Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
February 10, 2016

Table of Contents

Helpful Hints/Reference Document 2

External Criteria
Skeletal Muscle Relaxants 4
Narcotic Analgesics 5
Selective Serotonin Agonists 6
Antiemetic Agents 7
Proton Pump Inhibitors 8

Agenda 11

Pharmacotherapy Class Re-Reviews
Pharmacotherapy Review of Centrally Acting Skeletal Muscle Relaxants 12
Pharmacotherapy Review of Direct-Acting Skeletal Muscle Relaxants 40
Pharmacotherapy Review of GABA-Derivative Skeletal Muscle Relaxants 52
Pharmacotherapy Review of Skeletal Muscle Relaxants, Miscellaneous 73
Pharmacotherapy Review of Opiate Agonists 82
Pharmacotherapy Review of Opiate Partial Agonists 226
Pharmacotherapy Review of Selective Serotonin Agonists 291
Pharmacotherapy Review of Antiemetics, Antihistamines 391
Pharmacotherapy Review of Antiemetics, 5-HT_3 Receptor Antagonists 430
Pharmacotherapy Review of Antiemetics, Miscellaneous 510
Pharmacotherapy Review of Proton-Pump Inhibitors 569

New Drug Reviews
New Drug Review of Savaysa® 639
New Drug Review of Toujeo® 667

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).

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
- Benzodiazepines and barbiturates with the exception of those specified by the Alabama Medicaid Agency
- Agents used to promote smoking cessation, unless authorized for pregnant females or plan first recipients
- 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 in 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:

Maximum Unit Limitations
Early Refill
Brand Limit Switchover
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-9 code(s) may be used. Use of ICD-9 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic 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 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 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, 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 provided through a government or state sponsored drug assistance program for uninsured patients may be counted toward the stable therapy requirement. 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.

AGENDA

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

February 10, 2016
9:00 a.m. – 12:00 p.m.

---

1. Opening remarks…….……..……Chair
2. Approval of November 4, 2015 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…….…….University of Massachusetts 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, Miscellaneous – AHFS 562292
    - Proton-Pump Inhibitors – AHFS 562836
6. New Drug Reviews
    - Savaysa®
    - Toujeo®
7. Results of voting announced…….....……...……..Chair
8. Next meeting date
    - May 11, 2016
9. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Centrally Acting Skeletal Muscle Relaxants
AHFS Class 122004
February 10, 2016

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.[4-12] 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.

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 November 2013.

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®, Parafon Forte DSC®*	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			
Carisoprodol and aspirin	tablet	N/A	none†
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: Early Management of Persistent Non-Specific Low Back Pain (2009)**[13]	• The initial pharmacological treatment should be acetaminophen. • When acetaminophen alone provides insufficient pain relief, consider non-steroidal anti-inflammatory drugs and/or weak opioids. • Consider tricyclic antidepressants if other medicines provide insufficient pain relief. • Consider short-term use of strong opioids for patients in severe pain. • Skeletal muscle relaxants are not included among the pharmacological treatment options in this guideline.
American College of Physicians/American Pain Society: **Diagnosis and Treatment of Low Back Pain (2007)**[14]	• For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs. • Skeletal muscle relaxants are an option for short-term relief of acute low back pain, but all are associated with central nervous system adverse effects (primarily sedation). • There is no compelling evidence that skeletal muscle relaxants differ in efficacy or safety.
American College of Occupational and Environmental Medicine: **Low Back Disorders (2011)**[15]	Recommendations for the treatment of acute low back pain include: • Nonsteroidal anti-inflammatory drugs (NSAIDs). • Patients with known cardiovascular disease or multiple risk factors for cardiovascular disease should have risks and benefits of NSAID therapy for pain discussed. • Cytoprotective agents for patients with contraindications for non-steroidal anti-inflammatory drugs. • Acetaminophen if contraindications for NSAIDs. • Acetaminophen or aspirin as 1st-line therapy for patients with known or multiple risk factors for cardiovascular disease. • Skeletal muscle relaxants as 2nd-line treatment in select cases of moderate to severe acute low back pain not adequately controlled by NSAIDs. • Skeletal muscle relaxants are not recommended for mild to moderate acute low back pain or chronic use in subacute or chronic low back pain (other than acute exacerbations). • Limited use of opioids for severe acute low back pain without radicular pain.
American Academy of Neurology/Child Neurology Society: **Practice Parameter: Pharmacologic Treatment of Spasticity in Children and Adolescents with Cerebral Palsy (2010)**[16] **Reaffirmed July 2013**	• 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: management of multiple sclerosis in primary and secondary care**	• Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin. • Ensure that the drug has been tried at the optimal dose or the maximum dose the patients can tolerate. If a patient cannot tolerate baclofen or gabapentin, consider switching to the other. • A combination of baclofen and gabapentin may be considered.

Clinical Guideline	Recommendation(s)
(2014)[17]	• Consider tizanidine or dantrolene as a second-line options. • Consider benzodiazepines as a third-line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms. Combinations of medicines and other medicines such as anticonvulsants should only be used after seeking further specialist advice.
Department of Veteran Affairs/Department of Defense Clinical Practice Guideline Working Group: **Management of Stroke Rehabilitation (2010)[18]**	• Consider use of oral agents such as tizanidine and oral baclofen for spasticity especially if the spasticity is associated with pain, poor skin hygiene, or decreased function. Tizanidine should be used specifically for chronic stroke patients. • Diazepam and other benzodiazepines should be avoided during the stroke recovery. • Consider use of botulinum toxin, on its own, or in conjunction with oral medication for patients with 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 chronic lower extremity spasticity that cannot be effectively managed by oral medication or botulinum toxin.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the centrally acting 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 Centrally Acting Skeletal Muscle Relaxants[3-12]

Indication	Single Entity Agents						Combination Products	
	Carisoprodol	Chlorzoxazone	Cyclo-benzaprine	Metaxalone	Metho-carbamol	Tizanidine	Carisoprodol and Aspirin	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						✔		

†Injection formulation only.
‡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 individuals components listed below.

Table 4. Pharmacokinetic Parameters of the Centrally Acting Skeletal Muscle Relaxants[3-12]

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 (75)	1
Cyclobenzaprine	33 to 55	93	Liver	Renal (50)	ER: 32 IR: 18
Metaxalone	Not reported	Not reported	Liver	Not reported	8 to 9
Methocarbamol	100	Not reported	Liver	Renal (50 to 65)	1 to 2
Tizanidine	40	30	Liver	Renal (60)	2

ER=extended-release, IR=immediate-release

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Centrally Acting Skeletal Muscle Relaxants[4]

Generic Name(s)	Significance Level	Interaction	Mechanism
Centrally acting skeletal muscle relaxants (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, tizanidine)	1	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	1	Duloxetine	There is an increased risk of serotonin syndrome, therefore concomitant use is discouraged.
Cyclobenzaprine	1	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	1	Tramadol	Concomitant administration of tramadol and cyclobenzaprine increases the risk of seizures.
Tizanidine	1	Acyclovir	Tizanidine is primarily metabolized by the CYP1A2 isozyme. Although not studied, coadministration with acyclovir, 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)	Significance Level	Interaction	Mechanism
Tizanidine	1	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	1	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	1	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	1	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	1	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	1	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	1	Norfloxacin	Norfloxacin is a moderately potent inhibitor of CYP1A2-mediated metabolism of tizanidine. Concomitant use of norfloxacin with tizanidine

Generic Name(s)	Significance Level	Interaction	Mechanism
			increases tizanidine exposure and the risk of excessive sedation and hypotension.
Tizanidine	1	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	1	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	1	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	1	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	1	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.
Tizanidine	1	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.
Chlorzoxazone	2	Disulfiram	Disulfiram inhibits the metabolism of chlorzoxazone;

Generic Name(s)	Significance Level	Interaction	Mechanism
			therefore dose adjustment of chlorzoxazone should be considered.
Chlorzoxazone	2	Isoniazid	Isoniazid inhibits the metabolism of chlorzoxazone; therefore dose adjustment of chlorzoxazone should be considered.
Cyclobenzaprine	2	Escitalopram	There is an increased risk of serotonin syndrome, therefore concomitant use is discouraged.
Cyclobenzaprine	2	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	2	Guanfacine	Cyclobenzaprine may decrease the antihypertensive effect of guanfacine.
Cyclobenzaprine	2	Tricyclic antidepressants	There is an increased risk of serotonin syndrome, therefore concomitant use is discouraged.
Tizanidine	2	Fosphenytoin	Increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, and tremor).
Tizanidine	2	Lisinopril	Potentiation of hypotensive response.
Tizanidine	2	Phenytoin	Increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, and tremor).

Significance level 1=major severity, significance level 2=moderate severity.

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 individuals components listed below.

