenytoin, 55.8%; and phenytoin,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg vs diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg vs phenytoin 18 mg/kg	convulsive status epilepticus		electrical seizure activity within 20 minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes), side effects, outcomes 30 days posttreatment Secondary: Not reported	43.6% (P<0.02 between all groups). For subtle status epilepticus, no significant differences were seen between treatment groups (P<0.18). Lorazepam showed significantly higher frequency of treatment success compared to phenytoin in a pairwise comparison of patients with overt status epilepticus (P<0.002). Pairwise comparisons among other individual treatments showed no significant differences. There were no significant differences among any of the treatment groups with respect to adverse effects or 30-day posttreatment outcomes. Secondary: Not reported
Yasiry et al.[28] (2014) Phenobarbital vs lacosamide vs levetiracetam vs phenytoin vs	MA Patients with status epilepticus who have been resistant to initial therapy with benzodiazepines	N=Not reported (22 trials) Variable duration	Primary: Cessation of seizure activity Secondary: Not reported	Primary: Efficacy of levetiracetam was 68.5% (95% CI, 56.2 to 78.7), phenobarbital 73.6% (95% CI, 58.3 to 84.8), phenytoin 50.2% (95% CI, 34.2 to 66.1) and valproate 75.7% (95% CI, 63.7 to 84.8). Lacosamide studies were excluded from the meta-analysis due to insufficient data. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valproate				
Sedation				
Kienstra et al.[29] (2004) Pentobarbital 1.25 mg/kg to 2.5 mg/kg per titration protocol vs etomidate 0.1 mg/kg to 0.2 mg/kg per titration protocol	DB, PRO, RCT Children six months to six years of age requiring sedation for a head or neck computed tomography scan with American Society of Anesthesiologists physical status class I or II	N=57 1 day	Primary: Efficacy (success rate to complete the procedure with sedation) Secondary: Induction time, sedation time, total examination time	Primary: The success rate for the etomidate group was 57% (N=7) at total doses of up to 0.3 mg/kg and 76% (N=17) at total doses of up to 0.4 mg/kg compared to a success rate of 97% (N=33) for pentobarbital at a total dose of up to 5 mg/kg. The success rate for pentobarbital was significantly greater than the final etomidate group with a difference in proportions of 20.5% (95% CI, 1.9% to 44.4%; P=0.04). Secondary: Patients receiving etomidate had a significantly shorter induction time with a difference of means of 2.1 minutes (95% CI, 0.35 to 3.86; P=0.020), sedation time with a difference of means of 31.3 minutes (95% CI, 24.0 to 38.5; P<0.001), and total examination time with a difference of means of 53.1 minutes (95% CI, 40.8 to 65.3; P<0.001).
Moro-Sutherland et al.[30] (2000) Midazolam IV per titration protocol vs pentobarbital IV per titration protocol	PRO, RCT Children six months to six years of age requiring sedation for a head computed tomography scan with American Society of Anesthesiologists physical status class I or II	N=55 1 day	Primary: Efficacy (success rate to complete the procedure with sedation) Secondary: Induction time, sedation time	Primary: In the pentobarbital group, 97% (N=28) of patients were successfully scanned with good sedation compared to 11% (N=3) of patients in the midazolam group. Among the midazolam group an additional 8% (N=2) of patients had the scan completed despite incomplete sedation. Of the 21 patients (81%) given IV midazolam who were unsuccessfully sedated, 16 (61%) were subsequently sedated with the addition of IV pentobarbital to complete the imaging. Secondary: The mean level of sedation in the pentobarbital group was 5 on the Ramsay Scale (range, 4 to 6; SD±0.56). The mean induction time with pentobarbital was six minutes (range, 1 to 15 minutes; SD±4.1) and the mean sedation time was 86 minutes (range, 20 to 300 minutes; SD±69.2). The average induction and sedation times were not calculated for the midazolam group given only three patients were adequately sedated.
Malviya et al.[31] (2004)	PRO, RCT Children two to 12	N=70 1 day	Primary: Sedation scores (University of	Primary: Sedation scores were higher for the pentobarbital group compared to the chloral hydrate group, although were similar following the procedure and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pentobarbital 2 mg/kg IV in incremental doses titrated to a maximum of 5 mg/kg or 150 mg vs chloral hydrate 75 mg/kg to a maximum of 2 g PO as a single dose Note: midazolam in 0.05 mg/kg increments (incremental doses not to exceed 1 mg; total dose not to exceed 0.1 mg/kg) to augment sedation as deemed appropriate by nurse administrator for procedure completion.	years of age with American Society of Anesthesiologists physical status class I to III scheduled for sedation for magnetic resonance image scan		Michigan Sedation Scale) Secondary: Time to procedure onset, duration of procedure, minutes to discharge, percent requiring midazolam augmentation, adverse events	at discharge. Secondary: The mean time to procedure onset (±SD) was 9 (±6) minutes in the pentobarbital group and 28 (±14) minutes in the chloral hydrate group (P<0.05). The mean time of procedure duration (±SD) was 40 (±14) minutes in the pentobarbital group and 45 (±23) minutes in the chloral hydrate group. The mean time to procedure discharge (±SD) was 33 (±34) minutes in the pentobarbital group and 31 (±19) minutes in the chloral hydrate group. The percentage of patients requiring midazolam augmentation was 9% (N=3) in the pentobarbital group and 37% (N=13) in the chloral hydrate group (P<0.05). A total of five patients in the pentobarbital group experienced a paradoxical reaction (i.e., marked irritability, thrashing, and kicking). While the incidence of adverse events was similar in the two groups, the time to return to baseline activity was significantly longer in children who received pentobarbital (P=0.04). A total of 66% (N=21) of pentobarbital-treated patients did not return to baseline activity for more than eight hours versus 47% (N=15) of chloral hydrate-treated patients (P=NS). There were no differences in the incidence of agitation or restlessness between groups.
Miscellaneous				
Gerhardt et al.[32] (2011) Secobarbital 100 mg for one to two doses post-discharge	DB, PC, RCT Patients 18 to 65 years of age who presented to the emergency department with a migraine (with or	N=50 1 day	Primary: Change in perceived headache pain using a 100 mm visual analog scale Secondary:	Primary: The average change in reported headache pain for the placebo group was an increase of 3 mm (95% CI, −13 to 19 mm) at 24 hours after emergency department discharge. In the secobarbital group, the average change in reported headache pain was a decrease of 25 mm (95% CI, −13 to −38; P=0.01 vs placebo). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	without aura); patients underwent standard treatment in the emergency department (intravenous fluids, antiemetics, ketorolac, and opiate rescue therapy as required)		Difference in self-reported headache resolution rate	A total of 94% of patients receiving secobarbital self-reported partial or complete headache resolution (95 CI, 81 to 100) compared to 50% of patients receiving placebo (95% CI, 24 to 76; P=0.012). This translated to a number needed to treat of 2.3 patients treated with secobarbital to affect one additional partial or complete headache resolution.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SD=standard deviation, SR=systematic review, XO=crossover
Other abbreviations: CI=confidence interval, HR=hazard ratio, IV=intravenous, PO=by mouth

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Barbiturates

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amobarbital	injection	Amytal sodium®	$$$$$	N/A
Pentobarbital	injection	N/A	N/A	$$$$$
Phenobarbital	elixir, injection, tablet	N/A	N/A	$
Secobarbital	capsule	Seconal sodium®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The barbiturates are approved for the treatment of insomnia and for the induction of sedation. Some of the agents are also approved for use as an adjunct to anesthesia, as well as for the treatment of seizure disorders. Pentobarbital and phenobarbital are available in a generic formulation.[1-6]

Currently, there are no clinical guidelines that recommend the use of a barbiturate as first-line therapy for any condition in an outpatient setting.[8-17] There are few clinical trials available that directly compare the various agents. Studies suggest that the barbiturates are not as effective as other sedative-hypnotic agents.[18-32]

The use of barbiturates is associated with abuse and psychological/physical dependence. Individuals who have psychological dependence may increase the dosage or decrease the dosing interval. This behavior may result in a fatal overdose. Tolerance to the sedative-hypnotic effects occurs rapidly, and these agents lose their effectiveness

for sleep induction/maintenance after two weeks.[1-6] The use of barbiturates has been largely replaced by benzodiazepines.

There is insufficient evidence to support that one brand barbiturate is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand barbiturates within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand barbiturate is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics – Benzodiazepines
AHFS Class 282408
November 9, 2022

I. Overview

The benzodiazepines are approved for the treatment of anxiety disorders and insomnia.[1-13] Anxiety disorders include generalized anxiety disorder, panic disorder, posttraumatic stress disorder, and social phobia.[14] The agents approved for the treatment of anxiety include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam, and oxazepam.

The benzodiazepines that are approved solely for the treatment of insomnia include estazolam, flurazepam, temazepam, and triazolam.[1-13] The key diagnostic feature of primary insomnia is difficulty initiating or maintaining sleep for at least three months, which causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.[14] Insomnia may be considered either an acute or chronic disorder (especially if associated with underlying illnesses).

Some of the benzodiazepines are also approved for the treatment of seizure disorders (monotherapy, adjunctive therapy, Lennox-Gastaut syndrome, and status epilepticus) and for the management of acute alcohol withdrawal. Midazolam is a unique product compared to the other benzodiazepines; it is used for the induction/maintenance of general anesthesia and as a sedative (e.g., preoperative, prior to diagnostic/radiologic procedures, and intensive care unit sedation).[1-13]

Benzodiazepines potentiate the effects of gamma-aminobutyric acid and other inhibitory neurotransmitters.[1-13] Within the body there are three major benzodiazepine receptor subtypes. Benzodiazepine receptor subtype-1 is located throughout the central nervous system and is thought to mediate the anxiolytic, sedative and anticonvulsant properties of the benzodiazepines. Benzodiazepine receptor subtype-2 is located in the cortex, hippocampus, striatum, and spinal cord and is believed to mediate muscle relaxation, central nervous system depression, as well as psychomotor impairment. Depression of the central nervous system may range from mild impairment of task performance to hypnosis.[1,2] Benzodiazepine receptor subtype-3 is located throughout the body and glial cells, and is believed to contribute to tolerance and withdrawal when activated.[1,2] The benzodiazepines are mechanistically similar; however, they differ with regards to their pharmacokinetic properties. This includes onset, duration of action, and metabolism. Benzodiazepines with an active parent compound and rapid onset of action may produce euphoria and are more likely to be abused.[15-16] On September 23, 2020, the FDA released a publication to address labeling changes to the benzodiazepine class to improve the safe use of these agents. This action by the FDA is part of ongoing efforts to promote the public health by minimizing risks associated with inappropriate use of controlled substances. The update requires class-wide labeling changes for benzodiazepines to include the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions to help improve their safe use. Beyond requiring an update to the Boxed Warning, other required changes to the prescribing information encompass the Warnings and Precautions, Drug Abuse and Dependence, and Patient Counseling Information sections. Revisions to the patient Medication Guide will also be mandated to educate patients and caregivers about the associated risks of these therapies.[17]

The benzodiazepines that are included in this review are listed in Table 1. Prior to January 1, 2014, benzodiazepines were an excludable/optional drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90). This review encompasses all dosage forms and strengths, regardless of coverage status. All of the benzodiazepines are available in a generic formulation. This class was last reviewed in November 2020.

Table 1. Benzodiazepines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Alprazolam	extended-release tablet, oral concentrate, orally disintegrating tablet, tablet	Xanax®*, Xanax XR®*	alprazolam, alprazolam ER
Chlordiazepoxide	capsule	N/A	chlordiazepoxide

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Clonazepam	orally disintegrating tablet, tablet	Klonopin®*	clonazepam
Clorazepate	tablet	Tranxene T-Tab®*	clorazepate
Diazepam	injection, oral concentrate, oral solution, rectal gel, tablet	Diastat®*, Diastat AcuDial®*	Diastat®*†, Diastat AcuDial®*†, diazepam (excluding rectal gel)
Estazolam	tablet	N/A	estazolam
Flurazepam	capsule	N/A	flurazepam
Lorazepam	injection, oral concentrate, tablet, extended-release capsule	Ativan®*, Loreev XR®	lorazepam
Midazolam	injection, oral syrup	N/A	midazolam
Oxazepam	capsule	N/A	oxazepam
Temazepam	capsule	Restoril®*	temazepam
Triazolam	tablet	Halcion®*	triazolam

*Generic is available in at least one dosage form or strength.
†Generic product requires prior authorization.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the benzodiazepines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Benzodiazepines

Clinical Guideline	Recommendation(s)
National Institute for Clinical Excellence: **Generalized Anxiety Disorder and Panic Disorder in Adults: management (2011)**[18] Last updated June 2020	Drug treatment for people with generalized anxiety disorder (GAD) • If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI), specifically sertraline. • If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI), taking into account the following factors: o Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine). o The side-effect profile and the potential for drug interactions. o The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine). o The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference). • If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin. • Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. • Do not offer an antipsychotic for the treatment of GAD in primary care. • Before prescribing any medication, discuss the treatment options and any concerns the person with GAD has about taking medication. Explain fully the reasons for prescribing and provide written and verbal information on: o the likely benefits of different treatments o the different propensities of each drug for side effects, withdrawal syndromes and drug interactions o the risk of activation with SSRIs and SNRIs, with symptoms such as increased anxiety, agitation and problems sleeping o the gradual development, over one week or more, of the full anxiolytic effect o the importance of taking medication as prescribed and the need to continue treatment after remission to avoid relapse.

Clinical Guideline	Recommendation(s)
	• Take into account the increased risk of bleeding associated with SSRIs, particularly for older people or people taking other drugs that can damage the gastrointestinal mucosa or interfere with clotting (for example, non-steroidal anti-inflammatory drugs [NSAIDS] or aspirin). Consider prescribing a gastroprotective drug in these circumstances. • For people aged under 30 who are offered an SSRI or SNRI, warn them that these drugs are associated with an increased risk of suicidal thinking and self-harm in a minority of people under 30 and, see them within one week of first prescribing and, monitor the risk of suicidal thinking and self-harm weekly for the first month. • Review the effectiveness and side effects of the drug every two to four weeks during the first three months of treatment and every three months thereafter. • If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. <u>Panic disorder pharmacological interventions</u> • Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder. • Sedating antihistamines or antipsychotics should not be prescribed for the treatment of panic disorder. • Antidepressants should be the only pharmacologic intervention used in the longer term. The classes of antidepressants that have an evidence base for effectiveness are the selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs). At the time of this update (June 2020) escitalopram, sertraline, citalopram, paroxetine and venlafaxine are licensed for the treatment of panic disorder. • The following must be taken into account when deciding which medication to offer: o the age of the person o previous treatment response o risks: the likelihood of accidental overdose by the person being treated and by other family members if appropriate; the likelihood of deliberate self-harm, by overdose or otherwise (the highest risk is with TCAs) o tolerability o the possibility of interactions with concomitant medication (consult the interactions section of the BNF) o the preference of the person being treated o cost, where equal effectiveness is demonstrated. • All people who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects (including transient increase in anxiety at the start of treatment) and of the risk of discontinuation/withdrawal symptoms if the treatment is stopped abruptly or in some instances if a dose is missed or, occasionally, on reducing the dose of the drug. • People started on antidepressants should be informed about the delay in onset of effect, the time course of treatment, the need to take medication as prescribed, and possible discontinuation/withdrawal symptoms. Written information appropriate to the person's needs should be made available. • Unless otherwise indicated, an SSRI licensed for panic disorder should be offered. • If an SSRI is not suitable or there is no improvement after a 12-week course and if a further medication is appropriate, imipramine or clomipramine may be considered. Note that this is an off-label use for imipramine and clomipramine. • If there is no improvement after a 12-week course, an antidepressant from the alternative class (if another medication is appropriate) or another form of therapy should be offered.

Clinical Guideline	Recommendation(s)
	• People should be advised to take their medication as prescribed. This may be particularly important with short half-life medication in order to avoid discontinuation/withdrawal symptoms. • Stopping antidepressants abruptly can cause discontinuation/withdrawal symptoms. To minimize the risk of discontinuation/withdrawal symptoms when stopping antidepressants, the dose should be reduced gradually over an extended period of time.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)[19]**	• SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors. They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. • MAOIs appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies

Clinical Guideline	Recommendation(s)
	or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007; 2013 update)[20]**	General considerations • OCD is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. Initial treatment options • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include cognitive-behavioral therapy, SRIs, or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • Cognitive-behavioral therapy or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, FDA warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until four to six weeks after treatment initiation, and some may ultimately respond after as many as 10 to 12 weeks. • Patients not responding after 10 to 12 weeks may respond to a higher dose of the same medication. Changing treatments and pursuing sequential treatment trials • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Augmentation of SRIs with trials of different antipsychotic medications or with cognitive-behavioral therapy or augmentation of cognitive-behavioral therapy with an SRI. • Patients who do not respond to their first SRI may have their medication switched to a different SRI. A switch to venlafaxine is less likely to produce an adequate response. • For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can be considered. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone, pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.

Clinical Guideline	Recommendation(s)
American Psychological Association: **Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (2017)[21]**	• For adults with PTSD, psychotherapies are strongly recommended. • For adults with PTSD, offer one of the following (listed alphabetically): o Fluoxetine o Paroxetine o Sertraline o Venlafaxine • There is insufficient evidence to recommend for or against the following medications for treatment of adults with PTSD: o Risperidone o Topiramate
Department of Veterans Affairs/ Department of Defense: **The Management of Posttraumatic Stress Disorder and Acute Stress Disorder (2017)[22]**	<u>Treatment selection</u> • Individual, manualized trauma-focused psychotherapy is recommended over other pharmacologic and nonpharmacologic interventions for the primary treatment of PTSD. • When individual trauma-focused psychotherapy is not readily available or not preferred, pharmacotherapy or individual non-trauma-focused psychotherapy is recommended. With respect to pharmacotherapy and nontrauma-focused psychotherapy, there is insufficient evidence to recommend one over the other. <u>Pharmacotherapy</u> • Sertraline, paroxetine, fluoxetine, or venlafaxine is recommended as monotherapy for PTSD for patients diagnosed with PTSD who choose not to engage in or are unable to access trauma-focused psychotherapy. • Nefazodone, imipramine, or phenelzine is suggested as monotherapy for the treatment of PTSD if recommended pharmacotherapy, trauma-focused psychotherapy, or non-trauma-focused psychotherapy are ineffective, unavailable, or not in accordance with patient preference and tolerance. (NOTE: Nefazodone and phenelzine have potentially serious toxicities and should be managed carefully.) • Treatment of PTSD with quetiapine, olanzapine, and other atypical antipsychotics (except for risperidone, which is a Strong Against), citalopram, amitriptyline, lamotrigine, or topiramate as monotherapy are NOT suggested due to the lack of strong evidence for their efficacy and/or known adverse effect profiles and associated risks. • Treating PTSD with divalproex, tiagabine, guanfacine, risperidone, benzodiazepines, ketamine, hydrocortisone, or D-cycloserine are NOT recommended as monotherapy due to the lack of strong evidence for their efficacy and/or known adverse effect profiles and associated risks. • Treating PTSD with cannabis or cannabis derivatives is NOT recommended due to the lack of evidence for their efficacy, known adverse effects, and associated risks. • There is insufficient evidence to recommend for or against monotherapy or augmentation therapy for the treatment of PTSD with eszopiclone, escitalopram, bupropion, desipramine, doxepin, D-serine, duloxetine, desvenlafaxine, fluvoxamine, levomilnacipran, mirtazapine, nortriptyline, trazodone, vilazodone, vortioxetine, buspirone, hydroxyzine, cyproheptadine, zaleplon, and zolpidem. <u>Augmentation therapy</u> • The use of topiramate, baclofen, or pregabalin is NOT suggested as augmentation treatment of PTSD due to insufficient data and/or known adverse effect profiles and associated risks. • Combining exposure therapy with D-cycloserine is NOT suggested in the treatment of PTSD outside of the research setting. • Using atypical antipsychotics, benzodiazepines, and divalproex is NOT recommended as augmentation therapy for the treatment of PTSD due to low

Clinical Guideline	Recommendation(s)
	quality evidence or the absence of studies and their association with known adverse effects. • There is insufficient evidence to recommend the combination of exposure therapy with hydrocortisone outside of the research setting. • There is insufficient evidence to recommend for or against the use of mirtazapine in combination with sertraline for the treatment of PTSD. <u>Prazosin</u> • For global symptoms of PTSD, the use of prazosin is NOT suggested as mono- or augmentation therapy. • For nightmares associated with PTSD, there is insufficient evidence to recommend for or against the use of prazosin as mono- or augmentation therapy. <u>Combination therapy</u> • In partial- or non-responders to psychotherapy, there is insufficient evidence to recommend for or against augmentation with pharmacotherapy. • In partial- or non-responders to pharmacotherapy, there is insufficient evidence to recommend for or against augmentation with psychotherapy. • There is insufficient evidence to recommend for or against starting patients with PTSD on combination pharmacotherapy and psychotherapy.
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)[23]**	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments. • Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible. • When pharmacotherapy is utilized, the choice of a specific pharmacological agent should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects. • For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is: o Short-intermediate acting benzodiazepine receptor agonists or ramelteon. o Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful. o Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. o Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressant. o Other sedating agents. Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect. • Over-the-counter antihistamine or antihistamine/analgesic type drugs (over-the-counter "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data. • Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia. • Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments),

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	potential for dosage escalation, and rebound insomnia. • Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication. • Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia. • Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. • Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders. • Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.
American Academy of Sleep Medicine: **Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults (2017)[24]**	<u>Recommendations for treating sleep onset insomnia</u> • Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Recommendations are listed alphabetically. • Eszopiclone is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 14 minutes greater, compared to placebo (95% CI, 3 to 24 minute reduction). o Quality of Sleep: moderate-to-large improvement in quality of sleep, compared to placebo. • Ramelteon is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was nine minutes greater, compared to placebo (95% CI, 6 to 12 minute reduction). o Quality of Sleep: No improvement in quality of sleep, compared to placebo. • Temazepam is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 37 minutes greater, compared to placebo (95% CI, 21 to 53 minute reduction). o Quality of Sleep: Small improvement in quality of sleep, compared to placebo. • Triazolam is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was nine minutes greater, compared to placebo (95% CI, 4 to 22 minute reduction). o Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. • Zaleplon is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 10 minutes greater, compared to placebo (95% CI, 0 to 19 minute reduction). o Quality of Sleep: No improvement in quality of sleep, compared to placebo. • Zolpidem is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was five to 12 minutes greater, compared to placebo (95% CI, 0 to 19 minute reduction). o Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo.

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	Recommendations for treating sleep maintenance insomnia • Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Recommendations are listed alphabetically. • Doxepin is recommended as a treatment for sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 26 to 32 minutes longer, compared to placebo (95% CI, 18 to 40 minute improvement). o Wake After Sleep Onset: Mean reduction was 22 to 23 minutes greater, compared to placebo (95% CI, 14 to 30 minute reduction). o Quality of Sleep: Small-to-Moderate improvement in quality of sleep, compared to placebo. • Eszopiclone is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 28 to 57 minutes longer, compared to placebo (95% CI, 18 to 76 minute improvement). o Wake After Sleep Onset: Mean reduction was 10 to 14 minutes greater, compared to placebo (95% CI, 2 to 18 minute reduction). o Quality of Sleep: moderate-to-large improvement in quality of sleep, compared to placebo. • Temazepam is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 99 minutes longer, compared to placebo (95% CI, 63 to 135 minute improvement). o Wake After Sleep Onset: Not reported. o Quality of Sleep: Small improvement in quality of sleep, compared to placebo. • Suvorexant is recommended as a treatment for sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 10 minutes longer, compared to placebo (95% CI, 2 to 19 minute improvement). o Wake After Sleep Onset: Mean reduction was 16 to 28 minutes greater, compared to placebo (95% CI, 7 to 43 minute reduction). o Quality of Sleep: Not reported. • Zolpidem is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 29 minutes longer, compared to placebo (95% CI, 11 to 47 minute improvement). o Wake After Sleep Onset: Mean reduction was 25 minutes greater, compared to placebo (95% CI, 18 to 33 minute reduction). o Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. Not recommended for treating insomnia • The following drugs are not recommended for the treatment of sleep onset or sleep maintenance insomnia (versus no treatment) in adults: Diphenhydramine, Melatonin, Tiagabine, Trazodone, L-tryptophan, Valerian.
Department of Veterans Affairs and Department of Defense: **The Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea**	Treatment and management of chronic insomnia disorder – behavioral and psychological treatments • It is recommended that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. • Offer brief behavioral therapy for insomnia (BBT-I). • There is insufficient evidence to recommend for or against group versus individual CBT-I for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against internet-based CBT-I

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(2019)[25]	as an alternative to face-to-face based CBT-I for the treatment of chronic insomnia disorder. • CBT-I is suggested over pharmacotherapy as first-line treatment. • Offer CBT-I for the treatment of chronic insomnia disorder that is comorbid with another psychiatric disorder. • There is insufficient evidence to recommend for or against mindfulness meditation for the treatment of chronic insomnia disorder. • Sleep hygiene education is not suggested as a standalone treatment. Treatment and management of chronic insomnia disorder – complementary and integrative health treatments • Offer auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against acupuncture other than auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against aerobic exercise, resistive exercise, tai chi, yoga, and qigong for the treatment of chronic insomnia disorder. • Cranial electrical stimulation is not suggested. Treatment and management of chronic insomnia disorder – over-the-counter treatments • Diphenhydramine is not suggested. • Melatonin is not suggested. • Valerian and chamomile are not suggested. • Kava is not recommended. Treatment and management of chronic insomnia disorder – pharmacotherapy • In patients who are offered a short-course of pharmacotherapy for the treatment of chronic insomnia disorder, use of low-dose (i.e., 3 mg or 6 mg) doxepin or a non-benzodiazepine benzodiazepine receptor agonist is suggested. • There is insufficient evidence to recommend for or against the use of ramelteon for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against the use of suvorexant for the treatment of chronic insomnia disorder. • the use of antipsychotic drugs is not suggested for the treatment of chronic insomnia disorder. • The use of benzodiazepines is not suggested for the treatment of chronic insomnia disorder. • The use of trazodone is not suggested for the treatment of chronic insomnia disorder.
International League Against Epilepsy: **Updated International League Against Epilepsy Evidence Review of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and**	Adults with partial onset seizures • Carbamazepine, levetiracetam, phenytoin, and zonisamide are established treatments as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures. Valproic acid is probably effective and gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin are possibly effective for partial onset seizures. Clonazepam and primidone are potentially efficacious/effective. Children with partial-onset seizures • Oxcarbazepine is established as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures. Carbamazepine, phenobarbital, phenytoin, topiramate, valproic acid and vigabatrin may be effective and

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Syndromes (2013)[26]	clobazam, clonazepam, lamotrigine and zonisamide are potentially efficacious/ effective. Elderly adults with partial-onset seizures • Gabapentin and lamotrigine are effective as initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures. Carbamazepine may be effective and topiramate and valproic acid are potentially efficacious/effective. Adults with generalized-onset tonic-clonic seizures • Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective as initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures. Gabapentin, levetiracetam and vigabatrin are potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures. Children with generalized-onset tonic-clonic seizures • Carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective for children with newly diagnosed or untreated generalized onset tonic-clonic seizures. Oxcarbazepine is potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures. Children with absence seizures • Ethosuximide and valproic acid are established treatments for children with newly diagnosed or untreated absence seizures. Lamotrigine is possibly efficacious/effective as initial monotherapy. Gabapentin is inefficacious/ineffective for children with absence seizures. • Based on scattered reports, the following antiepileptic drugs may precipitate or aggravate absence seizures: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine and vigabatrin. No conclusion can be made about levetiracetam efficacy/effectiveness for absence seizures since the failed class III placebo-controlled trial was uninformative. Children with benign childhood epilepsy with centrotemporal spikes • Carbamazepine and valproic acid are possibly effective as initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes. Gabapentin, levetiracetam, oxcarbazepine, and sulthiame* are potentially efficacious/effective. Juvenile myoclonic epilepsy • Topiramate and valproic acid are potentially efficacious/effective for patients with newly diagnosed juvenile myoclonic epilepsy. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine and vigabatrin may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic-clonic seizures. There has been a report that lamotrigine may exacerbate seizures in juvenile myoclonic epilepsy.
National Institute for Clinical Excellence: **Epilepsies in children, young people and adults (2022)**[27]	Treatment with antiseizure medications • Develop an individualized antiseizure medication treatment strategy with the person, and their family and carers if appropriate. • Take into account any particular issues for older people starting an antiseizure medication, especially those with comorbidities. • Use a single antiseizure medication (monotherapy) to treat epilepsy whenever possible. • Review the diagnosis of epilepsy if seizures continue despite an optimal dose of

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	a first-line antiseizure medication. • If first-line monotherapy is unsuccessful and epilepsy diagnosis remains confirmed, try monotherapy with another antiseizure medication, using caution during the changeover period: o Increase the dose of the second medicine slowly while maintaining the dose of the first medicine. o If the second medicine is successful, slowly taper off the dose of the first medicine. o If the second medicine is unsuccessful, slowly taper off the dose of the second medicine and consider an alternative. • If monotherapy is unsuccessful, consider trying an add-on treatment. • When starting an add-on treatment, carefully titrate the additional medicine and review treatment frequently, including monitoring for adverse effects such as sedation. • If trials of add-on treatment do not result in a reduction in seizures, use the regimen that provides the best balance between effectiveness and tolerability of side effects. • Discuss with the person, and their family and carers as appropriate, the benefits of taking as few medicines as possible to maintain seizure freedom or control. When to start antiseizure medication • Start treatment with an antiseizure medication once the diagnosis of epilepsy is confirmed. • Consider starting treatment after a first unprovoked seizure if any of the following apply: o an examination identifies signs of neurological deficit o the electroencephalogram (EEG) shows unequivocal epileptic activity o after a discussion of the risk of further seizures, the person or their family or carers consider the risk unacceptable brain imaging shows a structural abnormality. Safety considerations • Follow Medicines and Healthcare products Regulatory Agency (MHRA) safety advice on switching between different manufacturers' products of a particular antiseizure medication. • Be aware that phenytoin is associated with an increased risk of serious skin reactions in people of Han Chinese or Thai family background. • Be aware that carbamazepine and potentially medicines with a similar chemical structure (such as oxcarbazepine and eslicarbazepine acetate) are associated with an increased risk of serious skin reactions in people of Han Chinese, Thai, European or Japanese family background. • Be aware that long-term treatment with some antiseizure medications (such as carbamazepine, phenytoin, primidone and sodium valproate) is associated with decreased bone mineral density and increased risk of osteomalacia. Follow the MHRA safety advice on antiepileptics: adverse effects on bone and consider vitamin D and calcium supplementation for people at risk. Antiseizure medications for women and girls • Give women and girls with epilepsy information and support that is tailored to their age-specific and developmental needs. Review regularly information provided about contraception, folic acid supplementation, conception, pregnancy, breastfeeding, caring for children, and menopause. • Discuss with women and girls with epilepsy who are able to have children (including young girls who are likely to need treatment when they are able to have children), and their families or carers if appropriate, the risks to an unborn

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	child of taking antiseizure medications during pregnancy, such as congenital malformations, neurodevelopmental impairments and fetal growth restriction. • Assess the risks and benefits of treatment with individual antiseizure medications when prescribing antiseizure medications for women and girls who are able to have children, now or in the future. Take into account the latest data on the risks to the unborn child and be aware that there are important uncertainties about the risks, particularly with newer drugs. Follow the MHRA safety advice on antiepileptic drugs in pregnancy. • Specifically, discuss the risks to the unborn child of using sodium valproate during pregnancy, including the increased risk with higher doses and polytherapy. Follow the MHRA safety advice on valproate use by women and girls. • Be aware that some antiseizure medications, for example, carbamazepine, oxcarbazepine, phenytoin and topiramate, can impair the effectiveness of hormonal contraceptives. • Be aware that oestrogen-containing hormonal contraceptives and hormone replacement therapy can impair the effectiveness of lamotrigine. • Explain that breastfeeding for most women and girls taking antiseizure medications is generally safe and should be encouraged. Support each mother to choose a feeding method that bests suits her and her family. • Decisions about antiseizure therapy and breastfeeding should be made between the woman or girl and the prescriber, and take into account the benefits of breastfeeding alongside the potential risks of the medication affecting the child. <u>Monitoring and review</u> • Arrange regular (at least annual) monitoring reviews for adults with epilepsy and any of the following: o a learning disability o drug-resistant epilepsy o a high risk of sudden unexpected death in epilepsy (SUDEP; see the section on reducing the risk of epilepsy-related death) o a serious comorbidity, such as complex psychosocial, cognitive or mental health problems o who are taking antiseizure medications associated with long-term side effects or drug interactions o who are able to get pregnant and are taking valproate or any other high-risk teratogenic antiseizure medication (see also the MHRA safety advice on antiepileptic drugs in pregnancy). • Discuss monitoring reviews with children and young people with epilepsy and their families and carers if appropriate, and agree a frequency for regular reviews that is: o individually tailored to the child or young person's needs, preferences and the nature of their epilepsy and o at least every 12 months. • Consider monitoring antiseizure medication levels in people with epilepsy and any of the following: o uncontrolled seizures o side effects from their medication o a specific clinical condition needing closer supervision (such as pregnancy or renal failure) o poor adherence to medication. • Explain to people with epilepsy and, if appropriate, their families and carers, that they can ask for a review of their care if they have concerns, need support or their care needs change, for example, to support medicines withdrawal, pregnancy planning or to review treatment if seizures recur. Provide contact details and

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	information on how to access epilepsy services.
American Academy of Neurology: **Evidence-Based Guideline Update: Medical Treatment of Infantile Spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (2012)**[28] Reaffirmed 2021	• To date, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone, and vigabatrin. • Low-dose adrenocorticotropic hormone should be considered as an alternative to high-dose adrenocorticotropic hormone for treatment of infantile spasms. • Adrenocorticotropic hormone or vigabatrin may be offered for short-term treatment of infantile spasms. Evidence suggests that adrenocorticotropic hormone may be offered over vigabatrin. • There is insufficient evidence to recommend the use of dexamethasone, prednisolone and methylprednisolone as being as effective as adrenocorticotropic hormone for short-term treatment of infantile spasms. • The data is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam, levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for the treatment of infantile spasms. • Hormonal therapy (adrenocorticotropic hormone or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. • A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
Infantile Spasms Working Group: **Infantile Spasms: A U.S. Consensus Report (2010)**[29]	• To improve outcomes in infantile spasms, the goals include early recognition and diagnosis, short-term treatment with a first-line therapy, timely electroencephalography evaluation to assess treatment effectiveness and prompt treatment modification if indicated. • Effective treatment should produce both cessation of spasms and resolution of hypsarrhythmia on electroencephalography. • The dose of the chosen first-line agent should be adjusted to achieve the maximum effective dose in as short amount of time as clinically indicated. • There is insufficient evidence to recommend the best approach in events of relapse. Possible treatment options include using the previously effective agent and dose, using the previously effective agent at the maximum dose or using a new agent. • Adrenocorticotropic hormone is considered first-line therapy for infantile spasms. There is insufficient evidence to recommend the optimal dose and duration of treatment, although short duration is preferable to avoid adverse events. Treatment with the maximum dose of adrenocorticotropic hormone should be continued for two weeks followed by taper and evaluation of treatment response. • Vigabatrin is considered first-line therapy for infantile spasms, especially in patients with comorbid tuberous sclerosis complex. Vigabatrin should be initiated at 50 mg/kg/day and increased up to 100 to 150 mg/kg/day if indicated. Efficacy should be assessed within two weeks following dose titration. Responders to treatment may continue therapy for six to nine months, with continued ophthalmic evaluation. • No recommendations can be given with regard to oral corticosteroids in the treatment of infantile spasms. • Ketogenic diet may be considered as second-line therapy when first-line therapies fail or are inappropriate. • Patients with refractory spasms, concomitant partial seizures or focal abnormalities on the electroencephalography may be evaluated for surgery.
European Federation of Neurological Societies: **Guideline on the Management of**	<u>Initial pharmacological treatment for generalized convulsive status epilepticus and non-convulsive status epilepticus</u> • The preferred treatment is intravenous administration of lorazepam 0.1 mg/kg; however, depending on the patients' general medical condition, treatment can be started at a lower dose of 4 mg, to be repeated if seizures continue for >10

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Status Epilepticus (2010)[30]	minutes after first injection. • If lorazepam is not available, diazepam 10 mg (route of administration not specified) directly followed by phenytoin (15 to 18 mg/kg) or equivalent fosphenytoin. • General management of refractory status epilepticus includes treatment in an intensive care unit. <u>Pharmacological treatment for refractory generalized convulsive status epilepticus and subtle status epilepticus</u> • Immediate infusions of anesthetic doses of midazolam, propofol or barbiturates are recommended due to the progressive risk of brain and systemic damage. • If midazolam is given, seizure suppression is recommended. This goal should be maintained for at least 24 hours. Simultaneous initiation of the chronic medication the patient with be treated with in the future should be initiated. • For elderly patients in whom intubation and artificial ventilation would not be justified, further non-anesthetizing anticonvulsants may be tried. <u>Pharmacological treatment for refractory non-convulsive status epilepticus</u> • Due to poor evidence and lack of any head-to-head trials, no recommendations can be made regarding which of the non-anaesthetizing anticonvulsants should be the drug of choice. • Recommendations include phenobarbital, valproic acid and levetiracetam. • If treatment regimen includes the administration of anesthetics, use the same protocol as refractory generalized convulsive status epilepticus.
American Epilepsy Society/ American Academy of Neurology: **Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults (2016)[31]**	<u>Initial therapy phase (five to 20 minutes)</u> • A benzodiazepine (specifically intramuscular (IM) midazolam, intravenous (IV) lorazepam, or IV diazepam) is recommended as the initial therapy of choice, given their demonstrated efficacy, safety, and tolerability. • Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration, compared with the three recommended benzodiazepines above, positions it as an alternative initial therapy rather than a drug of first choice. • For pre-hospital settings or where the three first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives. <u>Second therapy phase (begins when the seizure duration reaches 20 minutes and should conclude by the 40-minute mark when response or lack of response to the second therapy should be apparent)</u> • Reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any one of these options is better than the others. <u>Third therapy phase (begins when seizure duration reaches 40 minutes)</u> • There is no clear evidence to guide therapy in this phase. • If second therapy fails to stop the seizures, treatment considerations should include repeating second-line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).
American Academy of Neurology/ American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment**	• Lamotrigine use should be considered to decrease seizure frequency. • Lamotrigine use should be considered, and gabapentin use may be considered to decrease seizure frequency in patients aged ≥60 years. • Levetiracetam use may be considered to decrease seizure frequency. • Zonisamide use may be considered to decrease seizure frequency. • Vigabatrin use appears to be less efficacious than immediate-release carbamazepine use and may not be offered; furthermore, toxicity profile

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td>of New Onset Epilepsy (2018)[32]</td><td>precludes vigabatrin use as first-line therapy.
• Pregabalin use at 150 mg/day is possibly less efficacious than lamotrigine use at 100 mg/day.
• Evidence is insufficient to consider gabapentin, oxcarbazepine, or topiramate instead of carbamazepine.
• Evidence is insufficient to consider topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
• Data are lacking to support or refute use of third-generation antiepileptic drugs, clobazam, felbamate, or vigabatrin in treating new-onset epilepsy.
• Data are lacking to support or refute use of newer antiepileptic drugs in treating unclassified generalized tonic-clonic seizures.</td></tr>
<tr><td>American Academy of Neurology/ American Epilepsy Society: Efficacy and Tolerability of the New Antiepileptic Drugs II: Treatment of Refractory Epilepsy (2018)[33]</td><td><u>Summary of guidelines on the use of antiepileptic drugs (AEDs) in treatment-resistant epilepsy, based on Level A and B recommendations</u>
<table>
<tr><th>AED</th><th>Adjunctive focal adult</th><th>Focal mono-therapy</th><th>Idiopathic generalized epilepsy</th><th>Lennox-Gastaut syndrome</th><th>Adjunctive focal pediatric</th></tr>
<tr><td>Gabapentin</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>Yes</td></tr>
<tr><td>Lamotrigine</td><td>Yes</td><td>Yes</td><td>Yes (only in childhood absence epilepsy</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Levetiracetam</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td>Oxcarbazepine</td><td>Yes</td><td>Yes</td><td>No</td><td>No</td><td>Yes</td></tr>
<tr><td>Tiagabine</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td>Topiramate</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Zonisamide</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
</table>
• For treatment-resistant adult focal epilepsy (TRAFE), immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency. Lacosamide, eslicarbazepine, and extended-release topiramate use should also be considered to decrease seizure frequency in this population. Vigabatrin and rufinamide should be considered established as effective for decreasing seizure frequency in TRAFE but are not first-line agents (retinopathy risk with vigabatrin and modest benefit with rufinamide). Ezogabine use should be considered to decrease seizure frequency in this population but carries a serious risk of skin and retinal discoloration. Clobazam and extended-release oxcarbazepine use may be considered to decrease seizure frequency in TRAFE.
• Eslicarbazepine use may be considered to decrease seizure frequency as monotherapy for TRAFE. Data are insufficient to recommend the use of second- and the other third-generation AEDs as monotherapy in TRAFE.
• For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine use should be considered as add-on therapy to decrease seizure frequency in treating adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
• For Lennox-Gastaut syndrome, rufinamide use should be considered established as effective to decrease seizure frequency as add-on therapy, and clobazam use should be considered.
• For add-on therapy for treatment-resistant focal epilepsy, levetiracetam use should be considered to decrease seizure frequency (for ages one month to 16 years), zonisamide use should be considered to decrease seizure frequency (for ages six to 17 years), and oxcarbazepine use should be considered to decrease</td></tr>
</table>

Clinical Guideline	Recommendation(s)
	seizure frequency (for ages one month to four years). Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, pregabalin, rufinamide, tiagabine, or vigabatrin as add-on therapy for the treatment of these children or adolescents.
National Institute for Health and Clinical Excellence: **Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence (2011)**[34] **Reaffirmed 2019**	Drug regimens for assisted withdrawal • Prescribe and administer medication for assisted withdrawal within a standard clinical protocol. The preferred medication for assisted withdrawal is a benzodiazepine (chlordiazepoxide or diazepam). • Gradually reduce the dose of the benzodiazepine over seven to 10 days to avoid alcohol withdrawal recurring. • When managing alcohol withdrawal in the community, avoid giving people who misuse alcohol large quantities of medication to take home to prevent overdose or diversion (the drug being taken by someone other than the person it was prescribed for). Prescribe for installment dispensing, with no more than two days' medication supplied at any time. • Do not offer clomethiazole for community-based assisted withdrawal because of the risk of overdose and misuse. Interventions for moderate and severe alcohol dependence after successful withdrawal • After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention. • After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering disulfiram in combination with a psychological intervention to service users who have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable, or prefer disulfiram and understand the relative risks of taking the drug. Treatment for acute alcohol withdrawal • Offer pharmacotherapy to treat the symptoms of acute alcohol withdrawal. • Consider offering a benzodiazepine or carbamazepine. • Clomethiazole may be offered as an alternative to a benzodiazepine or carbamazepine. However, it should be used with caution, in inpatient settings only and according to the summary of product characteristics. Management of delirium tremens • Lorazepam is considered a first-line treatment option. • If symptoms persist or oral medication is declined, give parenteral lorazepam or haloperidol. Management of alcohol withdrawal seizures • In people with alcohol withdrawal seizures, consider offering a quick-acting benzodiazepine (e.g., lorazepam) to reduce the likelihood of further seizures. • Do not offer phenytoin to treat alcohol withdrawal seizures.