Table 6. Adverse Drug Events (%) Reported with the Centrally Acting Skeletal Muscle Relaxants[3-12]

Adverse Events	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine
Cardiovascular						
Arrhythmia	-	-	<1	-	-	✔
Bradycardia	-	-	-	-	✔	✔
Hypotension	✔	-	<1	-	✔	0 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	0 to 40	✔	✔	✔	✔	✔
Dyskinesia	-	-	-	-	-	✔
Fatigue	✔	-	1 to 3	-	-	9 to 16
Hallucinations	-	-	<1	-	-	3
Headache	2	✔	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	-	-	39 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[3-12]

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: 375 to 750 mg TID to QID	Safety and efficacy in children have not been established.	Tablets: 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 8 hours; maximum 3 g daily for no greater than 3 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: 4 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			
Carisoprodol and aspirin	Painful musculoskeletal disorders: Tablet: one to two tablets QID	Safety and efficacy in children have not been established.	Tablet: 200-325 mg
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.[19] (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.[20] (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.[21] (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.[22] (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.[23] (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.[24] (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.[25] (2003) Study 1: Cyclobenzaprine 5 mg TID vs cyclobenzaprine 10 mg TID vs placebo Study 2: 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: Study 1 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. Study 2 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: Study 1 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). Study 2 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.[26] (2009)	DB, RCT Adults with muscle	Study 1 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	Study 2: 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.[27] (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.[28] (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.[29] (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
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: 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 placebo	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; reflexes; clonus; spasm score; 8m walking time; motor skills and upper limb functions; activities of daily living; overall effect on function; efficacy and tolerability	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 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	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			living Secondary: Not reported	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 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	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	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
baclofen up to 60 mg			Secondary: Not reported	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 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
Simpson et al.[40] (2009) Tizanidine (TZD) 2 to 36 mg/day vs botulinum neurotoxin (BoNT) administered IM	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
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: 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

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®, Parafon Forte DSC®*	$$$-$$$$	$
Cyclobenzaprine	extended-release capsule, tablet*	Amrix®, Fexmid®*	$$$$$	$
Metaxalone	tablet	Skelaxin®*	$$$$$	$$$$
Methocarbamol	injection, tablet	Robaxin®*	$$$-$$$$	$
Tizanidine	capsule, tablet	Zanaflex®*	$$$$$	$
Combination Products				
Carisoprodol and aspirin	tablet	N/A	N/A	$$$
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.[3-12] 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.[17] For the management of stroke rehabilitation, guidelines recommend the use of tizanidine, dantrolene, or baclofen for spasticity resulting in pain.[18] Tizanidine should be used for chronic stroke patients. 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.[14-15,17] Skeletal muscle relaxants are considered a second-line treatment option in select cases of moderate to severe acute low back pain.[15] 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).[15] 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.[14,20,26-27]

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.[1-4,6-7] 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, 9-10] 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

1. Frontera, Joel and Verduzco-Gutierrez M. Spasticity. In: Walter R. Frontera, Julie K. Silver, Thomas D. Rizzo Jr., eds. Essentials of Physical Medicine and Rehabilitation: Musculoskeletal Disorders, Pain, and Rehabilitation. 3rd ed. Philadelphia, PA: Saunders; 2015. Available at: http://www.mdconsult.com. Accessed Sep 2015.
2. Montane, E. Vallana, A, Laporte, JR. Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. Neurology 2004;63:1357.
3. Zanaflex® [package insert]. Hawthorne, NY: Acorda Therapeutics, Inc.; Nov 2013.
4. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Sep]. Available from: http://online.factsandcomparisons.com.
5. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Sep]. Available from: http://www.thomsonhc.com/.
6. Soma® [package insert]. Somerset, NJ: Meda Pharmaceuticals, Inc.; Jan 2013.
7. Lorzone® [package insert]. Sayreville, NJ: Vertical Pharmaceuticals, Inc.; Nov 2014.
8. Parafon Forte DSC® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2012.
9. Amrix® [package insert]. Frazer, PA: Cephalon, Inc.; June 2013.
10. Fexmid® [package insert]. San Diego, CA: Victory Pharma, Inc.; August 2011.
11. Skelaxin® [package insert]. Bristol, TN: King Pharmaceuticals, Inc.; April 2008.
12. Robaxin® [package insert]. Milwaukee, WI: Schwarz Pharma; March 2011.
13. National Collaborating Centre for Primary Care. Low back pain. Early management of persistent non-specific low back pain. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009. Available at: http://www.nice.org.uk/CG88. Accessed Aug 2013.
14. Chou R, Qaseem A, Snow V, et al. Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147:478-91.
15. Low back disorders. In: Hegmann KT, editor(s). Occupational medicine practice guidelines. Evaluation and management of common health problems and functional recovery in workers. 3rd ed. Elk Grove Village (IL): American College of Occupational and Environmental Medicine (ACOEM); 2011. p. 333-796.
16. Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, Delgado MR, Hirtz D, Aisen M, Ashwal S, Fehlings DL, McLaughlin J, Morrison LA, Shrader MW, Tilton A, Vargus-Adams J. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2010;74:336-43.
17. National Institute for Health and Care Excellence. Multiple sclerosis: management of multiple sclerosis in primary and secondary care [guideline on the internet]. London, UK: National Institute for Health and Care Excellence; 2014 [cited 2014 Sep 22]. Available from: https://www.nice.org.uk/guidance/cg186.
18. Management of Stroke Rehabilitation Working Group. VA/DOD Clinical practice guideline for the management of stroke rehabilitation. J Rehabil Res Dev. 2010;47(9):1-43.
19. Serfer GT, Wheeler WJ, Sacks HJ, et al. Randomized, double-blind trial of carisoprodol 250 mg compared to placebo and carisoprodol 350 mg for the treatment of low back spasm. Curr Med Res Opin. 2010;26:91-99.
20. Rollings H, Management of acute musculoskeletal conditions-thoracolumbar strain or sprain: a double-blind evaluation comparing the efficacy and safety of carisoprodol with cyclobenzaprine hydrochloride. Curr Ther Res. 1983;34:917-28.
21. Boyles w, Glassman J, Soyka J. Management of acute musculoskeletal conditions: thoracolumbar strain or sprain. A double-blind evaluation comparing the efficacy and safety of carisoprodol with diazepam. Today's Thera Trends. 1983;1:1-16.
22. Bragstad A, Blikra G. Evaluation of a new skeletal muscle relaxant in the treatment of low back pain (a comparison of DS 103–282 with chlorzoxazone). Current Therapeutic Research 1979;26:39–43.
23. Ralph L, Look M, Wheeler W, et al. Double-blind, placebo-controlled trial of carisoprodol 250-mg tablets in the treatment of acute lower-back spasm. Curr Med Res Opin. 2008;2:551-8.
24. Hindle T. Comparison of carisoprodol, butabarbital, and placebo in treatment of the low back syndrome. California Medicine. 1972;117:7-11.
25. Borenstein DG, Korn S. Efficacy of a low-dose regimen of cyclobenzaprine hydrochloride in acute skeletal muscle spasm: results of two placebo-controlled trials. Clin Ther. 2003;25:1056-73.