American Psychiatric Association: **Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder (2018)**[35]	Selection of a Pharmacotherapy
	• Naltrexone or acamprosate should be offered to patients with moderate to severe alcohol use disorder who
	  o have a goal of reducing alcohol consumption or achieving abstinence,
	  o prefer pharmacotherapy or have not responded to nonpharmacological treatments alone, and
	  o have no contraindications to the use of these medications.
	• Disulfiram may be offered to patients with moderate to severe alcohol use disorder who
	  o have a goal of achieving abstinence,

Clinical Guideline	Recommendation(s)
	○ prefer disulfiram or are intolerant to or have not responded to naltrexone and acamprosate, ○ are capable of understanding the risks of alcohol consumption while taking disulfiram, and ○ have no contraindications to the use of this medication. • Topiramate or gabapentin may be offered to patients with moderate to severe alcohol use disorder who ○ have a goal of reducing alcohol consumption or achieving abstinence, ○ prefer topiramate or gabapentin or are intolerant to or have not responded to naltrexone and acamprosate, and ○ have no contraindications to the use of these medications. <u>Recommendations Against Use of Specific Medications</u> • Antidepressant medications should not be used for treatment of alcohol use disorder unless there is evidence of a co-occurring disorder for which an antidepressant is an indicated treatment. • In individuals with alcohol use disorder, benzodiazepines should not be used unless treating acute alcohol withdrawal or unless a co-occurring disorder exists for which a benzodiazepine is an indicated treatment. • For pregnant or breastfeeding women with alcohol use disorder, pharmacological treatments should not be used unless treating acute alcohol withdrawal with benzodiazepines or unless a co-occurring disorder exists that warrants pharmacological treatment. • Acamprosate should not be used by patients who have severe renal impairment. • For individuals with mild to moderate renal impairment, acamprosate should not be used as a first-line treatment and, if used, the dose of acamprosate be reduced compared with recommended doses in individuals with normal renal function. • Naltrexone should not be used by patients who have acute hepatitis or hepatic failure. • Naltrexone should not be used as a treatment for alcohol use disorder by individuals who use opioids or who have an anticipated need for opioids. <u>Treatment of Alcohol Use Disorder and Co-occurring Opioid Use Disorder</u> • In patients with alcohol use disorder and co-occurring opioid use disorder, naltrexone should be prescribed to individuals who ○ wish to abstain from opioid use and either abstain from or reduce alcohol use and ○ are able to abstain from opioid use for a clinically appropriate time prior to naltrexone initiation.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the benzodiazepines are noted in Tables 3 to 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Benzodiazepines (Drugs A to E)[1-13]

Indication	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Estazolam
Anxiety Disorders						
Management of anxiety disorders	✔ *†	✔		✔	✔ *‡	
Short-term relief of symptoms of anxiety	✔ *	✔		✔	✔ *‡	
Treatment of panic disorder, with or without agoraphobia	✔ *†§		✔			
Premedication for relief of anxiety and tension in patients who are to undergo surgical procedures					✔ ‡	
Premedication for the relief of anxiety and tension prior to cardioversion and to diminish the patient's recall of the procedure					✔ ‡	
Preoperative apprehension/anxiety		✔				
Sedative-Hypnotic						
Short-term management of insomnia						✔
Seizure Disorders						
Adjunct in partial seizures				✔		
Adjunct in status epilepticus and severe recurrent seizures					✔ ‡	
Adjunctive in convulsive disorders					✔ *	
Management of patients with absence seizures who failed succinimides			✔			
Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity					✔ ‖	
Monotherapy or adjunctive treatment of Lennox-Gastaut syndrome, akinetic and myoclonic seizures			✔			
Miscellaneous						
Acute alcohol withdrawal		✔		✔	✔ *‡	
Adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, and stiff-man syndrome					✔ *‡	

*Immediate-release formulation (tablet, concentrate and/or solution).

†Orally disintegrating tablet formulation.
‡Injection formulation.
§Extended-release formulation.
‖Rectal formulation.

Table 4. FDA-Approved Indications for the Benzodiazepines (Drugs F to T)[1-13]

Indication	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Anesthesia						
Induction of anesthesia, before administration of other anesthetic agents			✔ *			
Preanesthetic medication, producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery		✔ *				
Preoperative sedation/anxiolysis/amnesia			✔ *			
Sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures			✔ *†			
Sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting			✔ *			
Anxiety Disorders						
Management of anxiety disorders		✔ †		✔		
Short-term relief of symptoms of anxiety		✔ †		✔		
Sedative-Hypnotic						
Short-term management of insomnia	✔				✔	✔
Seizure Disorders						
Treatment of status epilepticus		✔ *				
Miscellaneous						
Acute alcohol withdrawal				✔		

*Injection formulation.
†Oral formulation(s).

IV. Pharmacokinetics

The pharmacokinetic parameters of the benzodiazepines are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Benzodiazepines[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Alprazolam	90	80	Liver	Renal (80) Feces (7)	ER: 10.7 to 15.8 IR: 6.3 to 26.9 ODT: 7.9 to 19.2
Chlordiazepoxide	Nearly complete	90 to 98	Liver	Renal (1 to 2)	10 to 48
Clonazepam	90	85	Liver	Renal (<1)	30 to 40
Clorazepate	91	97 to 98	Liver	Renal (62 to 67) Feces (15 to 19)	2.29
Diazepam	Oral: >90 Rectal: 90	95 to 99	Liver	Renal (75)	up to 48
Estazolam	Not reported	93	Not reported	Renal Feces (4)	10 to 24
Flurazepam	Not reported	97	Liver	Renal	2.3
Lorazepam	90 to 93	85 to 91	Liver (75)	Renal (88) Feces (7)	12
Midazolam	36	97	Liver	Renal (45 to 57)	1.8 to 6.4
Oxazepam	93	86 to 99	Liver	Renal (50)	2.8 to 8.6
Temazepam	Well absorbed	96	Not reported	Renal (80 to 90)	3.5 to 18.4
Triazolam	Well absorbed	89 to 94	Liver	Renal (80) Feces (9)	2.3

ER=extended-release, IR=immediate-release, ODT=orally disintegrating tablet

V. Drug Interactions

Major drug interactions with the benzodiazepines are listed in Table 6.

Table 6. Major Drug Interactions with the Benzodiazepines[2]

Generic Name(s)	Interaction	Mechanism
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Barbiturates	Concurrent use of triazolam and barbiturates may result in additive respiratory depression.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Centrally acting muscle relaxants	Concurrent use of benzodiazepines and centrally acting muscle relaxants may result in additive respiratory depression.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Flumazenil	Concurrent use of flumazenil and benzodiazepines may result in precipitation of seizures.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Mirtazapine	Concurrent use of mirtazapine and benzodiazepines may result in increased risk of CNS depression.

Generic Name(s)	Interaction	Mechanism
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Sodium oxybate	Concurrent use of sodium oxybate and benzodiazepines may result in an increase in sleep duration and central nervous system depression.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Tapentadol	Concurrent use of tapentadol and sedatives may result in an increase in central nervous system and respiratory depression.
Benzodiazepines (alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam)	Protease inhibitors	Concurrent use may lead to severe sedation and respiratory depression due to inhibition of hepatic metabolism.
Benzodiazepines (alprazolam, diazepam, midazolam, triazolam)	Azole antifungals	Increased and prolonged serum levels, central nervous system depression, and psychomotor impairment have been reported with benzodiazepines undergoing oxidative metabolism.
Benzodiazepines (diazepam)	Hydantoins	Serum hydantoin concentrations may be increased and phenytoin may increase the clearance of certain benzodiazepines.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam)	Nefazodone	Nefazodone may increase the pharmacologic effects of certain benzodiazepines due to CYP3A4 inhibition and decreased metabolic elimination. Impaired psychomotor performance and increased sedation may result from elevated benzodiazepine plasma concentrations.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam)	Rifamycins	Pharmacologic effects of certain benzodiazepines may be decreased by rifamycins due to CYP3A4 induction and increased metabolic elimination.
Benzodiazepines (alprazolam, clonazepam)	Carbamazepine	The pharmacologic effects of certain benzodiazepines may be decreased due to CYP3A4 induction by carbamazepine.
Benzodiazepines (diazepam, estazolam, midazolam)	Macrolides and ketolides	Central nervous system depression and prolonged sedation have been reported with the concurrent use of benzodiazepines and macrolides/ketolides.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Opioid analgesics	Concurrent use of opioid analgesics and benzodiazepines may result in additive respiratory depression
Benzodiazepines (midazolam)	Vasopressin receptor antagonists	Plasma concentrations of midazolam may be increased by vasopressin receptor antagonists.
Benzodiazepines (midazolam)	Delavirdine	Inhibition of CYP3A4 by delavirdine may decrease the metabolic elimination of certain benzodiazepines. Plasma concentrations and pharmacologic effects of certain benzodiazepines may be increased by delavirdine. Adverse effects, including the potential for serious cardiac arrhythmias, may result.
Benzodiazepines (alprazolam, clonazepam, midazolam, triazolam)	Idelalisib	Concurrent use of idelalisib and triazolam may result in increased triazolam concentrations.
Benzodiazepines (alprazolam, midazolam, triazolam)	Cobicistat	Concurrent use of cobicistat and triazolam may result in increased triazolam plasma concentrations

Generic Name(s)	Interaction	Mechanism
		and increased risk for serious adverse effects including, prolonged or increased sedation or respiratory depression.

VI. Adverse Drug Events

The most common adverse drug events reported with the benzodiazepines are listed in Tables 7 to 8. The boxed warnings are listed in Tables 9 to 11. The benzodiazepines share a number of similar adverse drug events. The most common adverse events are central nervous system-related, including ataxia, confusion, drowsiness, dizziness, and lightheadedness.[1-13] Long-acting benzodiazepines, or benzodiazepines with active metabolites, may have a higher incidence of residual daytime sedation and cognitive/psychomotor impairment. This may be more pronounced in elderly patients or patients with impaired elimination of benzodiazepines. Complex behaviors such as "sleep driving", as well as other behaviors, have been reported in patients who are not fully awake after taking a sedative-hypnotic.[1,2]

Misuse and dependence are a concern with the use of benzodiazepines. The risk of dependence increases with long-term therapy, high daily dose, use of high potency and rapid-onset benzodiazepines, history of substance abuse, chronic physical illness, chronic sleep disorders, and dysthymic or personality disorders.[36,37] Withdrawal symptoms may occur when benzodiazepines are discontinued, especially if therapy is abruptly stopped. Symptoms may include relapse of anxiety disorder or rebound/withdrawal syndromes. Withdrawal may occur within hours of discontinuation of a short-acting benzodiazepine or as late as one to two weeks with the use of long-acting agents. Factors that can predict the severity of withdrawal symptoms include long-term therapy, high daily dose, short benzodiazepine half-life, rapid taper rate, and concomitant substance abuse.[36,38]

Table 7. Adverse Drug Events (%) Reported with the Benzodiazepines (Drugs A to E)[1-13]

Adverse Events	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Estazolam
Cardiovascular						
Chest pain	1 to 10	-	-	-	-	-
Flushing	-	-	-	-	-	1 to 10
Hypotension	1 to 10	1 to 10	-	✔	✔	-
Palpitations	1 to 10	-	✔	-	-	1 to 10
Syncope	<10	-	-	-	-	-
Tachycardia	1 to 10	-	-	-	-	-
Vasodilation	-	-	-	-	✔	-
Central Nervous System						
Agitation	1 to 10	-	-	-	-	1 to 10
Akathisia	1 to 10	1 to 10	-	-	-	-
Amnesia	<1	-	✔	-	✔	1 to 10
Anxiety	-	-	-	✔	-	1 to 10
Apathy	-	-	-	-	-	1 to 10
Ataxia	>10	>10	✔	✔	✔	-
Attention disturbance	1 to 10	-	-	-	-	-
Behavior changes	-	-	✔	-	-	-
Cognitive disorder	>10	-	-	-	-	-
Coma	-	-	✔	-	-	-
Complex sleep-related behavior	-	-	-	-	-	<1
Confusion	1 to 10	1 to 10	✔	✔	✔	1 to 10

Adverse Events	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Estazolam
Coordination abnormal	>10	-	✔	-	-	1 to 10
Depersonalization	1 to 10	-	-	-	-	-
Depression	>10	-	✔	✔	✔	-
Derealization	1 to 10	-	-	-	-	-
Disinhibition	1 to 10	-	-	-	-	-
Disorientation	1 to 10	-	-	-	-	-
Dizziness	>10	1 to 10	✔	✔	-	1 to 10
Dream abnormalities	1 to 10	-	-	-	-	-
Drowsiness	>10	>10	✔	✔	✔	-
Dysdiadochokinesia	-	-	✔	-	-	-
Emotional lability	-	-	✔	-	-	1 to 10
Euphoria	-	-	-	-	-	1 to 10
Fatigue	>10	>10	✔	✔	✔	-
Fear	1 to 10	-	-	-	-	-
Fever	-	-	✔	-	-	<1
Hallucinations	1 to 10	-	✔	-	-	-
Hangover effect	-	-	-	-	-	1 to 10
Headache	1 to 10	-	✔	✔	✔	-
Hemiparesis	-	-	✔	-	-	-
Homicidal ideation	<1	-	-	-	-	-
Hostility	-	-	-	-	-	1 to 10
Hypersomnia	1 to 10	-	-	-	-	-
Hypoesthesia	1 to 10	-	-	-	-	-
Hypokinesia	-	-	-	-	-	1 to 10
Hypomania	<1	-	-	-	-	-
Hypotonia	-	-	✔	-	-	-
Hysteria	-	-	✔	-	-	-
Insomnia	1 to 10	-	✔	✔	-	-
Intellectual ability reduced	-	-	✔	-	-	-
Irritability	>10	>10	-	✔	-	-
Lethargy	1 to 10	-	-	-	-	-
Lightheadedness	>10	>10	-	✔	-	-
Malaise	1 to 10	-	-	-	-	-
Mania	<1	-	-	-	-	-
Memory impairment	>10	-	✔	✔	-	-
Mental impairment	1 to 10	>10	-	-	-	-
Nervousness	1 to 10	-	✔	✔	-	-

Adverse Events	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Estazolam
Nightmares	1 to 10	-	-	-	-	-
Paradoxical reactions	-	-	✔	-	✔	-
Paresthesia	1 to 10	-	-	-	-	1 to 10
Psychosis	-	-	✔	-	-	-
Restlessness	1 to 10	-	-	-	-	-
Sedation	>10	-	-	-	-	-
Seizure	1 to 10	-	✔	-	-	1 to 10
Sleep disturbances	-	-	-	-	-	1 to 10
Slurred speech	-	-	✔	✔	✔	-
Somnolence	>10	-	✔	-	-	>10
Stupor	-	-	-	-	-	1 to 10
Suicidal ideation/attempts	<1	-	✔	-	-	-
Talkativeness	1 to 10	-	-	-	-	-
Tremor	1 to 10	1 to 10	✔	✔	✔	1 to 10
Vasomotor disturbances	2	-	-	-	-	-
Vertigo	1 to 10	-	✔	-	✔	-
Dermatological						
Alopecia	-	-	✔	-	-	-
Dermatitis	1 to 10	1 to 10	-	-	-	1 to 10
Hirsutism	-	-	✔	-	-	-
Photosensitivity	-	1 to 10	-	-	-	-
Pruritus	-	-	-	-	-	1 to 10
Rash	1 to 10	>10	✔	✔	✔	1 to 10
Stevens-Johnson Syndrome	<1	-	-	-	-	-
Urticaria	-	-	-	-	-	1 to 10
Gastrointestinal						
Abdominal pain	1 to 10	-	✔	-	-	-
Anorexia	1 to 10	-	✔	-	-	-
Appetite increased/decreased	>10	>10	✔	✔	-	-
Change in appetite	-	-	-	-	-	1 to 10
Constipation	>10	-	✔	✔	✔	1 to 10
Dehydration	-	-	✔	-	-	-
Diarrhea	1 to 10	-	✔	✔	✔	-
Dyspepsia	1 to 10	-	-	-	-	-
Dysphagia	-	-	-	-	-	-
Encopresis	-	-	✔	-	-	-
Flatulence	-	-	-	-	-	1 to 10

Adverse Events	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Estazolam
Gastritis	-	-	✔	-	-	1 to 10
Gingival soreness	-	-	✔	-	-	-
Nausea	1 to 10	-	✔	✔	✔	-
Salivation decreased	-	>10	-	✔	-	-
Salivation increased	1 to 10	1 to 10	-	-	✔	-
Taste alteration	-	-	-	-	-	1 to 10
Tongue coated	-	-	✔	-	-	-
Vomiting	1 to 10	-	-	✔	-	-
Xerostomia	>10	>10	✔	✔	✔	1 to 10
Genitourinary						
Colpitis	-	-	✔	-	-	-
Dysmenorrhea	1 to 10	-	✔	-	-	-
Dysuria	-	-	✔	-	-	-
Ejaculation delayed	-	-	✔	-	-	-
Enuresis	-	-	✔	-	-	-
Impotence	-	-	✔	-	-	-
Incontinence	1 to 10	1 to 10	-	-	✔	-
Libido decreased	>10	>10	✔	✔	✔	-
Libido increased	1 to 10	1 to 10	✔	-	✔	-
Menstrual disorders	1 to 10	>10	-	-	-	1 to 10
Micturition difficulty	>10	>10	-	-	-	1 to 10
Micturition frequency	-	-	✔	-	-	1 to 10
Nocturia	-	-	✔	-	-	-
Sexual dysfunction	1 to 10	1 to 10	-	-	-	-
Urinary retention	-	-	✔	-	✔	-
Urinary tract infection	-	-	✔	-	-	-
Vaginal discharge/itching	-	-	-	-	-	1 to 10
Hematologic						
Anemia	-	-	✔	-	-	-
Eosinophilia	-	-	✔	-	-	-
Leukopenia	-	-	✔	-	-	-
Neutropenia	-	-	-	-	✔	-
Thrombocytopenia	-	-	✔	-	-	-
Hepatic						
Alkaline phosphatase increased	-	-	✔	-	-	-
Bilirubin increased	1 to 10	-	-	-	-	-
Hepatic failure	<1	-	-	-	-	-

Adverse Events	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Estazolam
Hepatitis	<1	-	-	-	-	-
Hepatomegaly	-	-	✔	-	-	-
Jaundice	<10	-	-	✔	✔	-
Liver enzymes increased	<10	-	✔	✔	-	-
Musculoskeletal						
Arthralgia	1 to 10	-	✔	-	-	-
Back pain	1 to 10	-	✔	-	-	-
Choreiform movements	-	-	✔	-	-	-
Dysarthria	>10	>10	✔	-	✔	-
Dyskinesia	1 to 10	-	-	-	-	-
Dystonia	1 to 10	-	-	-	-	-
Muscle cramps	1 to 10	1 to 10	-	-	-	-
Muscle pain	-	-	✔	-	-	-
Muscle spasm	-	-	-	-	-	<1
Muscle twitching	1 to 10	-	-	-	-	-
Muscle weakness	-	-	✔	-	-	-
Myalgia	1 to 10	-	✔	-	-	<1
Neck pain	-	-	-	-	-	<1
Rigidity	-	1 to 10	-	-	-	-
Weakness	1 to 10	-	-	-	✔	>10
Respiratory						
Allergic rhinitis	1 to 10	-	-	-	-	-
Apnea	-	-	-	-	✔	-
Asthma	-	-	-	-	✔	1 to 10
Bronchitis	-	-	✔	-	-	-
Chest congestion	-	-	✔	-	-	-
Cough	-	-	✔	-	-	1 to 10
Dyspnea	1 to 10	-	-	-	-	1 to 10
Hypersecretions	-	-	✔	-	-	-
Hyperventilation	1 to 10	-	-	-	-	-
Nasal congestion	>10	1 to 10	-	-	-	-
Pharyngitis	-	-	✔	-	-	-
Respiratory depression	-	-	✔	-	✔	-
Respiratory tract infection	-	-	✔	-	-	-
Rhinitis	-	-	✔	-	-	1 to 10
Rhinorrhea	-	-	✔	-	-	-
Shortness of breath	-	-	✔	-	-	-

Adverse Events	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Estazolam
Sinusitis	-	-	✔	-	-	1 to 10
Upper respiratory infection	1 to 10	-	-	-	-	-
Special Senses						
Blurred vision	1 to 10	-	✔	✔	✔	-
Diplopia	-	-	-	✔	✔	-
Eye movements abnormal	-	-	✔	-	-	-
Eye pain/swelling	-	-	-	-	-	1 to 10
Nystagmus	-	-	✔	-	-	-
Other						
Allergic reaction	-	-	✔	-	-	<1
Anaphylaxis	-	-	-	-	-	<1
Angioedema	<1	-	-	-	-	<1
Aphonia	-	-	✔	-	-	-
Chills	-	-	-	-	-	<1
Diaphoresis	1 to 10	-	-	-	-	1 to 10
Drug dependence	-	-	-	-	-	<1
Edema	-	-	✔	-	-	-
Falls	<1	-	-	-	-	-
Galactorrhea	<1	-	-	-	-	-
Gynecomastia	<1	-	-	-	-	-
Hyperprolactinemia	<1	-	-	-	-	-
Lymphadenopathy	-	-	✔	-	-	-
Pain with injection	-	-	-	-	✔	-
Peripheral edema	<1	-	-	-	-	-
Sleep apnea syndrome	<1	-	-	-	-	-
Tinnitus	<1	1 to 10	-	-	-	-
Weight changes	>10	>10	✔	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 8. Adverse Drug Events (%) Reported with the Benzodiazepines (Drugs F to T)[1-13]

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Cardiovascular						
Bigeminy	-	-	<1	-	-	-
Chest pain	✔	-	-	-	-	<1
Hypotension	✔	1 to 10	1 to 10	-	-	-
Palpitations	✔	-	-	-	-	-

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Syncope	-	-	-	✔	-	-
Tachycardia	-	-	-	-	-	<1
Central Nervous System						
Abnormal thinking	-	-	-	-	-	-
Agitation	-	-	<1	-	-	-
Akathisia	-	1 to 10	-	-	-	-
Amnesia	-	1 to 10	<1	-	<1	<1
Anxiety	-	-	-	-	1 to 10	-
Apathy	-	-	-	-	-	-
Apprehension	✔	-	-	-	-	-
Ataxia	✔	1 to 10	-	✔	<1	5
Coma	✔	-	-	-	-	-
Complex sleep-related behavior	-	-	-	-	<1	<1
Confusion	✔	1 to 10	-	-	1 to 10	<1
Delirium	-	-	<1	-	-	-
Depression	✔	1 to 10	-	-	-	<1
Disinhibition	-	<1	-	-	-	-
Disorientation	-	1 to 10	-	-	-	-
Dizziness	✔	1 to 10	-	✔	1 to 10	8
Dream abnormalities	-	-	-	-	-	<1
Drowsiness	✔	-	1 to 10	✔	1 to 10	14
Dysesthesia	-	-	-	-	-	<1
Dystonia	-	-	-	-	-	-
Euphoria	✔	<1	<1	-	1 to 10	<1
Faintness	✔	-	-	-	-	-
Fatigue	-	<1	-	-	1 to 10	<1
Hallucinations	✔	-	<1	-	-	-
Hangover effect	✔	-	-	-	1 to 10	-
Headache	✔	1 to 10	1 to 10	✔	1 to 10	10
Hyperkinesia	-	-	-	-	-	-
Hypokinesia	-	-	-	-	-	-
Incoordination	-	-	-	-	-	-
Irritability	✔	-	-	-	-	-
Lethargy	-	-	-	-	1 to 10	-
Lightheadedness	✔	-	-	-	-	5
Malaise	-	-	-	-	-	-
Memory impairment	✔	-	-	✔	-	<1

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Nervousness	✔	-	-	-	-	5
Nightmares	-	-	-	-	-	<1
Over sedation	-	-	1 to 10	-	-	-
Paradoxical reaction	✔	-	1 to 10	✔	<1	<1
Paranoid reaction	-	-	-	-	-	-
Paresthesia	-	-	-	-	-	<1
Restlessness	✔	-	-	-	-	-
Sedation	-	>10	-	-	-	<1
Seizure	-	<1	1 to 10	-	-	-
Sleep disturbances	-	-	-	-	-	-
Slurred speech	✔	-	-	-	-	<1
Speech disorder	-	-	-	-	-	-
Staggering	✔	-	-	-	-	-
Stimulation	-	-	-	-	-	-
Suicidal ideation	-	<1	-	-	-	-
Talkativeness	✔	-	-	-	-	-
Tremor	-	-	-	✔	-	-
Vertigo	-	<1	-	✔	1 to 10	-
Dermatological						
Dermatitis	-	1 to 10	-	-	-	<1
Flushing	✔	-	-	-	-	-
Pruritus	✔	-	-	-	-	-
Rash	✔	1 to 10	<1	✔	1 to 10	-
Gastrointestinal						
Abdominal pain	-	-	-	-	-	-
Anorexia	-	-	-	-	-	-
Appetite increased/decreased	✔	1 to 10	-	-	-	-
Bitter taste	✔	-	-	-	-	-
Constipation	✔	-	-	-	-	-
Cramps	-	-	-	-	-	<1
Diarrhea	✔	-	-	-	1 to 10	-
Dyspepsia	-	-	-	-	-	-
Gastrointestinal pain	✔	-	-	-	-	-
Heartburn	✔	-	-	-	-	-
Hiccups	-	-	1 to 10	-	-	-
Nausea	✔	1 to 10	1 to 10	-	-	5
Salivation increased	✔	<1	-	-	-	-

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Taste alteration	-	-	-	-	-	-
Upset stomach	✔	-	-	-	-	-
Vomiting	✔	-	1 to 10	-	<1	5
Weight changes	✔	1 to 10	-	-	-	-
Xerostomia	✔	-	-	-	-	<1
Genitourinary						
Impotence	-	-	-	-	-	-
Incontinence	-	-	-	✔	-	-
Libido changes	-	-	-	✔	1 to 10	<1
Decreased libido	-	-	-	-	-	-
Menstrual irregularities	-	<1	-	✔	-	-
Urinary retention	-	-	-	-	-	-
Hematologic						
Blood dyscrasias	-	<1	-	✔	<1	-
Granulocytopenia	✔	-	-	-	-	-
Leukopenia	✔	-	-	✔	-	-
Hepatic						
Aspartate aminotransferase increased	✔	-	-	-	-	-
Alkaline phosphatase increased	✔	-	-	-	-	-
Alanine aminotransferase increased	✔	-	-	-	-	-
Bilirubin increased	✔	-	-	-	-	-
Hepatic dysfunction	-	-	-	✔	-	-
Jaundice	✔	-	-	✔	-	-
Musculoskeletal						
Asthenia	-	<1	-	-	-	-
Dysarthria	✔	-	-	✔	1 to 10	<1
Joint pain	✔	-	-	-	-	-
Muscle spasticity	-	-	-	-	-	-
Myoclonic jerks	-	-	1 to 10	-	-	-
Weakness	✔	1 to 10	-	-	1 to 10	<1
Respiratory						
Apnea	✔	1 to 10	-	-	-	-
Bronchospasm	-	-	<1	-	-	-
Cough	-	-	1 to 10	-	-	-
Dyspnea	✔	-	-	-	-	-
Hyperventilation	-	1 to 10	-	-	-	-
Laryngospasm	-	-	<1	-	-	-

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Nasal congestion	-	1 to 10	-	-	-	-
Respiratory rate decreased	-	-	>10	-	-	-
Tidal volume decreased	-	-	>10	-	-	-
Special Senses						
Abnormal vision	-	-	-	-	-	-
Blurred vision	✔	-	-	✔	1 to 10	-
Cataract	-	-	-	-	-	-
Difficulty focusing	✔	-	-	-	-	-
Diplopia	-	-	-	✔	-	-
Eyes burning	✔	-	-	-	-	-
Nystagmus	-	-	1 to 10	-	-	-
Visual disturbances	-	1 to 10	-	-	-	<1
Other						
Anaphylaxis	-	-	-	-	<1	<1
Angioedema	-	-	-	-	<1	<1
Diaphoresis	✔	-	-	-	1 to 10	-
Drug dependence	✔	<1	1 to 10	✔	<1	-
Edema	-	-	-	✔	-	-
Falling	✔	-	-	-	-	-
Injection site reaction	-	-	1 to 10	-	-	-
Pain	✔	-	-	-	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 9. Boxed Warning for Benzodiazepines[1]

WARNING
WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS • Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation. • The use of benzodiazepines exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing benzodiazepines and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. • The continued use of benzodiazepines may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of benzodiazepines after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue benzodiazepines or reduce the dosage.

Table 10. Boxed Warning for Midazolam Injection[1]

WARNING
Adults and pediatrics: Intravenous midazolam hydrochloride has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam hydrochloride should be used only in hospital or ambulatory care settings, including physicians' and dental offices, that provide for continuous monitoring of respiratory and cardiac function (i.e., pulse oximetry). Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea (i.e., pulse oximetry). Hypoventilation, airway obstruction, and apnea can lead to hypoxia or cardiac arrest unless effective countermeasures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure. The initial dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional two or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 or 5 mg/mL formulation is recommended to facilitate slower injection. Doses of sedative medications in pediatric patients must be calculated on a mg/kg basis, and initial doses and all subsequent doses should always be titrated slowly. The initial pediatric dose of midazolam hydrochloride for sedation/anxiolysis/amnesia is age, procedure, and route dependent. Neonates: Midazolam hydrochloride should not be administered by rapid injection in the neonatal population. Rapid injection should be avoided in the neonatal population. Midazolam hydrochloride administered rapidly as an intravenous injection (less than two minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration.

Table 11. Boxed Warning for Midazolam Syrup[1]

WARNING
Midazolam syrup has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. Midazolam syrup has been associated with reports of respiratory depression, airway obstruction, desaturation, hypoxia, and apnea, most often when used concomitantly with other central nervous system depressants (e.g., opioids). Midazolam syrup should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices, that can provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for ventilation and intubation, and personnel trained in their use and skilled in airway management should be ensured. For deeply sedated patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

VII. Dosing and Administration

The usual dosing regimens for the benzodiazepines are listed in Table 12.

Table 12. Usual Dosing Regimens for the Benzodiazepines[1-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Alprazolam	Management of anxiety disorders, short-term relief of symptoms of anxiety: Oral concentrate (IR), orally disintegrating tablet (IR), tablet (IR): initial, 0.25 to 0.5 mg orally three times daily; may be increased to achieve a maximum therapeutic effect at every three to four days; maximum, 4 mg/day Treatment of panic disorder, with or without agoraphobia: Oral concentrate (IR), orally disintegrating tablet (IR), tablet (IR): initial, 0.5 mg orally three times daily; may increase dosage up to 1 mg every three to four days; usual dosage range is 1 to 10 mg/day Tablet (ER): initial, 0.5 to 1 mg orally in the morning; may increase dosage by up to 1 mg/day every three to four days; usual dosage range is 3 to 6 mg/day; maximum, 10 mg/day	Safety and efficacy in children have not been established.	Oral concentrate (IR): 1 mg/mL Orally disintegrating tablet (IR): 0.25 mg 0.5 mg 1 mg 2 mg Tablet (ER): 0.5 mg 1 mg 2 mg 3 mg Tablet (IR): 0.25 mg 0.5 mg 1 mg 2 mg
Chlordiazepoxide	Acute alcohol withdrawal: Capsule: initial, 25 to 100 mg, followed by repeated doses as needed; maximum, 300 mg/day Management of anxiety disorders, short-term relief of	Management of anxiety disorders, short-term relief of symptoms of anxiety ≥6 years of age: Capsule: 5 mg two to four times daily; may be increased to 10 mg two to three times	Capsule: 5 mg 10 mg 25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	symptoms of anxiety: Capsule: mild-to-moderate symptoms, 5 or 10 mg three to four times daily; severe symptoms, 20 or 25 mg three to four times daily Preoperative apprehension/ anxiety: Capsule: 5 to 10 mg three to four times daily on days preceding surgery	daily	
Clonazepam	Treatment of panic disorder, with or without agoraphobia: Orally disintegrating tablet, tablet: initial, 0.25 mg twice daily; increase by 0.125 to 0.25 mg twice daily every three days; maximum, 4 mg/day Management of patients with absence seizures who failed succinimides, monotherapy or adjunctive treatment of Lennox-Gastaut syndrome, akinetic and myoclonic seizures: Orally disintegrating tablet, tablet: initial, 1.5 mg/day divided into three doses; increase daily by 0.5 to 1 mg/day every three days; maximum, 20 mg/day	Management of patients with absence seizures who failed succinimides, monotherapy or adjunctive treatment of Lennox-Gastaut syndrome, akinetic and myoclonic seizures: Orally disintegrating tablet, tablet: ≤10 years of age (≤30 kg), 0.01 to 0.03 mg/kg/day divided two to three times daily; increase by 0.25 to 0.5 mg/day every three days; maximum, 0.2 mg/kg/day; >10 years of age (>30 kg): Initial, 1.5 mg/day divided into three doses; increase by 0.5 to 1 mg/day every three days; maximum, 20 mg/day	Orally disintegrating tablet: 0.125 mg 0.25 mg 0.5 mg 1 mg 2 mg Tablet: 0.5 mg 1 mg 2 mg
Clorazepate	Acute alcohol withdrawal: Tablet: day one: 30 mg initially, then 30 to 60 mg in divided doses for the remainder of the day; say two: 45 to 90 mg/day in divided doses; day three: 22.5 to 45 mg/day in divided doses; day four: 15 to 30 mg/day in divided doses; day five and thereafter: 7.5 to 15 mg/day in divided doses until the patient's condition is stable; maximum, 90 mg/day Management of anxiety disorders, short-term relief of symptoms of anxiety: Tablet: 15 to 60 mg/day in divided doses; usual daily dose is 30 mg/day; may be administered in a single dose at bedtime.	Adjunct in partial seizures: Tablet: nine to 12 years of age, 7.5 mg twice daily; increase by 7.5 mg/week; maximum, 60 mg/day; >12 years of age: 7.5 mg three times daily; increase by 7.5 mg/week; maximum, 90 mg/day	Tablet 3.75 mg 7.5 mg 15 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Adjunct in partial seizures: Tablet: 7.5 mg three times daily; may increase dose by 7.5 mg/week; maximum, 90 mg/day		
Diazepam	Acute alcohol withdrawal: Injection: initial, 10 mg IM/IV, then 5 to 10 mg in three to four hours, if necessary Oral concentrate, oral solution, tablet: 10 mg three to four times during the first 24 hours, reducing to 5 mg three to four times daily as needed Management of anxiety disorders, short-term relief of symptoms of anxiety: Injection: moderate symptoms: Initial, 2 to 5 mg IM/IV; repeat in three to four hours, if necessary; severe symptoms: initial, 5 to 10 mg IM/IV; repeat in three to four hours, if necessary Oral: 2 to 10 mg two to four times daily Premedication for the relief of anxiety and tension prior to cardioversion and to diminish the patient's recall of the procedure: Injection: 5 to 15 mg IV five to 10 minutes prior to the procedure Premedication for relief of anxiety and tension in patients who are to undergo surgical procedures (endoscopic procedure): Injection: 10 to 20 mg IV immediately prior to procedure or five to 10 mg IM 30 minutes prior to procedure Premedication for relief of anxiety and tension in patients who are to undergo surgical procedures: Injection: 10 mg IM (preferred route) before surgery	Management of anxiety disorders, short-term relief of symptoms of anxiety: Oral concentrate, oral solution, tablet: ≥6 months of age, 1 to 2.5 mg three to four times daily; increase gradually as needed and tolerated Adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, and stiff-man syndrome: Injection: 30 days to five years of age, 1 to 2 mg IM/IV, repeated every three to four hours, if necessary ≥5 years of age, 5 to 10 mg IM/IV, repeated every three to four hours, if necessary Oral concentrate, oral solution, tablet: ≥6 months of age, 1 to 2.5 mg three to four times daily; increase gradually as needed and tolerated Adjunctive in convulsive disorders: Oral concentrate, oral solution, tablet: ≥6 months of age: 1 to 2.5 mg three to four times daily; increase gradually as needed and tolerated Rectal gel: two to five years of age, 0.5 mg/kg; may repeat in four to 12 hours; six to 11 years of age, 0.3 mg/kg; may repeat in four to 12 hours; ≥12 years of age, 0.2 mg/kg; may repeat in four to 12 hours Adjunct in status epilepticus	Injection: 5 mg/mL Oral concentrate: 5 mg/mL Rectal gel: 2.5 mg 5-7.5-10 mg 12.5-15-17.5-20 mg Oral solution: 5 mg/5 mL Tablet: 2 mg 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, and stiff-man syndrome: Injection: initial, 5 to 10 mg IM/IV, then 5 to 10 mg in three to four hours, if necessary. Oral: 2 to 10 mg three to four times daily Adjunctive in convulsive disorders: Oral: 2 to 10 mg two to four times daily Rectal gel: 0.2 mg/kg; may repeat in four4 to 12 hours Adjunct in status epilepticus and severe recurrent seizures: Injection: initial, 5 to 10 mg (IV preferred); may be repeated at 10 to 15 minute intervals; maximum, 30 mg	and severe recurrent seizures: Injection: 30 days to five years of age: 0.2 to 0.5 mg (IV preferred) every two to five minutes; maximum, 5 mg; ≥5 years of age: 1 mg (IV preferred) every two to five minutes; maximum, 10 mg	
Estazolam	Short-term management of insomnia: Tablet: 1 to 2 mg at bedtime	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg
Flurazepam	Short-term management of insomnia: Capsule: 15 to 30 mg at bedtime	Safety and efficacy in children have not been established.	Capsule: 15 mg 30 mg
Lorazepam	Management of anxiety disorders, short-term relief of symptoms of anxiety: Oral concentrate, tablet: 2 to 3 mg/day divided into two to three daily doses Extended-release capsule: the recommended once daily dosage is equal to the total daily dose of lorazepam tablets Preanesthetic medication, producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery: Injection: 0.05 mg/kg IM two to three hours before procedure; maximum, 4 mg; 0.044 mg/kg or 2 mg IV (whichever is less);	Safety and efficacy in children have not been established.	Extended-release capsule: 1 mg 1.5 mg 2 mg 3 mg Injection: 2 mg/mL 4 mg/mL Oral concentrate: 2 mg/mL Tablet: 0.5 mg 1 mg 2 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maximum, 0.05 mg/kg or 4 mg Treatment of status epilepticus: Injection: 4 mg IV; may repeat dose in 10 to 15 minutes if needed		
Midazolam	Induction of anesthesia, before administration of other anesthetic agents: Injection: un-premedicated patients, 0.3 to 0.35 mg/kg IV; premedicated patients, 0.15 to 0.35 mg/kg IV Sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures (amnesia maintenance): Injection: incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary Preoperative sedation/ anxiolysis/amnesia: Injection: 0.07 to 0.08 mg/kg IM administered up to one hour before surgery; IV dosage must be individualized and titrated; some patients may respond to as little as 1 mg; no more than 2.5 mg should be given over a period of at least two minutes Sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures (continuous infusion): Injection: 0.01 to 0.05 mg/kg IV loading dose, followed by a continuous IV infusion at a rate of 0.02 to 0.10 mg/kg/hr	Preoperative sedation/anxiolysis/amnesia: Injection: non-neonatal: 0.1 to 0.15 mg/kg IM, six months to five years of age, 0.05 to 0.1 mg/kg IV; six to 12 years of age, 0.025 to 0.05 mg/kg IV; 12 to 16 years of age: refer to adult dosing Syrup: 0.25 to 1 mg/kg; maximum, 20 mg Sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting: Injection: <32 weeks, continuous IV infusion at a rate of 0.03 mg/kg/hr; ≥32 weeks, continuous IV infusion at a rate of 0.06 mg/kg/hour; non-neonatal, 0.05 to 0.2 mg/kg IV loading dose, followed by a continuous IV infusion at a rate of 0.06 to 0.12 mg/kg/hr	Injection: 1 mg/mL 5 mg/mL Syrup: 2 mg/mL
Oxazepam	Acute alcohol withdrawal: Capsule: 15 to 30 mg three to four times daily Management of anxiety disorders, short-term relief of symptoms of anxiety: Capsule: mild-to-moderate symptoms: 10 to 15 mg three to	Safety and efficacy in children <6 years of age have not been established. Absolute dosage for patients six to 12 years of age is not established. Management of anxiety	Capsule: 10 mg 15 mg 30 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	four times daily; severe symptoms: 15 to 30 mg three to four times daily	disorders, short-term relief of symptoms of anxiety: Capsule: mild-to-moderate symptoms: 10 to 15 mg three to four times daily; severe symptoms: 15 to 30 mg three to four times daily	
Temazepam	Short-term management of insomnia: Capsule: 7.5 to 30 mg at bedtime	Safety and efficacy in children have not been established.	Capsule: 7.5 mg 15 mg 22.5 mg 30 mg
Triazolam	Short-term management of insomnia: Tablet: 0.125 to 0.25 mg at bedtime; maximum, 0.5 mg	Safety and efficacy in children have not been established.	Tablet: 0.125 mg 0.25 mg

ER=extended-release, IM=intramuscular, IR=immediate-release, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the benzodiazepines are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Benzodiazepines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Alcohol Withdrawal				
Holbrook et al.[39] (1999) Benzodiazepines (chlordiazepoxide, diazepam, oxazepam, lorazepam) vs alternative active treatments (bromocriptine, carbamazepine, chlorpromazine, clonidine, doxepin, ethanol, hydroxyzine, paraldehyde, propranolol, thiamine) vs placebo	MA Patients being treated for acute alcohol withdrawal	N=1,286 (11 trials) Variable duration	Primary: Improvement of withdrawal symptoms, therapeutic success (CIWA-Ar score $\leq$10), adverse events, dropout rates Secondary: Not reported	Primary: In three studies with a similar outcome measures, the benzodiazepines were rated as more efficacious compared to placebo in relieving the symptoms of alcohol withdrawal within the first two days of withdrawal (OR, 3.28; 95% CI, 1.30 to 8.28). There were no significant differences in efficacy between individual benzodiazepines. In the nine trials that compared benzodiazepines with alternative active agents, there was no evidence of better efficacy of any alternative agent over a benzodiazepine. Three studies reported the number of adverse events and found no significant difference between benzodiazepines and the alternative treatments examined (OR, 0.67; 95% CI, 0.34 to 1.32). Data on study dropout rates were combined from five trials and indicated that fewer patients in the benzodiazepines group compared to the alternative treatment group dropped out within the first seven days of treatment (OR, 0.68; 95% CI, 0.47 to 0.97). Secondary: Not reported
Ntais et al.[40] (2005) Benzodiazepines alone or in	MA Patients with alcohol dependence who experienced	N=4,051 Variable duration	Primary: Severity of overall alcohol withdrawal syndrome, alcohol withdrawal	Primary: Compared to placebo, there was a benefit with the benzodiazepines against alcohol withdrawal seizures (P=0.01). Benzodiazepines had similar success rates as other drugs and offered a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination with other agents vs alternate benzodiazepines vs other agents (e.g., anticonvulsants) vs placebo	alcohol withdrawal		seizures, alcohol withdrawal delirium Secondary: Adverse events, discontinuation due to adverse events, withdrawal rate, mortality	benefit for seizure control against non-anticonvulsants (P=0.02), but not against anticonvulsants (95% CI, 0.46 to 8.65). Data on other comparisons were limited preventing informative quantitative synthesis for the various outcomes. Secondary: Compared to placebo, the number of withdrawals per arm tended to be less common among patients receiving benzodiazepine (P=0.22). No patients discontinued due to side effects in the benzodiazepine group and one patient discontinued treatment for this reason in the placebo group. No patients died in either the benzodiazepine groups or placebo groups. In those studies that compared benzodiazepines to other agents, there were no between-group differences in number of withdrawals per arm (P=0.54 for comparison with other drugs and P=0.75 for comparison with anticonvulsants). Two out of 901 benzodiazepine-treated patients died compared to five out of 1,275 patients receiving other agents. Patients receiving benzodiazepines had a higher incidence of side effects compared to patients receiving other agents (P=0.16) or anticonvulsants (P=0.47), though NS.
Kumar et al.[41] (2009) Lorazepam 8 mg/day (2 mg in the morning, 2 mg in the afternoon, 4 mg at night) for 2 days; the dose was reduced by 2 mg/day every 2 days vs	DB, RCT Male inpatients in a state of moderately severe, uncomplicated alcohol withdrawal	N=100 12 days	Primary: Withdrawal severity and changes in the CIWA-Ar scale Secondary: Not reported	Primary: There was no significant difference in withdrawal severity between patients receiving lorazepam or chlordiazepoxide at baseline or at any time during the study. Using an 11-item alcohol-withdrawal checklist, irritability (2.9 vs 0.4%; P<0.001), dizziness (0.9 vs 0.0%; P<0.001), and brisk reflexes (0.8 vs 0.2%; P<0.02) were more common with lorazepam than with chlordiazepoxide. Palpitations were more common with chlordiazepoxide than with lorazepam (0.9 vs 0.0%, respectively; P<0.001). The incidence of the remaining items (depressed mood, impaired concentration, anorexia, insomnia, fever, and gait ataxia) did not differ between the two groups. There were no symptoms of benzodiazepine withdrawal recorded during

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chlordiazepoxide 80 mg/day (20 mg in the morning, 20 mg in the afternoon, 40 mg at night) for 2 days; the dose was reduced by 20 mg per day every 2 days Dosing was down-titrated to zero across 8 treatment days.				the last four days of the study, nor were there impairing adverse events reported during this period. Secondary: Not reported
Caputo et al.[42] (2014) GATE 1 Oxazepam vs sodium oxybate	DB, MC, RCT Alcohol-dependent outpatients 21 to 75 years of age affected by uncomplicated AWS with CIWA-Ar score ≥10	N=126 10 days	Primary: Reduction of symptoms of AWS measured by the change in the total CIWA-Ar score from baseline Secondary: Not reported	Primary: A significant decrease of the mean total CIWA-Ar score from the baseline to the end of the study was found both in the sodium oxybate group (adjusted mean change from baseline of −15.62 ± 0.38; ANCOVA model P<0.0001) and in the oxazepam group (adjusted mean change from baseline of −16.27 ± 0.38; ANCOVA model P<0.0001), with no significant differences between the two treatments (ANCOVA model: estimated point 0.65 (95 % CI, −0.37 to 1.66) P=0.210). Secondary: Not reported
Anxiety Disorders				
Martin et al.[43] (2007) Alprazolam, diazepam, lorazepam vs	MA Patients with generalized anxiety disorder	N=2,326 (23 trials) 2 to 24 weeks	Primary: Withdrawals for any reason and withdrawals due to adverse events Secondary: Withdrawals due to lack of efficacy	Primary: The RR of withdrawal for any reason was 0.78 (95% CI, 0.62 to 1.00; P=0.05) in favor of benzodiazepines. The RR of withdrawal due to adverse events was 1.54 (95% CI, 1.17 to 2.03; P=0.002) indicating an increased risk for the benzodiazepine group. Secondary: The RR of withdrawal due to lack of efficacy was 0.29 (95% CI, 0.18 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				0.45; P<0.00001) in favor of benzodiazepines.
Moylan et al.[44] (2011) Alprazolam vs benzodiazepines	MA Patients ≥18 years of age with panic disorder or agoraphobia with panic attacks	N=631 (8 trials) Variable duration	Primary: PAF, HAM-A, proportion of panic attack-free patients, adverse events Secondary: Not reported	Primary: There was no significant difference in mean PAF improvement between alprazolam and other benzodiazepines (WMD in PAF of 0.6 panic attacks/week; 95% CI, -0.3 to 1.6). There was no difference in mean HAM-A improvement between alprazolam and other benzodiazepines (WMD, 0.8 points; 95% CI, -0.5 to 2.1). There was no significant difference between alprazolam and other benzodiazepines in the proportion of panic-attack free patients (RR, 1.1; 95% CI, 0.9 to 1.4). The most commonly reported adverse effect was sedation. There was no significant difference in the dropout rates due to adverse effects. There was no clinically significant difference in tolerability between alprazolam and comparative benzodiazepine. Secondary: Not reported
Mitte et al.[45] (2005) Benzodiazepines vs azapirones vs placebo	MA Patients with generalized anxiety disorder	N=12,053 (48 trials) Variable duration	Primary: Anxiety (HAM-A), depression (HAM-D) Secondary: Not reported	Primary: Active treatment reduced both anxiety and depression symptoms better than placebo. There were no significant differences in efficacy between the benzodiazepines and azapirones (P=NS). Significantly fewer patients in the benzodiazepine group dropped out of the study (20.5 vs 30.7%; P<0.05). Secondary: Not reported
Blanco et al.[46] (2003) Benzodiazepines,	MA Patients with social anxiety disorder	N=2,954 (23 trials) 6 to 20 weeks	Primary: Outcome data on the LSAS or a categorical	Primary: In terms of LSAS, no statistical difference was detected between medications or medication groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SSRIs, MAOIs, RIMAs, β-blockers, gabapentin, buspirone vs placebo			measure of status Secondary: CGI score	Secondary: In terms of responders, effect sizes of each medication group were: benzodiazepines (16.61), brofaromine (6.96), phenelzine (4.10), gabapentin (3.78), SSRIs (3.22), atenolol (1.36), and moclobemide (1.27). No statistical differences were detected between these Medications or medication groups.
van Balkom et al.[47] (1997) Benzodiazepines vs antidepressants vs psychological panic management vs exposure in vivo vs placebo	MA Patients with panic disorder (with or without agoraphobia)	N=5,011 (106 trials) Variable duration	Primary: Panic, agoraphobia, depression, and general anxiety Secondary: Not reported	Primary: Antidepressants, psychological panic management and antidepressants/ exposure in vivo demonstrated significant improvement in the reduction of panic, agoraphobia, depression, and anxiety compared to a control conditions. High-potency benzodiazepines showed significant improvement in panic, agoraphobia, and anxiety compared to control conditions. There were no significant differences between the treatments for panic disorder. Antidepressant test groups had significant improvements compared to other treatments except exposure in vivo in agoraphobia. A significantly greater improvement was noted in antidepressant/exposure in vivo compared to exposure in vivo alone and psychological panic management/exposure in vivo in treatment of depression and anxiety. Secondary: Not reported
Chessick et al.[48] (2006) Benzodiazepines vs	MA Patients with generalized anxiety disorder	N=5,908 (36 trials) 4 to 14 weeks	Primary: HAM-A, patient acceptability Secondary: Not reported	Primary: Using the HAM-A, lorazepam (WMD, 1.1; 95% CI, 0.29 to 1.91; P=0.008) and alprazolam (WMD, 1.1; 95% CI, 0.28 to 1.92; P=0.009) were more effective than buspirone, but diazepam was comparable in efficacy to buspirone (WMD, -0.20; 95% CI, -7.45 to 7.05; P=0.96).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
azapirones The MA also compared the azapirones to hydroxyzine, kava kava, placebo, venlafaxine and psychotherapy, but only the results from studies comparing the azapirones to the benzodiazepines are reported in this review.				Significantly fewer participants dropped out on benzodiazepine therapy compared to buspirone (RR, 1.24; 95% CI, 1.01 to 1.52; P=0.04). Patients receiving buspirone reported less drowsiness (P<0.00001), fatigue (P=0.00001), nervousness (P=0.0006), depression (P<0.00001), insomnia (P=0.01) and sleep problems (P=0.02) compared to benzodiazepines. Patients receiving benzodiazepines reported less nausea (P=0.03) and dizziness (P=0.02) compared to buspirone. In the trial that discontinued either diazepam or buspirone at either six or 12 weeks, neither group had worsening symptoms of anxiety but those on diazepam did show withdrawal symptoms at six weeks compared to those on buspirone (P<0.001). In the one extension trial with a taper off, 25% of patients on ipsapirone showed rebound anxiety symptoms compared to 40% of patients on lorazepam (P<0.001). Secondary: Not reported
Insomnia				
Holbrook et al.[49] (2000) Benzodiazepines vs zopiclone, diphenhydramine, glutethimide, promethazine, cognitive behavioral therapy, placebo	MA Patients with insomnia	N=2,672 (45 trials) 1 day to 6 weeks	Primary: Sleep latency, total sleep duration, adverse effects, dropout rates, cognitive function decline Secondary: Not reported	Primary: Using sleep records, benzodiazepines demonstrated a decrease in sleep latency by 4.2 minutes compared to placebo (95% CI, -0.7 to 9.2). Benzodiazepines demonstrated a significant increase in sleep duration compared to placebo by 61.8 minutes (95% CI, 37.4 to 86.2). Benzodiazepines were more likely to be associated with complaints of daytime drowsiness (OR, 2.4; 95% CI, 1.8 to 3.4) and dizziness/ lightheadedness (OR, 2.6; 95% CI, 0.7 to 10.3) compared to placebo. No difference was observed in dropout rates between the two groups. Pooled results from three trials indicated there was no significant difference between benzodiazepines and zopiclone in sleep latency, but benzodiazepine therapy may lead to a longer sleep by 23.1 minutes (95% CI, 5.6 to 40.6). There was no significant difference in adverse events among the treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				groups (OR, 1.5; 95% CI, 0.8 to 2.9). Comparisons between benzodiazepines and antihistamines did not detect any significant differences on sleep outcomes. Triazolam was found to be more effective in reducing sleep latency early in one trial, but efficacy decreased by the second week of treatment. Behavioral therapy efficacy was maintained throughout the nine-week follow-up. Secondary: Not reported
Smith et al.[50] (2002) Benzodiazepines or benzodiazepine receptor agonists vs behavioral treatment vs placebo	MA Patients with primary insomnia for ≥1 month	N=470 (21 trials) 1 to 10 weeks	Primary: Sleep latency, TST, number of awakenings, wake time after sleep onset, and sleep quality before and after treatment Secondary: Not reported	Primary: Sleep latency was reduced by 30% with pharmacological treatment compared to 43% with behavioral interventions. Pharmacotherapy increased TST by 12% compared to 6% with behavior therapy. Both pharmacotherapy and behavior therapy reduced number of awakenings per night by one. Wake time after sleep onset was reduced by 46% with pharmacotherapy and by 56% with behavior therapy. Pharmacotherapy improved sleep quality by 20% compared to 28% with behavior therapy. Overall, there were no differences in TST, number of awakenings, wake time after sleep onset, and sleep quality between benzodiazepine receptor agonists and behavioral therapy. The behavioral therapy group had a greater reduction in latency to sleep onset than the group that took the benzodiazepine receptor agonists (95% CI, 0.17 to 1.04). Secondary: Not reported
Nowell et al.[51]	MA	N=1,894	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1997) Benzodiazepines or benzodiazepine receptor agonists vs placebo	Adults <65 years of age with chronic insomnia	(22 trials) 4 to 35 days	Sleep latency, TST, number of awakenings, sleep quality Secondary: Not reported	Zolpidem and benzodiazepines were significantly more effective than placebo with regards to sleep latency, TST, number of awakenings and sleep quality (P<0.001). Secondary: Not reported
Buscemi et al.[52] (2007) Benzodiazepines, non-benzodiazepines, antidepressants vs placebo	MA Adults with chronic insomnia	105 trials 1 night to 6 months	Primary: Sleep latency, WASO, sleep efficiency, sleep quality, TST, adverse events Secondary: Not reported	Primary: Sleep latency assessed by PSG was significantly decreased for benzodiazepines (WMD, -10.0 minutes; 95% CI, -16.6 to -3.4), non-benzodiazepines (WMD, -12.8 minutes; 95% CI, -16.9 to -8.8) and antidepressants (WMD, -7.0 minutes; 95% CI, -10.7 to -3.3). Sleep latency assessed by sleep diaries was also significantly improved for benzodiazepines (WMD, -19.6 minutes; 95% CI, -23.9 to -15.3), non-benzodiazepines (WMD, -17.0 minutes; 95% CI, -20.0 to -14.0) and antidepressants (WMD, -12.2 minutes; 95% CI, -22.3 to -2.2). MA for WASO, sleep efficiency, sleep quality and TST measured by PSG and sleep diary were statistically significant and favored benzodiazepines and non-benzodiazepines vs placebo with the exception of PSG studies measuring WASO and TST, which were marginally nonsignificant. In contrast, PSG results significantly favored antidepressants vs placebo, but sleep diary results were fewer and non-significantly favored antidepressants for WASO and non-significantly favored placebo for TST. Indirect comparisons between benzodiazepines and non-benzodiazepines resulted in no significant difference in sleep latency; however, benzodiazepines were associated with more adverse events. Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in sleep latency or adverse events. Indirect comparisons between non-benzodiazepines and antidepressants resulted in a significantly greater sleep latency assessed by PSG but not by

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sleep diary for non-benzodiazepines. There was no significant difference in adverse events. All drug groups had a statistically significant higher risk of harm compared to placebo, although the most commonly reported adverse events were minor. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea. Secondary: Not reported
Glass et al.[53] (2008) Temazepam 15 mg for 2 weeks vs diphenhydramine 50 mg for 2 weeks vs placebo for 2 weeks	DB, PC, RCT, XO Elderly patients ≥70 years of age with primary insomnia	N=20 6 weeks	Primary: Subjective assessments of sleep recorded on sleep diaries Secondary: Morning-after psychomotor impairment (using the DSST and the MTT); morning-after memory impairment (using free-recall)	Primary: There was a significant difference in sleep quality scores with temazepam compared to diphenhydramine and placebo (both P<0.05). There was a significant difference in sleep-onset latency and TST with temazepam compared to placebo (P<0.05). There was a significant difference in the number of awakenings with diphenhydramine and temazepam compared to placebo (both P<0.05). Secondary: There were no changes in the DSST or the MTT scores with any treatment. No treatment effects could be detected on the memory assessment performed.
Piccione et al.[54] (1980) Triazolam 0.25 mg vs triazolam 0.50 mg vs	DB, XO Elderly patients >60 years of age with insomnia	N=27 5 days	Primary: Efficacy (questionnaire with subjective estimates of sleep latency, TST, number of awakenings, overall quality of sleep), side effects	Primary: The patients' global evaluation of effectiveness indicated that triazolam 0.25 and 0.50 mg improved sleep more than placebo (both P<0.05), while chloral hydrate 250 and 500 mg were not better than placebo. Triazolam 0.50 mg, but not 0.25 mg, was significantly better than chloral hydrate 250 mg (P<0.01) and 500 mg (P<0.05) in the global evaluation of effectiveness. There was no significant difference in sleep latency, TST and number of awakenings between placebo and either dose of chloral hydrate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chloral hydrate 250 mg vs chloral hydrate 500 mg vs placebo			Secondary: Not reported	Triazolam 0.25 mg significantly decreased sleep latency and increased TST compared to placebo (both P<0.05). Triazolam 0.50 mg significantly decreased the number of awakenings compared to placebo (P<0.01). Patients estimated their TST to be longer following the use of triazolam 0.25 mg as compared to chloral hydrate 250 or 500 mg (both P<0.05). There were no significant differences in reported side effects between the active treatments and placebo. Secondary: Not reported
Okawa et al.[55] (1978) Secobarbital 100 mg vs triazolam 0.5 mg vs placebo	DB, RCT, XO (two trials) Patients 18 to 60 years of age with a history of insomnia and two of the following: onset of sleep longer than 30 minutes, duration of sleep six hours or less, or experiencing three or more awakenings	N=76 2 nights	Primary: Patient preference questionnaire, success (defined as sleep onset in 30 minutes or less and sleep duration of six hours or more), adverse effects Secondary: Not reported	Primary: One trial compared triazolam to placebo and involved 19 patients. Sixteen patients preferred triazolam over placebo and three expressed no preference (P<0.001). Triazolam demonstrated greater efficacy over placebo in overall sleep (P<0.001), onset (P<0.001), duration (P<0.002) and number of awakenings (P<0.002). Triazolam was determined to be significantly more successful in 15 of 19 patients (P<0.004). No difference in next-morning alertness was noted between the two study groups. Seven patients receiving active treatment experienced mild-to-moderate adverse effects, with dizziness, drowsiness and headache as the most frequently reported. In comparison, three of the patients in the placebo group experienced mild-to-moderate side effects. The second trial was a combined study of 57 patients comparing triazolam and secobarbital. The results of the patient preference questionnaire were analyzed and showed a significant preference for triazolam (41 patients) over secobarbital (10 patients), with six having no preference for either agent (P<0.001). Significant improvement was seen with triazolam compared to secobarbital (P<0.001) in sleep onset, duration of sleep and number of awakenings. Feelings of alertness the next morning did not differ between treatment groups. Success was established in 73% of triazolam treated patients whereas only 30% of the secobarbital treated patients were determined successful (P<0.001). Thirteen patients in the secobarbital group reported adverse effects ranging from drowsiness and restlessness to dry mouth. More patients on triazolam reported side effects.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Seizures				
Conry et al.[56] (2014) Clobazam adjunctive therapy	ES, OL Patients 2 to 60 years of age from two RCTs taking clobazam as adjunctive therapy for Lennox-Gastaut syndrome	N=267 2 to 6 years	Primary: Changes in rates of drop seizures and total seizures Secondary: Responder rates (≥50, ≥75, or 100% decreases in seizure frequency vs baseline), sustained efficacy over time, and global evaluations; safety	Primary: The high median percentage decrease from baseline in average weekly rate of drop seizures (85 to 91%) was maintained through year five. The median percentage decrease in total seizures was also maintained, with an 85% reduction from baseline in those patients who had reached year five. Secondary: The percentages of patients with decreases of ≥50, ≥75, or 100% in their average weekly seizure rates from the previous blinded study baseline were consistent over the five-year trial span for both drop and total seizures. Over five years, 62 to 69% achieved at least a 75% reduction in drop seizures, and 50 to 65% attained a 75% or more reduction in total seizures while treated with clobazam. The majority of patients were assessed by both their physicians and caregivers as "very much improved" or "much improved" after one, two, and three years of treatment. During the open-label study, 60% of patients experienced ≥1 treatment-related adverse event. The most common adverse events during the open label extension were upper respiratory tract infection (28%) and pyrexia (19%). The upper respiratory tract infection and pneumonia events occurred predominantly in pediatric patients.
Isojarvi et al.[57] (2016) Clobazam: low dosage (target of 0.25 mg/kg/day [maximum 10 mg/day]), medium dosage (target of 0.5 mg/kg/day [maximum 20 mg/day]), and high	Post-hoc analysis of a DB, MC, PC, RCT Patients 2 to 60 years of age with a diagnosis of Lennox-Gastaut syndrome who were receiving stable doses of 1 to 3 AEDs (except	N=217 12 weeks	Primary: Seizure-related injuries Secondary: Adverse events	Primary: Patients receiving clobazam experienced significantly fewer seizure-related injuries than those receiving placebo (P<0.05). Compared with placebo (27.1%), the rates of seizure-related injuries were statistically significantly lower for the medium- (4.8%, P<0.001) and high-dosage (10.2%, P<0.03) clobazam groups, but not for the low-dosage clobazam group (12.1%). Secondary: A total of 32 patients experienced 53 adverse events that were considered to be seizure-related, of which 50 (94.3%) were mild or moderate in intensity. All severe seizure-related adverse events occurred in the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dosage (target of 1.0 mg/kg/day [maximum 40 mg/day]) vs placebo	benzodiazepines) for ≥30 days and were experiencing ≥2 drop seizures per week			group, with three patients experiencing one severe adverse event each (fall, contusion, or jaw fracture). In all treatment groups, all but one of the injuries were not serious, and most resolved by study end. The single serious adverse event (jaw fracture, which required surgery) occurred in a placebo-treated patient; this was the only seizure-related injury that required hospitalization.
Pavlidou et al.[58] (2006) Diazepam 0.33 mg/kg every 8 hours rectally for 1 day, followed by every 12 hours on day 2 vs no treatment	PRO, RCT Children 6 months to 3 years of age who experienced a first febrile seizure	N=139 3 years	Primary: Recurrence rates Secondary: Not reported	Primary: The 36-month recurrence rates in the no treatment group compared to the diazepam group were: 83 vs 38% (high-risk patients; P=0.005), 55 vs 35% (intermediate-risk patients; P=0.341), and 46 vs 33% (low-risk patients; P=0.412). Secondary: Not reported
Treiman et al.[59] (1998) Phenobarbital 15 mg/kg vs diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg vs lorazepam 0.1	DB, MC, RCT Adults with overt or subtle generalized convulsive status epilepticus	N=518 5 years	Primary: Success (defined as cessation of all motor and electrical seizure activity within 20 minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes), side effects, outcomes 30 days posttreatment	Primary: For treatment success in overt status epilepticus, a significant difference overall in the frequency of success was found, reported as: lorazepam, 64.9%; phenobarbital, 58.2%; diazepam/phenytoin, 55.8%; and phenytoin, 43.6% (P<0.02 between all groups). For subtle status epilepticus, no significant differences were seen between treatment groups (P<0.18). Lorazepam showed significantly higher frequency of treatment success compared to phenytoin in a pairwise comparison of patients with overt status epilepticus (P<0.002). Pairwise comparisons among other individual treatments showed no significant differences. There were no significant differences among any of the treatment groups with respect to adverse effects or 30-day posttreatment outcomes. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg vs phenytoin 18 mg/kg			Secondary: Not reported	Not reported
Appleton et al.[60] (2002) Lorazepam intravenous or rectally (dose not specified) vs diazepam intravenous or rectally (dose not specified)	MA Children 1 month to 16 years of age with acute tonic-clonic convulsions	N=102 1 year	Primary: Efficacy (cessation of the presenting convulsion, seizure recurrence within 24 hours of initial termination, need for additional drugs), safety (adverse events, admission to intensive care unit) Secondary: Not reported	Primary: Administration of one to two intravenous doses stopped the convulsion in 70% of lorazepam-treated patients compared to 65% of patients receiving intravenous diazepam (RR, 1.09; 95% CI, 0.77 to 1.54). A single dose of rectal lorazepam stopped the convulsion in all children (6/6), compared to 6/19 children treated with rectal diazepam (RR, 3.17; 95% CI, 1.63 to 6.14). Approximately 22% of intravenous lorazepam-treated children and 35% of intravenous diazepam-treated children experienced a further convulsion within 24 hours after presentation (RR, 0.63; 95% CI, 0.27 to 1.46). Approximately 4% of patients receiving intravenous lorazepam compared to 15% of patients receiving intravenous diazepam required additional antiepileptic drugs to terminate the presenting seizure (RR, 0.25; 95% CI, 0.03 to 2.03). The incidence of respiratory depression occurring in the lorazepam-treated group was 4% compared to 21% in the diazepam-treated group (RR, 0.18; 95% CI, 0.02 to 1.37). Secondary: Not reported
Chamberlain et al.[61] (2014) Lorazepam 0.1 mg/kg intravenous vs	DB, RCT Patients 3 months <18 years of age with convulsive status epilepticus	N=273 4 hours	Primary: Cessation of status epilepticus by 10 minutes without recurrence within 30 minutes, assisted ventilation	Primary: Cessation of status epilepticus for 10 minutes without recurrence within 30 minutes occurred in 101 of 140 (72.1%) in the diazepam group and 97 of 133 (72.9%) in the lorazepam group, with an absolute efficacy difference of 0.8% (95% CI, −11.4 to 9.8%). Twenty-six patients in each group required assisted ventilation (16.0 in the diazepam vs 17.6% in the lorazepam groups; absolute risk difference, 1.6%; 95% CI, −9.9 to 6.8%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diazepam 0.2 mg/kg intravenous Half of the treatment dose repeated at five minutes if necessary. If status epilepticus continued at 12 minutes, fosphenytoin was administered.			Secondary: Rates of seizure recurrence and sedation	Secondary: The rates of recurrent generalized convulsions within 60 minutes, excluding patients who failed the primary outcome, were 10.9% for diazepam and 10.3% for lorazepam and the rates of recurrence within four hours were 38.6 and 39.2%, respectively. The only statistically significant difference between treatment groups in any of the secondary outcomes was in the incidence of sedation, which occurred in 81 of 162 diazepam patients (50%) and 99 of 148 lorazepam patients (66.9%) (absolute risk difference, 16.9%; 95% CI, 6.1 to 27.7%).
Prasad et al.[62] (2014) Lorazepam intravenous vs diazepam intravenous or rectally vs phenytoin intravenous vs placebo	MA Patients with status epilepticus	N=2755 (18 studies) Variable duration	Primary: Efficacy and safety Secondary: Not reported	Primary: Intravenous diazepam demonstrated a greater reduction than placebo in the risk of non-cessation of seizures (RR, 0.73; 95% CI, 0.57 to 0.92), requirement for ventilatory support (RR, 0.39; 95% CI, 0.16 to 0.94), or continuation of status epilepticus requiring use of a different drug or general anaesthesia (RR, 0.73; 95% CI, 0.57 to 0.92). Intravenous lorazepam demonstrated a lower risk than placebo for non-cessation of seizures (RR, 0.52; 95% CI, 0.38 to 0.71) and for risk of continuation of status epilepticus requiring a different drug or general anaesthesia (RR, 0.52; 95% CI, 0.38 to 0.71). Intravenous lorazepam demonstrated a greater reduction than intravenous diazepam for the risk of non-cessation of seizures (RR, 0.64; 95% CI, 0.45 to 0.90) and had a lower risk for continuation of status epilepticus requiring a different drug or general anaesthesia (RR, 0.63; 95% CI, 0.45 to 0.88). Intravenous lorazepam demonstrated a greater reduction than intravenous phenytoin for risk of non-cessation of seizures (RR, 0.62; 95% CI, 0.45 to 0.86). Diazepam gel demonstrated a greater reduction than placebo gel in the risk of non-cessation of seizures (RR, 0.43; 95% CI, 0.30 to 0.62). Secondary: Not reported
Miscellaneous				
Leufkens et al.[63]	DB, PC, XO	N=18	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Alprazolam XR 1 mg vs alprazolam IR 1 mg vs placebo	Healthy individuals 20 to 45 years of age	Up to 5.5 hours after administration	Comparison of effects on actual driving ability (as assessed in a standard on-the-road driving test) measured by SDLP in centimeters) Secondary: Comparison of effects on cognitive and psychomotor functioning related to driving in a controlled laboratory setting	Both drug formulations significantly increased SDLP (P<0.001 for both IR and XR). However, mean SDLP after alprazolam XR was significantly lower than alprazolam IR (23.44 vs 27.68 cm, respectively; P<0.001). SDLP increased with approximately 8 cm in the IR group and 4 cm in the XR group as compared to placebo (19.5 cm with placebo; P<0.001 for both comparisons). No overall differences were found between placebo and either formulation of alprazolam in terms of mean speed and speed variability. Ten driving tests were terminated prematurely due to patients being too drowsy to continue (7/18 rides in the IR group and 3/18 rides in the XR group). Secondary: In terms of the divided attention task, performance was significantly impaired at 1 (P<0.001), 2.5 (P<0.001), and 5.5 hours (P<0.01) after administration of alprazolam IR 1 mg. The effects of the XR preparation were less severe than the IR formulation at one hour (P<0.05) and at 2.5 hours (P<0.5) but no longer at 5.5 hours postdose. A significant impairment on target detection by alprazolam IR compared to placebo was noted for all times of measurement (P<0.05). Alprazolam XR did not differ significantly from placebo one hour postdose; however, there was a significant difference at 2.5 and 5.5 hours (P<0.05 for both). In terms of the stop signal task, relative to placebo, the go reaction time was significantly longer after alprazolam IR (P<0.001) but not after alprazolam XR. In terms of the word learning test, placebo-drug comparisons demonstrated a significant impairing effect of alprazolam IR at one hour after administration but not with alprazolam XR.
Hindmarch et al.[64] (2006) Flurazepam 30 mg vs	DB, RCT, XO Healthy volunteers ≥65 years of age	N=24 Single dose treatment	Primary: Psychometric tests performed 8 hours after study medication (CFF, CRT, word recall,	Primary: There were no significant differences in psychometric tests between the zolpidem modified release treatment groups and placebo (P>0.05). Psychometric performance was significantly impaired with flurazepam compared to placebo for all tests with the exception of the DSST (P=0.0526).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
zolpidem modified release 6.25 mg vs zolpidem modified release 12.5 mg vs placebo			CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem modified release only) Secondary: Not reported	Ease of falling asleep and sleep quality were significantly improved with both doses of zolpidem modified release and with flurazepam (all P<0.05). Neither zolpidem modified release, nor flurazepam, modified perception of well-being on awakening. The frequency of adverse events was similar in all four treatment conditions. None of the adverse events was serious or led to withdrawal from the study. The plasma concentration ratio was 1.96 between the two doses of zolpidem modified release, which is consistent with dose linearity. Secondary: Not reported
Johnson et al.[65] (2006) Triazolam 0.25, 0.5 or 0.75 mg vs ramelteon 16, 80 or 160 mg vs placebo	DB, XO Adults with a history of sedative abuse	N=14 18 days	Primary: Subject-rated measures (drug liking, street value, pharmacological classification), observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word recall) Secondary: Not reported	Primary: Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures. Compared to placebo, all doses of ramelteon showed no significant effect on any of the subjective effect measures, including those related to potential for abuse (all P>0.05). In the pharmacological classification, 79% of patients identified the highest dose of ramelteon as placebo. Compared to placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all P>0.05). Secondary: Not reported

Study abbreviations**:** CI=confidence interval, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multi-center, NS=not significant, OL=open label, PC=placebo controlled, PRO=prospective trial, OR=odds ratio, RETRO=retrospective trial, RCT=randomized controlled trial, RR=relative risk, XO=crossover, WMD=weighted mean difference
Other abbreviations: AWS=alcohol withdrawal syndrome, CGI=Clinical Global Impression, CIWA-Ar=Clinical Institute Withdrawal Assessment of Alcohol Scale, CRT=choice reaction time, CPS=complex partial seizures, DSST=digit symbol substitution task, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, IR=immediate-release, LSAS=Lebowitz Social Anxiety Scale, LSEQ=Leeds sleep evaluation questionnaire, MAOI=monoamine oxidase inhibitor, MTT=manual tracking task, PAF=panic attack frequency, PSG=polysomnogram, RIMA=reversible inhibitor of monoamine-oxidase-A, SDLP=Standard Deviation of Lateral Position, SSRI=Selective serotonin reuptake inhibitor, XR=extended-release, TST=total sleep time, WASO=wake after sleep onset

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 14. Relative Cost of the Benzodiazepines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Alprazolam	extended-release tablet, oral concentrate, orally disintegrating tablet, tablet	Xanax®*, Xanax XR®*	$$$$$	$
Chlordiazepoxide	capsule	N/A	N/A	$
Clonazepam	orally disintegrating tablet, tablet	Klonopin®*	$$$$	$$
Clorazepate	tablet	Tranxene T-Tab®*	$$$$$	$$$$$
Diazepam	injection, oral concentrate, oral solution, rectal gel, tablet	Diastat®*, Diastat AcuDial®*	$$$$$	$$
Estazolam	tablet	N/A	N/A	$$$$
Flurazepam	capsule	N/A	N/A	$$$
Lorazepam	injection, oral concentrate, tablet, extended-release capsule	Ativan®*, Loreev XR®	$$$$$	$
Midazolam	injection, oral syrup	N/A	N/A	$
Oxazepam	capsule	N/A	N/A	$$
Temazepam	capsule	Restoril®*	$$$$$	$
Triazolam	tablet	Halcion®*	$$$$$	$

*Generic is available in at least one dosage form or strength.

N/A=Not available

X. Conclusions

The benzodiazepines are approved for the treatment of anxiety disorders and for the short-term treatment of insomnia. In addition, some of the agents are approved for the treatment of seizure disorders, acute alcohol withdrawal, as muscle relaxants, and for the induction/maintenance of general anesthesia.[1-13] The benzodiazepines are mechanistically similar; however, they differ with regards to their pharmacokinetic properties (e.g., onset and duration of action).[16,18] All of the benzodiazepines are available in a generic formulation.

The benzodiazepines that are approved for the treatment of anxiety include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam, and oxazepam. The American Psychiatric Association recommends the initial use of either a serotonin-norepinephrine reuptake inhibitor (SNRI) or a selective serotonin reuptake inhibitor (SSRI) for the treatment of panic disorder due to their favorable safety and tolerability profiles.[19] However, benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. They can be used concurrently with antidepressants to help control symptoms until the antidepressant takes effect, which is then followed by a slow tapering of the benzodiazepine.[19] For the long-term treatment of generalized anxiety disorder, the National Institute for Health and Clinical Excellence recommends the use of an SSRI as first-line therapy. Benzodiazepines should only be used as a short-term measure during crises.[18] Benzodiazepines have been shown to be more effective than placebo, and have demonstrated similar efficacy compared to agents in other classes for the treatment of anxiety disorders.[19,44,46-48] Guidelines do not give preference to one particular benzodiazepine over another. The risk of adverse events and physiological dependence must be considered when using the benzodiazepines.[17,19] Benzodiazepines are not recommended as monotherapy for the treatment of obsessive-compulsive disorder or posttraumatic stress disorder.[20-23]

Several benzodiazepines are approved for the short-term treatment of insomnia, including estazolam, flurazepam, temazepam, and triazolam. The American Academy of Sleep Medicine recommends the use of a short/intermediate-acting benzodiazepine, benzodiazepine receptor agonist, or ramelteon for the initial treatment of insomnia.[24] They do not give preference to one agent over another. Symptom pattern, treatment goals, past treatment responses, patient preference, comorbid conditions, contraindications, drug interactions, and adverse events should be considered when selecting a specific agent.[24] The frequency and severity of adverse events may be lower with benzodiazepine receptor agonists (e.g., eszopiclone, zaleplon, and zolpidem) due to their shorter half-lives.[24] Hypnotic treatments should be combined with behavioral and cognitive therapies.[24] Patients should be followed every few weeks during the initial treatment period to assess for effectiveness, adverse events, and the need for ongoing medication. Chronic use of hypnotic medications may be necessary in those individuals with severe/refractory insomnia or for those with chronic comorbid illnesses.[24] Results from clinical trials demonstrate that the benzodiazepines are effective for the short-term treatment of insomnia.[24-26,50,52-55]

Benzodiazepines may also be used for the treatment of seizure disorders, either as monotherapy or adjunctive therapy. It should be noted that other antiepileptic drugs are not currently included in the Preferred Drug Program. Diazepam is available in a rectal gel formulation, which is approved for the management of selected, refractory, patients with epilepsy who require intermittent use of diazepam to control bouts of increased seizure activity.[7]

In August 2016, the FDA announced class-wide changes to drug labeling was being required for the opioid and benzodiazepine classes because of serious risks associated with using these medications at the same time. The benzodiazepines now include a boxed warning in their labeling stating that concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing of these drugs should be reserved for use in patients for whom alternative treatment options are inadequate.[1-13] Subsequently, on September 23, 2020, the FDA released a publication to address labeling changes to the benzodiazepine class to improve the safe use of these agents. This action by the FDA is part of ongoing efforts to promote the public health by minimizing risks associated with inappropriate use of controlled substances. The update requires class-wide labeling changes for benzodiazepines to include the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions to help improve their safe use. In addition to the Boxed Warning update, other required changes to the prescribing information encompass the Warnings and Precautions, Drug Abuse and Dependence, and Patient Counseling Information sections. Revisions to the patient Medication Guide will also be mandated to educate patients and caregivers about the associated risks of these therapies.[17]

There is insufficient evidence to support that one brand benzodiazepine is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all benzodiazepines within the class reviewed, with the exception of diazepam rectal gel, are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Diazepam rectal gel provides a beneficial route of administration compared to other agents in this class. Therefore, patients should be allowed approval for this agent through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand benzodiazepine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics – Miscellaneous
AHFS Class 282492
November 9, 2022

I. Overview

The miscellaneous anxiolytics, sedatives, and hypnotics are used primarily for the treatment of anxiety disorders and insomnia. Anxiety disorders include generalized anxiety disorder, panic disorder, posttraumatic stress disorder, and social phobia.[1] The agents approved for the treatment of anxiety include buspirone, hydroxyzine, and meprobamate.[2-11] The exact mechanism of action of buspirone is unknown. It lacks anticonvulsant, muscle relaxant, or sedative properties, which are seen with other agents. The anxiolytic effects of hydroxyzine may be due to a suppression of activity in key regions of the subcortical area of the central nervous system. Meprobamate has been shown to have effects at multiple sites in the central nervous system, including the thalamus and limbic system.[2-11]

The key diagnostic feature of primary insomnia is difficulty initiating or maintaining sleep for at least three months, which causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.[1] Insomnia may be classified as episodic (symptoms last at least one month but less than three months), persistent (lasting three months or longer) or recurrent (two or more) episodes within the space of one year).[1] Eszopiclone, zaleplon, and zolpidem are approved for the treatment of insomnia.[4-11] These agents are considered benzodiazepine receptor agonists; however, they are more selective than traditional benzodiazepines and bind to the $GABA_A$ receptor complex. Compared to the benzodiazepines, they have a more rapid onset, shorter duration of action, and a lower risk of tolerance, dependence, and abuse. They are classified as Schedule IV controlled substances by federal regulation.[2-11] Ramelteon is a melatonin receptor agonist, which is also approved for the treatment of insomnia.[8] It is more selective for the melatonin type 1 (MT_1) and type 2 (MT_2) receptors as compared to the type 3 (MT_3) receptor in the suprachiasmatic nucleus of the hypothalamus.[8] The MT_1 and MT_2 receptors are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle. Ramelteon is not a controlled substance. Discontinuation after chronic administration did not produce withdrawal signs and it does not appear to produce physical dependence.[8]

Some of the miscellaneous agents are also approved for the management of acute alcohol withdrawal, for use as a sedative (e.g., preoperative, prior to procedures, and in intubated or mechanically ventilated patients), for the management of nausea/vomiting from surgical/diagnostic procedures, and for the treatment of pruritus. Dexmedetomidine is a selective $alpha_2$-adrenergic agonist with sedative properties.[11] Droperidol is a butyrophenone antipsychotic. The antiemetic effect is due to the blockade of dopamine stimulation of the chemoreceptor trigger zone.[2,3] Other effects include alpha-adrenergic blockade, peripheral vascular dilation, and reduction of the pressor effect of epinephrine.