26. Malanga GA, Ruoff GE, Weil AJ, et al. Cyclobenzaprine ER for muscle spasm associated with low back and neck pain: two randomized, double-blind, placebo-controlled studies of identical design. Curr Med Res Opin. 2009;25:1179-96.
27. Weil AJ, Ruoff GE, Nalamachu S, et al. Efficacy and tolerability of cyclobenzaprine extended release for acute muscle spasm: a pooled analysis. Postgrad Med. 2010;122:158-69.
28. Childers MK, Borenstein D, Brown RL Low-dose cyclobenzaprine vs combination therapy with ibuprofen for acute neck or back pain with muscle spasm: a randomized trial. Curr Med Res Opin. 2005 9:1485-93.
29. Khwaja SM, Minnerop M, Singer AJ. Comparison of ibuprofen, cyclobenzaprine or both in patients with acute cervical strain: a randomized controlled trial. CJEM. 2010;12:39-44.
30. Hennies O. A new skeletal muscle relaxant (DS 103–282) compared to diazepam in the treatment of muscle spasm of local origin. J Int Med Res. 1981;9:62–8.
31. Lapierre Y, Bouchard S, Tansey C, et al. Treatment of spasticity with tizanidine in multiple sclerosis. Can J Neurol Sci. 1987;14:513-7.
32. Smith C, Birnbaum G, Carter J, et al. Tizanidine treatment of spasticity caused by multiple sclerosis: results of a double-blind, placebo-controlled trial. Neurology. 1994;44(Supp 9):S34-42.
33. The United Kingdom Tizanidine Trial Group. A double-blind, placebo-controlled trial of tizanidine in the treatment of spasticity caused by multiple sclerosis. Neurology. 1994;44(Supp 9):S70-9.
34. Nance P, Bugaresti J, Shellenberger K, et al. Efficacy and safety of tizanidine in the treatment of spasticity in patients with spinal cord injury. Neurology. 1994;44(Suppl 9):S44-51.
35. Gelber D, Good D, Dromerick A, et al. Open-label dose-titration safety and efficacy study of tizanidine hydrochloride in the treatment of spasticity associated with chronic stroke.
36. Bass B, Weinshenker B, Rice G, et al. Tizanidine vs baclofen in the treatment of spasticity in patients with multiple sclerosis. Can J Neurol Sci. 1988;15:15-9.
37. Eyssette M, Rohmer F, Serratrice G, et al. Multi-center, double-blind trial of a novel antispastic agent, tizanidine, in spasticity associated with multiple sclerosis. Curr Med Res Opin. 1988;10:699-708.
38. Smolenski C, Muff S, Smolenski-Kautz S, et al. A double-blind comparative trial of new muscle relaxant, tizanidine (DS 103-282), and baclofen in the treatment of chronic spasticity in multiple sclerosis. Curr Med Res Opin. 1981;7:374-83.
39. Stien R, Nordal H, Oftedal S, et al. The treatment of spasticity in multiple sclerosis: a double-blind clinical trial of a new anti-spastic drug tizanidine compared to baclofen. Acta Neurol Scand. 1987;75:190-4.
40. Simpson DM, Gracies JM, Yablon SA, et al. Botulinum neurotoxin vs tizanidine in upper limb spasticity: a placebo-controlled study. J Neurol Neurosurg Psychiatry. 2009;80:380-5.
41. Dai AI, Wasay M, Awan S. Botulinum toxin type A with oral baclofen vs oral tizanidine: a nonrandomized pilot comparison in patients with cerebral palsy and spastic equinus foot deformity. J Child Neurol. 2008;23:1464-6.
42. Shakespeare D, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD001332. DOI: 10.1002/14651858.CD001332.
43. Taricco M, Adone R, Pagliacci C. Pharmacological interventions for spasticity following spinal cord injury. Cochrane Database of Systematic Review 2000, Issue 2. Art. No.: CD001131. DOI: 10.1002/14651858.CD001131.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Direct-Acting Skeletal Muscle Relaxants
AHFS Class 122008
February 10, 2016

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 capsules are available in a generic formulation. This class was last reviewed in November 2013.

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: Early Management of Persistent Non-Specific Low Back Pain (2009)**[10]	• The initial pharmacological treatment should be acetaminophen. • When acetaminophen alone provides insufficient pain relief, consider non-steroidal anti-inflammatory drugs and/or weak opioids. • Consider tricyclic antidepressants if other medicines provide insufficient pain relief. • Consider short-term use of strong opioids for patients in severe pain. • Skeletal muscle relaxants are not included among the pharmacological treatment options in this guideline.
American College of Physicians/American Pain Society: **Diagnosis and Treatment of Low Back Pain**	• For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs. • Skeletal muscle relaxants are an option for short-term relief of acute low back pain, but all are associated with central nervous system adverse effects

Clinical Guideline	Recommendation(s)
(2007)[11]	(primarily sedation). • There is no compelling evidence that skeletal muscle relaxants differ in efficacy or safety.
American College of Occupational and Environmental Medicine: **Low Back Disorders (2007)[12]**	Recommendations for the treatment of acute low back pain include: • Nonsteroidal anti-inflammatory drugs (NSAIDs). • Patients with known cardiovascular disease or multiple risk factors for cardiovascular disease should have risks and benefits of NSAID therapy for pain discussed. • Cytoprotective agents for patients with contraindications for non-steroidal anti-inflammatory drugs. • Acetaminophen if contraindications for non-steroidal anti-inflammatories. • Acetaminophen or aspirin as 1st-line therapy for patients with known or multiple risk factors for cardiovascular disease. • Skeletal muscle relaxants as 2nd-line treatment in select cases of moderate to severe acute low back pain not adequately controlled by NSAIDs. • Skeletal muscle relaxants are not recommended for mild to moderate acute low back pain or chronic use in subacute or chronic low back pain (other than acute exacerbations). • Limited use of opioids for severe acute low back pain without radicular pain.
American Academy of Neurology/Child Neurology Society: **Practice Parameter: Pharmacologic Treatment of Spasticity in Children and Adolescents with Cerebral Palsy (2010)[13]** **Reaffirmed July 2013**	• 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: management of multiple sclerosis in primary and secondary care (2014)[14]**	• Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin. • Ensure that the drug has been tried at the optimal dose or the maximum dose the patients can tolerate. If a patient cannot tolerate baclofen or gabapentin, consider switching to the other. • A combination of baclofen and gabapentin may be considered. • Consider tizanidine or dantrolene as a second-line options. • Consider benzodiazepines as a third-line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms. Combinations of medicines and other medicines such as anticonvulsants should only be used after seeking further specialist advice.
Department of Veteran Affairs/Department of Defense Clinical Practice Guideline Working Group: **Management of Stroke Rehabilitation (2010)[15]**	• Consider use of oral agents such as tizanidine and oral baclofen for spasticity especially if the spasticity is associated with pain, poor skin hygiene, or decreased function. Tizanidine should be used specifically for chronic stroke patients. • Diazepam and other benzodiazepines should be avoided during the stroke recovery. • Consider use of botulinum toxin, on its own, or in conjunction with oral medication for patients with 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 chronic lower extremity spasticity that cannot be effectively managed by oral medication or botulinum toxin.

Clinical Guideline	Recommendation(s)
Society for Ambulatory Anesthesiology: **Creation of a Guide for the Transfer of Malignant Hyperthermia Patient from Ambulatory Surgery Centers to Receiving Hospital Facility (2012)**[16]	• Intravenous dantrolene should be initiated prior to patient transfer to a receiving hospital facility. • This recommendation is supported by is supported by clinical research demonstrating that the likelihood of significant malignant hyperthermia complications doubles for every 30-minute delay in dantrolene administration.
European Malignant Hyperthermia Group: **Recognizing and Managing a Malignant Hyperthermia Crisis (2010)**[17]	• Administer dantrolene at 2 mg/kg. Infusions should be repeated until the cardiac and respiratory systems stabilize. • The maximum dose (10 mg/kg) may need to be exceeded.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the direct-acting 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 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

There are no significant drug interactions reported with the direct-acting skeletal muscle relaxants.[1] 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]

VI. Adverse Drug Events

The most common adverse drug events reported with the direct-acting skeletal muscle relaxants are listed in Table 5. The boxed warning for dantrolene is listed in Table 6.

Table 5. 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	✔
Incontinence	✔
Nocturia	✔
Urinary frequency	✔
Urinary retention	✔
Hematologic	
Aplastic anemia	✔
Leukopenia	✔
Lymphocytic lymphoma	✔
Thrombocytopenia	✔
Hepatic	
Hepatotoxicity	1

Adverse Events	Dantrolene
Musculoskeletal	
Back ache	✔
Myalgia	✔
Respiratory	
Dyspnea	✔
Respiratory depression	✔
Special Senses	
Diplopia	✔
Dysgeusia	✔
Epiphora	✔
Visual impairment	✔

✔ Percent not specified.

Table 6. 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 7.

Table 7. 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 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	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 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	Capsule: 25 mg 50 mg 100 mg Injection: 20 mg 250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	dictates Spasticity: Capsule: 25 to 100 mg orally three times daily	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	

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the direct-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. No controlled trials were found in the peer-reviewed literature regarding the use of dantrolene for malignant hyperthermia.

Table 8. 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.[18] (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.[19] (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 9. 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 in this class. It is approved for the management of spasticity, as well as for the prevention and treatment of malignant hyperthermia.[1-5] Dantrolene capsules are 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.[14,20] For the management of stroke rehabilitation, guidelines recommend the use of dantrolene, tizanidine or baclofen for spasticity resulting in pain.[15] 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.[7-8,18-19] There are limited studies directly comparing dantrolene to other antispasticity agents.[20]

Dantrolene is the treatment of choice for malignant hyperthermia.[16-17,21] 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.