Hetlioz® (tasimelteon) was FDA approved for treatment of Non-24-Hour Sleep-Wake Disorder (non-24) in 2014.[10] Tasimelteon is a melatonin receptor agonist with effects at the MT_1 and MT_2 receptors. Although the precise mechanism of tasimelteon in non-24 is unknown, these receptors are thought to be involved in the control of circadian rhythms.[10] This is the first FDA approval of a treatment for non-24, a chronic circadian rhythm disorder which occurs almost exclusively in persons who are completely blind, and the effectiveness of tasimelteon was evaluated in this population.[12] It has also gained approval for the treatment of Nighttime sleep disturbances in Smith-Magenis Syndrome in patients three to 15 years of age (oral suspension) and ≥16 years of age (capsule).[10]

In January 2013, the FDA released new recommendations that the dose of zolpidem be lowered due to new data suggesting that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Women appear to be more susceptible, as they eliminate zolpidem more slowly than men.[13] The FDA required the manufacturers of Ambien®, Ambien CR®, and Edluar® to lower the recommended dose. The recommended dose of zolpidem for women should be lowered from 10 to 5 mg for immediate-release products (Ambien®, Edluar®) and from 12.5 to 6.25 mg for extended-release products (Ambien CR®). For men, the labeling should recommend that health care professionals consider prescribing the lower

doses—5 mg for immediate-release products and 6.25 mg for extended-release products.[13] In May 2014, a similar safety communication was issued for eszopiclone, based on data that the 2 and 3 mg doses may be associated with impairment of driving skills, memory, and coordination lasting more than 11 hours without subjective awareness in some patients. A starting dose of 1 mg is now recommended in all patients.[14]

In April 2019, the FDA released a safety announcement advising that rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. A boxed warning is now required for eszopiclone, zaleplon, and zolpidem.[15]

The miscellaneous anxiolytics, sedatives, and hypnotics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation, with the exception of suvorexant and tasimelteon. This class was last reviewed in November 2020.

Table 1. Miscellaneous Anxiolytics, Sedatives, and Hypnotics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Buspirone	tablet	N/A	buspirone
Dexmedetomidine	injection	Precedex®*	dexmedetomidine
Droperidol	injection	N/A	droperidol
Eszopiclone	tablet	Lunesta®*	eszopiclone
Hydroxyzine	capsule, injection, solution, tablet	Vistaril®*	hydroxyzine
Meprobamate	tablet	N/A	meprobamate
Ramelteon	tablet	Rozerem®*	none
Tasimelteon	capsule, suspension	Hetlioz®	none
Zaleplon	capsule	N/A	zaleplon
Zolpidem	extended-release tablet, sublingual tablet, tablet	Ambien®*, Ambien CR®*, Edluar®	zolpidem

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous anxiolytics, sedatives, and hypnotics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Clinical Guideline	Recommendation(s)

National Institute for Clinical Excellence: **Generalized Anxiety Disorder and Panic Disorder in Adults: management (2011)**[16]
 	
Last updated June 2020
	Drug treatment for people with generalized anxiety disorder (GAD)
	• If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI), specifically sertraline.
	• If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI), taking into account the following factors:
	  ○ Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine).
	  ○ The side-effect profile and the potential for drug interactions.
	  ○ The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine).
	  ○ The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference).
	• If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin.
	• Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises.
	• Do not offer an antipsychotic for the treatment of GAD in primary care.

Clinical Guideline	Recommendation(s)
	• Before prescribing any medication, discuss the treatment options and any concerns the person with GAD has about taking medication. Explain fully the reasons for prescribing and provide written and verbal information on: o the likely benefits of different treatments o the different propensities of each drug for side effects, withdrawal syndromes and drug interactions o the risk of activation with SSRIs and SNRIs, with symptoms such as increased anxiety, agitation and problems sleeping o the gradual development, over one week or more, of the full anxiolytic effect o the importance of taking medication as prescribed and the need to continue treatment after remission to avoid relapse. • Take into account the increased risk of bleeding associated with SSRIs, particularly for older people or people taking other drugs that can damage the gastrointestinal mucosa or interfere with clotting (for example, non-steroidal anti-inflammatory drugs [NSAIDS] or aspirin). Consider prescribing a gastroprotective drug in these circumstances. • For people aged under 30 who are offered an SSRI or SNRI, warn them that these drugs are associated with an increased risk of suicidal thinking and self-harm in a minority of people under 30 and, see them within one week of first prescribing and, monitor the risk of suicidal thinking and self-harm weekly for the first month. • Review the effectiveness and side effects of the drug every two to four weeks during the first three months of treatment and every three months thereafter. • If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. <u>Panic disorder pharmacological interventions</u> • Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder. • Sedating antihistamines or antipsychotics should not be prescribed for the treatment of panic disorder. • Antidepressants should be the only pharmacologic intervention used in the longer term. The classes of antidepressants that have an evidence base for effectiveness are the selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs). At the time of this update (June 2020) escitalopram, sertraline, citalopram, paroxetine and venlafaxine are licensed for the treatment of panic disorder. • The following must be taken into account when deciding which medication to offer: o the age of the person o previous treatment response o risks: the likelihood of accidental overdose by the person being treated and by other family members if appropriate; the likelihood of deliberate self-harm, by overdose or otherwise (the highest risk is with TCAs) o tolerability o the possibility of interactions with concomitant medication (consult the interactions section of the BNF) o the preference of the person being treated o cost, where equal effectiveness is demonstrated. • All people who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects (including transient increase in anxiety at the start of treatment) and of the risk of discontinuation/withdrawal symptoms if the treatment is stopped abruptly or in some instances if a dose is missed or, occasionally, on reducing the dose of the drug. • People started on antidepressants should be informed about the delay in onset of

Clinical Guideline	Recommendation(s)
	effect, the time course of treatment, the need to take medication as prescribed, and possible discontinuation/withdrawal symptoms. Written information appropriate to the person's needs should be made available. • Unless otherwise indicated, an SSRI licensed for panic disorder should be offered. • If an SSRI is not suitable or there is no improvement after a 12-week course and if a further medication is appropriate, imipramine or clomipramine may be considered. Note that this is an off-label use for imipramine and clomipramine. • If there is no improvement after a 12-week course, an antidepressant from the alternative class (if another medication is appropriate) or another form of therapy should be offered. • People should be advised to take their medication as prescribed. This may be particularly important with short half-life medication in order to avoid discontinuation/withdrawal symptoms. • Stopping antidepressants abruptly can cause discontinuation/withdrawal symptoms. To minimize the risk of discontinuation/withdrawal symptoms when stopping antidepressants, the dose should be reduced gradually over an extended period of time.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)**[17]	• SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors (MAOI). They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. • MAOIs appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic

Clinical Guideline	Recommendation(s)
	disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007; 2013 update)[18]**	<u>General considerations</u> • OCD is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. <u>Initial treatment options</u> • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include cognitive-behavioral therapy, SRIs, or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • Cognitive-behavioral therapy or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, Food and Drug Administration (FDA) warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until four to six weeks after treatment initiation, and some may ultimately respond after as many as 10 to 12 weeks. • Patients not responding after 10 to 12 weeks may respond to a higher dose of the same medication. <u>Changing treatments and pursuing sequential treatment trials</u> • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Augmentation of SRIs with trials of different antipsychotic medications or with cognitive-behavioral therapy or augmentation of cognitive-behavioral therapy with an SRI. • Patients who do not respond to their first SRI may have their medication switched to a different SRI. A switch to venlafaxine is less likely to produce an adequate response. • For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can be considered. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone, pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of

Clinical Guideline	Recommendation(s)
	benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.
American Psychological Association: **Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (2017)[19]**	• For adults with PTSD, psychotherapies are strongly recommended. • For adults with PTSD, offer one of the following (listed alphabetically): o Fluoxetine o Paroxetine o Sertraline o Venlafaxine • There is insufficient evidence to recommend for or against the following medications for treatment of adults with PTSD: o Risperidone o Topiramate
Department of Veterans Affairs/ Department of Defense: **The Management of Posttraumatic Stress Disorder and Acute Stress Disorder (2017)[20]**	<u>Treatment selection</u> • Individual, manualized trauma-focused psychotherapy is recommended over other pharmacologic and nonpharmacologic interventions for the primary treatment of PTSD. • When individual trauma-focused psychotherapy is not readily available or not preferred, pharmacotherapy or individual non-trauma-focused psychotherapy is recommended. With respect to pharmacotherapy and nontrauma-focused psychotherapy, there is insufficient evidence to recommend one over the other. <u>Pharmacotherapy</u> • Sertraline, paroxetine, fluoxetine, or venlafaxine is recommended as monotherapy for PTSD for patients diagnosed with PTSD who choose not to engage in or are unable to access trauma-focused psychotherapy. • Nefazodone, imipramine, or phenelzine is suggested as monotherapy for the treatment of PTSD if recommended pharmacotherapy, trauma-focused psychotherapy, or non-trauma-focused psychotherapy are ineffective, unavailable, or not in accordance with patient preference and tolerance. (NOTE: Nefazodone and phenelzine have potentially serious toxicities and should be managed carefully.) • Treatment of PTSD with quetiapine, olanzapine, and other atypical antipsychotics (except for risperidone, which is a Strong Against), citalopram, amitriptyline, lamotrigine, or topiramate as monotherapy are NOT suggested due to the lack of strong evidence for their efficacy and/or known adverse effect profiles and associated risks. • Treating PTSD with divalproex, tiagabine, guanfacine, risperidone, benzodiazepines, ketamine, hydrocortisone, or D-cycloserine are NOT recommended as monotherapy due to the lack of strong evidence for their efficacy and/or known adverse effect profiles and associated risks. • Treating PTSD with cannabis or cannabis derivatives is NOT recommended due to the lack of evidence for their efficacy, known adverse effects, and associated risks. • There is insufficient evidence to recommend for or against monotherapy or augmentation therapy for the treatment of PTSD with eszopiclone, escitalopram, bupropion, desipramine, doxepin, D-serine, duloxetine, desvenlafaxine, fluvoxamine, levomilnacipran, mirtazapine, nortriptyline, trazodone, vilazodone, vortioxetine, buspirone, hydroxyzine, cyproheptadine, zaleplon, and zolpidem. <u>Augmentation therapy</u> • The use of topiramate, baclofen, or pregabalin is NOT suggested as augmentation treatment of PTSD due to insufficient data and/or known adverse effect profiles

Clinical Guideline	Recommendation(s)
	and associated risks. • Combining exposure therapy with D-cycloserine is NOT suggested in the treatment of PTSD outside of the research setting. • Using atypical antipsychotics, benzodiazepines, and divalproex is NOT recommended as augmentation therapy for the treatment of PTSD due to low quality evidence or the absence of studies and their association with known adverse effects. • There is insufficient evidence to recommend the combination of exposure therapy with hydrocortisone outside of the research setting. • There is insufficient evidence to recommend for or against the use of mirtazapine in combination with sertraline for the treatment of PTSD. <u>Prazosin</u> • For global symptoms of PTSD, the use of prazosin is NOT suggested as mono- or augmentation therapy. • For nightmares associated with PTSD, there is insufficient evidence to recommend for or against the use of prazosin as mono- or augmentation therapy. <u>Combination therapy</u> • In partial- or non-responders to psychotherapy, there is insufficient evidence to recommend for or against augmentation with pharmacotherapy. • In partial- or non-responders to pharmacotherapy, there is insufficient evidence to recommend for or against augmentation with psychotherapy. • There is insufficient evidence to recommend for or against starting patients with PTSD on combination pharmacotherapy and psychotherapy.
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)[21]**	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments. • Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible. • When pharmacotherapy is utilized, the choice of a specific pharmacological agent should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects. • For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is: o Short-intermediate acting benzodiazepine receptor agonists or ramelteon. o Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful. o Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. o Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressant. o Other sedating agents. Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect. • Over-the-counter antihistamine or antihistamine/analgesic type drugs (over-the-counter "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data. • Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia.

Clinical Guideline	Recommendation(s)
	• Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments), potential for dosage escalation, and rebound insomnia. • Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication. • Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia. • Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. • Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders. • Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.
American Academy of Sleep Medicine: **Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults (2017)**[22]	<u>Recommendations for treating sleep onset insomnia</u> • Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Recommendations are listed alphabetically. • Eszopiclone is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 14 minutes greater, compared to placebo (95% CI, 3 to 24 minute reduction). o Quality of Sleep: moderate-to-large improvement in quality of sleep, compared to placebo. • Ramelteon is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was nine minutes greater, compared to placebo (95% CI, 6 to 12 minute reduction). o Quality of Sleep: No improvement in quality of sleep, compared to placebo. • Temazepam is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 37 minutes greater, compared to placebo (95% CI, 21 to 53 minute reduction). o Quality of Sleep: Small improvement in quality of sleep, compared to placebo. • Triazolam is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was nine minutes greater, compared to placebo (95% CI, 4 to 22 minute reduction). o Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. • Zaleplon is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 10 minutes greater, compared to placebo (95% CI, 0 to 19 minute reduction). o Quality of Sleep: No improvement in quality of sleep, compared to placebo. • Zolpidem is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was five to 12 minutes greater, compared to placebo (95% CI, 0 to 19 minute reduction).

Clinical Guideline	Recommendation(s)
	○ Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. <u>Recommendations for treating sleep maintenance insomnia</u> • Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Recommendations are listed alphabetically. • Doxepin is recommended as a treatment for sleep maintenance insomnia (versus no treatment) in adults. ○ Total Sleep Time: Mean improvement was 26 to 32 minutes longer, compared to placebo (95% CI, 18 to 40 minute improvement). ○ Wake After Sleep Onset: Mean reduction was 22 to 23 minutes greater, compared to placebo (95% CI, 14 to 30 minute reduction). ○ Quality of Sleep: Small-to-Moderate improvement in quality of sleep, compared to placebo. • Eszopiclone is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. ○ Total Sleep Time: Mean improvement was 28 to 57 minutes longer, compared to placebo (95% CI, 18 to 76 minute improvement). ○ Wake After Sleep Onset: Mean reduction was 10 to 14 minutes greater, compared to placebo (95% CI, 2 to 18 minute reduction). ○ Quality of Sleep: moderate-to-large improvement in quality of sleep, compared to placebo. • Temazepam is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. ○ Total Sleep Time: Mean improvement was 99 minutes longer, compared to placebo (95% CI, 63 to 135 minute improvement). ○ Wake After Sleep Onset: Not reported. ○ Quality of Sleep: Small improvement in quality of sleep, compared to placebo. • Suvorexant is recommended as a treatment for sleep maintenance insomnia (versus no treatment) in adults. ○ Total Sleep Time: Mean improvement was 10 minutes longer, compared to placebo (95% CI, 2 to 19 minute improvement). ○ Wake After Sleep Onset: Mean reduction was 16 to 28 minutes greater, compared to placebo (95% CI, 7 to 43 minute reduction). ○ Quality of Sleep: Not reported. • Zolpidem is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. ○ Total Sleep Time: Mean improvement was 29 minutes longer, compared to placebo (95% CI, 11 to 47 minute improvement). ○ Wake After Sleep Onset: Mean reduction was 25 minutes greater, compared to placebo (95% CI, 18 to 33 minute reduction). ○ Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. <u>Not recommended for treating insomnia</u> • The following drugs are not recommended for the treatment of sleep onset or sleep maintenance insomnia (versus no treatment) in adults: Diphenhydramine, Melatonin, Tiagabine, Trazodone, L-tryptophan, Valerian.
Department of Veterans Affairs and Department of Defense: **The Management of Chronic Insomnia**	<u>Treatment and management of chronic insomnia disorder – behavioral and psychological treatments</u> • It is recommended that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. • Offer brief behavioral therapy for insomnia (BBT-I).

Clinical Guideline	Recommendation(s)
Disorder and Obstructive Sleep Apnea (2019)[23]	• There is insufficient evidence to recommend for or against group versus individual CBT-I for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against internet-based CBT-I as an alternative to face-to-face based CBT-I for the treatment of chronic insomnia disorder. • CBT-I is suggested over pharmacotherapy as first-line treatment. • Offer CBT-I for the treatment of chronic insomnia disorder that is comorbid with another psychiatric disorder. • There is insufficient evidence to recommend for or against mindfulness meditation for the treatment of chronic insomnia disorder. • Sleep hygiene education is not suggested as a standalone treatment. <u>Treatment and management of chronic insomnia disorder – complementary and integrative health treatments</u> • Offer auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against acupuncture other than auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against aerobic exercise, resistive exercise, tai chi, yoga, and qigong for the treatment of chronic insomnia disorder. • Cranial electrical stimulation is not suggested. <u>Treatment and management of chronic insomnia disorder – over-the-counter treatments</u> • Diphenhydramine is not suggested. • Melatonin is not suggested. • Valerian and chamomile are not suggested. • Kava is not recommended. <u>Treatment and management of chronic insomnia disorder – pharmacotherapy</u> • In patients who are offered a short-course of pharmacotherapy for the treatment of chronic insomnia disorder, use of low-dose (i.e., 3 mg or 6 mg) doxepin or a non-benzodiazepine benzodiazepine receptor agonist is suggested. • There is insufficient evidence to recommend for or against the use of ramelteon for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against the use of suvorexant for the treatment of chronic insomnia disorder. • the use of antipsychotic drugs is not suggested for the treatment of chronic insomnia disorder. • The use of benzodiazepines is not suggested for the treatment of chronic insomnia disorder. • The use of trazodone is not suggested for the treatment of chronic insomnia disorder.
American Society for Gastrointestinal Endoscopy: **Sedation and Anesthesia in Gastrointestinal Endoscopy (2018)[24]**	• All patients undergoing endoscopic procedures should be evaluated to assess their risk of sedation related to pre-existing medical conditions. • The combination of an opioid and benzodiazepine is a safe and effective regimen for achieving minimal to moderate sedation for upper endoscopy and colonoscopy in patients without risk factors for sedation-related adverse events. • Using an appropriate adjunctive agent (e.g., diphenhydramine, promethazine, or droperidol) is suggested in combination with conventional sedative drugs in select clinical circumstances. • Providers should undergo specific training in the administration of endoscopic

Clinical Guideline	Recommendation(s)
	sedation and possess the skills necessary for the diagnosis and management of sedation-related adverse events, including rescue from a level of sedation deeper than that intended. • The routine monitoring of blood pressure, oxygen saturation, and heart rate in addition to clinical observation for changes in cardiopulmonary status is recommended during all endoscopic procedures using sedation. Supplemental oxygen administration should be considered for moderate sedation and should be administered during deep sedation. Supplemental oxygen should be administered if hypoxemia is anticipated or develops. • Capnography monitoring should be considered for patients undergoing endoscopy targeting deep sedation. • Anesthesia provider–administered sedation should be considered for complex endoscopic procedures or patients with multiple medical comorbidities or at risk for airway compromise. • Endoscopists should use propofol-based sedation (endoscopist-directed or anesthesia-provider administered) when it is expected to improve patient safety, comfort, procedural efficiency, and/or successful procedure completion.
Society for Ambulatory Anesthesia: **Consensus Guidelines for the Management of Postoperative Nausea and Vomiting (2020)**[25]	Pediatric postoperative nausea and vomiting (PONV) management • Low risk prophylaxis: No treatment or 5-HT_3 receptor antagonist or dexamethasone. • Medium risk prophylaxis: 5-HT_3 receptor antagonist + dexamethasone. • High risk prophylaxis: 5-HT_3 receptor antagonist + dexamethasone + consider total intravenous anesthesia. • Rescue treatment: Use anti-emetic from different class than prophylactic drug-droperidol, promethazine, dimenhydrinate, metoclopramide; may also consider acupuncture/acupressure. Adult PONV management • One to two risk factors prophylaxis: Give two agents (5-HT_3 receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • More than two risk factors prophylaxis: Give three or four agents (5-HT_3 receptor antagonists, antihistamines, corticosteroids, dopamine antagonists, propofol anesthesia, NK-1 receptor antagonists, anticholinergics, acupuncture). • Rescue treatment: Use anti-emetic from different class than prophylactic drug.
National Institute for Health and Clinical Excellence: **Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence (2011)**[26] **Reaffirmed 2019**	Drug regimens for assisted withdrawal • Prescribe and administer medication for assisted withdrawal within a standard clinical protocol. The preferred medication for assisted withdrawal is a benzodiazepine (chlordiazepoxide or diazepam). • Gradually reduce the dose of the benzodiazepine over seven to 10 days to avoid alcohol withdrawal recurring. • When managing alcohol withdrawal in the community, avoid giving people who misuse alcohol large quantities of medication to take home to prevent overdose or diversion (the drug being taken by someone other than the person it was prescribed for). Prescribe for installment dispensing, with no more than two days' medication supplied at any time. • Do not offer clomethiazole for community-based assisted withdrawal because of the risk of overdose and misuse. Interventions for moderate and severe alcohol dependence after successful withdrawal • After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention. • After a successful withdrawal for people with moderate and severe alcohol

Clinical Guideline	Recommendation(s)
	dependence, consider offering disulfiram in combination with a psychological intervention to service users who have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable, or prefer disulfiram and understand the relative risks of taking the drug. Treatment for acute alcohol withdrawal • Offer pharmacotherapy to treat the symptoms of acute alcohol withdrawal. • Consider offering a benzodiazepine or carbamazepine. • Clomethiazole may be offered as an alternative to a benzodiazepine or carbamazepine. However, it should be used with caution, in inpatient settings only and according to the summary of product characteristics. Management of delirium tremens • Lorazepam is considered a first-line treatment option. • If symptoms persist or oral medication is declined, give parenteral lorazepam or haloperidol. Management of alcohol withdrawal seizures • In people with alcohol withdrawal seizures, consider offering a quick-acting benzodiazepine (e.g., lorazepam) to reduce the likelihood of further seizures. • Do not offer phenytoin to treat alcohol withdrawal seizures.

American Psychiatric Association: **Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder (2018)**[27]	Selection of a Pharmacotherapy
	• Naltrexone or acamprosate should be offered to patients with moderate to severe alcohol use disorder who
	  o have a goal of reducing alcohol consumption or achieving abstinence,
	  o prefer pharmacotherapy or have not responded to nonpharmacological treatments alone, and
	  o have no contraindications to the use of these medications.
	• Disulfiram may be offered to patients with moderate to severe alcohol use disorder who
	  o have a goal of achieving abstinence,
	  o prefer disulfiram or are intolerant to or have not responded to naltrexone and acamprosate,
	  o are capable of understanding the risks of alcohol consumption while taking disulfiram, and
	  o have no contraindications to the use of this medication.
	• Topiramate or gabapentin may be offered to patients with moderate to severe alcohol use disorder who
	  o have a goal of reducing alcohol consumption or achieving abstinence,
	  o prefer topiramate or gabapentin or are intolerant to or have not responded to naltrexone and acamprosate, and
	  o have no contraindications to the use of these medications.
	
	Recommendations Against Use of Specific Medications
	• Antidepressant medications should not be used for treatment of alcohol use disorder unless there is evidence of a co-occurring disorder for which an antidepressant is an indicated treatment.
	• In individuals with alcohol use disorder, benzodiazepines should not be used unless treating acute alcohol withdrawal or unless a co-occurring disorder exists for which a benzodiazepine is an indicated treatment.
	• For pregnant or breastfeeding women with alcohol use disorder, pharmacological treatments should not be used unless treating acute alcohol withdrawal with benzodiazepines or unless a co-occurring disorder exists that warrants pharmacological treatment.
	• Acamprosate should not be used by patients who have severe renal impairment.

Clinical Guideline	Recommendation(s)
	• For individuals with mild to moderate renal impairment, acamprosate should not be used as a first-line treatment and, if used, the dose of acamprosate be reduced compared with recommended doses in individuals with normal renal function. • Naltrexone should not be used by patients who have acute hepatitis or hepatic failure. • Naltrexone should not be used as a treatment for alcohol use disorder by individuals who use opioids or who have an anticipated need for opioids. <u>Treatment of Alcohol Use Disorder and Co-occurring Opioid Use Disorder</u> • In patients with alcohol use disorder and co-occurring opioid use disorder, naltrexone should be prescribed to individuals who o wish to abstain from opioid use and either abstain from or reduce alcohol use and o are able to abstain from opioid use for a clinically appropriate time prior to naltrexone initiation.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous anxiolytics, sedatives, and hypnotics are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (Drugs B-L)[2-11]

Indication	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Anxiety Disorders					
Management of generalized anxiety disorders	✔				
Short-term relief of symptoms of anxiety	✔				
Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested					✔
Sedative-Hypnotic					
Sedation when used as premedication and following general anesthesia					✔
Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting; administer by continuous infusion not to exceed 24 hours		✔			
Sedation of non-intubated patients prior to and/or during surgical and other procedures		✔			
Treatment of insomnia (shown to decrease sleep latency and improve sleep maintenance)				✔	
Miscellaneous					
Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus					✔
To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures			✔		

Table 4. FDA-Approved Indications for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (Drugs M-Z)[2-11]

Indication	Meprobamate	Ramelteon	Tasimelteon	Zaleplon	Zolpidem
Anxiety Disorders					
Management of anxiety disorders	✔				
Short-term relief of symptoms of anxiety	✔				
Sedative-Hypnotic					

Indication	Meprobamate	Ramelteon	Tasimelteon	Zaleplon	Zolpidem
Short-term treatment of insomnia (shown to decrease the time to sleep onset for up to 30 days in controlled clinical studies; it has not been shown to increase total sleep time or decrease the number of awakenings; the clinical trials performed in support of efficacy ranged from a single night to five weeks in duration; the final formal assessments of sleep latency were performed at the end of treatment)				✔	
Short-term treatment of insomnia characterized by difficulties with sleep initiation (shown to decrease sleep latency for up to 35 days in controlled clinical studies)					✔ *
Insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep (not indicated for the treatment of middle-of-the night awakening when the patient has fewer than four hours of bedtime remaining before the planned time of waking)					✔ †
Treatment of insomnia characterized by difficulty with sleep onset		✔			
Short-term treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset)					✔ ‡
Miscellaneous					
Treatment of Non-24-Hour Sleep-Wake Disorder			✔		
Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS)			✔		

*Immediate-release formulations (sublingual tablet [Edluar®] and tablet).
†Immediate-release formulations (sublingual tablet [Intermezzo®]).
‡Extended-release formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Buspirone	Variable	86	Liver	Renal (29 to 63) Feces (18 to 38)	2 to 3
Dexmedetomidine	SubQ: 81	94	Liver	Renal (95) Feces (4)	2.0 to 2.7
Droperidol	Complete	Extensive	Liver	Renal (75) Feces (22)	2
Eszopiclone	Rapidly absorbed	Not reported	Liver	Renal	5 to 6
Hydroxyzine	Rapidly absorbed orally	Not reported	Liver	Not reported	3 to 20
Meprobamate	Well absorbed	0 to 30	Liver	Renal (10 to 20)	9 to 11
Ramelteon	1.8	82	Liver	Renal (84) Feces (4)	1.0 to 2.6
Tasimelteon	38.3	90	Liver	Renal (80) Feces (4)	1.3
Zaleplon	30	60	Liver	Renal (71) Feces (17)	1
Zolpidem	70	93	Liver	Renal (<1)	2.5 to 3.0

V. Drug Interactions

Major drug interactions with the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 6.

Table 6. Major Drug Interactions with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[3]

Generic Name(s)	Interaction	Mechanism
Buspirone	Linezolid	Serotonin syndrome (e.g., agitation, altered consciousness, ataxia, myoclonus, overactive, reflexes, shivering) may occur in some patients. Unless patients are carefully observed for signs and symptoms of serotonin syndrome, do not coadminister.
Buspirone	Tranylcypromine	Concurrent use of buspirone and tranylcypromine may result in hypertensive crisis.
Buspirone	Phenelzine	Concurrent use of phenelzine and buspirone may result in hypertensive crisis.
Buspirone	Isocarboxazid	Concurrent use of isocarboxazid and buspirone may result in hypertensive crisis.
Buspirone	Monoamine oxidase inhibitors	Concurrent use of buspirone and monoamine oxidase inhibitors may result in hypertensive crisis.
Buspirone	Clozapine	Concurrent use of clozapine and buspirone may result in an increased risk of gastrointestinal bleeding and hyperglycemia.
Buspirone	Procarbazine	Concurrent use of buspirone and procarbazine may result in hypertensive crisis.
Buspirone, dexmedetomidine, droperidol, eszopiclone, hydroxyzine, meprobamate, ramelteon,	CNS Depressants	Concurrent use may result in increased risk of respiratory and CNS depression.

Generic Name(s)	Interaction	Mechanism
suvorexant, zaleplon, zolpidem		
Droperidol	Ziprasidone	The combination of ziprasidone and droperidol may have cause additive prolongation of the QT interval.
Droperidol	Neuroleptics (molindone, clozapine, perphenazine, trifluprom azine, remoxipride, acetophenazine, bromperidol, tiapride, pipamperone)	Concurrent use of droperidol and neuroleptics may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Fluoroquinolones	Concurrent use of droperidol and fluoroquinolones may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Tricyclic antidepressants, monoamine oxidase inhibitors, phenothiazines	Concurrent use of droperidol and tricyclic antidepressants may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Class I and III antiarrhythmics	Concurrent use of droperidol and antiarrhythmic agents may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Diuretics	Concurrent use of droperidol and diuretics may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Laxatives	Concurrent use of droperidol and laxatives may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Antimalarials	Concurrent use of droperidol and antimalarials may result in an increased risk of cardiotoxicity (QT prolongation, torsade de pointes, cardiac arrest).
Droperidol	Calcium channel blockers	Concurrent use of droperidol and calcium channel blockers may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Tyrosine kinase inhibitors	Concurrent use of droperidol and tyrosine kinase inhibitors may result in an increased risk of QT interval prolongation.
Eszopiclone, zaleplon	Ketoconazole	Concurrent use of eszopiclone or zaleplon and ketoconazole may result in increased plasma concentrations of eszopiclone or zaleplon.
Eszopiclone	Selected strong CYP3A4 inhibitors (nelfinavir, saquinavir, delavirdine, lopinavir, tipranavir, posaconazole, boceprevir, telaprevir, cobicistat, atazanavir)	Concurrent use of eszopiclone and selected strong CYP3A4 inhibitors may result in increased plasma concentrations of eszopiclone.
Hydroxyzine	QT prolonging	Concurrent use of hydroxyzine and QT prolonging agents may

Generic Name(s)	Interaction	Mechanism
	agents	result in increased risk of QT interval prolongation.
Ramelteon	Fluvoxamine	Plasma concentrations of ramelteon may be increased by coadministration of fluvoxamine. Inhibition of CYP1A2 by fluvoxamine may decrease the metabolic elimination of ramelteon/zolpidem.
Tasimelteon	Selected strong CYP1A2 inhibitors (abiraterone, ciprofloxacin, enoxacin, fluvoxamine)	Concurrent use of tasimelteon and selected strong CYP1A2 inhibitors may result in increased tasimelteon exposure and increased risk of tasimelteon adverse events.
Tasimelteon	Selected strong CYP1A2 inducers (phenytoin, carbamazepine, primidone, phenobarbital, rifampin, rifabutin, fosphenytoin, St john's wort, rifapentine, enzalutamide)	Concurrent use of tasimelteon and selected strong CYP3A4 inducers may result in decreased tasimelteon exposure with reduced tasimelteon efficacy.
Zolpidem	Human immunodeficiency virus protease inhibitors	Inhibition of CYP3A4 by protease inhibitors may decrease the metabolic elimination and increase plasma concentrations of eszopiclone and zolpidem.
Zolpidem	Carbamazepine	Concurrent use of carbamazepine and zolpidem may result in decreased zolpidem plasma concentrations.
Zolpidem	Ciprofloxacin	Concurrent use of ciprofloxacin and zolpidem may result in increased zolpidem plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Tables 7 and 8. The boxed warnings are listed in Tables 9 and 10. Meprobamate, eszopiclone, suvorexant, zaleplon, and zolpidem are classified as Schedule IV controlled substances by federal regulation because of their abuse potential. The risk of abuse and dependence increases with the dose, duration of treatment, and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol/drug abuse or psychiatric disorders.

Table 7. Adverse Drug Events (%) Reported with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (A to L)[2]

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Cardiovascular					
Arrhythmia	-	✔	-	-	-
Atrial fibrillation	-	2 to 9	-	-	-
Atrioventricular block	-	✔	-	-	-
Bradycardia	<1	5 to 42	-	-	-
Cardiac arrest	-	✔	✔	-	-
Cardiomyopathy	<1	-	-	-	-
Chest pain	≥1	-	-	1 to 10	-
Extrasystoles	-	✔	-	-	-
Heart block	-	✔	-	-	-
Heart failure	<1	-	-	-	-
Hypertension	<1	✔	✔	<1	-
Hypotension	<1	24 to 56	✔	-	-
Hypovolemia	-	3	-	-	-
Myocardial infarction	<1	✔	-	-	-
Peripheral edema	-	3 to 7	-	1 to 10	-
QTc prolongation	-	-	✔	-	-
Supraventricular tachycardia	-	✔	-	-	-
Syncope	<1	-	-	-	-
T-wave inversion	-	✔	-	-	-
Tachycardia	-	25	✔	-	-
Torsades de pointes	-	-	✔	-	-
Ventricular arrhythmia	-	✔	-	-	-
Ventricular tachycardia	-	✔	✔	-	-
Central Nervous System					
Abnormal gait	-	-	-	<1	-
Agitation	-	✔	-	<1	-
Anger	2	-	-	-	-
Anxiety	-	5 to 9	✔	1 to 3	-
Ataxia	<1	-	-	<1	-
Cerebrovascular attack	<1	-	-	-	-
Chills	-	-	✔	-	-

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Complex sleep-related activities	-	-	-	<1	-
Confusion	2	✔	-	≤3	-
Delirium	-	✔	-	-	-
Depression	-	-	✔	1 to 4	-
Dizziness	12	✔	✔	5 to 7	✔
Dream disturbances	≥1	-	-	1 to 3	-
Drowsiness	10	-	✔	-	✔
Dysphoria	-	-	✔	-	-
Emotional lability	-	-	-	<1	-
Euphoria	-	-	-	<1	-
Excitement	2	-	-	-	-
Extrapyramidal symptoms	<1	-	✔	-	-
Fever	-	✔	-	<1	-
Hallucinations	<1	✔	✔	1 to 3	✔
Headache	6	✔	-	15 to 21	✔
Hostility	-	-	-	<1	-
Hyperactivity	-	-	✔	-	-
Illusion	-	✔	-	-	-
Incoordination	1	-	-	-	-
Involuntary movements	-	-	-	-	✔
Lightheadedness	3	-	-	-	-
Memory impairment	-	-	-	<1	-
Malaise	-	-	-	<1	-
Migraine	-	-	-	1 to 10	-
Nervousness	5	-	-	≤5	✔
Neuralgia	-	✔	-	≤3	-
Neuritis	-	✔	-	<1	-
Neuroleptic malignant syndrome	-	-	✔	-	-
Neuropathy	-	-	-	<1	-
Neurosis	-	-	-	<1	-
Numbness	2	-	-	-	-
Paresthesia	1	-	-	<1	✔
Parkinsonism	<1	-	-	-	-
Personality disorders	<1	-	-	-	-
Psychosis	<1	-	-	-	-
Restlessness	-	-	✔	-	-
Seizure	<1	✔	-	-	✔
Somnolence	-	-	-	8 to 10	-
Speech disorder	-	✔	-	-	-
Suicidal ideation	<1	-	-	-	-
Tremor	1	-	-	<1	✔

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Vertigo	-	-	-	<1	-
Dermatological					
Alopecia	-	-	-	<1	-
Contact dermatitis	-	-	-	<1	-
Ecchymosis	<1	-	-	-	-
Eczema	-	-	-	<1	-
Erythema multiforme	-	-	-	<1	-
Maculopapular rash	-	-	-	<1	-
Photosensitivity reaction	-	-	-	<1	-
Pruritus	-	-	-	1 to 4	✔
Rash	1	-	-	3 to 4	✔
Urticaria	-	-	-	<1	✔
Vesiculobullous rash	-	-	-	<1	-
Endocrine and Metabolic					
Acidosis	-	✔	-	-	-
Breast enlargement	-	-	-	<1	-
Breast neoplasm	-	-	-	<1	-
Cholelithiasis	-	-	-	<1	-
Galactorrhea	<1	-	-	-	-
Gout	-	-	-	<1	-
Gynecomastia	-	-	-	≤3	-
Mastitis	-	-	-	<1	-
Thyroid abnormality	<1	-	-	-	-
Gastrointestinal					
Abdominal pain	-	✔	-	-	-
Anorexia	<1	-	-	<1	-
Colitis	-	-	-	<1	-
Dehydration	-	-	-	<1	-
Diarrhea	2	✔	-	2 to 4	-
Dysgeusia	-	-	-	8 to 34	-
Dyspepsia	-	-	-	2 to 6	-
Dysphagia	-	-	-	<1	-
Gastrointestinal ulcer	-	-	-	<1	-
Irritable colon	<1	-	-	-	-
Melena	-	-	-	<1	-
Nausea	8	3 to 11	-	4 to 5	-
Rectal hemorrhage	<1	-	-	<1	-
Thirst	-	✔	-	-	-
Tongue edema	-	-	-	<1	-
Ulcerative stomatitis	-	-	-	<1	-
Vomiting	-	✔	-	≤3	-

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Xerostomia	-	3 to 4	-	3 to 7	✔
Genitourinary					
Amenorrhea	-	-	-	<1	-
Cystitis	-	-	-	<1	-
Dysmenorrhea	-	-	-	≤3	-
Dysuria	-	-	-	<1	-
Enuresis	<1	-	-	-	-
Hematuria	-	-	-	<1	-
Kidney calculus	-	-	-	<1	-
Kidney pain	-	-	-	<1	-
Libido decreased	-	-	-	≤3	-
Menorrhagia	-	-	-	<1	-
Menstrual irregularities	<1	-	-	-	-
Oliguria	-	✔	-	<1	-
Pelvic inflammatory disease	<1	-	-	-	-
Pyelonephritis	-	-	-	<1	-
Urethritis	-	-	-	<1	-
Urinary frequency	-	-	-	<1	-
Urinary incontinence	-	-	-	<1	-
Urinary retention	-	1	-	-	-
Urinary tract infection	-	-	-	≤3	-
Vaginal hemorrhage	-	-	-	<1	-
Vaginitis	-	-	-	<1	-
Vulvovaginal dryness	-	-	-	-	-
Hematologic					
Anemia	-	✔	-	-	-
Eosinophilia	<1	-	-	-	-
Leukopenia	<1	-	-	-	-
Thrombocytopenia	<1	-	-	-	-
Thrombophlebitis	-	-	-	<1	-
Hepatic					
Alkaline phosphatase increased	-	✔	-	-	-
Alanine transaminase increased	-	✔	-	-	-
Aspartate aminotransferase increased	-	✔	-	-	-
Gamma-glutamyl transpeptidase increased	-	✔	-	-	-
Hepatic impairment	-	✔	-	-	-
Hepatitis	-	-	-	<1	-
Hepatomegaly	-	-	-	<1	-
Hyperbilirubinemia	-	✔	-	-	-
Liver damage	-	-	-	<1	-

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Transaminases increased	<1	-	-	-	-
Laboratory Test Abnormalities					
Blood urea nitrogen increased	-	✔	-	-	-
Hypercholesterolemia	-	-	-	<1	-
Hyperkalemia	-	✔	-	-	-
Hypocalcemia	-	1	-	-	-
Hypoglycemia	-	✔	-	-	-
Hypokalemia	-	-	-	<1	-
Musculoskeletal					
Cogwheel rigidity	<1	-	-	-	-
Dyskinesia	<1	-	-	-	-
Dystonia	<1	-	-	-	-
Muscle spasms	<1	-	-	-	-
Myasthenia	-	-	-	<1	-
Myopathy	-	-	-	<1	-
Neck rigidity	-	-	-	<1	-
Restless leg syndrome	<1	-	-	-	-
Rigors	-	✔	-	-	-
Weakness	2	-	-	-	-
Respiratory					
Apnea	-	✔	-	-	-
Asthma	-	-	-	<1	-
Bronchitis	-	-	-	<1	-
Bronchospasm	-	✔	✔	-	-
Dyspnea	<1	✔	-	<1	-
Epistaxis	<1	-	-	<1	-
Hypercapnia	-	✔	-	-	-
Hyperventilation	<1	-	-	-	-
Hypoventilation	-	✔	-	-	-
Hypoxia	-	✔	-	-	-
Laryngospasm	-	-	✔	-	-
Nasal congestion	≥1	-	-	-	-
Pleural effusion	-	2	-	-	-
Pulmonary congestion	-	✔	-	-	-
Respiratory acidosis	-	✔	-	-	-
Respiratory depression	-	37	-	-	✔
Throat irritation	≥1	-	-	-	-
Upper respiratory tract infection	-	-	-	-	-
Wheezing	-	≤1	-	-	-
Special Senses					
Blurred vision	2	-	-	-	✔

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Conjunctivitis	<1	-	-	<1	-
Dry eyes	-	-	-	<1	-
Mydriasis	-	-	-	<1	-
Nystagmus	-	-	-	<1	-
Photophobia	-	-	-	<1	-
Photopsia	-	✔	-	-	-
Tinnitus	≥1	-	-	<1	-
Vestibular disorder	-	-	-	<1	-
Visual disturbance	<1	✔	-	-	-
Other					
Accidental injury	-	-	-	≤3	-
Allergic reaction	<1	-	-	<1	✔
Anaphylaxis	-	-	✔	<1	-
Angioedema	<1	-	-	<1	-
Diaphoresis	1	✔	-	<1	-
Edema	<1	-	-	<1	-
Facial edema	-	-	-	<1	-
Heat stroke	-	-	-	<1	-
Hemorrhage	-	✔	-	-	-
Herpes zoster	-	-	-	<1	-
Infection	-	-	-	5 to 10	-
Pain	1	✔	-	4 to 5	-
Serotonin syndrome	<1	-	-	-	-
Shivering	-	-	✔	-	-
Twitching	-	-	-	<1	-
Viral infection	-	-	-	3	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 8. Adverse Drug Events (%) Reported with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (M to Z)[2]

Adverse Events	Meprobamate	Ramelteon	Tasimelteon	Zaleplon	Zolpidem
Cardiovascular					
Angina	-	-	-	<1	-
Arrhythmia	✔	-	-	-	-
Bigeminy	-	-	-	<1	-
Bundle branch block	-	-	-	<1	-
Cardiospasm	-	-	-	<1	-
Chest pain	-	-	-	≥1	1 to 10
Electrocardiogram changes	✔	-	-	-	-
Hypertension	-	-	-	<1	<1

Adverse Events	Meprobamate	Ramelteon	Tasimelteon	Zaleplon	Zolpidem
Hypotension	-	-	-	<1	<1
Hypotensive crisis	✔	-	-	-	-
Palpitation	✔	-	-	<1	1 to 10
Pericardial effusion	-	-	-	<1	-
Peripheral edema	✔	-	-	≤1	-
Syncope	✔	-	-	<1	<1
Tachycardia	✔	-	-	-	<1
Vasodilation	-	-	-	<1	-
Ventricular extrasystoles	-	-	-	<1	-
Ventricular tachycardia	-	-	-	<1	-
Central Nervous System					
Abnormal dreams	-	-	10	-	-
Abnormal thinking	-	-	-	≥1	-
Agitation	-	-	-	-	<1
Amnesia	-	-	-	2 to 4	1 to 10
Anxiety	-	-	-	≤1	1 to 10
Apathy	-	-	-	-	1 to 10
Ataxia	✔	-	-	<1	1 to 10
Attention disturbance	-	-	-	-	1 to 10
Burning sensation	-	-	-	-	1 to 10
Cerebrovascular attack	-	-	-	<1	<1
Chills	✔	-	-	-	-
Central nervous system stimulation	-	-	-	<1	-
Cognition decreased	-	-	-	-	<1
Complex sleep-related activities	-	✔	-	<1	<1
Concentration decreased	-	-	-	-	<1
Confusion	-	-	-	≤1	1 to 10
Delusions	-	-	-	<1	-
Depersonalization	-	-	-	<1 to 2	1 to 10
Depression	-	2	-	≥1	1 to 10
Disinhibition	-	-	-	-	1 to 10
Disorientation	-	-	-	-	1 to 10
Dizziness	✔	4 to 5	-	7 to 9	1 to 12
Dream disturbances	-	-	-	-	1 to 10
Drowsiness	✔	-	-	-	1 to 10
Drugged feeling	-	-	-	-	1 to 10
Emotional lability	-	-	-	-	<1
Euphoria	✔	-	-	-	1 to 10
Excitement	✔	-	-	-	-
Fatigue	-	3 to 4	-	-	1 to 10
Fever	✔	-	-	≥1	1 to 10

Adverse Events	Meprobamate	Ramelteon	Tasimelteon	Zaleplon	Zolpidem
Hallucinations	-	-	-	≤1	1 to 10
Headache	✔	-	17	30 to 42	3 to 19
Hypoesthesia	-	-	-	<1 to 2	1 to 10
Illusion	-	-	-	-	<1
Insomnia	-	3	-	-	1 to 10
Lethargy	-	-	-	-	1 to 10
Lightheadedness	-	-	-	-	1 to 10
Memory impairment	-	-	-	-	1 to 10
Malaise	-	-	-	<1 to 2	-
Migraine	-	-	-	≥1	<1
Mood disorder	-	-	-	-	1 to 10
Nervousness	-	-	-	≥1	-
Overstimulation	✔	-	-	-	-
Paresthesia	✔	-	-	3	<1 to 10
Sleep disorder	-	-	-	-	1 to 10
Somnolence	-	3 to 5	-	5 to 6	6 to 15
Speech disorder	✔	-	-	-	<1
Stress	-	-	-	-	1 to 10
Stupor	-	-	-	-	<1
Temperature regulation altered	-	-	-	-	1 to 10
Tremor	-	-	-	2	1 to 10
Vertigo	✔	-	-	≤1	1 to 10
Dermatological					
Alopecia	-	-	-	<1	-
Contact dermatitis	✔	-	-	-	-
Ecchymosis	✔	-	-	<1	-
Erythema multiforme	✔	-	-	-	-
Petechiae	✔	-	-	-	-
Photosensitivity reaction	-	-	-	≤1	-
Pruritus	-	-	-	≥1	<1
Purpura	✔	-	-	<1	-
Rash	✔	-	-	≥1	1 to 10
Stevens-Johnson syndrome	✔	-	-	-	-
Urticaria	-	-	-	-	1 to 10
Wrinkling	-	-	-	-	1 to 10
Endocrine and Metabolic					
Cholelithiasis	-	-	-	<1	-
Cyanosis	-	-	-	<1	-
Diabetes mellitus	-	-	-	<1	-
Goiter	-	-	-	<1	-
Ketosis	-	-	-	<1	-

Adverse Events	Meprobamate	Ramelteon	Tasimelteon	Zaleplon	Zolpidem
Gastrointestinal					
Abdominal pain	-	-	-	6	1 to 10
Anorexia	-	-	-	<1 to 2	-
Appetite disorder	-	-	-	-	1 to 10
Bleeding gums	-	-	-	<1	-
Colitis	-	-	-	≤1	-
Constipation	-	-	-	≥1	1 to 10
Dehydration	-	-	-	-	-
Diarrhea	✔	-	-	-	1 to 10
Dysgeusia	-	2	-	≥1	-
Dyspepsia	-	-	-	≥1	1 to 10
Dysphagia	-	-	-	-	<1
Flatulence	-	-	-	-	1 to 10
Gastroenteritis	-	-	-	<1	1 to 10
Gastroesophageal reflux	-	-	-	-	1 to 10
Gastrointestinal ulcer	-	-	-	<1	-
Hiccup	-	-	-	-	1 to 10
Intestinal obstruction	-	-	-	<1	-
Nausea	✔	3	-	6 to 8	1 to 10
Proctitis	✔	-	-	-	-
Rectal hemorrhage	-	-	-	<1	-
Stomatitis	✔	-	-	-	-
Tongue edema	-	-	-	<1	-
Ulcerative stomatitis	-	-	-	<1	-
Vomiting	✔	-	-	-	1 to 10
Xerostomia	-	-	-	≥1	1 to 10
Genitourinary					
Anuria	✔	-	-	-	-
Cystitis	-	-	-	-	<1
Dysmenorrhea	-	-	-	3 to 4	-
Dysuria	-	-	-	<1	1 to 10
Hematuria	-	-	-	<1	-
Impotence	-	-	-	<1	-
Incontinence	-	-	-	<1	<1
Menorrhagia	-	-	-	-	1 to 10
Oliguria	✔	-	-	-	-
Renal failure	-	-	-	-	<1
Urinary retention	-	-	-	<1	-
Urinary tract infection	-	-	7	-	1 to 10
Vaginitis	-	-	-	-	<1
Vulvovaginal dryness	-	-	-	-	1 to 10

Adverse Events	Meprobamate	Ramelteon	Tasimelteon	Zaleplon	Zolpidem
Hematologic					
Agranulocytosis	✔	-	-	-	-
Anemia	-	-	-	<1	<1
Aplastic anemia	✔	-	-	-	-
Eosinophilia	✔	-	-	<1	-
Leukocytosis	-	-	-	<1	-
Leukopenia	✔	-	-	-	<1
Lymphadenopathy	-	-	-	<1	<1
Lymphocytosis	-	-	-	<1	-
Porphyria exacerbation	✔	-	-	-	-
Thrombocytopenic purpura	✔	-	-	-	-
Thrombophlebitis	-	-	-	<1	-
Hepatic					
Abnormal hepatic function	-	-	-	-	<1
Alanine transaminase increased	-	-	10	<1	-
Aspartate aminotransferase increased	-	-	-	<1	-
Hyperbilirubinemia	-	-	-	<1	-
Liver function tests abnormal	-	-	-	<1	-
Laboratory Test Abnormalities					
Cortisol decreased	-	1	-	-	-
Hyperglycemia	-	-	-	<1	<1
Hyperuricemia	-	-	-	<1	-
Hypoglycemia	-	-	-	<1	-
Hypothyroidism	-	-	-	<1	-
Prolactin increased	-	✔	-	-	-
Testosterone decreased	-	✔	-	-	-
Musculoskeletal					
Arthralgia	-	2	-	≥1	1 to 10
Arthritis	-	-	-	≥1	-
Back pain	-	-	-	≥1	1 to 10
Balance disorder	-	-	-	-	1 to 10
Dysarthria	-	-	-	<1	-
Dystonia	-	-	-	<1	-
Hypertonia	-	-	-	1	-
Involuntary muscle contractions	-	-	-	-	1 to 10
Myalgia	-	2	-	≥1	1 to 10
Myasthenia	-	-	-	<1	-
Myositis	-	-	-	<1	-
Neck pain	-	-	-	-	1 to 10
Osteoporosis	-	-	-	<1	-
Psychomotor retardation	-	-	-	-	1 to 10

Adverse Events	Meprobamate	Ramelteon	Tasimelteon	Zaleplon	Zolpidem
Weakness	✔	-	-	5 to 7	1 to 10
Respiratory					
Bronchitis	-	-	-	≥1	-
Bronchospasm	✔	-	-	-	-
Dyspnea	-	-	-	-	<1
Epistaxis	-	-	-	≤1	-
Pharyngitis	-	-	-	-	1 to 10
Pulmonary embolus	-	-	-	<1	-
Sinusitis	-	-	-	-	1 to 10
Throat irritation	-	-	-	-	1 to 10
Upper respiratory tract infection	-	3	7	-	1 to 10
Special Senses					
Accommodation impaired	✔	-	-	-	-
Asthenopia	-	-	-	-	1 to 10
Blurred vision	-	-	-	-	1 to 10
Conjunctivitis	-	-	-	≥1	-
Depth perception altered	-	-	-	-	1 to 10
Diplopia	-	-	-	-	1 to 10
Ear pain	-	-	-	≤1	-
Eye pain	-	-	-	3 to 4	-
Eye redness	-	-	-	-	1 to 10
Glaucoma	-	-	-	<1	-
Hyperacusis	-	-	-	1 to 2	-
Parosmia	-	-	-	1 to 2	-
Photophobia	-	-	-	<1	-
Ptosis	-	-	-	<1	-
Scleritis	-	-	-	-	<1
Tinnitus	-	-	-	-	1 to 10
Visual disturbance	-	-	-	<1 to 2	1 to 10
Other					
Allergic reaction	-	-	-	-	1 to 10
Anaphylaxis	✔	✔	-	<1	<1
Angioedema	-	✔	-	<1	<1
Angioneurotic edema	✔	-	-	-	-
Binge eating	-	-	-	-	1 to 10
Diaphoresis	-	-	-	-	<1
Edema	-	-	-	-	<1
Facial paralysis	-	-	-	<1	-
Falling	-	-	-	-	<1
Flu-like syndrome	-	-	-	-	1 to 10
Hypersensitivity	✔	-	-	-	-

Adverse Events	Meprobamate	Ramelteon	Tasimelteon	Zaleplon	Zolpidem
Influenza	-	1	-	-	-
Lactose intolerance	-	-	-	<1	-
Somnambulism	-	-	-	-	<1
Thrombosis	-	-	-	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 9. Boxed Warning for Droperidol[2]

WARNING
Cases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation, and some cases have been fatal. Due to its potential for serious proarrhythmic effects and death, reserve droperidol for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes) have been reported in patients treated with droperidol. Based on these reports, all patients should undergo a 12-lead electrocardiogram prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, do not administer droperidol. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, perform electrocardiogram monitoring prior to treatment and continue for two to three hours after completing treatment to monitor for arrhythmias. Droperidol is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome. Administer droperidol with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, hypomagnesemia, or administration of other drugs known to increase the QT interval). Other risk factors may include age greater than 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and intravenous opiates. Initiate droperidol at a low dose and adjust upward, with caution, as needed to achieve the desired effect.

Table 10. Boxed Warning for Eszopiclone, Zaleplon, and Zolpidem[2]

WARNING
Complex sleep behaviors including sleepwalking, sleep-driving, and engaging in other activities while not fully awake may occur following use of these agents. Some of these events may result in serious injuries, including death. Discontinue immediately if a patient experiences a complex sleep behavior

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 11.

Table 11. Usual Dosing Regimens for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2-11]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Buspirone	Management of anxiety disorders; short-term relief of symptoms of anxiety: Tablet: 5 to 7.5 mg twice daily; increase by 5 mg/day every two to three days as needed; maximum, 60 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 7.5 mg 10 mg 15 mg 30 mg
Dexmedetomidine	Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting; administer by continuous infusion not to exceed 24 hours: Injection: 1 µg/kg intravenous over 10 minutes, then 0.2 to 0.7	Safety and efficacy in children have not been established.	Injection: 80 µg/20 mL 200 µg/2 mL 200 µg/50 mL 400 µg/4 mL 400 µg/100 mL 1,000 µg/10 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	µg/kg/hour Sedation of non-intubated patients prior to and/or during surgical and other procedures: Injection: 1 µg/kg intravenous over 10 minutes, then 0.2 to 1.0 µg/kg/hour		
Droperidol	To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures: Injection: 2.5 mg; additional 1.25 mg doses may be given to achieve desired effect	To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures in patients two to 12 years of age: Injection: 0.1 mg/kg To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures in patients >12 years of age: Injection: 2.5 mg	Injection: 2.5 mg/mL
Eszopiclone	Treatment of insomnia: Tablet: 1 mg immediately before bedtime; maximum, 3 mg	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 3 mg
Hydroxyzine	Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested: Injection: 50 to 100 mg intramuscular stat, then every four to six hours as needed Capsule, syrup, tablet: 50 to 100 mg four times daily Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus: Capsule, syrup, tablet: 25 mg three to four times per day Sedation when used as premedication and following general anesthesia: Injection: 25 to 100 mg intramuscular Capsule, syrup, tablet: 50 to 100 mg	Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested in patients ≥6 years of age: Capsule, syrup, tablet: 50 to 100 mg daily in divided doses Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested in patients <6 years of age: Capsule, syrup, tablet: 50 mg daily in divided doses Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated	Capsule: 25 mg 50 mg 100 mg Oral solution: 10 mg/5 mL 50 mg/25 mL Tablet: 10 mg 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		pruritus in patients ≥6 years of age: Capsule, syrup, tablet: 50 to 100 mg daily in divided doses Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus in patients <6 years of age: Capsule, syrup, tablet: 50 mg daily in divided doses Sedation when used as premedication and following general anesthesia: Injection: 0.5 mg/lb Capsule, syrup, tablet: 0.6 mg/kg	
Meprobamate	Management of anxiety disorders, short-term relief of symptoms of anxiety: Tablet: 1,200 to 1,600 mg/day in three to four doses; maximum, 2,400 mg	Management of anxiety disorders, short-term relief of symptoms of anxiety in patients six to 12 years of age: Tablet: 200 to 600 mg/day in two to three divided doses	Tablet: 200 mg 400 mg
Ramelteon	Treatment of insomnia characterized by difficulty with sleep onset: Tablet: 8 mg within 30 minutes of going to bed; maximum, 8 mg	Safety and efficacy in children have not been established.	Tablet: 8 mg
Tasimelteon	Treatment of Non-24-Hour Sleep-Wake Disorder: Capsule: 20 mg taken one hour before bedtime, at the same time every night Treatment of nighttime sleep disturbances in Smith-Magenis syndrome: Capsule: 20 mg taken one hour before bedtime, at the same time every night	Treatment of nighttime sleep disturbances in Smith-Magenis syndrome in patients ≥16 years of age: Capsule: 20 mg taken one hour before bedtime, at the same time every night Treatment of nighttime sleep disturbances in Smith-Magenis syndrome in patients 3 to 15 years of age: Suspension: Body weight ≤28 kg, 0.7 mg/kg one hour before bedtime; body weight >28 kg, 20	Capsule: 20 mg Suspension: 4 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		mg one hour before bedtime	
Zaleplon	Short-term treatment of insomnia: Capsule: 10 mg immediately before bedtime; maximum, 20 mg	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg
Zolpidem	Short-term treatment of insomnia characterized by difficulties with sleep initiation: Immediate release sublingual tablet (Edluar®), tablet: 5 mg for women and 5 or 10 mg for men, immediately before bedtime with at least seven to eight hours remaining before the planned time of awakening Insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep: Immediate release sublingual tablet (Intermezzo®): 1.75 mg for women and 3.5 mg for men, taken only once per night if needed; take only if four hours of bedtime remain before the planned time of waking Insomnia characterized by difficulties with sleep onset and/or sleep maintenance: Extended release tablet: 6.25 mg for women, and 6.25 or 12.5 mg for men, immediately before bedtime with at least seven to eight hours remaining before the planned time of awakening	Safety and efficacy in children have not been established.	Extended release tablet (Ambien CR®): 6.25 mg 12.5 mg Immediate release tablet (Ambien®): 5 mg 10 mg Sublingual tablet: 1.75 mg (Intermezzo®) 3.5 mg (Intermezzo®) 5 mg (Edluar®) 10 mg (Edluar®)

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous anxiolytics, sedatives, and hypnotics are summarized in Table 12.

Table 12. Comparative Clinical Trials with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Anxiety				
Gammans et al.[28] (1992) Buspirone 10 to 60 mg/day vs placebo	MA Adult outpatients with generalized anxiety disorder	N=509 (8 trials) 4 weeks	Primary: HAM-A score, HAM-D score, CGI score to determine responders Secondary: Not reported	Primary: Overall, patients treated with buspirone demonstrated significant (P<0.001) improvement over baseline in total HAM-A scores compared to placebo. Significantly more buspirone-treated patients (54%) were classified as responders than placebo-treated patients (28%) (P<0.001). Patients with GAD and concurrent depressive symptoms exhibited significantly greater improvement with buspirone compared to placebo (P<0.01 to P<0.03 depending upon the parameter measured and severity of depressive symptoms). Weekly ratings indicated that buspirone produced a progressively increasing anxiolytic response relative to placebo throughout the four-week DB treatment period in patients with GAD and coexisting depressive symptoms (P<0.05 at week one for HAM-D and P<0.05 at week two for HAM-A). Secondary: Not reported
Lader et al.[29] (1998) Buspirone 20 mg/day vs hydroxyzine 50 mg/day	DB, MC, PC, RCT Adult outpatients with GAD	N=244 6 weeks	Primary: HAM-A scores Secondary: CGI, MADRS, HAD Scale, FARD, Tyrer Withdrawal Symptom Scale	Primary: Hydroxyzine (P<0.02), but not buspirone (P=NS), significantly improved HAM-A scores over placebo after 28 days of treatment. HAM-A scores were not significantly different between hydroxyzine and buspirone. Secondary: Significantly (P<0.02) more patients on hydroxyzine improved CGI scores than placebo. There was no significant difference between buspirone and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				With respect to the MADRS, both buspirone and hydroxyzine patients were significantly better than placebo (P<0.001). HAD scores for both depression (P<0.01 for buspirone, P<0.02 for hydroxyzine) and anxiety (P<0.001 for both buspirone and hydroxyzine) were significantly better with the active drugs compared to placebo. The FARD total scores (P<0.001 for both buspirone and hydroxyzine) were also significantly better than placebo. There was no rebound with respect to HAM-A or other efficacy variables following placebo substitution at day 28. Both the buspirone and hydroxyzine patients continued to improve. No significant withdrawal symptoms for either active drug were detected on the Tyrer Scale. Both active treatments were well tolerated. The only side effects affecting more than 5% of the exposed patients were headache and migraine (6.1%) in the buspirone-treated patients (0% in hydroxyzine and 2.5% in placebo patients) and somnolence in the hydroxyzine group (9.9%) as compared to 4.9% in the buspirone and none in the placebo group.
Llorca et al.[30] (2002) Hydroxyzine 50 mg/day or bromazepam* 6 mg/day vs placebo	DB, MC, PG, RCT Adult outpatients with GAD	N=334 18 weeks	Primary: HAM-A scores Secondary: Responder and remission rates, change in CGI-S scale score and HAD scale score, maintenance of treatment efficacy, evaluation of rebound and withdrawal symptoms, safety	Primary: Mean change in HAM-A scores from baseline was significantly greater for hydroxyzine (-12.16) compared to placebo (-9.64; P=0.019). Bromazepam was also significantly more effective than placebo in decreasing HAM-A scores (P<0.03). Secondary: Results at endpoint for percentage of responders (P=0.003), remission rates (P=0.028), change in CGI-S scale score (P=0.001), HAD scale score (P=0.008), and maintenance of efficacy (P=0.022) on day 84 also confirmed the efficacy of hydroxyzine over placebo. The study showed no statistically significant difference between hydroxyzine and bromazepam; however, the study was not designed or powered to detect differences between these two active treatments. Efficacy was significantly maintained vs placebo in 86.5% of patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the hydroxyzine group (P=0.022) and in 88.1% of patients in the bromazepam group (P=0.010) until day 84. In the placebo, hydroxyzine, and bromazepam groups, only 10.1%, 14.7% and 14.0% of patients, respectively, experienced at least one adverse event considered to be related to treatment. Safety results were comparable in the 3 groups with the exception of drowsiness, which was reported most frequently in the bromazepam group (7.9%), followed by hydroxyzine (3.9%) and then placebo (1.8%). There were no statistically significant differences between each treatment group with regards to rebound effect. Differences in withdrawal symptoms that reached statistical significance were the following: hydroxyzine induced more sweating than placebo (P=0.048) and bromazepam induced more sleep disturbances than placebo (P=0.002).
Blanco et al.[31] (2003) Benzodiazepines, SSRIs, MAOIs, RIMAs, β-blockers, gabapentin, buspirone vs placebo	MA Patients with social anxiety disorder	N=2,954 (23 trials) 6 to 20 weeks	Primary: Outcome data on the LSAS or a categorical measure of status Secondary: CGI score	Primary: In terms of LSAS, no statistical difference was detected between medications or medication groups. Secondary: In terms of responders, effect sizes of each medication group were: benzodiazepines (16.61), brofaromine (6.96), phenelzine (4.10), gabapentin (3.78), SSRIs (3.22), atenolol (1.36), and moclobemide (1.27). No statistical differences were detected between these medications or medication groups.
Insomnia				
Zammit et al.[32] (2004) Eszopiclone 2 to 3 mg vs	DB, MC, PC, RCT Adults 21 to 64 years of age with chronic primary insomnia	N=308 6 weeks	Primary: Efficacy (PSG and patient reports), next day residual effects (DSST), tolerance, rebound insomnia, safety	Primary: Eszopiclone 2 and 3 mg had significantly less time to sleep onset ($P \leq 0.001$ and $P \leq 0.0001$, respectively), more TST ($P \leq 0.01$ and $P \leq 0.0001$), better SE ($P \leq 0.001$ and $P \leq 0.0001$), and enhanced quality and depth of sleep (both $P<0.05$) across the DB period compared to placebo. Eszopiclone 3 mg ($P \leq 0.01$) but not 2 mg significantly improved sleep maintenance compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			Secondary: Not reported	Median DSST scores showed no decrement in psychomotor performance relative to baseline and did not differ from placebo in either eszopiclone group. There was no evidence of tolerance or rebound insomnia after therapy discontinuation. Treatment was well tolerated; unpleasant taste was the most common adverse event reported with eszopiclone. Secondary: Not reported
Krystal et al.[33] (2003) Eszopiclone 3 mg vs placebo	DB, MC, PC, RCT Adults with chronic insomnia	N=788 6 months	Primary: SL, WASO, NAW, TST, quality of sleep, next-day ratings of ability to function, daytime alertness, sense of physical well-being, safety Secondary: Not reported	Primary: At the first week and each month for the study duration, eszopiclone produced significant and sustained improvements in SL, WASO, NAW, number of nights awakened per week, TST, and quality of sleep compared to placebo (all $P \leq 0.003$). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo (all $P \leq 0.002$). There was no evidence of tolerance and the most common adverse events were unpleasant taste and headache. Secondary: Not reported
Walsh et al.[34] (2007) Eszopiclone 3 mg vs placebo	DB, MC, PC, RCT Adults 21 to 64 years of age with primary insomnia	N=830 26 weeks	Primary: Patient-reported sleep measures (SL, WASO, TST, NAW, sleep quality, daytime alertness, ability to concentrate, physical well-	Primary: Patient-reported sleep and daytime function improved more with eszopiclone than with placebo at all months ($P<0.001$). Eszopiclone reduced ISI scores to below clinically meaningful levels for 50% of patients (vs 19% of patients with placebo; $P<0.05$) at six months. Lower mean scores on the FSS and the ESS were observed in the eszopiclone group relative to placebo for each month and the month one to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			being, and ability to function), ISI, FSS, ESS, Medical Outcomes Study SF-36, Work Limitations Questionnaire, safety (assessments performed at baseline, treatment months one to six, and two weeks after discontinuation of treatment) Secondary: Not reported	six average (P<0.05). SF-36 domains of Physical Functioning, Vitality, and Social Functioning were improved with eszopiclone vs placebo for the month one to six average (P<0.05). Similarly, improvements were observed for all domains of the Work Limitations Questionnaire with eszopiclone vs placebo for the month one to six average (P<0.05). There was no evidence of rebound insomnia after discontinuation of eszopiclone as SL, WASO and TST remained significantly improved from baseline (all P<0.001). There were no between-treatment differences observed during the discontinuation period except for a significantly greater SL on the first night after discontinuation with eszopiclone vs placebo (45 vs 30 minutes; P=0.015). No significant group differences were observed in mean Benzodiazepine Withdrawal Symptom Questionnaire scores (3.0 with eszopiclone and 2.3 with placebo; P=0.12), or overall adverse event rates (15.2% for eszopiclone and 11.1% for placebo; P value not reported). Unpleasant taste (19.7 vs 1.1%; P<0.001), somnolence (8.8 vs 3.2%; P=0.0029), and myalgia (6.0 vs 2.9; P=0.047) were reported in significantly more patients receiving eszopiclone than those receiving placebo. Secondary: Not reported
Joffe et al.[35] (2009) Eszopiclone 3 mg for 4 weeks vs placebo for 4 weeks Each treatment	DB, PC, RCT, XO Perimenopausal and postmenopausal women 40 to 65 years of age with sleep-onset and/or sleep-maintenance insomnia co-occurring with hot flashes and depressive and/or	N=59 11 weeks Each treatment period was separated by a 2-week washout period	Primary: Changes in the ISI scale Secondary: Diary-based sleep parameters (WASO, SE, sleep-onset latency, TST, NAW); number of hot flashes/night sweats, depressive	Primary: The ISI score was reduced by 8.7 more points with eszopiclone than with placebo (P<0.0001). The ISI score was 7 or less after four weeks of treatment in 87% of women on eszopiclone and in 34% of women on placebo. Secondary: SL was reduced by 17.8 more minutes with eszopiclone than with placebo (P=0.04). For both treatment periods together, WASO was reduced by 37.7 minutes more with eszopiclone than placebo (P=0.05), SE improved by 14.6% more with eszopiclone than with placebo (P=0.01), and TST increased by 66.5 minutes more with eszopiclone than with placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
period was separated by a 2-week washout period.	anxiety symptoms		symptoms (via MADRS), anxiety symptoms (assessed via BAI), MENQOL, and functional impairment, safety	(P=0.01). Among patients with anxiety symptoms at baseline, BAI scores were reduced by a mean of 1.5 more with eszopiclone than with placebo (P=0.03). Quality of life (P=0.0002) and functional disability (P=0.09) improved more on eszopiclone than on placebo. Among those with depressive symptoms at baseline, MADRS scores were reduced by a mean of 7.4 more points with eszopiclone than with placebo (P=0.0004). Compared to placebo, eszopiclone had a significant effect on depressive symptoms during the second (P=0.003), but not first, treatment period. There was a significant reduction in nighttime hot flashes with eszopiclone compared to placebo (reduction by 1.5 nighttime hot flashes; P=0.047), but the effect on daytime symptoms was not different. Compared to placebo, eszopiclone had a significant effect on nighttime hot flashes during the second (P=0.0006), but not first, treatment period. Overall, the treatment was well tolerated. The only adverse event occurring in >5% of the population was metallic taste on eszopiclone (25%).
Scharf et al.[36] (2005) Eszopiclone 1 to 2 mg vs placebo	DB, MC, PC, RCT Community-dwelling elderly patients (mean age 72.3 years) with primary insomnia	N=231 2 weeks	Primary: Patient-reported efficacy (SL, TST) Secondary: WASO, NAW, number and length of naps, quality of sleep, depth of sleep, ratings of daytime alertness, sense of physical well-being, morning sleepiness, ability	Primary: Patients treated with eszopiclone 1 and 2 mg had a significantly shorter SL compared to placebo (P<0.05 and P=0.0034, respectively). The eszopiclone 2-mg group (P=0.0003) but not the 1-mg group (P>0.1) had significantly longer TST compared to placebo. Secondary: Compared to placebo, patients receiving eszopiclone 2 mg had significantly less WASO but similar NAW per night (P>0.1). Patients receiving eszopiclone 2 mg had significantly fewer (P=0.028) and shorter in duration (P=0.011) daytime naps, higher ratings of sleep quality (P=0.0006) and depth (P=0.0015), better daytime alertness (P=0.022) and sense of physical well-being (P=0.047) compared to patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			to function, quality of life (Q-LES-Q), safety	placebo. The differences between eszopiclone 2 mg and placebo were marginally significant for morning sleepiness (P=0.055) and ability to function (P=0.058). Duration of nap was significantly shorter in the eszopiclone 1-mg group compared to the placebo group (P<0.05); however, there were no other significant differences in any other secondary efficacy endpoints. Compared to placebo, the eszopiclone 2-mg group had significantly higher quality of life scores on five of the 16 Q-LES-Q domains (physical health, mood, household activities, leisure time activities and medications; P<0.05). The differences between eszopiclone 2 mg and placebo were marginally significant for the Q-LES-Q global score (P=0.064). There were no significant differences between eszopiclone 1 mg and placebo for any of the Q-LES-Q dimensions. Eszopiclone was well tolerated with unpleasant taste reported as the most frequent treatment-related adverse event.
Ancoli-Israel et al.[37] (2010) Eszopiclone 2 mg vs placebo	DB, MC, PC, RCT Patients 65 to 85 years of age with primary insomnia	N=388 12 weeks Treatment was followed by a two week, SB run out period	Primary: Change from baseline sTST Secondary: Change from baseline in sSL and WASO	Primary: After 12 weeks, the mean sTST was 360.08 minutes with eszopiclone compared to 297.86 minutes at baseline (mean change of 63.24 minutes). This was significantly greater than placebo (P<0.0001). Secondary: There was a greater improvement in sSL with eszopiclone compared to placebo (mean decrease of 24.62 vs 19.92 minutes; respectively; P=0.0014). Patients receiving eszopiclone experienced a greater decrease in WASO compared to those receiving placebo (mean decrease of 36.4 vs 14.8 minutes; P<0.0001). The reported NAW per night was reduced (P≤0.01), and the quality (P<0.001) and depth of sleep (P≤0.001) was improved at all time points with eszopiclone compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a significantly greater decrease in naps per week over the first three weeks of treatment with eszopiclone (1.2 naps per week decrease) vs placebo (0.4 naps per week; P=0.006), but not at subsequent time points. Similar results were obtained for total nap time per week. Patients receiving eszopiclone had significantly greater improvements in ISI total scores than those receiving placebo at all time points (all P<0.001). The percentage of patients with ISI total scores categorized as "no insomnia" and "sub-threshold insomnia" was greater in the eszopiclone group (78.0% at week 12) than in the placebo group (61.1%; P<0.05). Changes in self-reported daytime alertness, ability to function, ability to concentrate, and sense of physical well-being were significantly increased with eszopiclone compared to placebo at all times points (all P≤0.001). Patients receiving eszopiclone had significant improvements in the vitality scale of the SF-36 at week six (P=0.04) and week 12 (P=0.008), and in the general health scale at week 12 (P=0.009) compared to placebo. There were no significant differences on the other SF-36 individual scale scores, or on the mental or physical component summary scores among the treatment groups. On the SDS, there were significant improvements observed in the eszopiclone group compared to the placebo group for the social life and family life/home responsibilities items (both P≤0.03) at week six, but not at week 12. There was no significant difference on the work/school item at either time point. The overall incidence of adverse events was 59.3% for eszopiclone and 50.5% for placebo. The most common adverse events reported in the eszopiclone group were headache (13.9 vs 12.4% for placebo), unpleasant taste (12.4 vs 1.5% for placebo), and nasopharyngitis (5.7 vs 6.2% for placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lettieri et al.[38] (2009) Eszopiclone 3 mg 30 minutes prior to PSG (premedication) vs placebo 30 minutes prior to PSG (premedication)	DB, PC, RCT Patients 18 to 64 years of age with newly diagnosed obstructive sleep apnea who were initiating CPAP	N=117 4 to 6 weeks	Primary: CPAP compliance during the initial four to six weeks of therapy Secondary: CPAP titration quality as assessed by WASO), TST, total arousal index, SL, SE, AHI	Primary: CPAP was used on a higher percentage of nights in the eszopiclone group than in the placebo group (75.9 vs 60.1%, respectively; P=0.005). Eszopiclone was associated with more hours of use per night during nights used (4.8 vs 3.9 hours, respectively; P=0.03) and for more hours per night for all nights of the study period (4.0 vs 2.9 hours, respectively; P=0.03). The percentage of days with >4 hours of use also was greater among the eszopiclone group (59.2 vs 37.0%, respectively; P=0.007). Good compliance (>4 hours of use per night on >70% of nights) was observed in more patients pretreated with eszopiclone than with placebo (53.1 vs 27.1%, respectively; P=0.009). Secondary: Premedication with eszopiclone improved the quality of CPAP titration PSG compared to placebo as evidenced by shortened SL (19.4 vs 31.8 minutes, respectively; P=0.08), improved SE (87.8 vs 80.1%, respectively; P=0.002), expanded TST (350.9 vs 319.7 minutes, respectively; P=0.007), and decreased WASO (39.3 vs 59.9 minutes, respectively; P=0.009). The residual AHI tended to be lower following eszopiclone premedication (6.4 vs 12.8 events/hour, respectively; P=0.08).
Lettieri et al.[39] (2009) Eszopiclone 3 mg for 2 weeks vs placebo for 2 weeks To promote adherence with CPAP, OL use of	DB, PC, RCT Patients 18 to 64 years of age with newly diagnosed obstructive sleep apnea who were initiating CPAP	N=160 24 weeks	Primary: Adherence to CPAP at week 24 Secondary: Rate of CPAP discontinuation and OL use of sedative-hypnotic agents	Primary: Patients receiving eszopiclone used CPAP for 64.4% of nights compared to 45.2% of nights in those receiving placebo (P=0.003). In the eszopiclone and placebo groups, CPAP was used for 3.57 vs 2.42 hours per night, respectively for all study nights (P=0.005) and for 4.05 vs 3.02 hours per night, respectively for nights when CPAP was used (P=0.019). Secondary: The mean duration of regular use of CPAP was 13.3 weeks for the placebo group and 17.6 weeks for the eszopiclone group (P=0.005). The mean time to discontinuation of CPAP for the placebo and eszopiclone groups was 17.2 and 19.7 weeks, respectively (P=0.033).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sedative-hypnotic agents was allowed after the first 4 weeks of treatment.				A total of 24.7% of patients requested OL non-benzodiazepines. This request was more frequent among those receiving placebo than eszopiclone (31% vs 19%; P=0.084). The mean duration of hypnotic use (9.7 days) was similar for both groups. Adverse events were reported in 7.1% of patients and did not differ between the groups.
Menza et al.[40] (2010) Eszopiclone 2 to 3 mg vs placebo	DB, MC, PC, PG, RCT Patients 35 to 85 years of age with Parkinson's disease and sleep maintenance insomnia or SL insomnia, as well as clinically significant daytime distress or impairment secondary to insomnia	N=30 6 weeks	Primary: Patient-reported TST Secondary: WASO, NAW and SII, quality of sleep, quality of life (assessed via PDQ-8), motor function (assessed via UPDRS), severity and change (assessed via CGI), ability to function, daytime alertness, fatigue severity (assessed via FSS), caregiver quality of life and depression (assessed via MCBI and CES-D)	Primary: There was no significant difference in the improvement seen in TST among the groups (66.5 minutes with eszopiclone vs 47.0 minutes with placebo; P=0.1099). Secondary: There were significant differences in NAW (P=0.035), quality of sleep (P=0.018), and CGI-improvement in sleep (P=0.035) among the groups. There was no significant difference in WASO (P=0.071). There were no differences in the UPDRS motor, activities of daily living, therapeutic complications, mood or Schwab subscales. There were no significant differences in SL, FSS, SII, PDQ-8, Ability to Function Scale, the MCBI caregiver burden, the CES-D, or the Daytime Alertness Scale. Overall, 30% of patients reported adverse events; 33% of patients receiving eszopiclone and 27% of patients receiving placebo.
Pollack et al.[41] (2011) Eszopiclone 3 mg for 3 weeks	DB, PC, RCT, XO Patients 18 to 64 years of age with PTSD with associated sleep	N=24 7 weeks	Primary: Changes in scores on the SPRINT and PSQI scales Secondary:	Primary: Eszopiclone was associated with significant improvement in PTSD symptomatology as measured by the SPRINT compared to placebo (P=0.032). Eszopiclone was associated with a significantly greater reduction in PSQI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 3 weeks Each treatment period was separated by a 1-week washout period.	disturbance		CAPS, SL and TST	score compared to placebo (P=0.011). Secondary: In phase 1, the CAPS was also significantly reduced with eszopiclone compared to placebo (P=0.003). SL was significantly reduced with eszopiclone compared to placebo (P=0.044). There was no significant difference in TST among the treatment groups (P=0.061). Adverse events with eszopiclone were of mild to moderate severity, with the most common comprising unpleasant taste (32%), sedation (16%), and headaches (12%).
McCall et al.[42] (2010) Eszopiclone 3 mg vs placebo All patients started with one week of OL fluoxetine; patients experiencing insomnia after this period were randomized to 8 weeks of eszopiclone or placebo in addition to the OL fluoxetine.	DB, PC, RCT Patients 18 to 70 years of age with depression and insomnia	N=60 8 weeks	Primary: DLRF subscale of the Basis-32 Secondary: Safety	Primary: Final DLRF scores were better (lower) in the eszopiclone group than in the placebo group (0.81±0.64 vs 1.2±0.72). Secondary: The only meaningful adverse event reported, was unpleasant taste, and it occurred in 46% of patients treated with eszopiclone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosenberg et al.[43] (2005) Eszopiclone 1, 2, 3 or 3.5 mg vs placebo	DB, PC, RCT Healthy adult volunteers with transient insomnia	N=436 1 night	Primary: Efficacy and next-morning effects evaluated by PSG, DSST and self-report Secondary: Not reported	Primary: Patients treated with eszopiclone had significantly less PSG LPS (all doses except 1 mg; P≤0.0001), WASO (all doses; P≤0.05) and NAW (3 and 3.5 mg doses; P<0.005), and greater SE (all doses; P≤0.02) compared to placebo. Self-reported efficacy results were similar to PSG. Self-reported morning sleepiness scores were significantly better for eszopiclone 3 and 3.5 mg compared to placebo (P<0.05). Treatment was well tolerated by patients, and the most common treatment-related adverse event was unpleasant taste. Secondary: Not reported
Krystal et al.[44] (2012) Eszopiclone 3 mg vs placebo	Post hoc analysis of a 6-month PC, RCT Patients diagnosed with chronic primary insomnia	N=195 6 months	Primary: Determination of the distribution of baseline WASO; continuous analysis of the relationship between baseline WASO severity and drug-placebo difference at month one and six; and categorical efficacy analyses of subgroups delimited by the following WASO thresholds: 0, 30, 45, 60, and 90 minutes Secondary:	Primary: The baseline WASO distribution was: <30 minutes, 32.2%; >0 to <45 minutes, 41.5%; >30 to <90 minutes, 33.0%; >45 to <90 minutes, 23.7%; >90 minutes, 22.6%. A relationship between greater baseline WASO severity and a significantly greater drug-placebo difference in efficacy for WASO was evident. Eszopiclone was found to have significant sleep maintenance efficacy at each time point across the entire range of WASO severity studied. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	
Rosenberg et al.[45] SUNRISE-1 (2019) Lemborexant 5 mg QHS or lemborexant 10 mg QHS vs zolpidem tartrate ER 6.25 mg QHS vs placebo	AC, DB, DD, MC, PC, PG, RCT Males ≥65 and females ≥55 years of age with a diagnosis of insomnia based on DSM-5, history of sWASO ≥60 minutes at least three nights per week in the previous four weeks, regular time spent in bed (between seven and nine hours), evidence of sleep maintenance insomnia, ISI score ≥13	N=1,006 4 weeks	Primary: Change from baseline for mean LPS on Days 29/30 as measured by PSG Secondary: Change from baseline for SE and WASO on Days 29/30, change from baseline for mean WASO in the second half of the night (WASO2H) on Days 29/30, safety	Primary: Treatment with both lemborexant 5 mg and 10 mg demonstrated significantly greater mean decreases from baseline in LPS on Days 29/30 compared to placebo (-19.5 and -21.5 vs -7.9 minutes, respectively). Treatment with zolpidem ER demonstrated a mean decrease from baseline in LPS on Days 29/30 compared to placebo (-7.5 vs -7.9 minutes, respectively). Secondary: Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater increases from baseline in SE (measured by PSG) at one month compared to placebo (12.9 and 14.1 vs 5.4%, respectively), as well as WASO (measured by PSG) at one month of treatment compared to placebo (-43.9 and -46.4 vs -18.6 minutes, respectively). The mean increase from baseline in SE was 9.1% for the zolpidem ER group and the mean decrease from baseline in WASO was -36.5 minutes. Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater decreases from baseline in WASO2H at one month (-27.2 and -28.8 vs -8.9 minutes, respectively). The mean decrease was -21.4 minutes in the zolpidem ER group. Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater decreases from baseline in sSOL at one month compared to placebo (-25.2 and -24.8 vs -8.1). The mean decrease was -17.0 in the zolpidem ER group. The overall incidence of treatment-emergent adverse events was similar among treatment groups. Non-serious adverse events were deemed to be mild or moderate in severity. A total of six individuals (four in the zolpidem group and two in the lemborexant 5 mg group) reported eight serious adverse; none were deemed to be treatment-related. Sleep paralysis was reported by one individual in the lemborexant 5 mg group and three in the lemborexant 10 mg group, although all were reported as mild in severity.
Kärppä et al.[46]	DB, MC, PC, PG,	N=971	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SUNRISE-2 (2020) Lemborexant 5 mg QHS or lemborexant 10 mg QHS vs placebo	RCT Adults ≥18 years of age with a diagnosis of insomnia based on DSM-5, history of sSOL ≥30 minutes and/or sWASO ≥60 minutes on at least three nights per week in the previous four weeks, regular time spent in bed (between seven and nine hours), ISI score ≥15	52 weeks	Change from baseline in sSOL at month six Secondary: Change from baseline in sSE and sWASO at month six compared to placebo	Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater decreases from baseline in median sSOL compared to placebo at month six (-21.81 and -28.21 vs -11.43 minutes, respectively; P<0.0001 for both strengths). Secondary: Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater increases from baseline at month six compared to placebo in both sSE (LSM, 14.19 and 14.31 vs 9.64%; P=0.0001 for 5 mg group and <0.0001 for 10 mg group) and sWASO (LSM, -46.75 and -41.95 vs -29.28; P=0.0005 [5 mg] and P=0.0105 [10 mg]). A greater proportion of sleep onset responders was seen with lemborexant 5 mg and 10 mg compared with placebo at month six (31.2 and 30.1 vs 17.7%, respectively; P<0.001 [both strengths]). A greater proportion of sleep maintenance responders was seen with lemborexant 5 mg and 10 mg compared with placebo at month six (35.0 and 30.0 vs 20.4%, respectively; P<0.001 [5 mg] and P<0.05 [10 mg]). Both lemborexant 5 mg and 10 mg demonstrated significant greater increases from baseline in sTST compared with placebo at month six (LSM, 69.95 and 74.08 vs 51.40 minutes, respectively; P=0.0034 [5 mg] and P=0.0004 [10 mg], respectively).
Uchimura et al.[47] (abstract) (2011) Ramelteon 4 and 8 mg vs placebo	DB, PC, RCT Japanese adults with chronic insomnia	N=1,130 Duration not reported	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported There was no statistically significant difference between ramelteon and placebo in the change in subjective SL (P value not reported). Significant improvement was observed in the change in subjective TST with ramelteon 8 mg at week one (P value not reported). Post hoc analyses indicated that treatment with ramelteon 8 mg resulted in a reduction in subjective SL in individuals with smaller fluctuations