XII. References

1. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Sep]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Sep]. Available from: http://www.thomsonhc.com/.
3. Dantrium® capsules [package insert]. Rochester, MI: JHP Pharmaceuticals; March 2012.
4. Dantrium® injection [package insert]. Rochester, MI: JHP Pharmaceuticals; November 2008.
5. Ryanodex® injection [package insert]. Woodcliff Lake, NJ: Eagle Pharmaceuticals, Inc.; July 2014.
6. Frontera, Joel and Verduzco-Gutierrez M. Spasticity. In: Walter R. Frontera, Julie K. Silver, Thomas D. Rizzo Jr., eds. Essentials of Physical Medicine and Rehabilitation: Musculoskeletal Disorders, Pain, and Rehabilitation. 3rd ed. Philadelphia, PA: Saunders; 2015. Available at: http://www.mdconsult.com. Accessed Sep 2015.
7. Haslam, RHA, et al. Dantrolene sodium in children with spasticity. Arch Phys Med Rehabil 1974;55:384-388.
8. Joynt, RL, Leonard, JA. Dantrolene sodium suspension in treatment of spastic cerebral palsy. Dev Med Child Neurol. 1980;22:755-67.
9. Saper, CB. Autonomic disorders and their management. In: Goldman L, Ausiello D, eds. Cecil Medicine. 23rd ed. Philadelphia, PA: Saunders Elsevier; 2008. Available at: http://www.mdconsult.com. Accessed August 2013.National Collaborating Centre for Primary Care.
10. Low back pain. Early management of persistent non-specific low back pain. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009. Available at: http://www.nice.org.uk/CG88. Accessed August 2013.
11. Chou R, Qaseem A, Snow V, et al. Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147:478-91.
12. Hegmann KT, ed. Low back disorders. In: Glass LS, editor(s). Occupational medicine practice guidelines: evaluation and management of common health problems and functional recovery in workers. 2nd ed. Elk Grove Village (IL): American College of Occupational and Environmental Medicine (ACOEM); 2007. p. 366. Available at: http://www.guideline.gov/content.aspx?id=12540. Accessed February 2011.
13. Larach MG, Dirksen SJ, Belani KG, Brandom BW, Metz KM, Policastro MA, et al. Special article: Creation of a guide for the transfer of care of the malignant hyperthermia patient from ambulatory surgery centers to receiving hospital facilities. Anesth Analg. 2012 Jan;114(1):94-100. doi: 10.1213/ANE.0b013e3182373b4a.
14. National Institute for Health and Care Excellence. Multiple sclerosis: management of multiple sclerosis in primary and secondary care [guideline on the internet]. London, UK: National Institute for Health and Care Excellence; 2014 [cited 2014 Sep 22]. Available from: https://www.nice.org.uk/guidance/cg186.
15. Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2010;74:336-43.
16. Larach MG, Dirksen SJ, Belani KG, et al. Creation of a Guide for the Transfer of Care of the Malignant Hyperthermia Patient from Ambulatory Surgery Centers to Receiving Hospital Facilities. Anesthesia & Analgesia. 2012;114(1):94-100.
17. Management of Stroke Rehabilitation Working Group. VA/DOD Clinical practice guideline for the management of stroke rehabilitation. J Rehabil Res Dev. 2010;47(9):1-43.
18. Ketel, WV, Kolb, ME. Long-term treatment with dantrolene sodium of stroke patients with spasticity limiting the return of function. Curr Med Res Opin. 1984; 9:161-9.
19. Katrak, PH, et al. Objective assessment of spasticity, strength, and function with early exhibition of dantrolene sodium after cerebrovascular analogue saccular accident; a randomized, double-blind controlled study. Arch Phys Med Rehab 1992;73:4-9.
20. Shakespeare D, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD001332. DOI: 10.1002/14651858.CD001332.
21. Gronert GA et al. Malignant hyperthermia. In: Miller, RD, ed. Miller's Anesthesia. 7th ed. Philadelphia, PA: Elsevier, Churchill Livingstone, 2009. Available at: http://www.mdconsult.com. Accessed August 2013.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of GABA-Derivative Skeletal Muscle Relaxants
AHFS Class 122012
February 10, 2016

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.[1-5] 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. 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] Baclofen is an analog of GABA and inhibits both monosynaptic and polysynaptic reflexes at the spinal level to cause muscle relaxation.[1-5]

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 tablets are available in a generic formulation. This class was last reviewed in November 2013.

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, tablet*	Gablofen®, Lioresal Intrathecal®	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: Early Management of Persistent Non-Specific Low Back Pain (2009)[8]**	• The initial pharmacological treatment should be acetaminophen. • When acetaminophen alone provides insufficient pain relief, consider non-steroidal anti-inflammatory drugs and/or weak opioids. • Consider tricyclic antidepressants if other medicines provide insufficient pain relief. • Consider short-term use of strong opioids for patients in severe pain. • Skeletal muscle relaxants are not included among the pharmacological treatment options in this guideline.
American College of Physicians/American Pain Society: **Diagnosis and Treatment of Low Back Pain (2007)[9]**	• For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs. • Skeletal muscle relaxants are an option for short-term relief of acute low back pain, but all are associated with central nervous system adverse effects (primarily sedation). • There is no compelling evidence that skeletal muscle relaxants differ in efficacy or safety.
American College of Occupational and	Recommendations for the treatment of acute low back pain include: • Nonsteroidal anti-inflammatory drugs (NSAIDs).

Clinical Guideline	Recommendation(s)
Environmental Medicine: **Low Back Disorders (2007)[10]**	• Patients with known cardiovascular disease or multiple risk factors for cardiovascular disease should have risks and benefits of NSAID therapy for pain discussed. • Cytoprotective agents for patients with contraindications for non-steroidal anti-inflammatory drugs. • Acetaminophen if contraindications for non-steroidal anti-inflammatories. • Acetaminophen or aspirin as 1st-line therapy for patients with known or multiple risk factors for cardiovascular disease. • Skeletal muscle relaxants as 2nd-line treatment in select cases of moderate to severe acute low back pain not adequately controlled by NSAIDs. • Skeletal muscle relaxants are not recommended for mild to moderate acute low back pain or chronic use in subacute or chronic low back pain (other than acute exacerbations). • Limited use of opioids for severe acute low back pain without radicular pain.
American Academy of Neurology/Child Neurology Society: **Practice Parameter: Pharmacologic Treatment of Spasticity in Children and Adolescents with Cerebral Palsy (2010)[11]** **Reaffirmed July 2013**	• 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: management of multiple sclerosis in primary and secondary care (2014)[12]**	• Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin. • Ensure that the drug has been tried at the optimal dose or the maximum dose the patients can tolerate. If a patient cannot tolerate baclofen or gabapentin, consider switching to the other. • A combination of baclofen and gabapentin may be considered. • Consider tizanidine or dantrolene as a second-line options. • Consider benzodiazepines as a third-line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms. Combinations of medicines and other medicines such as anticonvulsants should only be used after seeking further specialist advice.
Department of Veteran Affairs/Department of Defense Clinical Practice Guideline Working Group: **Management of Stroke Rehabilitation (2010)[13]**	• Consider use of oral agents such as tizanidine and oral baclofen for spasticity especially if the spasticity is associated with pain, poor skin hygiene, or decreased function. Tizanidine should be used specifically for chronic stroke patients. • Diazepam and other benzodiazepines should be avoided during the stroke recovery. • Consider use of botulinum toxin, on its own, or in conjunction with oral medication for patients with 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 chronic lower extremity spasticity that cannot be effectively managed by oral medication or botulinum toxin.

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. 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 GABA-derivative Skeletal Muscle Relaxants[1-5]

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[1-5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Baclofen	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]

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[1-5]

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

Adverse Events	Baclofen
Depression	✔
Disorientation	✔
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	✔

Adverse Events	Baclofen
Myalgia	✔
Respiratory	
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[1-5]

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	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.	Intrathecal injection: 50 µg/mL 500 µg/mL 1,000 µg/mL 2,000 µg/mL Tablet: 10 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	700 µg/day) Tablet: maintenance, 40 to 80 mg per day divided in three or four doses	Tablet: safety and efficacy have not been established in pediatric patients <12 years of age	

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.[14] (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
Spasticity				
Brar et al.[15] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sachais et al.[16] (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
Feldman et al.[17] (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.[18] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gilmartin et al.[19] (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 month, 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 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.[20] (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.[21] (2009) Baclofen	RCT Children with intractable, spastic	N=17 6 months	Primary: Changes on visual analogue scale for individually	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
intrathecal infusion vs placebo	cerebral palsy		formulated problems and the caregiver assistance scale of the Pediatric Evaluation of Disability Inventory self-care domain Secondary: Not reported	Pediatric Evaluation of Disability Inventory scores did not change significantly among the treatment groups. Secondary: Not reported
Krach et al.[22] (2010) Baclofen intrathecal infusion vs placebo	RETRO Adults and children with cerebral palsy	N=708 8 years	Primary: Survival probabilities Secondary: Not reported	Primary: Survival after eight years was 92% in the baclofen group and 82% in the 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
Ordia et al.[23] (1996) Baclofen intrathecal infusion	OL Patients with severe spasticity of spinal cord origin refractory to oral baclofen or who experienced intolerable side effects	N=59 Variable duration	Primary: Rigidity (Ashworth Scale score) Secondary: Not reported	Primary: 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.[24] (1997)	OL Patients 17 to 39	N=11 3 months	Primary: Muscle tone (Ashworth Scale	Primary: Lower-extremity Ashworth Scale scores decreased from 3.5 points before treatment to 2.2 points after three months of treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Baclofen intrathecal infusion	with acquired brain injury, severe, progressive spasticity, and dystonia refractory to maximal medical therapy, which interfered with activities of daily living		score) Secondary: Not reported	(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.[25] (2009) Baclofen intrathecal infusion	PRO Children with spasticity and/or dystonia	N=25 6 months	Primary: Attainment of individual goals measured with the 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	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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Utilities Index Mark (III) for health-related quality of life	The Health Utilities Index Mark (III) did not show a statistically significant change post-implant; however, the results were slightly improved.
Brochard et al.[26] (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 (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.[27] (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,	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°