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(within ±30 minutes) of subjective SL at baseline, in those with a shorter (<1 year) history of insomnia, and in individuals who had not used benzodiazepines (P value not reported). Ramelteon was safe and well tolerated up to 16 mg nightly.
Kohsaka et al.[48] (abstract) (2011) Ramelteon 4, 8, 16, or 32 mg vs placebo	DB, PC, XO Japanese patients with chronic insomnia	N=65 Each dose was given for two nights over five study periods	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Ramelteon 8 and 32 mg significantly shortened the mean LPS when compared to placebo (P value not reported). Overall changes in sleep architecture were modest (<3% changes vs placebo; P value not reported), with increases in stage 1 and decreases in stage 3/4. When compared to SL data from a similarly designed United States study, there was no evidence of any ethnic differences in the efficacy of ramelteon between Japanese and United States patients. Overall, ramelteon 8 mg showed the most favorable balance between sleep-promoting effects and tolerability (P value not reported). Ramelteon was well tolerated, the most common adverse effect was somnolence, which was similar to placebo at doses up to 8 mg, but increased with higher doses (P value not reported). Next-day residual effects occurred no more frequently with ramelteon at any dose than with placebo (P value not reported).
Wang-Weigand et al.[49] (2011) Ramelteon 8 mg vs placebo	PC, RCT Adults 18 to 64 years of age with chronic insomnia	N=552 Nightly treatment for 3 weeks with a one week, placebo run-out period to assess rebound insomnia	Primary: Patient reported SL at week three Secondary: Patient reported SL at week one and two, patient reported TST, patient reported WASO, patient	Primary and secondary: There was a reduction in the average patient reported SL (as measured by the PSQ-IVRS) at weeks one, two, and three, when compared to placebo; however, none of these reductions reached statistical significance (P value not reported). There were no significant differences seen between ramelteon and placebo at any time point regarding the following patient-reported parameters: TST, WASO, NAW, or sleep quality (P value not reported). There was no evidence of rebound insomnia detected during the placebo run-out period for the groups that had received placebo or ramelteon.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			reported NAW, and sleep quality (all assessed each week), safety	Headache and somnolence occurred in more than 3% of subjects in either group. Overall, the proportion of subjects with any treatment-related adverse events was similar between the ramelteon and placebo-groups (16.5 vs 15.4%, respectively; P-value not reported).
Wang-Weigand et al.[50] (2009) Ramelteon 8 mg vs placebo	DB, PC, RCT (pooled analysis of 4 trials) Patients 18 to 83 years of age with chronic insomnia	N=1,122 Duration varied among included trials	Primary: LS mean LPS for nights one and two for each included trial Secondary: Safety	Primary: At nights one and two, mean LPS was 43.3 minutes for the placebo group and 30.2 minutes, resulting in a between-group difference of 13.1 minutes (P<0.001). Secondary: The total number of adverse events was similar for ramelteon 8 mg (209 [36.5%]) and placebo (192 [34.3%]) (P value not reported). The most common adverse events were headache and somnolence.
Zammit et al.[51] (2009) Ramelteon 8 or 16 mg vs placebo	DB, MC, PC, RCT, SD Healthy patients 18 to 64 years of age	N=289 1 night	Primary: LPS assessed by PSG Secondary: PSG assessed endpoints include TST, WASO, and NAW after persistent sleep onset; subjective measures include SL, TST, WASO, NAW after persistent sleep onset, and overall sleep quality, safety	Primary: Treatment with ramelteon 8 mg resulted in a significant decrease in LS mean LPS when compared to placebo (12.2 vs 19.7 minutes; P=0.004). Treatment with ramelteon 16 mg resulted in a numeric decrease in LS mean LPS when compared to placebo; however, this decrease did not reach statistical significance (14.8 vs 19.7 minutes; P=0.065). Secondary: Treatment with ramelteon 8 and 16 mg resulted in significant increases in the LS mean TST when compared to placebo (8 mg: 436.8 vs 419.7 minutes; P=0.009 and 16 mg: 433.1 vs 419.7 minutes; P=0.043). There were no significant changes in any other objective or subjective measures of sleep. A total of 31 subjects (10.7%) reported at least one adverse event during the study. The incidence rates were 12.4, 13.3, and 6.4% for the placebo, ramelteon 8 and 16 mg groups, respectively. Most adverse events were mild or moderate in severity and the most commonly reported adverse event was somnolence.
Erman et al.[52] (2006) Ramelteon 4 to 32 mg	DB, MC, PC, RCT, 5-period XO Men and non-pregnant, non-	N=107	Primary: Mean LPS Secondary: TST, WASO,	Primary: All tested doses of ramelteon resulted in statistically significant reductions in LPS compared to placebo (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	lactating women 18 to 64 years of age with chronic insomnia		percentage of sleep time in each sleep stage, subjective sleep quality, next-day performance and alertness, safety	All tested doses of ramelteon resulted in statistically significant increases in TST compared to placebo (P=0.001). No significant differences in WASO (P=0.470), percentage of time spent in the different sleep stages and subjective sleep quality (P=0.525) were reported between the ramelteon groups and the placebo group. There were no differences between the placebo group and any ramelteon dose group on next-day performance and alertness (P values not reported). The safety of ramelteon at each dose was similar to that of placebo and the most commonly reported adverse events were headache, somnolence, and sore throat.
Mayer et al.[53] (2009) Ramelteon 8 mg vs placebo	DB, PC, RCT Patients ≥18 years of age with chronic primary insomnia	N=451 6 months	Primary: LPS (measured by PSG) Secondary: TST (measured by PSG), total time spent in each sleep stage, latency to REM, self-reported efficacy	Primary: Greater reductions in LPS occurred with ramelteon compared to placebo (P<0.05 for each time point). A greater change from baseline occurred with ramelteon (54 to 56%) compared to placebo (30 to 47%). Secondary A greater increase in TST occurred with ramelteon (381.1 minutes) compared to placebo (365.7 minutes) at week one (P<0.001), but not at any other time points. There were no significant changes in percent of time spent in Stage 1 or REM sleep with ramelteon vs placebo. There was a significant increase in percent of time spent in Stage 2 sleep and a significant decrease in time spent in Stage 3/4 with ramelteon compared to placebo (P values not reported). There was a greater reduction in subjective SL with ramelteon compared to placebo at week one, as well as months one and five (P<0.05). There

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				were no significant reductions at other time points between the treatment groups. There were no significant differences between ramelteon and placebo at any time point on the following measures: subjective TST, subjective NAW and sleep quality. No significant differences in sWASO was observed between ramelteon (90.89 minutes) and placebo (79.54 minutes) at any time point except month six (P=0.036). There were no significant differences on measures of morning level of alertness and ability to concentrate, or immediate/delayed morning recall between the treatment groups. No rebound insomnia was observed during the placebo run-out period. There were no differences between the treatment groups with regards to measures of withdrawal during the placebo run-out period.
Uchiyama et al.[54] (2011) Ramelteon 8 mg vs placebo	DB, MC, PC, RCT Japanese patients 20 to 85 years of age with primary insomnia	N=1,605 2 weeks	Primary: Mean patient-reported SL during week one of treatment Secondary: Mean SL during week two of treatment, mean patient-reported TST for week one and for week two, patient's global impression of treatment, rebound insomnia, and safety	Primary: The mean SL was reduced in week one in both the ramelteon and placebo groups (-15.98 and -11.73 minutes, respectively; P=0.0010). Secondary: The mean SL decreased further in week two in both groups; however, the difference between the groups of -2.36 minutes in favor of ramelteon did not achieve statistical significance (P=0.1093). Ramelteon increased TST significantly more than placebo at week one (difference in LS mean, 4.2 minutes; P=0.0484), but not at week two (2.4 minutes; P=0.2378). The mean NAW reported by patients in the ramelteon group was significantly less than that in the placebo group at week two (difference in LS mean of -0.07; P=0.0469) but not for week 1 (-0.04; P=0.2592). The mean sleep quality score with ramelteon was significantly smaller than that with placebo for week one (difference in LS mean, -0.12;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.0174), but not week two (-0.06; P=0.2059). There was no evidence of rebound insomnia with ramelteon during the run-out period. The mean total score for patients' global impression of treatment improved significantly with ramelteon compared to placebo at the end of week one (1.52 vs 1.59; P=0.0041) and week two (1.45 vs 1.53; P=0.0028). The proportion of patients scoring individual items as ''improved'' was significantly higher for ramelteon than placebo at weeks one and two for time to fall asleep (week one, 53.1 vs 44.3%; P=0.0100, week two, 58.3 vs 52.5%; P=0.0434), TST (week one, 42.0 vs 34.0%; P=0.0121, week two, 47.6 vs 38.8%; P=0.0031), sleep quality (week one, 56.4 vs 48.2%; P=0.0115, week two, 62.5 vs 56.1%; P=0.0463), and usefulness of treatment (week one, 58.2 vs 47.6%; P=0.0008, week two, 64.6 vs 56.8%; P=0.0123), but not for daytime distress (week one, 33.4 vs 31.9%; P=0.9116, week two, 42.7 vs 37.7%; P=0.0881). A total of 26.4% of patients in the ramelteon group and 20.5% of patients in the placebo group reported at least one treatment-emergent adverse event. All events were mild or moderate in severity. The most common adverse event leading to discontinuation was nasopharyngitis.
Uchiyama et al.[55] (2011) Ramelteon 4 to 16 mg	MC, SB Japanese patients 20 to 85 years of age with primary insomnia	N=222 24 weeks	Primary: Adverse events, residual effects, rebound insomnia, withdrawal symptoms, and dependence Secondary: Subjective SL and TST	Primary: During the study, 77.4% of patients reported adverse events. The most frequent reported adverse events were nasopharyngitis, inflammation of upper respiratory tract, eczema, elevated γ-glutamyltransferase, laryngopharyngitis, and headache. Endocrine adverse events that were considered drug-related included metrorrhagia, dysmenorrhea, polymenorrhea, increased estradiol, increased cortisol, and decreased cortisol. The mean change in next-morning residual scores significantly improved from baseline with ramelteon (P<0.05). The mean change from baseline in SL at week 24 and the placebo run-out period using the full analysis set with 8 mg were -30.4 and -28.6 minutes in the group continuously treated with ramelteon, which confirms the lack

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of rebound insomnia. Ramelteon was not associated with withdrawal symptoms and there was no evidence of dependence. Secondary: Mean subjective SL decreased significantly during the study. In the group that continuously received ramelteon 8 mg, it decreased from a baseline of 70.5 to 54.4 minutes after one week (P<0.0001) and 33.8 minutes after 20 weeks (P<0.0001), then plateaued until the end of the study. The mean subjective TST was 5.52 hours at baseline, increasing to 5.78 hours at week one (P<0.0001) and 6.30 hours at week 20 (P<0.0001), and remained stable until the end of the study.
Gooneratne et al.[56] (2010) Ramelteon 8 mg vs placebo	DB, PC, RCT Patients ≥60 years of age with obstructive sleep apnea and insomnia symptoms	N=21 4 weeks	Primary: Objective change in SOL using PSG Secondary: PSQI, (ISI, FOSQ, quality of life (SF-36)	Primary: Using PSG, there was a 10.7 minute decrease in SOL in the ramelteon arm compared to a 17.8 minute increase in the placebo arm (difference, 28.5 minutes; P=0.008). For self-reported SOL, there was no significant difference among the two study arms (−1.3 minutes; P=0.9). Neither objective nor subjective SE differed significantly between study arms. Secondary: There were no significant differences in the PSQI, ISI, FOSQ, or SF-36 among the treatment groups. The adverse events reported with ramelteon were diarrhea, skin ulcer, sinusitis, and fracture after being hit by a bicyclist. For placebo, the adverse events were abdominal pain and nausea. All adverse events were thought to be unrelated to study drug treatments, and none were serious adverse events.
Liu et al.[57] (2012) Ramelteon	MA Patients with chronic insomnia	N=8 trials Duration varied	Primary: Subjective and polysomnographic SL, TST and latency to REM	Primary: There were significant improvements in all outcomes (subjective and polysomnographic SL, TST and latency to REM), except for the percentage of REM.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Secondary: Not reported	By subgroup analysis, subjective SL was reduced only in the patients 18 to 64 years of age. For the safety, ramelteon was not associated with higher risk ratio of any frequent adverse events comparing with control. Secondary: Not reported
Dobkin et al.[58] (2009) Ramelteon 8 mg	OL, PRO Patient population not specified	N=20 6 weeks	Primary: Patient reported LPS Secondary: Patient reported endpoints include TST, WASO, total number of nighttime awakenings, SE, and number of hot flashes/ night sweats; other secondary endpoints include sleep impairment (assessed via the SII), daytime functioning, daytime alertness, quality of life (assessed via the MENQOL), mood (assessed via the BDI), CGI-S, and CGI-I, safety	Primary: Treatment with ramelteon resulted in improvements in LPS at week six when compared to baseline (24.0±15.0 vs 46.2±19.8 minutes; P<0.001). The average improvement across all participants was 22 minutes. Secondary: Treatment with ramelteon 8 mg resulted in improvements at week six when compared to baseline in the following parameters: TST (420±38 vs 336±62 minutes; P<0.001), SE (0.91±0.06 vs 0.80±0.10; P<0.001), night time awakenings (1.86±1.53 vs 2.32±1.36; P<0.05), and hot flashes (1.52±1.32 vs 2.31±1.95; P<0.05). There were no significant improvements in WASO at any time period throughout the study when compared to baseline. Significant improvements were observed in patient reported sleep quality (P<0.001), daytime dysfunction (P<0.01), daytime alertness (P<0.001), SII scores (P<0.001), MENQOL scores (P<0.01), BDI scores (P<0.001), and anxiety (P<0.001). At the end of this trial, 55% of women were considered “responders” according to the CGI-I scale. Insomnia severity, assessed by the CGI-S, also improved over baseline (3.14 vs 4.65; P<0.001). Of the subjects treated with ramelteon in this trial, 40% reported side effects. The most frequently reported side effects included headaches, daytime fatigue/fogginess, dry mouth, lightheadedness, and dizziness. Most side effects were mild and transient.
Richardson et al.[59] (2009)	OL, PRO	N=1,213	Primary: Adverse events,	Primary: There were no noteworthy changes in vital signs, physical examinations,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ramelteon 8 or 16 mg Subjects >65 years of age received 8 mg/day, subjects 18 to 64 years of age received 16 mg/day.	Adults with primary insomnia	48 weeks	changes in vital signs, laboratory values, 12-ECG, and results of physical examination Secondary: Safety	clinical chemistry, hematology, or urinalysis values. There were also no ECG changes to suggest adverse cardiac effects. Consistent statistically significant (P≤0.05) decreases in free thyroxine and free testosterone (in older men) were detected. Duration of menses increased by approximately one day. In both groups, those older and younger than 65, subjective SL and TST improved by month one and was sustained during the one-year period. At six months and one year, CGI indices were improved. During the placebo run-out period, SL did increase but did not return to baseline. Secondary: A total of 69.8% of patients reported at least one adverse event. There was no difference in adverse event incidence between those older and younger than 65 (P value not reported). The overall incidence of adverse events was similar at six months and one year.
Gross et al.[60] (2009) Ramelteon 8 mg All patients continued to take their antidepressant; dose reductions were permitted at any time but no dose increases were permitted during the study period.	OL, PRO Patients 18 to 80 years of age with GAD and related insomnia	N=27 10 weeks	Primary: CGI-I, CGI-S, daytime sleepiness (assessed via ESS), HAMA, and patient reported sleep diaries Secondary: Safety	Primary: The addition of ramelteon 8 mg resulted in significant improvement over baseline in the following study parameters: time to fall asleep (34.67±29.26 vs 77.52±47.73 minutes; P<0.001), TST (7.52±1.22 vs 5.02±0.96 hours; P<0.001), CGI-S Insomnia (1.67±0.73 vs 4.30±0.47; P<0.001), CGI-I Insomnia (1.59±0.64 vs 3.85±0.36; P<0.001), HAMA (3.96±2.97 vs 8.26±2.94; P<0.001), ESS (5.48±3.27 vs 11.56±2.14; P<0.001), CGI-S Anxiety (1.25±0.64 vs 2.85±0.66; P<0.001), CGI-I Anxiety (1.41±0.50 vs 2.33±0.78; P<0.001). Secondary: The most common adverse events regarding ramelteon use were headache upon stopping ramelteon (7.4%), daytime tiredness (3.7%), and depression (3.7%). All side effects were reported as transient.
Roth et al.[61] (2006) Ramelteon 4 mg	DB, PC, RCT Patients 64 to 93 years of age with	N=829 5 weeks	Primary: SL at week one Secondary:	Primary: Significant reductions in SL at week one were reported with both ramelteon 4 mg (70.2 vs 78.5 minutes; P=0.008) and 8 mg (70.2 vs 78.5 minutes; P=0.008) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ramelteon 8 mg vs placebo	chronic primary insomnia		TST at weeks one, three and five; reductions in SL at weeks three and five; sleep diaries; rebound insomnia and withdrawal effects during the seven-day placebo run out	Secondary: Patients continued to report reduced SL at week three with ramelteon 8 mg (P=0.003) and at week five with ramelteon 4 and 8 mg (P=0.028 and P<0.001, respectively) compared to placebo. Patient-reported TST at weeks one and three was significantly longer compared to placebo for ramelteon 4 mg (324.6 vs 313.9 minutes; P=0.004 and 336.0 vs 324.3 minutes; P=0.007, respectively). TST for ramelteon 4 mg at five weeks and for ramelteon 8 mg at weeks one, three and five were longer than placebo but did not reach statistical significance (P values >0.05). Analyses of other sleep parameters obtained via sleep diaries (e.g., NAW, ease of falling back asleep after an awakening and sleep quality) yielded no statistically significant differences among groups at weeks one, three and five. There was no evidence of significant rebound insomnia or withdrawal effects following treatment discontinuation. Incidence of adverse events was 51.5, 54.8 and 58.0% of patients in the placebo, 4 and 8 mg ramelteon groups, respectively.
Roth et al.[62] (2005) Ramelteon 16 mg vs ramelteon 64 mg vs placebo Doses were given	DB, PC, MC, RCT Healthy adult volunteers with transient insomnia (35 to 60 years of age with total sleep duration 6.5 to 8.5 hours, a usual SL of 30 minutes or less, a habitual bedtime between 8:30 PM and midnight)	N =375	Primary: Mean LPS as measured by PSG Secondary: TST, WASO, percentage of sleep time in each sleep stage, NAW, residual effects assessed by DSST and post-sleep questionnaire, safety	Primary: Participants who had received either ramelteon dosage had significantly shorter LPS relative to placebo (both P<0.001). Secondary: Participants who had received ramelteon 16 or 64 mg had significantly longer TST compared to participants who had received placebo (P=0.007 and P=0.033, respectively). There were no significant differences between the ramelteon groups and placebo with regard to WASO, percentage of sleep time in each sleep stage, and NAW. No significant differences in DSST scores were reported among the

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>30 minutes before bedtime.</td><td></td><td></td><td></td><td>groups, but ramelteon 64 mg was associated with statistically significant declines in subjective levels of alertness (P=0.020) and ability to concentrate (P=0.043) compared to placebo.

No serious adverse events were reported.</td></tr>
<tr><td>Michelson et al.[63] (2014)

Suvorexant 30 mg nightly for elderly patients and 40 mg nightly for non-elderly patients

vs

placebo</td><td>DB, PC, RCT

Patients ≥18 years of age with primary insomnia</td><td>N=779

1 year</td><td>Primary:
Safety and tolerability

Secondary:
sTST, sTSO</td><td>Primary:
Similar proportions of patients treated with suvorexant or placebo discontinued because of adverse events. The most common adverse events that were increased for suvorexant versus placebo were somnolence, fatigue, and dry mouth. Somnolence was the adverse event with the highest incidence for discontinuations, (suvorexant 20/521 [4%] vs placebo 2/258 [1%]). Somnolence was most common in the first three months (57/527 [11%] for suvorexant vs 6/258 [2%] for placebo) and was less commonly reported by the second three months (11/425 [3%] for suvorexant vs 1/254 [<1%] for placebo). There were no clinically meaningful differences between groups in vital signs or laboratory values.

Secondary:
Over the first month, the suvorexant group showed significant improvements in sTST and sTSO compared with the placebo group. The improvements were maintained throughout the one-year phase.</td></tr>
<tr><td>Herring et al.[64] (2016)

Suvorexant 15 mg nightly for elderly patients and 20 mg nightly for non-elderly patients

vs

placebo</td><td>Pooled analysis from 2 identical DB, PC, RCTs

Non-elderly (18 to 64 years of age) and elderly (≥ 65 years of age) patients with insomnia</td><td>N=493 suvorexant; N=767 placebo

3 months</td><td>Primary:
Change from baseline in sleep diary and PSG measures of sleep maintenance (sTST, WASO) and sleep onset (sTSO, LPS)

Secondary:
Safety</td><td>Primary:
Change from baseline in sleep diary and PSG measures of sleep maintenance
<table>
<tr><th></th><th>Month 1</th><th>Month 1 P-value (vs placebo)</th><th>Month 3</th><th>Month 3 P-value (vs placebo)</th></tr>
<tr><td colspan="5">Diary measures</td></tr>
<tr><td>sTST, minutes</td><td>18.4</td><td>P<0.001</td><td>16.0</td><td>P<0.001</td></tr>
<tr><td>sTSO, minutes</td><td>-5.6</td><td>P<0.05</td><td>-5.9</td><td>P<0.001</td></tr>
<tr><td>sWASO, minutes</td><td>-6.6</td><td>P<0.01</td><td>-4.7</td><td>P<0.05</td></tr>
<tr><td colspan="5">PSG measures</td></tr>
<tr><td>LPS, minutes</td><td>-9.1</td><td>P<0.001</td><td>-4.6</td><td>NS</td></tr>
<tr><td>WASO, minutes</td><td>-25.4</td><td>P<0.001</td><td>-23.1</td><td>P<0.001</td></tr>
<tr><td>TST, minutes</td><td>34.7</td><td>P<0.001</td><td>27.5</td><td>P<0.001</td></tr>
</table>
Secondary:
Patients treated with suvorexant had generally similar incidences of any</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				adverse events or discontinuations due to adverse events compared with placebo. The proportion of patients with serious adverse events was similar among the treatment groups. The proportion of patients that had drug-related adverse events was somewhat higher with suvorexant, but none of the drug-related adverse events were serious. The most common adverse event that was increased for suvorexant versus placebo was next-day somnolence (6.7 vs 3.3%). Somnolence rarely resulted in discontinuation and was mostly mild or moderate in severity.
Scharf et al.[65] (1994) Zolpidem 10 to 15 mg vs placebo	DB, MC, PC, PG, RCT Adults with chronic insomnia	N=75 5 weeks	Primary: LPS, SE, sleep maintenance, sleep quality, effects on sleep stages, residual drug effects, safety Secondary: Not reported	Primary: Zolpidem had a significant (P<0.05) effect on LPS and SE from weeks two through five in the 10-mg group and at weeks two through six in the 15-mg group. Polysomnographic measures of sleep maintenance were not significantly different among the three treatment groups (P>0.05). Patients receiving zolpidem 15 mg reported significantly better quality of sleep than those receiving the 10 mg dose at week two and placebo at week five. Stages 1, 2, and 3 to 4 sleep were not significantly affected by either the 10- or 15-mg doses of zolpidem compared to placebo. However, there were significant (P<0.05) decreases in REM sleep at weeks three and four with zolpidem 15 mg compared to placebo. There was no evidence of residual effect with zolpidem 10 or 15 mg. There was no evidence of tolerance at either dose. The only significant treatment difference was in the percent of time in Stage 3 to 4 sleep (P<0.05 for both zolpidem doses compared to placebo). There were no significant treatment differences between the 10-mg zolpidem group and the placebo group in LPS, SE, WTDS or sleep quality during the post treatment period when zolpidem was discontinued. The 15-mg zolpidem group did not differ significantly from the placebo group on LPS or SE on the first night post treatment, but did result in a significantly greater WTDS and poorer quality of sleep (P<0.05 compared to placebo)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				during the first night post treatment. Comparison of the subsequent two nights post treatment showed no significant differences between zolpidem 15 mg and placebo on any of these variables. Overall, the incidence of treatment emergent adverse events in the zolpidem groups was similar to those in the placebo group. While none of the adverse events were severe, two patients in the 15-mg zolpidem group withdrew from the study: one patient experienced drowsiness, dizziness, and nausea; and one patient experienced visual disturbance and over sedation. The 15-mg zolpidem dosage provided no clinical advantage over the 10 mg zolpidem dosage. Secondary: Not reported
Roehrs et al.[66] (2011) Zolpidem 10 mg vs placebo	DB, PC, RCT Patients 21 to 70 years of age with primary insomnia	N=33 12 months	Primary: Number of zolpidem or placebo choices made, total number of zolpidem or placebo capsules chosen, and given a placebo or zolpidem choice on a given night, the nightly number of capsules taken Secondary: Not reported	Primary: On weekly telephone interviews, patients reported taking 73 to 89% of the single nightly capsules each month while at home. The groups did not differ in the average percentage of capsules used over the 12 months (placebo, 81% vs zolpidem, 84%). Over the three one-week laboratory self-administration assessments, the zolpidem group selected zolpidem (80.3%) more often than placebo (P<0.020). The placebo group showed no color preference, choosing the red capsule 51% of opportunities and the blue capsule 49% of opportunities. Overall, the zolpidem group self-administered more zolpidem capsules than placebo capsules (P<0.001). In the zolpidem group, the total number of capsules chosen, whether placebo or zolpidem, did not differ over months one, four, and 12. The total number of placebo capsules self-administered by the placebo group increased significantly during month four and month 12 compared to month one (P<0.02). Within the zolpidem group, the nightly number of placebo vs zolpidem capsules self-administered each month did not differ. On average, the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				zolpidem group self-administered a 9.1 mg dose nightly in month one, a 9.4 mg dose in month four, and a 9.4 mg dose in month 12. In the placebo group, the nightly number of capsules increased over time (P<0.02). The percent of patients increasing the dose did not differ between the zolpidem and placebo groups and did not change from month four to month 12. A significantly greater percent of patients receiving zolpidem compared to placebo decreased the dose they self-administered in month four and month 12 compared to month one (P<0.001). The self-administration rates did not differ when at the laboratory vs at home for patients receiving zolpidem. These rates also did not differ over the three assessments. Secondary: Not reported
Roth et al.[67] (1995) Zolpidem 5, 7.5, 10, 15, 20 mg vs placebo Statistical analyses were primarily performed between zolpidem 7.5 and 10 mg and placebo.	DB, PC, PG, RCT Healthy adult volunteers with transient insomnia	N=462 SD	Primary: SL, sleep duration, SE (TST divided by time in bed) NAW (sleep maintenance), effect on sleep stages, next day psychomotor performance and alertness (DSST, Symbol Copying Tests, Visual Analog Scales on the Morning Questionnaire) Secondary: Not reported	Primary: Compared to placebo, zolpidem 7.5 and 10 mg significantly decreased SL, increased sleep duration and efficiency, and reduced the NAW (all P<0.05). Subjective quality of sleep was also rated significantly better with both doses of zolpidem compared to placebo (both P<0.001). Increasing the dose above 10 mg did not result in a corresponding increase in hypnotic efficacy. Treatment with zolpidem had no effect on stage 1, stage 2 and stages 3 to 4 sleep. Significantly less REM sleep was reported in the zolpidem groups compared to the placebo group (both P<0.001). Zolpidem 7.5 or 10 mg had no significant effect on next day psychomotor performance and alertness. No statistically significant differences in the overall side effects were found between zolpidem doses of 7.5 mg (4.9%) or 10 mg (6.7%) and placebo (7.8%). Higher doses of zolpidem were associated with more side effects (17.6% with 15 mg [P=0.069 vs placebo] and 31.4% with 20 mg [P<0.001 vs placebo]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Randall et al.[68] (2012) Zolpidem 5 or 10 mg vs placebo	DB, PC, RCT Adults 23 to 70 years of age with chronic primary insomnia	N=91 8 months	Primary: Polysomnographic sleep parameters and morning subject assessments of sleep on two nights in months one and eight Secondary: Not reported	Primary: Relative to placebo, zolpidem significantly increased overall TST and SE, reduced SL and wake after sleep onset when assessed at months one and eight. Overall, subjective evaluations of efficacy were not shown among treatment groups. Secondary: Not reported
Krystal et al.[69] (2008) Zolpidem ER 12.5 mg vs placebo Treatments were taken 3 to 7 nights per week.	DB, MC, PC, RCT Patients 18 to 64 years of age with chronic primary insomnia	N=1,025 26 weeks	Primary: Score on the PGI, Item 1, (aid to sleep) at week 12 of the treatment period in the ITT population Secondary: Scores on CGI-I, PGI, PMQ, TST, WASO, SOL, quality of sleep, and NAW in the ITT population	Primary: At week 12, PGI, Item 1 (aid to sleep) was scored as favorable (i.e., "helped me sleep") by 89.8% of zolpidem patients vs 51.4% of placebo patients (P<0.0001). Secondary: The percentage of patients who reported a treatment benefit on the PGI (Items 1 to 4) was higher in the zolpidem ER group compared to placebo at each four-week interval during the 24-week treatment period (all P<0.0001). The percentage of patients who obtained a positive evaluation on the CGI-I scale was greater in the zolpidem ER group compared to the placebo group at all four-week intervals during the 24-week treatment period (all P<0.0001). At every time point, results on the PMQ were greater for patients in the zolpidem ER group compared to the placebo group for the TST (P<0.0001), WASO (P<0.0001), SOL (P≤0.0014), quality of sleep (P<0.0001), and NAW (month one; P=0.0515, months two to six; P<0.0001). Patients in the zolpidem ER group demonstrated improvements in their

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ability to concentrate in the morning at each month throughout the treatment period, as compared to those in the placebo group (months one to five; P<0.0001, month six; P=0.0014). Patients in the zolpidem ER group had sustained reductions in their level of sleepiness in the morning compared to placebo at each month throughout the treatment period (P<0.0001). The most common adverse events occurring at a higher frequency in the zolpidem extended-release group than in the placebo group were headache, anxiety, somnolence, dizziness, fatigue, disturbance inattention, irritability, nausea, and sinusitis.
Fava et al.[70] (2011) Zolpidem ER 12.5 mg vs placebo Patients were also receiving OL escitalopram 10 mg daily.	DB, MC, PC, PG, RCT Patients 21 to 64 years of age with major depressive disorder and associated insomnia	N=358 24 weeks Two phases were included Phase 1 was 8 weeks; responders (≥50% in 17-item $HDRS_{17}$) at week 8 continued to receive an additional 16 weeks of therapy in phase 2	Primary: Change from baseline in subjective TST Secondary: Subjective LSO, NAW, WASO, sleep quality, sleep-related next-day functioning, $HDRS_{17}$ SIS score, PGI-IT, CGI-I, CGI-S, MGH-CPFQ, Q-LES-Q, safety	Primary: Phase 1 During phase 1, treatment with zolpidem ER led to significantly greater improvements in TST when compared to treatment with placebo (P<0.0001). Phase 2 During phase 2, treatment with zolpidem ER led to improvements in TST that were significant at weeks 12 and 16 (P<0.05 for both), but not at weeks 20 and 24 (P value not reported). Secondary: Phase 1 Treatment with zolpidem ER led to significantly greater improvement in TST at each assessment. The LSM difference between the treatment groups in the change from baseline TST ranged from 37.9 to 45.5 minutes (P<0.0001 for all comparisons). The group receiving zolpidem ER had a TST of approximately seven hours at week eight, compared to approximately five hours at baseline (P<0.0001 vs placebo for improvement over baseline). Treatment with zolpidem ER led to significantly greater improvements in WASO, LSO, NAW, and sleep quality when compared to treatment with placebo (P<0.001 for all comparisons at all time points). Total improvement in insomnia-only $HDRS_{17}$ was also significantly greater in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the group receiving zolpidem ER compared to those receiving placebo (P<0.001 for all time points). Treatment with zolpidem ER also produced favorable results on all domains of the SIS, except mental fatigue, when compared to treatment with placebo at week eight (P<0.05). There were no significant differences at week eight between the two groups on the improvement in functioning and quality of life on the Q-LES-Q; however, at week eight, there were greater improvements seen in the MGH-CPFQ total score, wakefulness/alertness, energy, memory/recall, and mental acuity in those patients receiving zolpidem ER compared to those receiving placebo (P<0.05). There were no significant improvements found with zolpidem ER compared to placebo on motivation/enthusiasm, attention focus/sustain, or ability to find words, at week eight. Treatment with zolpidem ER was also associated with greater improvements than placebo in some aspects of sleep-related next-day functioning, including morning energy, sleep impact on daily activities, and morning concentration ability. Decreases seen in the $HDRS_{17}$ scores at week eight were comparable between the two treatment groups; at the end of phase 1 58.4 and 63.7% of patients in the placebo and zolpidem ER groups, respectively, met the criteria for depression treatment response. PGI-IT scores were superior in the group receiving zolpidem ER compared to those in the placebo group (P<0.001) and both CGI-S and CGI-I scores were comparable between the groups throughout phase 1. Phase 2 During phase 2, treatment with zolpidem ER continued to show significantly greater improvement at each visit in the NAW and sleep quality, when compared to treatment with placebo (P value not reported). For WASO, treatment with zolpidem ER resulted in significant improvements over treatment with placebo at weeks 16 and 20 and there were no significant differences between the treatment groups in LSO during phase 2 (P value not reported). The $HDRS_{17}$ total score of insomnia-only items demonstrated significantly greater improvement in the zolpidem ER group throughout phase 2 (P<0.05 for all time points).

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				Treatment with zolpidem ER was associated with significant differences on all of the SIS domain scores at week 24, except mental fatigue (P<0.05). There were no differences between the groups in any of the MGH-CPFQ subscales at week 24 (P-value not reported). Treatment with zolpidem ER resulted in improvements over placebo on the physical health/activities and medication satisfaction subscales of Q-LES-Q (P<0.05); however, treatment with placebo resulted in improvements over zolpidem ER on the school/course work subscale (P<0.05). Both groups experienced improvements in depression treatment remission and depression symptoms; however, these improvements were not significantly different between groups (P value not reported). PGI-IT scores indicated insomnia treatment was rated higher with zolpidem ER compared to placebo (P<0.001). Ratings of severity and mental illness by clinicians were comparable between the two groups throughout phase 2. A greater percentage of patients treated with zolpidem ER experienced at least one adverse event during phase 1 when compared to patients treated with placebo (72.9 vs 66.3%; P value not reported). The most common adverse events that occurred more frequently in the group receiving zolpidem ER, compared to the placebo group, include nausea, somnolence, dry mouth, dizziness, fatigue, upper respiratory tract infection, and decreased libido. During phase 2, 57.3% of zolpidem ER-treated patients and 60% of placebo-treated patients experienced an adverse event (P value not reported). The most frequently reported events among both treatment groups include headache, diarrhea, and nasopharyngitis.
Fava et al.[71] (2009) Zolpidem ER 12.5 mg	DB, MC, PC, PG, RCT Patients 21 to 64 years of age with	N=383 8 weeks	Primary: Change from baseline to week eight in subjective TST	Primary: At week eight, the mean TST increased from baseline by 106 minutes in the group receiving zolpidem ER and by 68.2 minutes in the placebo group (LSM in the change from baseline between groups 39.4 minutes, 90% CI, 24.81 to 53.99; P<0.0001).

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vs placebo All patients received OL escitalopram 10 mg/day.	insomnia and comorbid GAD		Secondary: Subjective SOL, NAW, WASO, sleep quality, HAMA, BAI, SIS, MGH-CPFQ, SDS, safety	Secondary: From week one through week eight, mean TST was significantly greater in the group receiving zolpidem ER when compared to those receiving placebo (P<0.0001). Significant improvements in SOL, WASO, NAW, and quality of sleep were observed throughout the treatment period with zolpidem ER vs placebo based on the difference in LSM change from baseline (P<0.0001 for all comparisons). Significant improvements were also seen with MSQ measures of sleep-related next-day symptoms, including morning energy, morning concentration, and impact of sleep on daily activities (P<0.0001 for all comparisons). The change from baseline in PGI-IT for the zolpidem ER-treated group was significantly greater when compared to the placebo-treated group (P<0.0001 for all comparisons). At week two, there was a significant difference in favor of treatment with zolpidem ER on all seven items of the SIS (P<0.0001 for six comparisons; P<0.01 for one comparison). This improvement was sustained to week eight on four of the seven items: daily activities (P=0.107), emotional impact (P<0.0001), energy/fatigue (P<0.001), and satisfaction with sleep (P<0.0001). Between group differences in the total MGH-CPFQ score were significant at week four but not at week eight (P=0.0586). There were statistically significant differences between groups at one or both of the time points for three of seven items. There was statistically significantly greater improvement in the zolpidem ER group on three items (motivation, wakefulness/alertness, and energy) at week four (P<0.05) and on two items (wakefulness/alertness and energy) at week eight (P<0.01). The mean HAMA total scores decreased for both groups throughout the study. At week eight, HAMA total scores for both the group receiving zolpidem ER and the group receiving placebo showed comparable reductions (-13.3 vs -12.5, respectively; P=0.4095). Rates of treatment response in the group receiving zolpidem ER and the group receiving placebo were similar at week eight (63.4 vs 64.2%, respectively; P=0.8564).

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				Both treatment groups demonstrated at least a 40% reduction in the BAI at week one and continued to improve throughout the study. By week six, there was a difference in favor of the placebo group that as also present at week eight. There were no significant differences in Q-LES-Q between groups at week eight and there were no significant differences between groups in SDS scores at any time point measured. Treatment-emergent adverse events that occurred in at least 10% of patients and either group but with a higher incidence in the group receiving zolpidem ER included dizziness, nausea, and fatigue. Six patients receiving zolpidem ER experienced seven events of non-global amnesia between two and 59 days of taking the study medication. One patient in each group experienced one serious adverse event. Laboratory values, vital signs, and physical examination findings revealed no meaningful changes or clinically relevant differences between groups.
Erman et al.[72] (2008) zolpidem ER 12.5 mg vs placebo Zolpidem ER or placebo was to be taken nightly or at least 3 times per week.	DB, PC, RCT (subset analysis) Adults under 65 years of age with chronic insomnia	N=1,012 24 weeks	Primary: Change from baseline to week 12 in the Time Management and Output scales of the WLQ Secondary: Change from baseline to week four and to week 24 in the Time Management and Output scales of the WLQ, or premature discontinuation	Primary: At week 12, treatment with zolpidem ER 12.5 resulted in a 4.86 point reduction in the Output Scale (95% CI, -8.37 to -1.36; P=0.0066) and a 7.29 point reduction in the Time Management Scale (95% CI, -10.77 to -3.81; P<0.0001) vs placebo. Secondary: At week four, scores for the Output Scale and the Time Management Scale were significantly lower than at baseline (P value not reported). The decrease was significantly greater with zolpidem ER than for placebo for both the Output Scale (-9.59 vs -2.16; P<0.0001) and the Time Management Scale (-12.22 vs -3.85; P<0.0001).
Roth et al.[73] (2013)	DB, MC, PC, PG, RCT	N=295	Primary: LSO after MOTN,	Primary: Zolpidem SL tablets significantly (P<0.0001) decreased LSO over four

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Zolpidem SL tablets 3.5 mg vs placebo	Adults with primary insomnia and difficulty returning to sleep after MOTN	28 nights	adverse events Secondary: Not reported	weeks (baseline, 68.1 minutes; zolpidem SL tablets, 38.2 minutes) compared to placebo (baseline, 69.4 minutes; placebo, 56.4 minutes). Ratings of morning sleepiness/alertness significantly (P=0.0041) favored the zolpidem SL tablets group on nights medication was taken but not on other nights. Participants in the zolpidem SL tablets group took the study drug on 62% of nights during the four weeks; members of the placebo group took study medication on 64% of nights. Adverse events were generally mild and at the same rate (19.3% of participants) in both groups. There were no treatment-related serious adverse events, and one adverse event-related study discontinuation from the placebo group. Dosing/week did not increase across the study. Secondary: Not reported
Roth et al.[74] (2008) Zolpidem 1.75 or 3.5 mg SL vs placebo Subjects were awakened 4 hours after lights out, dosed with zolpidem SL or placebo, kept awake for 30 minutes, and then returned to bed for 30 minutes.	DB, PC, XO Adults with insomnia characterized by difficulty returning to sleep following MOTN awakenings	N=82 3 2-night treatment periods Each treatment period consisted of 2 consecutive nights of dosing separated by a washout of 5 to 12 days.	Primary: LPS following MOTN comparing zolpidem SL 3.5 mg to placebo Secondary: TST, SE, sleep quality, subjective SOL, subjective TST, and mean LPS for zolpidem SL 1.75 compared to placebo (all assessed after MOTN); according to the statistical analysis plan, if any test of a secondary endpoint did not attain	Primary: Treatment with zolpidem SL 3.5 mg resulted in a significant improvement in LPS after MOTN compared to treatment with placebo (9.69 vs 28.12 minutes; P<0.001 vs placebo, P<0.001 vs zolpidem SL 1.75 mg). Secondary: Treatment with zolpidem SL 1.75 mg resulted in a significant improvement in LPS after MOTN compared to treatment with placebo (16.89 vs 28.12 minutes; P<0.001). Treatment with zolpidem SL 1.75 mg resulted in improvements in the following parameters: TST after MOTN (197.80 vs 183.12 minutes; P<0.001), subjective SOL after MOTN (28.58 vs 40.43 minutes; P<0.001), and subjective TST after MOTN (162.36 vs 148.61 minutes; P<0.011). Treatment with zolpidem SL 3.5 mg resulted in improvements in the following parameters: TST after MOTN (208.99 vs 183.12 minutes; P<0.001 vs placebo, P=0.005 vs zolpidem SL 1.75 mg), subjective SOL after MOTN (25.23 vs 40.43 minutes; P<0.001), and subjective TST after MOTN (172.51 vs 148.61 minutes; P<0.011). The endpoints of WASO after MOTN and NAW after MOTN failed to reach significance for either dose of zolpidem SL compared to placebo. Treatment with zolpidem SL 3.5 mg resulted in the greater improvement

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			statistical significance, then inferential analyses of secondary endpoints would cease and no further inferential assessment of remaining secondary endpoints would be made, safety	in sleep quality compared to treatment with placebo (P<0.001) and compared to treatment with zolpidem SL 1.75 mg (P=0.018). Sleep quality ratings in the group receiving zolpidem SL 1.75 mg were not significantly different than the group receiving placebo. No serious adverse events occurred and no subject discontinued the study due to an adverse event. Out of the 82 included subjects, 14 reported an adverse event. All adverse events were mild in severity and transient.
Staner et al.[75] (2010) Zolpidem 10 mg SL tablet vs zolpidem 10 mg tablet	DB, MC, RCT, XO Patients 18 to 65 years of age with primary insomnia	N=70 SD	Primary: LPS, SOL, time spent in sleep stage 1 Secondary: TST, WASO, SE index, total time spent awake, time spent in stage 2, time spent in slow wave sleep; time spent in REM sleep; REM SL, LSEQ, DSST, CFF Test	Primary: Zolpidem SL shortened the LPS by about 34% or 10.3 minutes (P=0.001), SOL with about 8.6 minutes (P<0.01) and time spent in sleep stage 1with about 7.4 minutes (P<0.01) compared to zolpidem. Secondary: There were no significant differences on in TST and WASO among the treatment groups. The TST was 432 minutes for zolpidem SL and 425 minutes for zolpidem. WASO was 31 and 30 minutes for zolpidem SL and zolpidem, respectively. There was a significant difference in SE index (P<0.05) and total time spent awake (P<0.05), favoring zolpidem SL. No differences were found between the treatments for the sleep architecture parameters time spent in sleep stage 1, slow wave sleep, REM and REM SL. The difference found for time spent in stage 2 reached statistical significance (P<0.05), favoring zolpidem SL. There were no significant differences in LSEQ scores among the treatment groups. There were no significant differences in the way patients rated their subjective feelings of alertness, contentedness and calmness on the visual analog scale. There were no significant differences in DSST between the two treatments. CFF Test results indicated that, during the descending

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				runs, patients had a lower flicker fusion threshold after zolpidem SL than after zolpidem (P<0.05). There were no between-treatment differences for the ascending runs. Both routes of administration were well tolerated with a similar overall incidence of adverse events. The most common adverse events with zolpidem SL were somnolence and dysgeusia. Nausea, dysgeusia, somnolence and dizziness were the most common adverse events with zolpidem.
Valente et al.[76] (2013) Zolpidem 5 and 10 mg SL vs zolpidem 10 mg oral	DB, DD, OL, RCT Healthy volunteers	N=58 Duration not specified	Primary: PSG and post-sleep questionnaires Secondary: Not reported	Primary: A significant main treatment effect was evident considering the SOL and persistent SL. An earlier sleep onset was induced by SL zolpidem 10 mg (SOL; P<0.004 and persistent SL; P<0.006) and SL zolpidem 5 mg (SOL; P<0.025 and persistent SL; P<0.046) compared to oral zolpidem 10 mg. Subjects that received SL zolpidem 10 mg reported an earlier sleep onset (latency to sleep and latency until persistent sleep) when compared to subjects from other groups (P<0.005). Secondary: Not reported
Staner et al.[77] (2009) Zolpidem 5 mg SL tablet vs zolpidem 10 mg SL tablet vs zolpidem 10 mg tablet	OL, RCT, XO Healthy volunteers in a post-nap model of insomnia	N=21 SD	Primary: LPS, SOL, latency to stage 1, TST, SE, awakening after sleep onset, REM SL, stage 4 duration Secondary: Not reported	Primary: For zolpidem 10 mg SL tablets, LPS was significantly decreased by 6.11 minutes as compared to zolpidem 10 mg tablets (P<0.05). Zolpidem 10 mg SL tablets decreased SOL by 5.81 minutes as compared to zolpidem 10 mg tablets (P<0.05). Zolpidem 10 mg SL tablets decreased latency to stage 1 by 6.17 minutes as compared to zolpidem 10 mg tablets (P<0.05). Similar differences were demonstrated for sleep initiation parameters between zolpidem 5 and 10 mg SL tablets (7.28 minute difference for LPS, 6.69 minute difference for SOL and 6.06 minute difference for latency to stage 1; all P<0.05). There were no significant differences in the three sleep initiation parameters between zolpidem 5 and 10 mg SL tablets.

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				There were no significant differences between the three treatments for sleep maintenance parameters, including TST, SE or awakening after sleep onset. There were no differences in sleep maintenance between zolpidem 5 and 10 mg SL tablets. Significant treatment effects were evidenced for REM SL and stage 4 duration. Both REM SL and stage 4 duration were similar with zolpidem 5 and 10 mg SL tablets. Both parameters were significantly shorter in patients receiving zolpidem 5 mg SL tablets compared to zolpidem 10 mg tablets (REM SL, -19.22 minutes; P<0.01, stage 4 duration, -11.89 minutes; P<0.01). There were no differences in sleep architecture between zolpidem 5 and 10 mg SL tablets. No differences were detected in subjective sleep parameters as indicated by a lack of significant treatment effect on any of the LSEQ variables. Next-day residual effects were comparable between treatments. Vigilance, psychomotor performances, attention and concentration were comparable between treatments. The most frequent adverse events were somnolence, headache and fatigue. All were of moderate or mild intensity and resolved spontaneously. Secondary: Not reported
Castro et al.[78] (2020) Zolpidem 5 mg SL tablet vs zolpidem 10 mg tablet Treatments administered at	DD, RCT Adults 20 to 64 years of age with insomnia who reported nocturnal awakenings predominantly before 3:00 a.m. and who had not used psychoactive drugs in the 30 preceding days	N=67 3 months	Primary: Clinical improvement Secondary: Adverse events	Primary: There was clinical improvement in 37 (55%) participants after completing the protocol: 23 (68%) in the sublingual group and 14 (42%) in the oral group (P=0.05). Most of these participants (n=23) improved after week six. Additionally, 11 (16%) participants presented early improvement followed by symptom recurrence, and there was no clinical improvement in 19 (28%) participants. Both treatments decreased middle-of-the-night awakenings by an average of -3.1±2.3 days/week and increased total sleep time by 1.5 hours. Changes in sleep quality and insomnia severity scores were also favorable and comparable between groups: variation depended on continuation of treatment. Regarding PSG findings, sleep latency decreased more in the

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bedtime, and "as needed" following middle-of-the-night awakenings				sublingual group than the oral group (-14±42 vs 10±29 min; P=0.03). Secondary: The investigators registered 152 adverse events, 58 (38%) unrelated to the study medication, 69 (45%) possibly related, and 25 (16%) probably/certainly related. Headache, sleepiness, and dizziness were the most likely events to be treatment related. The proportion of patients with adverse events did not differ between groups, but the number of treatment-related adverse events leading to discontinuation was higher in the oral group than the sublingual group (29%, n=24 vs 13%, n=9; two-sided P=0.02).
Beaulieu-Bonneau et al.[79] (2017) Initial six-week acute treatment with CBT, delivered alone (CBT; N=80) or combined with zolpidem 10 mg nightly (COMB; N=80) This was followed by a six-month extended treatment during which those receiving CBT initially were further randomized to extended monthly CBT sessions (CBT–CBT) or no additional	RCT Adults ≥30 years of age with chronic insomnia	N=160 24 months	Primary: ISI, sleep diary measures (SOL, WASO, TST, and SE) at 12 and 24 months Secondary: Not reported	Primary: For ISI total scores, there was a significant treatment condition effect at the 6-month follow-up (P<0.001), with post hoc tests revealing significantly lower ISI scores in the COMB-taper group than in the other groups (from 8.7 to 9.0). There were no significant between-group differences at the 12-month follow-up (P=0.17), and the simple main effect failed to reach significance at 24-month follow-up (P=0.09). There was no significant group effect for any of the four sleep diary variables (P>0.18) at 12-months. At the 24-month follow-up, a significant treatment effect was found for WASO and SE, with post hoc tests revealing a similar pattern as the one observed at the 6-month follow-up, i.e., a significantly shorter WASO and a higher SE in the COMB-taper condition compared to the other three conditions (WASO: 46.2 vs. 59.7 to 71.7 min, SE: 86.9 vs. 81.2 to 83.7%). The treatment group effect was not significant for SOL or TST at the 24-month follow-up. Secondary: Not reported

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treatment (CBT-no tx), and those receiving combined treatment initially were randomized to extended monthly CBT while zolpidem medication was tapered (COMB-taper) or extended CBT combined with medication as needed (COMB-prn; 10 pills per month)				
Elie et al.[80] (1999) Zaleplon 5 to 20 mg or zolpidem 10 mg vs placebo	DB, MC, PC, RCT Adults with primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders	N=615 4 weeks	Primary: Patient's assessment of SL Secondary: Patient's assessment of sleep duration, sleep quality, NAW, rebound insomnia, withdrawal effects, safety	Primary: Median SL was significantly lower with zaleplon 10 and 20 mg than with placebo during all four weeks of treatment, and with zaleplon 5 mg and zolpidem 10 mg for the first three weeks. Secondary: Zaleplon 20 mg significantly ($P<0.05$) increased sleep duration compared to placebo in all but week three of the study, while zolpidem 10 mg significantly ($P<0.05$) increased sleep duration at all time points. Mean scores for sleep quality were significantly ($P<0.05$) better than with placebo during week one with zaleplon 10 mg and 20 mg, and for all weeks with zolpidem 10 mg. No significant differences were observed in NAW between the placebo and active treatment groups. The number of patients treated with zaleplon showing rebound insomnia was not significantly different from placebo on the first night after discontinuation of four weeks of treatment. Significant differences in SL

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				(P<0.05) and NAW (P<0.01) were noted in patients treated with zolpidem 10 mg. On the second night after discontinuation of treatment, there were significantly more patients (P<0.05) showing rebound insomnia for the NAW with zaleplon 10 and 20 mg than with placebo, and on the third night there were significantly fewer patients (P<0.05) showing rebound for the NAW with zaleplon 20 mg. There was no evidence of withdrawal symptoms after discontinuation of four weeks of zaleplon treatment. Significantly more patients who had received zolpidem than placebo reported withdrawal effects on the first night after treatment was discontinued; however, there was no statistically significant difference on the second or third night between the two groups. The frequency of adverse events in the active treatment groups did not differ significantly from that in the placebo group. The study did not report any direct comparisons between the zaleplon.
Huedo et al.[81] (2012) Eszopiclone, zaleplon, or zolpidem vs placebo	MA DB, PG, PC, RCTs of eszopiclone, zaleplon, or zolpidem	N=4,378 Duration varied	Primary: Polysomnographic and subjective SL Secondary: Waking after sleep onset, NAW, TST, SE, and subjective sleep quality	Primary: Significant improvements (reductions) in primary outcomes were documented: polysomnographic SL (weighted standardized mean difference; 95% CI, -0.57 to -0.16) and subjective SL (-0.33, -0.62 to -0.04) compared to placebo. Analyses of weighted mean raw differences showed that the active agents decreased polysomnographic SL by 22 minutes (-33 to -11 minutes) compared to placebo. Secondary: No significant results were identified in the secondary outcomes.
Uchimura et al.[82] (2012) Eszopiclone 1, 2, and 3 mg vs	DB, PC, RCT, XO Japanese patients with primary insomnia	N=72 10 nights	Primary: Sleep measures from PSG and subjective patient reports Secondary: Not reported	Primary: All active treatments produced significant improvement in objective and subjective SL compared to placebo (P<0.05 for all comparisons); linear dose-response relationships were observed for eszopiclone. PSG-determined WASO, SE, and NAW, and patient-reported measures of WASO, NAW, sleep quality, sleep depth, and daytime functioning significantly improved following treatment with eszopiclone 2 mg and 3

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zolpidem 10 mg vs placebo				mg and zolpidem 10 mg vs placebo (P<0.05). Eszopiclone at all doses increased TST and stage 2 sleep time (P<0.001 for both comparisons), but did not alter REM or slow-wave sleep. Eszopiclone was generally well tolerated; the most frequently reported adverse event was mild dysgeusia. Secondary: Not reported
Pinto et al.[83] (2016) Eszopiclone 3 mg vs zopiclone 7.5 mg	DB, DD, NI, RCT Patients 20 to 64 years of age	N=199 4 weeks	Primary: ISI after four weeks of treatment Secondary: PSG measures including TST, SE, and SL	Primary: No significant differences were observed between groups regarding ISI values (P=0.588). The primary efficacy analysis demonstrated the non-inferiority of eszopiclone over zopiclone. Secondary: At the end of the study, a significant difference between the zopiclone and eszopiclone groups regarding TST was found (P=0.039), with a longer duration observed in the latter. A difference between the groups (P=0.018) was also observed for SE, indicating greater values in the eszopiclone group (mean sleep efficiency of 90% for eszopiclone vs 86% for zopiclone). However, there was no difference between the two groups regarding SL (P=0.151) and time awake (P=0.097).
Erman et al.[84] (2008) Eszopiclone 1 mg for 2 nights vs eszopiclone 2 mg for 2 nights vs eszopiclone 2.5 mg for 2 nights	MC, RCT, XO Patients 21 to 64 years of age with primary insomnia; with a 3 to 7 day washout between XO treatments	N=65 2 nights for each treatment	Primary: LPS Secondary: SE, WASO, WTDS, NAW, and patient-reported variables	Primary: All active treatments reduced median LPS by 42 to 55% compared to placebo (P<0.05). The median LPS was 13.1 minutes for eszopiclone 3 mg and zolpidem 10 mg. The median LPS was 29.0, 16.8, 15.5, and 13.8 minutes for the placebo, eszopiclone 1, 2, and 2.5 mg dose groups, respectively. The two highest doses of eszopiclone (2.5 and 3 mg) and zolpidem demonstrated significantly lower LPS when compared to eszopiclone 1 mg (P<0.05). Secondary: Significant differences were found between all active treatments in SE compared to placebo (P<0.05). Eszopiclone 2, 2.5, and 3 mg, and zolpidem 10 mg demonstrated significantly higher SE when compared to eszopiclone 1 mg (P<0.05).

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vs eszopiclone 3 mg for 2 nights vs zolpidem 10 mg for 2 nights vs placebo for 2 nights There was a 3 to 7 day washout between XO treatments				Treatment with eszopiclone 3 mg resulted in significant differences compared to treatment with placebo for WASO, WTDS, and NAW. Eszopiclone 2.5 mg demonstrated significant differences compared to placebo for WASO and WTDS. Neither of the lower doses of eszopiclone nor zolpidem 10 mg was different from placebo for WASO or WTDS. Comparisons of eszopiclone 3 mg and zolpidem 10 mg were not significantly different for WASO (P=0.12), for WTDS (P=0.07), or for NAW (P=0.10). Treatment with eszopiclone 2 and 3 mg and zolpidem 10 mg showed improvements in patient-reported measures of sleep relative to placebo. Both doses of eszopiclone and zolpidem 10 mg significantly improved sSL, sTST, quality of sleep, and depth of sleep relative to placebo (P<0.05). Eszopiclone 2 and 3 mg and zolpidem 10 mg were significantly different from placebo for subject reported NAW and sWASO (P<0.05). Morning sleepiness was significantly less with eszopiclone 3 mg compared to placebo (P<0.05). Evening ratings of daytime alertness were significantly increased with eszopiclone 2 mg and with zolpidem 10 mg compared to placebo (P<0.05), and daytime ability to function was significantly improved for eszopiclone 2 and 3 mg and zolpidem 10 mg compared to placebo (P<0.05). The most common adverse events were headache, unpleasant taste, somnolence, dizziness, and nausea. The overall rate of central nervous system adverse events was 7.9% for placebo, 6.2 to 12.5% for the eszopiclone groups, and 23.4% for zolpidem 10 mg.
Zammit et al.[85] (2009) Ramelteon 8 mg vs zolpidem 10 mg vs	DB, MC, PC, XO Adults over the age of 65 with self-reported chronic insomnia	N=33 Each study drug was taken for one night each with a 4 to 10 day washout period between	Primary: SOT composite score Secondary: Equilibrium scores on the SOT, SOT ratios, SQTT scores, and memory tests,	Primary: There were no differences between placebo and ramelteon on the SOT (P=0.837). Secondary: There were no significant differences between placebo and ramelteon on turn time (P=0.776) or turn sway (P=0.982). Treatment with zolpidem, the positive control, did result in significant impairments on the SOT, turn time, and turn sway (P<0.001 for all). Immediate and delayed memory recall were not significantly different with ramelteon (P=0.683 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Subjects were administered the study drug 30 minutes prior to bedtime and were awakened 2 hours after dosing to evaluate balance.		treatments.	safety	P=0.650, respectively); however, immediate recall declined significantly with zolpidem (P=0.002). Adverse events were infrequent and none were serious. The same proportion of subjects in the ramelteon and placebo groups reported adverse events (21.2%) compared to 39.4% of subjects in the zolpidem group. Adverse events that occurred in at least two subjects in any group include dizziness, headache, nausea, and somnolence.
Huang et al.[86] (2011) Zaleplon 10 mg vs zolpidem 10 mg	AC, DB, RCT Patients 20 to 65 years of age with primary insomnia	N=48 2 weeks	Primary: Change in subjective SL from baseline to week two Secondary: Sleep duration, NAW, sleep quality and incidence of rebound insomnia	Primary: There was a significant reduction in subjective SL in the zaleplon group (reduced from 63.0 minutes to 31.6 minutes; P<0.05) and zolpidem group (reduced from 61.9 minutes to 30.0 minutes; P<0.05). There was no significant difference between the zaleplon group and zolpidem group in SL (P=0.084). Secondary: There was no significant difference in sleep duration, NAW, or sleep quality among the groups. None of the patients experienced rebound insomnia. The most frequently reported adverse effects were headache, dizziness, anxiety and urinary tract infection. There was no significant difference in the frequency of each adverse effect between the zaleplon and zolpidem groups.
Dunbar et al.[87] (2004) Zaleplon 5 to 20 mg vs zolpidem 5 to 10 mg	MA Patients 16 to 85 years of age with insomnia	N=1,539 (6 trials)	Primary: SOL, TST, quality of sleep, adverse events, rebound insomnia Secondary: Not reported	Primary: Of the two studies that directly compared SOL, one study reported a significantly shorter SL with zaleplon (P<0.001), whereas the other study reported results in favor of zolpidem (P=0.03). Of the two studies that directly compared TST, one study reported that sleep duration was significantly less in the zaleplon group (290.7 vs 308.6 minutes for zolpidem; P=0.05) but another study found no difference (eight hours for zaleplon vs 8.3 hours on zolpidem).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
		4 weeks		Patients on zaleplon were less likely to experience an improvement in sleep quality than those on zolpidem (OR, 0.66; 95% CI, 0.51 to 0.87). There was no statistically significant difference in the frequency of treatment-emergent adverse events (OR, 0.86; 95% CI, 0.62 to 1.20). One study reported that patients taking zaleplon were less likely to suffer withdrawal symptoms on the first night of the placebo run-out phase than those on zolpidem (1.5 and 7.1% respectively; P=0.01). Combined results from two trials noted that patients receiving zaleplon were less likely to experience rebound insomnia compared to those on zolpidem (SL OR, 0.27; 95% CI, 0.17 to 0.44, sleep duration OR, 0.25; 95% CI, 0.15 to 0.41, and NAW OR, 0.34; 95% CI, 0.18 to 0.61). In a XO study, 62.3% of patients favored zolpidem compared to 37.7% of patients who favored zaleplon (P=0.08). Secondary: Not reported
Zammit et al.[88] (2006) Zaleplon 10 mg for 2 nights vs zolpidem 10 mg for 2 nights vs placebo for	DB, PC, RCT, XO Patients 18 to 65 years of age with primary sleep-maintenance insomnia	N=37	Primary: LPS and TST, daytime SL Secondary: Not reported	Primary: LPS after the administration of zaleplon 10 mg, zolpidem 10 mg, and placebo was 14.9, 11.7, and 42.2 minutes, respectively (overall P<0.001), which made the LPS with active agents shorter by approximately 27 and 31 minutes (P<0.001 for both comparisons). TST was significantly longer with zaleplon 10 mg and zolpidem 10 mg than placebo by approximately 22 and 30 minutes, respectively (overall P<0.001). Daytime SL was not significantly different between the zaleplon 10 mg and placebo groups (P>0.136); however, it was shorter with zolpidem 10 mg compared to placebo (overall P<0.001) when tested at four (P<0.001), five (P<0.001), and seven (P<0.05) hours, respectively, after dose administration. There was no significant difference between the zaleplon 10 mg and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Each treatment period was separated by a 5- or 12-day washout period.				placebo in patients' subjective level of alertness or ability to concentrate. Patients reported significantly less alertness after the SLT performed at four hours after dosing with zolpidem 10 mg compared to placebo (overall P=0.005). Daytime subjective reports of ability to concentrate following zolpidem 10 mg were significantly worse than following placebo when tested after the SLT at four, five, and six hours after treatment (overall P<0.05). Secondary: Not reported
Danjou et al.[89] (1999) Zaleplon 10 mg vs zolpidem 10 mg vs placebo	DB, XO Healthy volunteers, mean age 29.5 years	N=36 13 days	Primary: Subjective and objective measurements of residual effects when study drug was given five, four, three, or two hours before morning awakening, tests included DSST, CFF threshold, CRT, Memory Test, Sternberg Memory Scanning Task, LARS, LSEQ, adverse events Secondary: Not reported	Primary: No residual effects were demonstrated after zaleplon 10 mg, when administered as little as two hours before waking, on either subjective or objective assessments. Zolpidem 10 mg showed significant residual effects on DSST and memory after administration up to five hours before waking and CRT, CFF threshold and Sternberg Memory Scanning Task after administration up to four hours before waking. Residual effects of zolpidem were apparent in all objective and subjective measurements when the drug was administered later in the night. There were no serious adverse experiences during the study; all adverse events were mild-to-moderate. Overall, the number of subjects who reported any adverse experience after administration of study drug was similar for zaleplon and placebo (11 and 33% regardless of the time of drug administration) but was significantly higher following zolpidem (56 to 72%) when zolpidem was administered two, three, four, and five hours before awakening (P values not reported). Secondary: Not reported
Verster et al.[90] (2002) Zaleplon 10 mg	DB, XO Healthy volunteers with mean age 24.0	N=30 SD with at least a 5-day	Primary: Driving ability (standard deviation of the lateral	Primary: Zaleplon 10 and 20 mg did not significantly impair driving ability four hours after middle-of-the-night administration (significant difference defined as P<0.0125).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs zaleplon 20 mg vs zolpidem 10 mg vs zolpidem 20 mg vs placebo This was a 2-part study with the first part evaluating the effect of ethanol and the second part evaluating the effects of zaleplon and zolpidem. Only the second part of the study was reported in this review.	years	washout period	position, standard deviation of speed, memory, psychomotor performance) (subjects given study medication five hours after going to bed and awakened three hours after dose, driving test performed four hours after awakened, memory and psychomotor tests performed six hours after awakened) Secondary: Not reported	Relative to placebo, after zolpidem 10 mg, standard deviation of the lateral position (amount of weaving of the car) was significantly elevated but the magnitude of the difference was small and not likely to be of clinical importance (difference, 2.87 cm; P<0.005). Standard deviation of speed (speed variability) was not significantly different for zolpidem 10 mg than placebo (P=0.256). Zolpidem 20 mg significantly increased SDLP and speed variability (both P<0.001). Memory and psychomotor test performances were unaffected after both doses of zaleplon and zolpidem 10 mg. Zolpidem 20 mg significantly impaired performance on psychomotor and memory tests. (Note: the recommended dose for zolpidem is 10 mg immediately before bedtime.) Secondary: Not reported
Piccione et al.[91] (1980) Triazolam 0.25 mg vs	DB, XO Elderly patients >60 years of age with insomnia	N=27 5 days	Primary: Efficacy (questionnaire with subjective estimates of SL, TST, NAW, overall quality of	Primary: The patients' global evaluation of effectiveness indicated that triazolam 0.25 and 0.50 mg improved sleep more than placebo (both P<0.05), while chloral hydrate 250 and 500 mg were not better than placebo. Triazolam 0.50 mg, but not 0.25 mg, was significantly better than chloral hydrate 250 mg (P<0.01) and 500 mg (P<0.05) in the global evaluation of effectiveness.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triazolam 0.50 mg vs chloral hydrate 250 mg vs chloral hydrate 500 mg vs placebo			sleep), side effects Secondary: Not reported	There was no significant difference in SL, TST and NAW between placebo and either dose of chloral hydrate. Triazolam 0.25 mg significantly decreased SL and increased TST compared to placebo (both P<0.05). Triazolam 0.50 mg significantly decreased the NAW compared to placebo (P<0.01). Patients estimated their TST to be longer following the use of triazolam 0.25 mg as compared to chloral hydrate 250 or 500 mg (both P<0.05). There were no significant differences in reported side effects between the active treatments and placebo. Secondary: Not reported
Johnson et al.[92] (2006) Triazolam 0.25, 0.5 or 0.75 mg vs ramelteon 16, 80 or 160 mg vs placebo	DB, XO Adults with a history of sedative abuse	N=14 18 days	Primary: Subject-rated measures (drug liking, street value, pharmacological classification), observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word recall) Secondary: Not reported	Primary: Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures. Compared to placebo, all doses of ramelteon showed no significant effect on any of the subjective effect measures, including those related to potential for abuse (all P>0.05). In the pharmacological classification, 79% of patients identified the highest dose of ramelteon as placebo. Compared to placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all P>0.05). Secondary: Not reported
Hindmarch et al.[93] (2006) Flurazepam 30 mg	DB, RCT, XO Healthy volunteers ≥65 years of age	N=24 SD treatment	Primary: Psychometric tests performed 8 hours after study	Primary: There were no significant differences in psychometric tests between the zolpidem modified release treatment groups and placebo (P>0.05). Psychometric performance was significantly impaired with flurazepam

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs zolpidem modified release 6.25 mg vs zolpidem modified release 12.5 mg vs placebo			medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem modified release only) Secondary: Not reported	compared to placebo for all tests with the exception of the DSST (P=0.0526). Ease of falling asleep and sleep quality were significantly improved with both doses of zolpidem modified release and with flurazepam (all P<0.05). Neither zolpidem modified release, nor flurazepam, modified perception of well-being on awakening. The frequency of adverse events was similar in all four treatment conditions. None of the adverse events was serious or led to withdrawal from the study. The plasma concentration ratio was 1.96 between the two doses of zolpidem modified release, which is consistent with dose linearity. Secondary: Not reported
Holbrook et al.[94] (2000) Benzodiazepines vs zopiclone, diphenhydramine, glutethimide, promethazine, cognitive behavioral therapy, placebo	MA Patients with insomnia	N=2,672 (45 trials) 6 weeks	Primary: SL, total sleep duration, adverse effects, dropout rates, cognitive function decline Secondary: Not reported	Primary: Using sleep records, benzodiazepines demonstrated a decrease in SL by 4.2 minutes compared to placebo (95% CI, -0.7 to 9.2). Benzodiazepines demonstrated a significant increase in sleep duration compared to placebo by 61.8 minutes (95% CI, 37.4 to 86.2). Benzodiazepines were more likely to be associated with complaints of daytime drowsiness (OR, 2.4; 95% CI, 1.8 to 3.4) and dizziness/ lightheadedness (OR, 2.6; 95% CI, 0.7 to 10.3) compared to placebo. No difference was observed in dropout rates between the two groups. Pooled results from three trials indicated there was no significant difference between benzodiazepines and zopiclone in SL, but benzodiazepine therapy may lead to a longer sleep by 23.1 minutes (95% CI, 5.6 to 40.6). There was no significant difference in adverse events among the treatment groups (OR, 1.5; 95% CI, 0.8 to 2.9).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Comparisons between benzodiazepines and antihistamines did not detect any significant differences on sleep outcomes. Triazolam was found to be more effective in reducing SL early in one trial, but efficacy decreased by the second week of treatment. Behavioral therapy efficacy was maintained throughout the nine-week follow-up. Secondary: Not reported
Buscemi et al.[95] (2007) Benzodiazepines, non-benzodiazepines, antidepressants vs placebo	MA Adults with chronic insomnia	105 trials 1 night to 6 months	Primary: SL, WASO, SE, sleep quality, TST, adverse events Secondary: Not reported	Primary: SL assessed by PSG was significantly decreased for benzodiazepines (WMD, -10.0 minutes; 95% CI, -16.6 to -3.4), non-benzodiazepines (WMD, -12.8 minutes; 95% CI, -16.9 to -8.8) and antidepressants (WMD, -7.0 minutes; 95% CI, -10.7 to -3.3). SL assessed by sleep diaries was also significantly improved for benzodiazepines (WMD, -19.6 minutes; 95% CI, -23.9 to -15.3), non-benzodiazepines (WMD, -17.0 minutes; 95% CI, -20.0 to -14.0) and antidepressants (WMD, -12.2 minutes; 95% CI, -22.3 to -2.2). MA for WASO, SE, sleep quality and TST measured by PSG and sleep diary were statistically significant and favored benzodiazepines and non-benzodiazepines vs placebo with the exception of PSG studies measuring WASO and TST, which were marginally nonsignificant. In contrast, PSG results significantly favored antidepressants vs placebo, but sleep diary results were fewer and non-significantly favored antidepressants for WASO and non-significantly favored placebo for TST. Indirect comparisons between benzodiazepines and non-benzodiazepines resulted in no significant difference in SL; however, benzodiazepines were associated with more adverse events. Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in SL or adverse events. Indirect comparisons between non-benzodiazepines and antidepressants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				resulted in a significantly greater SL assessed by PSG but not by sleep diary for non-benzodiazepines. There was no significant difference in adverse events. All drug groups had a statistically significant higher risk of harm compared to placebo, although the most commonly reported adverse events were minor. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea. Secondary: Not reported
Smith et al.[96] (2002) Benzodiazepines or benzodiazepine receptor agonists vs behavioral treatment vs placebo	MA Patients with primary insomnia for ≥1 month	N=470 (21 trials)	Primary: SL, TST, NAW, WASO, and sleep quality before and after treatment Secondary: Not reported	Primary: SL was reduced by 30% with pharmacological treatment compared to 43% with behavioral interventions. Pharmacotherapy increased TST by 12% compared to 6% with behavior therapy. Both pharmacotherapy and behavior therapy reduced NAW per night by one. WASO was reduced by 46% with pharmacotherapy and by 56% with behavior therapy. Pharmacotherapy improved sleep quality by 20% compared to 28% with behavior therapy. Overall, there were no differences in TST, NAW, WASO, and sleep quality between benzodiazepine receptor agonists and behavioral therapy. The behavioral therapy group had a greater reduction in LSO than the group that took the benzodiazepine receptor agonists (95% CI, 0.17 to 1.04). Secondary: Not reported
Nowell et al.[97] (1997)	MA	N=1,894 (22 trials)	Primary: SL, TST, NAW,	Primary: Zolpidem and benzodiazepines were significantly more effective than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Benzodiazepines or benzodiazepine receptor agonists vs placebo	Adults <65 years of age with chronic insomnia	4 to 35 days	sleep quality Secondary: Not reported	placebo with regards to SL, TST, NAW and sleep quality (P<0.001). Secondary: Not reported
Post-Operative Nausea and Vomiting				
Schaub et al.[98] (2012) Droperidol vs placebo (or no treatment)	MA RCTs testing prophylactic droperidol in adults undergoing general anaesthesia and reporting on post-operative nausea and vomiting	N=25 trails Duration varied	Primary: Prevention of nausea and vomiting; adverse events Secondary: Not reported	Primary: For the prevention of early nausea (within six hours postoperatively), the RR was 0.45 (95% CI, 0.35 to 0.58) and the number needed to treat was 7, 4, and 2 for low, medium and high baseline risk. For the prevention of early vomiting the RR was 0.65 (95% CI, 0.57 to 0.74), and the number needed to treat was 11, 6, and 4 respectively. For the prevention of late nausea (within 24 hours) the RR was 0.74 (95% CI, 0.62 to 0.87) and the number needed to treat was 15, 8, and 5 respectively. For the prevention of late vomiting the RR was 0.61 (95% CI, 0.47 to 0.80) and the number needed to treat was 10, 5, and 3 respectively. Droperidol decreased the risk of headache but increased the risk of restlessness. There were no differences in the incidences of sedation or dizziness. Two patients receiving droperidol 0.625 mg had extrapyramidal symptoms. Cardiac toxicity data were not reported. Secondary: Not reported
Atsuta et al.[99] (2017) Droperidol 1.25 mg	DB, RCT Patients 20 to 80 years of age scheduled to undergo elective	N=186 72 hours	Primary: Overall and cumulative incidence of vomiting	Primary: The overall incidence of vomiting for 72 hours post-craniotomy was significantly lower in the fosaprepitant group (12.8%) than in the droperidol group (38%; P<0.001; RR, 0.336; 95% CI, 0.186 to 0.605). The cumulative incidence of vomiting was significantly lower in the fosaprepitant group than in the droperidol group (HR, 0.30; 95% CI, 0.16