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and ankle joints Secondary: Not reported	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.[28] (2009) Baclofen intrathecal infusion	RETRO Ambulant children with cerebral palsy	N=21 5 to 75 months	Primary: Ashworth Scale score, Gillette Functional Assessment Questionnaire score, use of walking aids, and joint angle at which the stretch reflex was triggered Secondary: Not reported	Primary: The mean Ashworth score decreased by 1.4 points (P<0.001). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Margetis et al.[29] (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
Loubser et al.[30] (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.[31] (2009)	DB, RCT Adults with	N=80 6 weeks	Primary: Functional analysis (Pedersen's scale,	Primary: Both eperisone and baclofen significantly improved functionality of lower limbs vs baseline (eperisone, –9.1%; P<0.01, baclofen, –8.3%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Baclofen 60 mg/day vs eperisone 300 mg/day	moderate to severe spastic palsy		muscular tone, joint range of motion, 10-meter walking time); physiological and pathological reflexes; and electromyography (Hmax/Mmax amplitude ratio and the Wartenberg test) Secondary: Not reported	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. 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.[32] (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.[33] (1988) Tizanidine up to 24 mg vs baclofen up to 60	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:	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg			Not reported	
Smolenski et al.[34] (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.[35] (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.[36] (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	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	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
botulinum type A 20 to 24 units/kg			pediatric neurologist 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, tablet*	Lioresal Intrathecal®, Gablofen®	$$$$$	$$

*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.[1-4] Baclofen tablets are available in a generic formulation.

For the management of multiple sclerosis, guidelines recommend initial treatment with baclofen or gabapentin for bothersome regional or global spasticity or spasms.[11] For the management of stroke rehabilitation, guidelines recommend the use of baclofen, dantrolene, or tizanidine for spasticity resulting in pain.[13] 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.[14-36] 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.[31-36]

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.[1-5]

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.

XII. References

1. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Sep]. Available from: http://online.factsandcomparisons.com.
2. Baclofen: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2015 [cited 2015 Sep 24]. Available from: http://www.utdol.com/utd/index.do.
3. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Sep]. Available from: http://www.thomsonhc.com/.
4. Lioresal Intrathecal® [package insert]. Minneapolis, MN: Medtronic, Inc.; 2013 May.
5. Gablofen® [package insert]. Hazelwood MO: Mallinckrodt Brand Pharmaceuticals, Inc.; 2015 Feb.
6. Frontera, Joel and Verduzco-Gutierrez M. Spasticity. In: Walter R. Frontera, Julie K. Silver, Thomas D. Rizzo Jr., eds. Essentials of Physical Medicine and Rehabilitation: Musculoskeletal Disorders, Pain, and Rehabilitation. 3rd ed. Philadelphia, PA: Saunders; 2015. Available at: http://www.mdconsult.com. Accessed Sep 2015.
7. Montane, E. Vallana, A, Laporte, JR. Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. Neurology 2004; 63: 1357.
8. National Collaborating Centre for Primary Care. Low back pain. Early management of persistent non-specific low back pain [guideline on the internet]. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 [cited 2013 Aug 28]. Available at: http://www.nice.org.uk/CG88.
9. Chou R, Qaseem A, Snow V, et al. Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147:478-491.
10. Hegmann KT, ed. Low back disorders. In: Glass LS, editor(s). Occupational medicine practice guidelines: evaluation and management of common health problems and functional recovery in workers 2nd ed [guideline on the internet]. Elk Grove Village (IL): American College of Occupational and Environmental Medicine (ACOEM); 2007 [cited 2013 Aug 28]. p. 366. Available at: http://www.guideline.gov/content.aspx?id=12540.
11. Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, Delgado MR, Hirtz D, Aisen M, Ashwal S, Fehlings DL, McLaughlin J, Morrison LA, Shrader MW, Tilton A, Vargus-Adams J. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2010;74:336-43.
12. National Institute for Health and Care Excellence. Multiple sclerosis: management of multiple sclerosis in primary and secondary care [guideline on the internet]. London, UK: National Institute for Health and Care Excellence; 2014 [cited 2014 Sep 22]. Available from: https://www.nice.org.uk/guidance/cg186.
13. Management of Stroke Rehabilitation Working Group. VA/DOD Clinical practice guideline for the management of stroke rehabilitation. J Rehabil Res Dev. 2010;47(9):1-43.
14. Sanders JC, Gerstein N, Torgeson E, et al. Intrathecal baclofen for postoperative analgesia after total knee arthroplasty. J Clin Anesth 2009;21:486-92.
15. Brar S, Smith M, Nelson L, et al. Evaluation of treatment protocols on minimal to moderate spasticity in multiple sclerosis. Arch Phys Med Rehabil 1991;72:186-9.
16. Sachais B, Logue J, Carey M. Baclofen, a new antispastic drug. A controlled, multicenter trial in patients with multiple sclerosis. Arch Neurol 1977;34:422-8.
17. Feldman R, Kelly-Hayes M, Conomy J, et al. Baclofen for spasticity in multiple sclerosis. Double-blind crossover and three-year study. Neurology 1978;28:1094.
18. Gerszten P, Albright A, Barry M. Effect on ambulation of continuous intrathecal baclofen infusion. Pediatr Neurosurg 1997;27:40-44.
19. Gilmartin R, Bruce D, Abbott R, et al. Intrathecal baclofen for management of spastic cerebral palsy: multicenter trial. J Child Neurol 2000;15:71-77.
20. Van Schaeybroeck P, Nuttin B, Lagae L, et al. Intrathecal baclofen for intractable cerebral spasticity: a prospective placebo-controlled, double-blind study. Neurosurgery 2000;46:603-612.
21. Hoving MA, van Raak EP, Spincemaille GH, et al. Efficacy of intrathecal baclofen therapy in children with intractable spastic cerebral palsy: a randomized controlled trial. Eur J Paediatr Neurol 2009;13:240-6.
22. Krach LE, Kriel RL, Day SM, et al. Survival of individuals with cerebral palsy receiving continuous intrathecal baclofen treatment: a matched-cohort study. Dev Med Child Neurol 2010;52:672-6.

23. Ordia J, Fischer E, Adamski E, et al. Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. J Neurosurg 1996;85:452-457.
24. Meythaler J, McCary A, Hadley M. Prospective assessment of continuous intrathecal infusion of baclofen for spasticity caused by acquired brain injury: a preliminary report. J Neurosurg 1997;87:415-419.
25. Ward A, Hayden S, Dexter M, et al. Continuous intrathecal baclofen for children with spasticity and/or dystonia: Goal attainment and complications associated with treatment. J Paediatr Child Health 2009;45:720-6.
26. Brochard S, Lempereur M, Filipetti P, et al. Changes in gait following continuous intrathecal baclofen infusion in ambulant children and young adults with cerebral palsy. Dev Neurorehabil 2009;12:397-405.
27. Horn TS, Yablon SA, Chow JW, et al. Effect of intrathecal baclofen bolus injection on lower extremity joint range of motion during gait in patients with acquired brain injury. Arch Phys Med Rehabil 2010;91:30-4.
28. Brochard S, Remy-Neris O, Filipetti P, et al. Intrathecal baclofen infusion for ambulant children with cerebral palsy. Pediatr Neurol 2009;40:265-70.
29. Margetis K, Korfias S, Boutos N, et al. Intrathecal baclofen therapy for the symptomatic treatment of hereditary spastic paraplegia. Clin Neurol Neurosurg. 2014 Aug;123:142-5.
30. Loubser P, Narayan R, Sandin K, et al. Continuous infusion of intrathecal baclofen: long-term effects on spasticity in spinal cord injury. Paraplegia 1991;29:48-64.
31. Bresolin N, Zucca C, Pecori A, et al. Efficacy and tolerability of eperisone and baclofen in spastic palsy: a double-blind randomized trial. Adv Ther 2009;26:563-73.
32. Bass B, Weinshenker B, Rice G, et al. Tizanidine vs baclofen in the treatment of spasticity in patients with multiple sclerosis. Can J Neurol Sci 1988;15:15-19.
33. Eyssette M, Rohmer F, Serratrice G, et al. Multicenter, double-blind trial of a novel antispastic agent, tizanidine, in spasticity associated with multiple sclerosis. Curr Med Res Opin 1988;10:699-708.
34. Smolenski C, Muff S, Smolenski-Kautz S, et al. A double-blind comparative trial of new muscle relaxant, tizanidine (DS 103-282), and baclofen in the treatment of chronic spasticity in multiple sclerosis. Curr Med Res Opin 1981;7:374-83.
35. Stien R, Nordal H, Oftedal S, et al. The treatment of spasticity in multiple sclerosis: a double-blind clinical trial of a new anti-spastic drug tizanidine compared to baclofen. Acta Neurol Scand 1987;75:190-4.
36. Dai AI, W5HTy M, Awan S. Botulinum toxin type A with oral baclofen vs oral tizanidine: a nonrandomized pilot comparison in patients with cerebral palsy and spastic equinus foot deformity. J Child Neurol 2008;23:1464-6.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skeletal Muscle Relaxants, Miscellaneous
AHFS Class 122092
February 10, 2016

I. Overview

Orphenadrine is the only miscellaneous skeletal muscle relaxant that is currently available and it is 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 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 November 2013.

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

*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: Early Management of Persistent Non-Specific Low Back Pain (2009)**[4]	• The initial pharmacological treatment should be acetaminophen. • When acetaminophen alone provides insufficient pain relief, consider non-steroidal anti-inflammatory drugs and/or weak opioids. • Consider tricyclic antidepressants if other medicines provide insufficient pain relief. • Consider short-term use of strong opioids for patients in severe pain. • Skeletal muscle relaxants are not included among the pharmacological treatment options in this guideline.
American College of Physicians/American Pain Society: **Diagnosis and Treatment of Low Back Pain (2007)**[5]	• For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs. • Skeletal muscle relaxants are an option for short-term relief of acute low back pain, but all are associated with central nervous system adverse effects (primarily sedation). • There is no compelling evidence that skeletal muscle relaxants differ in efficacy or safety.
American College of Occupational and Environmental Medicine: **Low Back Disorders (2007)**[6]	Recommendations for the treatment of acute low back pain include: • Nonsteroidal anti-inflammatory drugs (NSAIDs). • Patients with known cardiovascular disease or multiple risk factors for cardiovascular disease should have risks and benefits of NSAID therapy for pain discussed. • Cytoprotective agents for patients with contraindications for non-steroidal

Clinical Guideline	Recommendation(s)
	anti-inflammatory drugs. • Acetaminophen if contraindications for non-steroidal anti-inflammatories. • Acetaminophen or aspirin as 1st-line therapy for patients with known or multiple risk factors for cardiovascular disease. • Skeletal muscle relaxants as 2nd-line treatment in select cases of moderate to severe acute low back pain not adequately controlled by NSAIDs. • Skeletal muscle relaxants are not recommended for mild to moderate acute low back pain or chronic use in subacute or chronic low back pain (other than acute exacerbations). • Limited use of opioids for severe acute low back pain without radicular pain.

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
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[3]

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

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Skeletal Muscle Relaxants, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Orphenadrine	2	Haloperidol	Mechanism unknown. Orphenadrine is an analogue of diphenhydramine with anticholinergic properties. Worsening of schizophrenia symptoms, decreased haloperidol serum concentration, and tardive dyskinesia have been reported when anticholinergic agents were used with haloperidol.
Orphenadrine	2	Phenothiazines	Orphenadrine is an analogue of diphenhydramine with anticholinergic properties. The concurrent use of anticholinergic agents may reduce oral absorption of phenothiazines, antagonize the

Generic Name(s)	Significance Level	Interaction	Mechanism
			behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects.
Orphenadrine	2	Potassium chloride	Orphenadrine may slow gastrointestinal motility, delaying potassium chloride tablet passage through the gastrointestinal tract.

Significance level 1=major severity, significance level 2=moderate severity.

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]

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

Adverse Events	Orphenadrine
Cardiovascular	
Palpitations	✔
Shock	✔
Tachycardia	✔
Central Nervous System	
Agitation	✔
Confusion	✔
Dizziness	✔
Drowsiness	✔
Dyskinesia	✔
Euphoria	✔
Excitement	✔
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	

Adverse Events	Orphenadrine
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

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tervo et al.[9] (1976) 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	DB, PC, RCT Patients with acute LBP	N=25 7 days	Primary: Mean duration of disability; subjective impressions of the treatments Secondary: Objective clinical examinations (gait, sitting posture, scoliosis, spinal flexion, muscle spasm, Lasegue)	Primary: Treatment with orphenadrine significantly reduced the mean duration of 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

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

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	$

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

X. Conclusions

Orphenadrine is the only miscellaneous skeletal muscle relaxant that is currently available, and it is approved for the symptomatic relief of pain associated with acute musculoskeletal disorders.[1-3] It 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; however, there were no studies found in the medical literature that directly compared orphenadrine to other skeletal muscle relaxants.[1-3,7-10]

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.

XII. References

1. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Sep]. Available from: http://online.factsandcomparisons.com.
2. Norflex™ [package insert]. Northridge, CA*:* 3M Pharmaceuticals; 2007 Apr.
3. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Sep]. Available from: http://www.thomsonhc.com/.
4. National Institute for Health and Care Excellence (NICE). Low back pain: Early management of persistent non-specific low back pain [guideline on the internet]. London (UK): NICE; 2009 [cited 2013 Aug 30]. Available from: http://www.nice.org.uk/CG88.
5. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147:478-91.
6. Hegmann KT, ed. Low back disorders. In: Glass LS, editor(s). Occupational medicine practice guidelines: evaluation and management of common health problems and functional recovery in workers. 3rd ed. Elk Grove Village (IL): American College of Occupational and Environmental Medicine (ACOEM); 2011. p. 333. Available at: http://www.guideline.gov/content.aspx?id=38438.
7. Gold R. Orphenadrine citrate: sedative or muscle relaxant? Clin Ther. 1978;1:451-3.
8. Klinger N, Wilson R, Kanniainen C, et al. Intravenous orphenadrine for the treatment of lumbar paravertebral muscle strain. Curr Ther Res. 1988;43:247-54.
9. Tervo T, Petaja L, Lepisto P. A controlled clinical trial of a muscle relaxant analgesic combination in the treatment of acute lumbago. Br J Clin Pract. 1976;30:62-4.
10. Hoivik H, Moe N. Effect of a combination of orphenadrine/paracetamol tablets ('Norgesic') on myalgia: a double-blind comparison with placebo in general practice. Curr Med Res Opin. 1083;8:531-5.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Opiate Agonists
AHFS Class 280808
February 10, 2016

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]

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 pharmacotherapy treatments.[8] Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence.[4-6] 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.[8,9] Patients may also experience withdrawal symptoms when a dose is missed. In addition, there is no ceiling to its effects and an overdose can be fatal. Compared to full agonists, buprenorphine (partial agonist) has a lower potential for abuse and is safer in an overdose situation.[9]

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.[10] An additional safety communication regarding the risks of using tramadol in children aged 17 years and younger was released in September 2015. The FDA is reviewing available information on the rare but serious risk of slowed or difficult breathing and will communicate final conclusions when the review is complete.[11] In November 2010, the FDA recommended against the continued prescribing and use of propoxyphene-containing products and asked manufacturers to voluntarily remove these products from the United States market. The decision was based on the results of a new study, which showed that when propoxyphene was taken at therapeutic doses, there were significant changes to the electrical activity of the heart (prolonged QT, PR, and QRS intervals).[12] In January 2011, the FDA also asked manufacturers to limit the amount of acetaminophen in prescription drug products (which are predominantly combinations of acetaminophen and opioids) to 325 mg per dosage form to make these products safer for patient to use.[13] In January 2014 the FDA recommended health care professionals discontinue prescribing and dispensing prescription combination drug products that contain more than 325 mg of acetaminophen. More than half of manufacturers have voluntarily complied with the initial 2011 FDA request. However, some prescription combination drug products containing more than 325 mg of acetaminophen per dosage unit remain available.[14] Over the last several years, the FDA has made great efforts to curb the rapidly-escalating problem of misuse and abuse of extended-release and long-acting opioids. Emphasis has been placed on the development of abuse-deterrent opioid formulations, and a Risk Evaluation and Mitigation Strategy

(REMS) has been implemented to educate prescribers on the dangerous risks associated with the prescription and utilization of opioid medications.[15]

In September 2013, the FDA announced labeling changes for all extended-release and long-acting opioids, and the changes were finalized in April 2014. Safety labeling across the class now includes an updated indication stating that these agents are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or otherwise inadequate. The FDA requires a new boxed warning regarding the risk of neonatal opioid withdrawal syndrome when these agents are used during pregnancy, and also requires the manufacturers of extended-release and long-acting opioids to conduct postmarket studies further assessing the known risks of misuse, abuse, hyperalgesia, addiction, overdose, and death. These changes are incorporated into the aforementioned REMS program.[16]