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fosaprepitant 150 mg Dexamethasone 9.9 mg was given to all patients, except those with diabetes	craniotomy		Secondary: Overall and cumulative incidence of PONV, incidence of vomiting, frequency of vomiting, nausea score, and use of rescue antiemetic use	to 0.56; P<0.001). Secondary: There was no significant difference between the groups in the overall incidence of PONV for 72 hours (44.7% for fosaprepitant vs 54.3% for droperidol; P=0.24). There were no significant differences in nausea score or antiemetic use between the two groups, although the nausea score and nausea incidence were lower in the fosaprepitant group at 6 to 24 hours.
Non-24-hour sleep-wake disorder				
Lockley et al.[100] (2015) SET and RESET Tasimelteon 20 mg one hour prior to bedtime vs placebo	DB, MC, PC, RCT Totally blind patients 18 to 75 years of age with non-24 hour sleep-wake disorder	*SET:* N=84 6 months *RESET:* N=20 20 weeks	*SET:* Primary: Proportion of entrained patients (patients having an internal circadian period of ≤24.1 hours and CI including 24.0 hours); proportion of patients who had a clinical response (entrainment at month one or month seven plus clinical improvement, measured by the Non-24 Clinical Response Scale) Secondary: Not reported	*SET:* Primary: Circadian entrainment occurred in eight (20%) of 40 patients in the tasimelteon group compared with one (3%) of 38 patients in the placebo group at month one (difference 17%; 95% CI, 3.2 to 31.6; P=0.0171). Nine (24%) of 38 patients showed a clinical response, compared with none of 34 in the placebo group (difference 24%; 95% CI, 8.4 to 39.0; P=0.0028). Secondary: Not reported *RESET:* Primary: Nine (90%) of ten patients in the tasimelteon group maintained entrainment, whereas only two (20%) of ten patients withdrawn to placebo maintained entrainment (difference 70%; 95% CI, 26.4 to 100.0; P=0.0026). Secondary: No deaths were reported in either study, and discontinuation rates due to adverse events were comparable between the tasimelteon (3 [6%] of 52 patients) and placebo (2 [4%] of 52 patients) treatment courses.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			RESET: Primary: Proportion of non-entrained patients Secondary: Safety	
Smith-Magenis Syndrome				
Polymeropoulos et al.[101] (2021) Tasimelteon 20 mg capsule one hour prior to bedtime for adults or weight-based oral suspension dosing for pediatric patients vs placebo	DB, RCT Genetically confirmed patients with Smith-Magenis syndrome, aged 3 to 39, with sleep complaints	N=26 9 weeks (DB) >3 months (OL)	Primary: Improvement of sleep quality and total sleep time on the worst 50% of nights Secondary: Actigraphy and behavioral parameters	Primary: Treatment with tasimelteon showed a difference of 0.4 increase in average sleep quality on the worst 50% of nights (tasimelteon, 2.8; placebo, 2.4; P=0.0139). Total sleep time on the worst 50% of nights resulted in a difference of 18.5 minutes increase for tasimelteon compared to placebo (tasimelteon, 419.3 minutes; placebo, 400.9 minutes; P=0.0556). Secondary: Secondary endpoints complemented and extended the conclusions from the primary endpoints showing improvement in overall sleep quality (tasimelteon, 0.6; placebo, 0.2; P=0.0155) and total sleep time as determined by diary (tasimelteon, 40.9; placebo, 19.8; P=0.0134). Further, actigraphy-based measurement of total sleep time also showed improvement (tasimelteon, 20.2; placebo, 1.9; P=0.0218). Patients treated for ≥90 days in the open-label study showed persistent efficacy.
Sedation				
Fraser et al.[102] (2013) Dexmedetomidine or propofol vs benzodiazepine	MA RCTs consisting of critically ill, mechanically ventilated adults requiring sedation regimen	N=1,235 Duration varied	Primary: Duration of intensive care unit length of stay, duration of mechanical ventilation, delirium prevalence, and/or short-term mortality	Primary: Compared to a benzodiazepine sedative strategy, a nonbenzodiazepine sedative strategy was associated with a shorter intensive care unit length of stay (difference, 1.62 days; 95% CI, 0.68 to 2.55; P=0.0007) and duration of mechanical ventilation (difference, 1.9 days; 95% CI, 1.70 to 2.09; P<0.00001) but a similar prevalence of delirium (risk ratio, 0.83; 95% CI, 0.61 to 1.11; P=0.19) and short-term mortality rate (risk ratio, 0.98; 95% CI, 0.76 to 1.27; P=0.88). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	

Drug regimen abbreviations: ER=extended release, SL=sublingual
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, ITT=intent to treat, LS=least square, LSM=least squares mean, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, SD=single dose, XO=crossover, WMD=weighted mean difference
Miscellaneous abbreviations: AHI=apnea hypopnea index, BAI=Beck Anxiety Inventory, CAPS=Clinician Administered PTSD Scale, CBT=cognitive-behavioral therapy, CES-D=Center for Epidemiologic Studies Depression Scale, CFF=Critical Flicker Fusion, CGI=Clinical Global Impression, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impressions-Severity, CPAP=Continuous positive airway pressure, CRT=Choice Reaction Time, CTT=Continuous Tracking Test, DLRF=Daily Living and Role Functioning, DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSST=Digit-Symbol Substitution Test, ECG=electrocardiogram, ESS=Epworth Sleepiness Scale, FARD=Ferreri Anxiety Rating Diagram, FOSQ=Functional Outcomes of Sleepiness Questionnaire, FSS=Fatigue Severity Scale, HAD=Hospital Anxiety and Depression, HAMA=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, $HDRS_{17}$=Hamilton Depression Rating Scale 17-item, ISI=Insomnia Severity Index, LPS=latency to persistent sleep, LSAS=Liebowitz Social Anxiety Scale, LSEQ=Leeds Sleep Evaluation Questionnaire, LSO=latency to sleep onset, MADRS=Montgomery-Åsberg Depression Rating Scale, MAOI=monoamine oxidase inhibitors, MCBI=Multidimensional Caregiver Burden Inventory, MENQOL=Menopause-Related Quality of Life, MGH-CFPQ=Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, MOTN=middle-of-the-night awakening, NAW=number of awakenings, PDQ-8=Parkinson Disease Questionnaire Short Form, PGI=Patient Global Impression, PGI-IT= Patient Global Impression of Insomnia Treatment, PMQ=Patient Morning Questionnaire, PSG=polysomnography, PSQI=Pittsburg Sleep Quality Index, PSQ-IVRS=Post-Sleep Questionnaire Interactive Voice Response System, PTSD=posttraumatic stress disorder, Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire, REM=rapid eye movement, RIMA=reversible inhibitors of monoamine oxidase-A, SDS=Sheehan Disability Scale, sSE=subjective sleep efficiency, SE=sleep efficiency, SF-36=Short Form-36, SII=Sleep Impairment Index, SIS=Sleep Impact Scale, SL=sleep latency, sSOL= subjective sleep onset latency, SOL=sleep onset latency, SOT=Sensory Organization Test, SPRINT=Short PTSD Rating Interview, SQTT=Step Quick Turn Test, SSRI=selective serotonin-reuptake inhibitor, sTSO=subjective time to sleep onset, sTST=subject reported total sleep time, sWASO=subjective wake time after sleep onset, TST=total sleep time, WASO=wake time after sleep onset, WLQ=Work Life Questionnaire, WTDS=wake time during sleep

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 13. Relative Cost of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Buspirone	tablet	N/A	N/A	$
Dexmedetomidine	injection	Precedex®*	$$$$$	$$$$$
Droperidol	injection	N/A	N/A	$
Eszopiclone	tablet	Lunesta®*	$$$$$	$
Hydroxyzine	capsule, solution, tablet	Vistaril®*	$$$$$	$
Meprobamate	tablet	N/A	N/A	$$$$$
Ramelteon	tablet	Rozerem®*	$$$	$$
Tasimelteon	capsule, suspension	Hetlioz®	$$$$$	N/A
Zaleplon	capsule	N/A	N/A	$
Zolpidem	extended-release tablet, sublingual tablet, tablet	Ambien®*, Ambien CR®*, Edluar®	$$$$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The miscellaneous anxiolytics, sedatives, and hypnotics are used primarily for the treatment of anxiety disorders and insomnia. In addition, some agents are approved for the treatment of acute alcohol withdrawal, management of procedural nausea/vomiting, treatment of Non-24-Hour Sleep-Wake Disorder (non-24), nighttime sleep disturbances in Smith-Magenis Syndrome, as well as treatment of pruritus. All of the products are available in a generic formulation, with the exception of tasimelteon.

The agents that are approved for the treatment of anxiety disorders include buspirone, hydroxyzine, and meprobamate.[2-3] The American Psychiatric Association recommends the initial use of either a serotonin-norepinephrine reuptake inhibitor (SNRI) or a selective serotonin reuptake inhibitor (SSRI) for the treatment of panic disorder due to their favorable safety and tolerability profiles.[17] Buspirone and sedating antihistamines are not effective as monotherapy for the treatment of panic disorder.[16-17] For the long-term treatment of generalized anxiety disorder, the National Institute for Health and Clinical Excellence recommends the use of an SSRI as first-line therapy.[16] Sedating antihistamines are one of several options for the short-term, immediate treatment of generalized anxiety disorder.[16] Buspirone is not recommended for the initial treatment of obsessive-compulsive disorder or posttraumatic stress disorder.[18-20] The available guidelines do not provide any recommendations regarding the use of meprobamate for the treatment of anxiety disorders.[16-20]

Eszopiclone, ramelteon, zaleplon, and zolpidem are approved for the treatment of insomnia.[2-11] The American Academy of Sleep Medicine recommends the use of a short/intermediate-acting benzodiazepine, benzodiazepine receptor agonist, or ramelteon for the initial treatment of insomnia.[21] They do not give preference to one agent over another. Symptom pattern, treatment goals, past treatment responses, patient preference, comorbid conditions, contraindications, drug interactions and adverse events should be considered when selecting a specific agent.[21,22] The Department of Veterans Affairs/Department of Defense recommends that all adult patients receive cognitive behavioral therapy for insomnia as the initial treatment for chronic insomnia disorder. If cognitive behavioral therapy alone is unsuccessful, a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, should be used to decide whether to add pharmacological therapy.[23] The frequency and severity of adverse events may be lower with benzodiazepine receptor agonists (e.g., eszopiclone, zaleplon, and zolpidem) and ramelteon than benzodiazepines due to their shorter half-lives.[21] Hypnotic treatments should be combined with behavioral and cognitive therapies.[22] Patients should be followed every few weeks during the initial treatment period to assess for effectiveness, adverse events and the need for ongoing medication. Chronic use of hypnotic medications may be necessary in those individuals with severe/refractory insomnia or for those with chronic comorbid illnesses.[22] Results from clinical trials demonstrate that these agents are effective for the treatment of insomnia. Relatively few studies were found in the medical literature directly comparing the efficacy and safety of these agents.

Tasimelteon is the first FDA-approved treatment for non-24, a chronic circadian rhythm disorder which occurs almost exclusively in persons who are completely blind.[10,12] It has also gained approval for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome in patients three to 15 years of age (oral suspension) and ≥16 years of age (capsule).[10] Smith-Magenis Syndrome is a rare genetic disorder that affects multiple organ systems, including a circadian defect which leads to severely disrupted sleep patterns.

There is insufficient evidence to support that one brand miscellaneous anxiolytic, sedative, or hypnotic agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous anxiolytic, sedative, or hypnotic agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous anxiolytic, sedative, or hypnotic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Orexin Receptor Antagonists
AHFS Class 282440
November 9, 2022

I. Overview

The key diagnostic feature of primary insomnia is difficulty initiating or maintaining sleep for at least three months, which causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.[1] Insomnia may be classified as episodic (symptoms last at least one month but less than three months), persistent (lasting three months or longer) or recurrent (two or more) episodes within the space of one year).[1] Suvorexant (Belsomra®) was Food and Drug Administration (FDA) approved in 2014 for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Suvorexant is a selective antagonist of orexin receptors (OX1R and OX2R). Orexin A and orexin B are neuropeptides that promote wakefulness. Blocking the binding of orexin to the orexin receptors is thought to suppress wakefulness.[2-4] Lemborexant (Dayvigo®) was FDA approved in 2019 for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Lemborexant is a competitive orexin receptor antagonist that binds to both OX1R and OX2R with stronger inhibition effect to OX2R.[5] Daridorexant (Quviviq®) is the third agent approved in this class.[6] These agents are Schedule IV controlled substances, producing similar effects as zolpidem in an abuse liability study.[4-6]

The orexin receptor antagonists included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. None of the products are available in a generic formulation. These agents were previously included in the miscellaneous anxiolytics, sedatives, and hypnotics AHFS class.

Table 1. Orexin Receptor Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Daridorexant	tablet	Quviviq®	none
Lemborexant	tablet	Dayvigo®	none
Suvorexant	tablet	Belsomra®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the orexin receptor antagonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Orexin Receptor Antagonists

Clinical Guideline	Recommendation(s)

American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)**[7]	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments.
	• Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible.
	• When pharmacotherapy is utilized, the choice of a specific pharmacological agent should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects.
	• For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is:
	  ○ Short-intermediate acting benzodiazepine receptor agonists or ramelteon.
	  ○ Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful.

Clinical Guideline	Recommendation(s)
	○ Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. ○ Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressant. ○ Other sedating agents. Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect. • Over-the-counter antihistamine or antihistamine/analgesic type drugs (over-the-counter "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data. • Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia. • Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments), potential for dosage escalation, and rebound insomnia. • Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication. • Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia. • Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. • Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders. • Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.
American Academy of Sleep Medicine: **Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults (2017)**[8]	<u>Recommendations for treating sleep onset insomnia</u> • Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Recommendations are listed alphabetically. • Eszopiclone is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. ○ Sleep Latency: Mean reduction was 14 minutes greater, compared to placebo (95% CI, 3 to 24 minute reduction). ○ Quality of Sleep: moderate-to-large improvement in quality of sleep, compared to placebo. • Ramelteon is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. ○ Sleep Latency: Mean reduction was nine minutes greater, compared to placebo (95% CI, 6 to 12 minute reduction). ○ Quality of Sleep: No improvement in quality of sleep, compared to placebo. • Temazepam is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. ○ Sleep Latency: Mean reduction was 37 minutes greater, compared to placebo (95% CI, 21 to 53 minute reduction). ○ Quality of Sleep: Small improvement in quality of sleep, compared to

Clinical Guideline	Recommendation(s)
	placebo. • Triazolam is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was nine minutes greater, compared to placebo (95% CI, 4 to 22 minute reduction). o Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. • Zaleplon is recommended as a treatment for sleep onset insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was 10 minutes greater, compared to placebo (95% CI, 0 to 19 minute reduction). o Quality of Sleep: No improvement in quality of sleep, compared to placebo. • Zolpidem is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Sleep Latency: Mean reduction was five to 12 minutes greater, compared to placebo (95% CI, 0 to 19 minute reduction). o Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. <u>Recommendations for treating sleep maintenance insomnia</u> • Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Recommendations are listed alphabetically. • Doxepin is recommended as a treatment for sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 26 to 32 minutes longer, compared to placebo (95% CI, 18 to 40 minute improvement). o Wake After Sleep Onset: Mean reduction was 22 to 23 minutes greater, compared to placebo (95% CI, 14 to 30 minute reduction). o Quality of Sleep: Small-to-Moderate improvement in quality of sleep, compared to placebo. • Eszopiclone is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 28 to 57 minutes longer, compared to placebo (95% CI, 18 to 76 minute improvement). o Wake After Sleep Onset: Mean reduction was 10 to 14 minutes greater, compared to placebo (95% CI, 2 to 18 minute reduction). o Quality of Sleep: moderate-to-large improvement in quality of sleep, compared to placebo. • Temazepam is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 99 minutes longer, compared to placebo (95% CI, 63 to 135 minute improvement). o Wake After Sleep Onset: Not reported. o Quality of Sleep: Small improvement in quality of sleep, compared to placebo. • Suvorexant is recommended as a treatment for sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 10 minutes longer, compared to placebo (95% CI, 2 to 19 minute improvement). o Wake After Sleep Onset: Mean reduction was 16 to 28 minutes greater, compared to placebo (95% CI, 7 to 43 minute reduction). o Quality of Sleep: Not reported. • Zolpidem is recommended as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. o Total Sleep Time: Mean improvement was 29 minutes longer, compared to

Clinical Guideline	Recommendation(s)
	placebo (95% CI, 11 to 47 minute improvement). ○ Wake After Sleep Onset: Mean reduction was 25 minutes greater, compared to placebo (95% CI, 18 to 33 minute reduction). ○ Quality of Sleep: Moderate improvement in quality of sleep, compared to placebo. Not recommended for treating insomnia • The following drugs are not recommended for the treatment of sleep onset or sleep maintenance insomnia (versus no treatment) in adults: Diphenhydramine, Melatonin, Tiagabine, Trazodone, L-tryptophan, Valerian.
Department of Veterans Affairs and Department of Defense: **The Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea (2019)**[9]	Treatment and management of chronic insomnia disorder – behavioral and psychological treatments • It is recommended that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. • Offer brief behavioral therapy for insomnia (BBT-I). • There is insufficient evidence to recommend for or against group versus individual CBT-I for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against internet-based CBT-I as an alternative to face-to-face based CBT-I for the treatment of chronic insomnia disorder. • CBT-I is suggested over pharmacotherapy as first-line treatment. • Offer CBT-I for the treatment of chronic insomnia disorder that is comorbid with another psychiatric disorder. • There is insufficient evidence to recommend for or against mindfulness meditation for the treatment of chronic insomnia disorder. • Sleep hygiene education is not suggested as a standalone treatment. Treatment and management of chronic insomnia disorder – complementary and integrative health treatments • Offer auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against acupuncture other than auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against aerobic exercise, resistive exercise, tai chi, yoga, and qigong for the treatment of chronic insomnia disorder. • Cranial electrical stimulation is not suggested. Treatment and management of chronic insomnia disorder – over-the-counter treatments • Diphenhydramine is not suggested. • Melatonin is not suggested. • Valerian and chamomile are not suggested. • Kava is not recommended. Treatment and management of chronic insomnia disorder – pharmacotherapy • In patients who are offered a short-course of pharmacotherapy for the treatment of chronic insomnia disorder, use of low-dose (i.e., 3 mg or 6 mg) doxepin or a non-benzodiazepine benzodiazepine receptor agonist is suggested. • There is insufficient evidence to recommend for or against the use of ramelteon for the treatment of chronic insomnia disorder. • There is insufficient evidence to recommend for or against the use of suvorexant for the treatment of chronic insomnia disorder. • the use of antipsychotic drugs is not suggested for the treatment of chronic

Clinical Guideline	Recommendation(s)
	insomnia disorder. • The use of benzodiazepines is not suggested for the treatment of chronic insomnia disorder. • The use of trazodone is not suggested for the treatment of chronic insomnia disorder.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the orexin receptor antagonists are noted in Table 3.

Table 3. FDA-Approved Indications for the Orexin Receptor Antagonists[4-6]

Indication	Daridorexant	Lemborexant	Suvorexant
Treatment of patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance	✔	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the orexin receptor antagonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Orexin Receptor Antagonists[3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Daridorexant	62	>99	Liver	Renal (28) Feces (57)	8
Lemborexant	Not reported	94	Liver	Renal (29.1) Feces (57.4)	17 to 19
Suvorexant	82	>99	Liver	Renal (23) Feces (66)	12

V. Drug Interactions

Major drug interactions with the orexin receptor antagonists are listed in Table 5.

Table 5. Major Drug Interactions with the Orexin Receptor Antagonists[3]

Generic Name(s)	Interaction	Mechanism
Lemborexant	Strong, moderate, and weak CYP3A inhibitors (e.g., itraconazole, clarithromycin, verapamil, etc.)	Concurrent use with a strong, moderate, or weak CYP3A inhibitor increases lemborexant AUC and Cmax which may increase the risk of lemborexant adverse reactions.
Daridorexant	Strong and moderate CYP3A inhibitors	Concomitant use with a strong or moderate CYP3A4 inhibitor increases exposure to daridorexant, which may increase the risk of adverse reactions.
Daridorexant, lemborexant	Strong and moderate CYP3A inducers (e.g., rifampin, carbamazepine, efavirenz, bosentan, modafinil, etc.)	Concurrent use with a strong or moderate CYP3A inducer decreases orexin receptor antagonist exposure, which may reduce lemborexant efficacy.
Lemborexant	CYP2B6 substrates (e.g., bupropion, methadone, etc.)	Concurrent use of lemborexant decreases the AUC of drugs that are CYP2B6 substrates, which may result in reduced efficacy for these concomitant medications.
Daridorexant, suvorexant	CNS Depressants	Concurrent use may result in increased risk of respiratory and CNS depression.
Suvorexant	CYP3A4 inhibitors	Concurrent use of suvorexant and selected CYP3A4 inhibitors may result in increased plasma concentrations of suvorexant.

VI. Adverse Drug Events

The most common adverse drug events reported with the orexin receptor antagonists are listed in Table 6. Lemborexant and suvorexant are classified as Schedule IV controlled substances by federal regulation because of their abuse potential.

Table 6. Adverse Drug Events (%) Reported with the Orexin Receptor Antagonists[2]

Adverse Events	Daridorexant	Lemborexant	Suvorexant
Central Nervous System			
Abnormal dreams	-	≤2	2
Complex sleep-related disorder	✔	<1	-
Dizziness	3	-	3
Drowsiness	<6	7 to 10	2 to 7
Fatigue	<6	7 to 10	-
Hallucinations	✔	-	✔
Headache	6 to 7	5 to 6	7
Hypnogenic hallucinations	-	<1	✔
Nightmares	-	≤2	-
Sleep paralysis	✔	1 to 2	✔
Suicidal ideation	-	-	✔
Gastrointestinal			
Diarrhea	-	-	2
Nausea	3	-	-
Xerostomia	-	-	2
Laboratory Test Abnormalities			
Hypercholesterolemia	-	-	✔
Musculoskeletal			
Weakness	-	-	✔
Respiratory			
Cough	-	-	2
Upper respiratory tract infection	-	-	2

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the orexin receptor antagonists are listed in Table 7.

Table 7. Usual Dosing Regimens for the Orexin Receptor Antagonists[4-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Daridorexant	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance: Tablet: 25 to 50 mg taken no more than once per night and within 30 minutes of going to bed, with ≥7 hours remaining before awakening	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg
Lemborexant	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance: Tablet: 5 mg taken no more than once per night, immediately before going to bed with at least seven hours before planned time of awakening; maximum, 10 mg once per night	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Suvorexant	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance: Tablet: 10 mg taken no more than once per night and within 30 minutes of going to bed, with ≥7 hours remaining before awakening; maximum, 20 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 15 mg 20 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the orexin receptor antagonists are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Orexin Receptor Antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insomnia				
Mignot et al.[10] (2022) Study 1: Daridorexant 50 mg vs daridorexant 25 mg vs placebo Study 2: Daridorexant 25 mg vs daridorexant 10 mg vs placebo	Two DB, MC, PC, RCT Adults ≥18 years of age with a diagnosis of insomnia	N=930 (Study 1) N=924 (Study 2) 3 months	Primary: Change from baseline in WASO and LPS, measured by polysomnography Secondary: Change from baseline in self-reported total sleep time and the sleepiness domain score of the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ)	Primary: In study 1, WASO and LPS were reduced among participants in the daridorexant 50 mg group compared with participants in the placebo group at month one (least squares mean [LSM] difference, −22.8 min; 95% CI, −28.0 to −17.6; P<0.0001 for WASO; –11.4 min; 95% CI, −16.0 to −6.7; P<0.0001 for LPS) and month three (−18.3 min; 95% CI, −23.9 to −12.7; P<0.0001 for WASO; −11.7 min; 95% CI, −16.3 to −7.0; P<0.0001 for LPS). WASO and LPS were reduced among participants in the daridorexant 25 mg group compared with the placebo group at month one (LSM difference, −12.2 min; 95% CI, −17.4 to −7.0; P<0.0001 for WASO; –8.3 min; 95% CI, −13.0 to −3.6; P=0.0005 for LPS) and month three (−11.9 min; 95% CI, −17.5 to −6.2; P<0.0001 for WASO; −7.6 min; 95% CI, −12.3 to −2.9; P=0.0015 for LPS). In study 2, WASO was reduced among participants in the daridorexant 25 mg group compared with participants in the placebo group at month one (LSM difference, −11.6 min; 95% CI, −17.6 to −5.6; P=0.0001) and month three (−10.3 min; 95% CI, −17.0 to −3.5; P=0.0028), whereas no significant differences in LPS were observed at month one or month three. Compared with the placebo group, no significant differences were observed among participants in the daridorexant 10 mg group for WASO (P=0.37 at month one; P=0.57 at month three) or LPS (P=0.38 at month one; P=0.32 at month three). Secondary: Compared with placebo, participants in the daridorexant 50 mg group had improved self-reported total sleep time at month one (LSM difference, 22.1 min; 95% CI, 14.4 to 29.7; P<0.0001) and month three (19.8 min; 95% CI, 10.6 to 28.9; P<0.0001), and IDSIQ sleepiness domain scores at month one (–1.8; 95% CI, –2.5 to –1.0; P<0.0001) and month three (–1.9; 95% CI, –2.9 to –0.9; P=0.0002). Compared with the placebo group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				participants in the daridorexant 25 mg group had improved self-reported total sleep time at month one (LSM difference, 12.6 min; 95% CI, 5.0 to 20.3; P=0.0013) and month three (9.9 min; 95% CI, 0.8 to 19.1; P=0.033), but not IDSIQ sleepiness domain scores (–0.8; 95% CI, –1.5 to 0.01; P=0.055 at month one; –1.0; 95% CI, –2.0 to 0.01; P=0.053 at month three). Compared with the placebo group, participants in the daridorexant 25 mg group had significant improvement in self-reported total sleep time at month one (LSM difference, 16.1 min; 95% CI, 8.2 to 24.0; P<0.0001) and month three (19.1; 95% CI, 10.1 to 28.0; P<0.0001), but not in IDSIQ sleepiness domain scores (–0.8; 95% CI, –1.6 to 0.1; P=0.073 at month one; –1.3; 95% CI, –2.2 to –0.3; P=0.012 at month three).
Rosenberg et al.[11] SUNRISE-1 (2019) Lemborexant 5 mg QHS or lemborexant 10 mg QHS vs zolpidem tartrate ER 6.25 mg QHS vs placebo	AC, DB, DD, MC, PC, PG, RCT Males ≥65 and females ≥55 years of age with a diagnosis of insomnia based on DSM-5, history of sWASO ≥60 minutes at least three nights per week in the previous four weeks, regular time spent in bed (between seven and nine hours), evidence of sleep maintenance insomnia, ISI score ≥13	N=1,006 4 weeks	Primary: Change from baseline for mean LPS on Days 29/30 as measured by PSG Secondary: Change from baseline for SE and WASO on Days 29/30, change from baseline for mean WASO in the second half of the night (WASO2H) on Days 29/30, safety	Primary: Treatment with both lemborexant 5 mg and 10 mg demonstrated significantly greater mean decreases from baseline in LPS on Days 29/30 compared to placebo (-19.5 and -21.5 vs -7.9 minutes, respectively). Treatment with zolpidem ER demonstrated a mean decrease from baseline in LPS on Days 29/30 compared to placebo (-7.5 vs -7.9 minutes, respectively). Secondary: Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater increases from baseline in SE (measured by PSG) at one month compared to placebo (12.9 and 14.1 vs 5.4%, respectively), as well as WASO (measured by PSG) at one month of treatment compared to placebo (-43.9 and -46.4 vs -18.6 minutes, respectively). The mean increase from baseline in SE was 9.1% for the zolpidem ER group and the mean decrease from baseline in WASO was -36.5 minutes. Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater decreases from baseline in WASO2H at one month (-27.2 and -28.8 vs -8.9 minutes, respectively). The mean decrease was -21.4 minutes in the zolpidem ER group. Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater decreases from baseline in sSOL at one month compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo (-25.2 and -24.8 vs -8.1). The mean decrease was -17.0 in the zolpidem ER group. The overall incidence of treatment-emergent adverse events was similar among treatment groups. Non-serious adverse events were deemed to be mild or moderate in severity. A total of six individuals (four in the zolpidem group and two in the lemborexant 5 mg group) reported eight serious adverse; none were deemed to be treatment-related. Sleep paralysis was reported by one individual in the lemborexant 5 mg group and three in the lemborexant 10 mg group, although all were reported as mild in severity.
Kärppä et al.[12] SUNRISE-2 (2020) Lemborexant 5 mg QHS or lemborexant 10 mg QHS vs placebo	DB, MC, PC, PG, RCT Adults ≥18 years of age with a diagnosis of insomnia based on DSM-5, history of sSOL ≥30 minutes and/or sWASO ≥60 minutes on at least three nights per week in the previous four weeks, regular time spent in bed (between seven and nine hours), ISI score ≥15	N=971 52 weeks	Primary: Change from baseline in sSOL at month six Secondary: Change from baseline in sSE and sWASO at month six compared to placebo	Primary: Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater decreases from baseline in median sSOL compared to placebo at month six (-21.81 and -28.21 vs -11.43 minutes, respectively; P<0.0001 for both strengths). Secondary: Treatment with lemborexant 5 mg and 10 mg demonstrated significantly greater increases from baseline at month six compared to placebo in both sSE (LSM, 14.19 and 14.31 vs 9.64%; P=0.0001 for 5 mg group and <0.0001 for 10 mg group) and sWASO (LSM, -46.75 and -41.95 vs -29.28; P=0.0005 [5 mg] and P=0.0105 [10 mg]). A greater proportion of sleep onset responders was seen with lemborexant 5 mg and 10 mg compared with placebo at month six (31.2 and 30.1 vs 17.7%, respectively; P<0.001 [both strengths]). A greater proportion of sleep maintenance responders was seen with lemborexant 5 mg and 10 mg compared with placebo at month six (35.0 and 30.0 vs 20.4%, respectively; P<0.001 [5 mg] and P<0.05 [10 mg]). Both lemborexant 5 mg and 10 mg demonstrated significant greater increases from baseline in sTST compared with placebo at month six (LSM, 69.95 and 74.08 vs 51.40 minutes, respectively; P=0.0034 [5 mg] and P=0.0004 [10 mg], respectively).
Michelson et al.[13]	DB, PC, RCT	N=779	Primary:	Primary:

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>(2014)

Suvorexant 30 mg nightly for elderly patients and 40 mg nightly for non-elderly patients

vs

placebo</td><td>Patients ≥18 years of age with primary insomnia</td><td>1 year</td><td>Safety and tolerability

Secondary:
sTST, sTSO</td><td>Similar proportions of patients treated with suvorexant or placebo discontinued because of adverse events. The most common adverse events that were increased for suvorexant versus placebo were somnolence, fatigue, and dry mouth. Somnolence was the adverse event with the highest incidence for discontinuations, (suvorexant 20/521 [4%] vs placebo 2/258 [1%]). Somnolence was most common in the first three months (57/527 [11%] for suvorexant vs 6/258 [2%] for placebo) and was less commonly reported by the second three months (11/425 [3%] for suvorexant vs 1/254 [<1%] for placebo). There were no clinically meaningful differences between groups in vital signs or laboratory values.

Secondary:
Over the first month, the suvorexant group showed significant improvements in sTST and sTSO compared with the placebo group. The improvements were maintained throughout the one-year phase.</td></tr>
<tr><td>Herring et al.[14] (2016)

Suvorexant 15 mg nightly for elderly patients and 20 mg nightly for non-elderly patients

vs

placebo</td><td>Pooled analysis from 2 identical DB, PC, RCTs

Non-elderly (18 to 64 years of age) and elderly (≥ 65 years of age) patients with insomnia</td><td>N=493 suvorexant; N=767 placebo

3 months</td><td>Primary:
Change from baseline in sleep diary and PSG measures of sleep maintenance (sTST, WASO) and sleep onset (sTSO, LPS)

Secondary:
Safety</td><td>Primary:
Change from baseline in sleep diary and PSG measures of sleep maintenance
<table>
<tr><th></th><th>Month 1</th><th>Month 1 P-value (vs placebo)</th><th>Month 3</th><th>Month 3 P-value (vs placebo)</th></tr>
<tr><td colspan="5">Diary measures</td></tr>
<tr><td>sTST, minutes</td><td>18.4</td><td>P<0.001</td><td>16.0</td><td>P<0.001</td></tr>
<tr><td>sTSO, minutes</td><td>-5.6</td><td>P<0.05</td><td>-5.9</td><td>P<0.001</td></tr>
<tr><td>sWASO, minutes</td><td>-6.6</td><td>P<0.01</td><td>-4.7</td><td>P<0.05</td></tr>
<tr><td colspan="5">PSG measures</td></tr>
<tr><td>LPS, minutes</td><td>-9.1</td><td>P<0.001</td><td>-4.6</td><td>NS</td></tr>
<tr><td>WASO, minutes</td><td>-25.4</td><td>P<0.001</td><td>-23.1</td><td>P<0.001</td></tr>
<tr><td>TST, minutes</td><td>34.7</td><td>P<0.001</td><td>27.5</td><td>P<0.001</td></tr>
</table>
Secondary:
Patients treated with suvorexant had generally similar incidences of any adverse events or discontinuations due to adverse events compared with placebo. The proportion of patients with serious adverse events was similar among the treatment groups. The proportion of patients that had drug-related adverse events was somewhat higher with suvorexant, but none of the drug-related adverse events were serious. The most common adverse event that was increased for suvorexant versus placebo was next-</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				day somnolence (6.7 vs 3.3%). Somnolence rarely resulted in discontinuation and was mostly mild or moderate in severity.

Drug regimen abbreviations: ER=extended release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, ITT=intent to treat, LS=least square, LSM=least squares mean, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, SD=single dose, XO=crossover, WMD=weighted mean difference
Miscellaneous abbreviations: DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, ISI=Insomnia Severity Index, LPS=latency to persistent sleep, PSG=polysomnography, sSE=subjective sleep efficiency, SE=sleep efficiency, sSOL= subjective sleep onset latency, SOL=sleep onset latency, sTSO=subjective time to sleep onset, sTST=subject reported total sleep time, sWASO=subjective wake time after sleep onset, TST=total sleep time, WASO=wake time after sleep onset

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
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IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Orexin Receptor Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Daridorexant	tablet	Quviviq®	$$$$$	N/A
Lemborexant	tablet	Dayvigo®	$$$$$	N/A
Suvorexant	tablet	Belsomra®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The orexin receptor antagonists are indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.[2-6] The American Academy of Sleep Medicine lists the orexin receptor antagonists as an option for the treatment of sleep maintenance insomnia.[8] Symptom pattern, treatment goals, past treatment responses, patient preference, comorbid conditions, contraindications, drug interactions and adverse events should be considered when selecting a specific agent for the treatment of insomnia.[7,8] The Department of Veterans Affairs/Department of Defense recommends that all adult patients receive cognitive behavioral therapy for insomnia as the initial treatment for chronic insomnia disorder. If cognitive behavioral therapy alone is unsuccessful, a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, should be used to decide whether to add pharmacological therapy.[9]

There is insufficient evidence to support that one brand orexin receptor antagonist is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand orexin receptor antagonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand orexin receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Review of Livtencity® (maribavir)
AHFS Class 081892 (Antivirals, Miscellaneous)
November 9, 2022

I. Overview

Maribavir (Livtencity®) is a cytomegalovirus (CMV) pUL97 kinase inhibitor indicated for the treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet.[1-3] This is the first drug approved for use in this specific population. Maribavir received Breakthrough Therapy and Priority Review designations for this indication.[4]

Table 1. Antivirals, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Maribavir	tablet	Livtencity®	none

PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antivirals are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antivirals, Miscellaneous

Clinical Guideline	Recommendation(s)
American Society for Transplantation and Cellular Therapy Series: **Cytomegalovirus treatment and management of resistant or refractory infections after hematopoietic cell transplantation (2021)**[5]	Treatment of resistant and refractory cytomegalovirus (CMV) • Treat in consultation with an infectious disease specialist. • Antiviral selection is individualized based on a combination of known or suspected resistance genotype mutations, previous drug exposure and acceptable toxicity profile. • Upon clinical suspicion of CMV resistance, switching drug class, confirming genotypic resistance mutations, and reducing immunosuppression is recommended if feasible. • Ganciclovir is the medication most commonly affected by CMV resistance due to UL97 phosphotransferase mutations. If high-level UL97 resistance mutations are detected (>5-fold increase in ganciclovir IC50) a switch to foscarnet is recommended. However, certain low-level UL97 resistance mutations (M460I, C592G, L595W) are usually manageable with higher-dose ganciclovir (7.5 to 10 mg/kg q12h). Preemptive use of filgrastim therapy may mitigate myelosuppression from high-dose ganciclovir dosing. • For refractory CMV without known resistant mutations, optimize dosing of current ganciclovir as appropriate, switch to foscarnet as next-line option, then consider maribavir through early access or trial participation for investigational agents. • Combination therapy is generally not recommended due to the absence of data on efficacy and the additive risk of nephrotoxicity and myelotoxicity. • The recommended treatment duration is at least two to four weeks of optimally selected and dosed anti-CMV medication, guided clinically by resolution of disease symptoms and aiming to achieve undetectable CMV viremia, if present, for at least two consecutive assays.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antivirals are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Antivirals, Miscellaneous[1-3]

Indication	Maribavir
Treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant cytomegalovirus (CMV) infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antivirals are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antivirals, Miscellaneous[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (Hours)
Maribavir	Not reported	98	Hepatic (% not reported)	Fecal (14) Renal (61)	4.3

V. Drug Interactions

Major drug interactions with the miscellaneous antivirals are listed in Table 5.

Table 5. Major Drug Interactions with the Miscellaneous Antivirals[2]

Generic Name(s)	Interaction	Mechanism
Maribavir	Ganciclovir	Concurrent use of ganciclovir and maribavir may result in decreased ganciclovir efficacy.
Maribavir	Valganciclovir	Concurrent use of maribavir and valganciclovir may result in decreased valganciclovir efficacy.
Maribavir	Select CYP3A4 Inducers (e.g., Rifampin, Mitotane, Rifabutin, Fosphenytoin, St John's Wort, Enzalutamide, Lumacaftor, Apalutamide)	Concurrent use of maribavir and select CYP3A4 inducers may result in decreased maribavir exposure and potential for decreased maribavir efficacy.
Maribavir	Phenobarbital	Concurrent use of maribavir and phenobarbital may result in decreased maribavir exposure and potential for decreased maribavir efficacy.
Maribavir	Carbamazepine	Concurrent use of carbamazepine and maribavir may result in decreased maribavir exposure and potential for decreased maribavir efficacy.
Maribavir	Phenytoin	Concurrent use of maribavir and phenytoin may result in decreased maribavir exposure and potential for decreased maribavir efficacy.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antivirals are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Antivirals, Miscellaneous[1]

Adverse Events	Maribavir
Central Nervous System	
Fatigue	12
Taste disorder	46
Gastrointestinal	
Diarrhea	19
Nausea	21
Vomiting	14
Hematologic	
Hemoglobin decreased	1 to 32
Neutrophils decreased	2 to 4
Platelet count decreased	5 to 18
Laboratory Test Abnormalities	
Serum creatinine increased	7 to 33
Other	
Infection	23

✓ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antivirals are listed in Table 7.

Table 7. Usual Dosing Regimens for the Antivirals, Miscellaneous[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Maribavir	Treatment of patients with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet: Tablet: 400 mg (two 200 mg tablets) taken orally twice daily with or without food	Treatment of patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet: Tablet: 400 mg (two 200 mg tablets) taken orally twice daily with or without food	Tablet: 200 mg

CMV=cytomegalovirus

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antivirals are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Antivirals, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cytomegalovirus				
Avery et al.[6] (2021) SOLSTICE Maribavir 400 mg twice daily vs investigator-assigned therapy (IAT; valganciclovir/ganciclovir, foscarnet, or cidofovir) Treatment for 8 weeks with 12 weeks of follow-up	AC, MC, OL Hematopoietic-cell and solid-organ transplant recipients ≥12 years of age with documented CMV infection refractory to the most recent treatment	N=352 20 weeks	Primary: Confirmed CMV clearance at end of week eight Secondary: Composite of confirmed CMV viremia clearance and symptom control at the end of week eight, maintained through week 16 (eight weeks beyond the treatment phase); safety	Primary: A higher proportion of patients in the maribavir group achieved confirmed CMV viremia clearance at week eight than in the IAT group (55.7% [131/235] vs 23.9% [28/117]; adjusted difference, 32.8%; 95% CI, 22.80 to 42.74%; P<0.001). Secondary: A higher proportion of patients randomized to maribavir versus IAT demonstrated CMV viremia clearance and symptom control at the end of week eight, maintained through week 16 (key secondary endpoint; 18.7% vs 10.3%; adjusted difference, 9.5%; 95% CI, 2.02 to 16.88%; P=0.01). This effect was consistent at weeks 12 (22.6% vs 10.3%; P<0.001) and 20 (18.3% vs 9.4%; P=0.008). Rates of treatment-emergent adverse events were similar between groups (maribavir, 97.4%; IAT, 91.4%). Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%). Fewer patients discontinued treatment due to treatment-emergent adverse events with maribavir (13.2%) than IAT (31.9%). One patient per group had fatal treatment-related treatment-emergent adverse events.

Drug regimen abbreviations: IV=intravenous
Study abbreviations: AC=active-controlled, DB=double blind, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial
Other abbreviations: AIDS=acquired immunodeficiency virus, CMV=cytomegalovirus, HCT=hematopoietic cell transplantation, HIV=human immunodeficiency virus, HSV=herpes simplex virus

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
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IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

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Table 9. Relative Cost of the Antivirals, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Maribavir	tablet	Livtencity®	$$$$$	N/A

N/A=Not available.

X. Conclusions

Maribavir (Livtencity®) is a cytomegalovirus (CMV) pUL97 kinase inhibitor indicated for the treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant cytomegalovirus (CMV) infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet.[1-3] This is the first drug approved for use in this specific population. In the SOLSTICE trial, a higher proportion of patients in the maribavir group achieved confirmed CMV viremia clearance at week eight than in the investigator-assigned therapy group (55.7 vs 23.9%; P<0.001).[6] Guidelines have not been updated since the approval of maribavir, but the American Society for Transplantation and Cellular Therapy Series recommends "for refractory CMV without known resistant mutations, optimize dosing of current ganciclovir as appropriate, switch to foscarnet as next-line option, then consider maribavir through early access or trial participation for investigational agents."[5]

Maribavir (Livtencity®) is used in a specific patient population. Because this agent has a narrow indication with limited usage, and very specific criteria must be met prior to initiating therapy, it should be managed through the

medical justification portion of the prior authorization process. Maribavir (Livtencity®) offers no significant clinical advantage over other alternatives in general use.

XI. Recommendations

Maribavir (Livtencity®) is not recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred agents within the miscellaneous antivirals class.

XII. References

1. Lexicomp Online Database [database on the Internet]. Hudson (OH): Lexicomp Inc.: 2022 [cited 2022 Aug]. Available from: http://online.lexi.com. Subscription required to view.
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