Another regulatory change regarding hydrocodone and acetaminophen combination products occurred on October 6, 2014, as the DEA re-scheduled hydrocodone and acetaminophen combination products from schedule III to schedule II.[17]

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 remifentanil and tapentadol. This class was last reviewed in November 2013. 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^	Alfenta®*	alfentanil
Codeine	tablet	N/A	codeine
Fentanyl	buccal lozenge, buccal tablet, injection, nasal spray, sublingual spray, sublingual tablet, transdermal patch	Abstral®, Actiq®*, Duragesic®*, Fentora®, Lazanda®, Sublimaze®*, Subsys®	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	Dolophine®*, Methadose®*	methadone
Morphine	epidural, injection, rectal suppository, solution, tablet	Astramorph-PF®, Duramorph®, Infumorph®	morphine
Oxycodone	capsule, oral concentrate, solution, tablet	Oxecta®, Roxicodone®*	oxycodone
Oxymorphone	injection, tablet	Opana®*	oxymorphone
Remifentanil	injection^	Ultiva®	none
Sufentanil	injection^	Sufenta®*	sufentanil
Tapentadol	extended-release tablet, tablet	Nucynta®, Nucynta ER®	none
Tramadol	extended-release capsule, extended-release tablet, tablet	Conzip ER®*, Ultram®*, Ultram ER®*	tramadol
Combination Products			
Codeine and acetaminophen	elixir, suspension, tablet	Capital w/Codeine®, Tylenol-Codeine No.3®*, Tylenol-	codeine and acetaminophen

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
		Codeine No.4®*	
Codeine, butalbital, acetaminophen, and caffeine	capsule	Fioricet With Codeine®*	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
Dihydrocodeine, aspirin, and caffeine	capsule	Synalgos-DC®*	dihydrocodeine, aspirin, and caffeine
Hydrocodone and acetaminophen	solution, tablet	Hycet®*, Lorcet HD®*, Lorcet Plus®*, Lortab®*, Norco®*, Verdrocet®*, Vicodin®*, Vicodin ES®*, Vicodin HP®*, Xodol®*, Zamicet®*	hydrocodone and acetaminophen
Hydrocodone and ibuprofen	tablet	Ibudone®*, Reprexain®*, Vicoprofen®*, Xylon®*	hydrocodone and ibuprofen
Opium and belladonna	rectal suppository	N/A	opium and belladonna
Oxycodone and acetaminophen	extended-release tablet, solution, tablet	Percocet®*, Primlev®, Xartemis XR®	oxycodone and acetaminophen
Oxycodone and aspirin	tablet	Percodan®*	oxycodone and aspirin
Oxycodone and ibuprofen	tablet	N/A	oxycodone and ibuprofen
Tramadol and acetaminophen	tablet	Ultracet®*	tramadol and acetaminophen

*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 (2015)**[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 (7 to 10), moderate pain (4 to 6) and mild pain (1 to 3). • Pain associated with oncology emergency should be addressed while treating the underlying condition. <u>General principles of opioid treatment</u> • The appropriate dose is that which relieves the patient's pain throughout the dosing interval without causing unmanageable adverse effects. • Titrate with caution in patients with risk factors such as decreased renal/hepatic function, chronic lung disease, upper airway compromise, sleep

Clinical Guideline	Recommendation(s)
	apnea, and poor performance status. • 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 provide adequate pain relief while avoiding the toxicities of the non-opioid component. • Monitor for aberrant drug-taking behaviors. • Risk Evaluation and Mitigation Strategies (REMS) programs are currently in place for all transmucosal fentanyl products; long-acting, extended-release formulations of opioids (e.g. hydrocodone ER, hydromorphone ER, morphine ER, oxycodone ER, oxymorphone ER, tapentadol ER); methadone tablets and solutions indicated for use as analgesics; and fentanyl or buprenorphine-containing transdermal systems. <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. • When possible, use the same opioid for short-acting and extended-release forms. • Increase the dose of extended-release 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. • 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 one hour as needed. <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 severe pain should receive rapid titration of short-acting opioids. • For opioid-naïve patients whose pain intensity is moderate at presentation, the pathways are quite similar to those for severe pain, with slower titration of short-acting opioids. • Opioid-naïve patients experiencing mild pain intensity should receive nonopioid analgesics, such as NSAIDs or acetaminophen, or treatment with consideration of slower titration of short-acting opioids. • Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended-release or long-acting formulations of opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain. Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment. <u>Management of pain in opioid-tolerant patients</u> • Opioid-tolerant patients are those chronically taking opioids for pain relief. 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."

Clinical Guideline	Recommendation(s)
	• In order to achieve adequate analgesia in opioid-tolerant patients who are experiencing breakthrough pain of intensity greater than or equal to 4, or a pain intensity less than 4 without meeting goals for pain control and function, the previous 24-hour total oral or intravenous opioid requirement must be calculated and the new "rescue" dose must be increased by an opioid dose equivalent to 10 to 20% of the total opioid taken in the previous 24 hours. • Efficacy and adverse effects should be assessed every 60 minutes for orally administered opioids and every 15 minutes for intravenous opioids to determine a subsequent dose. Upon assessment, if the pain score remains unchanged or is increased, administration of 50 to 100% of the previous rescue dose is recommended. <u>Selecting an appropriate opioid</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. • In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice. • Morphine and hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. • Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone. • 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. • The methods of administering analgesics that are widely accepted within clinical practice include "around the clock", "as needed", and "patient-controlled analgesia." • "Around the clock" dosing is provided to chronic pain patients for continuous

Clinical Guideline	Recommendation(s)
	pain relief. A "rescue dose" should also be provided as a subsequent treatment for patients receiving "around the clock" doses. Rescue doses of short acting opioids should be provided for pain that is not relieved by regularly scheduled, "around the clock" doses. Opioids administered on an "as needed" basis are for patients who have intermittent pain with pain-free intervals. The "as needed" method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows a patient to control a device that delivers a bolus of analgesic "on demand". • No single opioid is optimal for all patients. When considering opioid rotation, defined as changing to an equivalent dose of an alternative opioid to avoid adverse effects, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. • Subsequent treatment is based upon the patient's continued pain rating score. All approaches for all pain intensity levels must include administering regular doses of opioids with rescue doses as needed, management of constipation, and psychosocial support and education for patients and their families. • Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's goals of comfort and function is mandated at each contact. • If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patients should be converted to an extended-release oral medication (if feasible) or another extended-release formulation (i.e., transdermal fentanyl) or long-acting agent (i.e., methadone). The subsequent treatment is based upon the patients' continued pain rating score. Rescue doses of the short acting formulation of the same long acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by extended-release opioids. • Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety. • Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, other individual characteristics of the patient such as age, and physical condition. • Opioids alone may not provide the optimal therapy, but when used in conjunction with nonopioid analgesics, such as an NSAID or adjuvant, and psychological and physical approaches, they can help to improve patient outcomes. • Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or, in some cases, to counter the adverse events associated with opioids. • The term adjuvant refers to medications that are coadministered to manage an adverse event of an opioid or to adjuvant analgesics that are added to enhance analgesia. Adjuvant may also include drugs for neuropathic pain. Clinically, adjuvant analgesics consist of anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch). • Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, visceral pain, and to reduce systemic opioid requirement, and are particularly important in treating neuropathic pain that is resistant to opioids. • Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain. Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic interventions. Attentions should be focused on psychosocial support and providing education to patients and families.

Clinical Guideline	Recommendation(s)
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 (2012)**[20]	• Treatment of mild pain (WHO Step 1 analgesics):
	  o Acetaminophen or NSAIDs.
	• Treatment of moderate pain (WHO Step 2 analgesics):
	  o Acetaminophen, aspirin, or an NSAID plus a weak immediate-release opioid such as codeine, dihydrocodeine, tramadol, or propoxyphene or a strong opioid at low doses such as morphine or oxycodone.
	  o New opioid formulations may improve drug administration for patients with moderate pain. These include controlled release formulations of codeine, dihydrocodeine, tramadol, morphine and oxycodone in dosages appropriate for moderate pain.
	  o Additional options include low-dose formulations of transdermal fentanyl and of transdermal buprenorphine.
	• Treatment of severe pain (WHO Step III analgesics):
	  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 Methadone is an alternative treatment option, but may be more complicated to use because of its pharmacokinetic parameters. Methadone should be initiated by physicians with experience and expertise in its use.
	  o Strong opioids may be combined with a nonopioid analgesic (step 1).
	  o Patients with severe pain that need urgent relief should be treated with parenteral opioids
	• Opioid doses should be titrated to effect as rapidly as possible, with around-

Clinical Guideline	Recommendation(s)
	the-clock dosing and an as-needed 'breakthrough dose' (usually=10% of total daily dose) to manage transient pain exacerbations. If more than four 'breakthrough doses' per day are necessary, opioid treatment with a slow-release formulation should be initiated. • Reduction in opioid dose may be achieved by using a co-analgesic, such an antidepressant, neuroleptic psychoactive drug or anticonvulsant. Such combinations may also alleviate refractory side effects such as constipation, nausea, vomiting and central nervous system toxicity. Other strategies include the continued use of anti-emetics, laxatives, major tranquilizers, and psychostimulants; also, switching to another opioid agonist and/or another route may allow titration to adequate analgesia without the same disabling effects. • Neuropathic pain may not be adequately controlled by opioids alone; combination with co-analgesics may improve pain control. Steroids should be considered in case of nerve compression. There is sufficient evidence for use of bisphosphonates for refractory bone pain, but not for general use as first-line therapy of bone pain.

National Opioid Use Guideline Group: **Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain (2010)**[21]	<u>Conducting an opioid trial</u>
	• During an opioid trial, select the most appropriate opioid for trial therapy using a stepped approach, and consider safety.
	• Mild-to-moderate pain:
	  o First-line therapy: codeine or tramadol. There is a lower risk of overdose and addiction with these agents than stronger opioids. Tramadol is associated with seizures in patients at high seizure risk, or when combined with medications that increase serotonin levels (e.g., selective serotonin reuptake inhibitors).
	  o Second-line therapy: morphine, oxycodone or hydromorphone.
	• Severe pain:
	  o First-line therapy: morphine, oxycodone or hydromorphone. Oxycodone, hydromorphone and hydrocodone may have a higher abuse liability than morphine.
	  o Second-line therapy: fentanyl. Before starting fentanyl, ensure the patient is fully opioid tolerant.
	  o Third-line therapy: methadone. Titration of methadone is hazardous due to its very long half life leading to drug accumulation.
	• Start with a low dosage, increase dosage gradually and monitor opioid effectiveness until optimal dose is attained.
	• Chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200 mg/day of morphine or equivalent.
	• When initiating opioid therapy for patients at higher risk for misuse, prescribe only for well-defined somatic or neuropathic pain conditions, start with lower doses and titrate in small-dose increments, and monitor closely for signs of drug-related behaviors.
	• Meperidine is not recommended for use in chronic non-cancer pain. Oral meperidine has poor bioavailability and is less effective than codeine. Normeperidine can accumulate with frequent use of parenteral doses of meperidine, causing seizures and delirium.
	• Use acetaminophen-opioid combinations with caution to avoid acetaminophen toxicity.
	• Titrate controlled-release formulations with caution to avoid overdose and misuse. Each controlled-release tablet can contain a much higher opioid dose than immediate-release formulations, and can easily be converted to immediate release by biting or crushing the tablet.
	• Parenteral opioids are not recommended for use in chronic non-cancer pain. The parenteral route has higher risk of overdose, abuse and addiction, and

Clinical Guideline	Recommendation(s)

	infection.
	
	<u>Monitoring long-term opioid therapy</u>
	• For patients experiencing unacceptable adverse effects or insufficient opioid effectiveness from one particular opioid, try prescribing a different opioid or discontinuing therapy.
	• For patients receiving opioids for a prolonged period who may not have had an appropriate trial of therapy, take steps to ensure that long-term therapy is warranted and dose is optimal.
	
	<u>Treating specific populations with long-term opioid therapy</u>
	• Opioid therapy in elderly patients can be safe and effective. They cause less organ toxicity than NSAIDs and appear to cause less cognitive impairment than benzodiazepines. Among strong opioids, oxycodone and hydromorphone may be preferred over oral morphine because they are less likely to cause constipation and sedation. Controlled-release formulations are recommended due to compliance. There is no evidence controlled-release formulations are more effective than immediate-release formulations. For breakthrough pain or activity-related pain, immediate release formulations can be used.
	• A trial of opioid therapy may be considered for adolescent patients with well-defined somatic or neuropathic pain conditions when non-opioid alternatives have failed, risk of opioid misuse is assessed as low, close monitoring is available, and consultation, if feasible, is included in the treatment plan.
	• Pregnant patients taking long-term opioid therapy should be tapered to the lowest effective dose slowly enough to avoid withdrawal symptoms, and then therapy should be discontinued if possible.
	• Patients with a psychiatric diagnosis are at greater risk for adverse effects from opioid treatment. Usually in these patients, opioids should be reserved for well-defined somatic or neuropathic pain conditions. Titrate more slowly and monitor closely; seek consultation where feasible.
	
	<u>Managing opioid misuse and addiction in chronic non-cancer pain patients</u>
	• For patients with chronic non-cancer pain who are addicted to opioids, three treatment options should be considered: methadone or buprenorphine treatment, structured opioid therapy, or abstinence-based treatment.
	• Indications for methadone treatment are any of the following:
	  o Failed trial of structured opioid therapy.
	  o Using opioids by injection, snorting, or crushing tablets.
	  o Accessing opioids from multiple physicians or from the “street”.
	  o Addiction to opioids and to other drugs/substances.
	• Indications for buprenorphine treatment are similar to those for methadone treatment. Buprenorphine could be preferred over methadone for:
	  o Patients who are at higher risk of methadone toxicity.
	  o Adolescents and young adults.
	  o Patients in communities where methadone treatment is unavailable.
	• An ideal candidate for a structured opioid therapy trial would be an opioid-addicted patient with chronic non-cancer pain who:
	  o Has a well-defined somatic or neuropathic pain condition for which opioids have been shown to be effective.
	  o Is well-known to the physician.
	  o Is not currently addicted to cocaine, alcohol or other drugs.
	  o Is not accessing opioids.
	• Abstinence-based treatment can be a patient preference or used when methadone or buprenorphine treatment is not available.

American Society of	• Pharmacologic management of chronic pain includes anticonvulsants,

Clinical Guideline	Recommendation(s)
Anesthesiologists/ American Society of Regional Anesthesia and Pain Medicine: **Practice Guidelines for Chronic Pain Management (2010)**[22]	antidepressants, benzodiazepines, N-methyl-D-aspartate (NMDA) receptor antagonists, NSAIDs, opioid therapy, skeletal muscle relaxants, and topical agents. • Anticonvulsants should be used as part of a multimodal strategy for patients with neuropathic pain. • Tricyclic antidepressants should be used as part of a multimodal strategy for patients with chronic pain. • Serotonin–norepinephrine reuptake inhibitors should be used as part of a multimodal strategy for a variety of chronic pain patients. • Selective serotonin reuptake inhibitors may be considered specifically for patients with diabetic neuropathy. • As part of a multimodal pain management strategy, extended-release oral opioids should be used for neuropathic or back pain patients, and transdermal, sublingual, and immediate-release oral opioids may be used. • For selected patients, NMDA receptor antagonists (e.g., neuropathic pain), NSAIDs (e.g., back pain), and topical agents (e.g., peripheral neuropathic pain) may be used; benzodiazepines and skeletal muscle relaxants may be considered. • A strategy for monitoring and managing side effects, adverse effects, and compliance should be considered for all patients undergoing any long-term pharmacologic therapy.

Veterans Health Administration, Department of Defense: **Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (2010)**[23]	<u>General considerations</u>
	• A trial of opioid therapy is indicated for a patient with chronic pain who meets all of the following criteria:
	  o Moderate to severe pain that has failed to adequately respond to non-opioid and non-drug therapeutic interventions.
	  o The potential benefits of opioid therapy are likely to outweigh the risks.
	  o The patient is fully informed and consents to the therapy.
	  o Clear and measurable treatment goals are established.
	
	<u>Initiation phase</u>
	• There is no evidence to recommend for or against the selection of any specific opioid:
	  o Select a specific opioid formulation that matches the individual's needs and specific medical conditions.
	  o Consider patient preference, and agent that allows administration by the least in visual analogue scale route.
	  o Consider the ease of drug administration, patient's prior experience with, and level of tolerance to opioid medications, potential risk for misuse, and abuse patterns.
	  o Transdermal fentanyl should be avoided in opioid naïve patients.
	• Start the opioid therapy trial with a low dose and with one medication at a time.
	• For continuous chronic pain, an agent with a long duration of action, such as controlled-release morphine or methadone is recommended. Short-acting opioids can be started, and later converted to long acting opioids.
	• Treatment of continuous chronic pain should be initiated with opioids on a defined and scheduled basis.
	• For episodic chronic pain, consider short-acting opioids (such as morphine, oxycodone, or hydrocodone), trying one medication at a time on an as needed basis. Long-acting opioids should not be used on an as needed basis.
	
	<u>Titration phase</u>
	• Titration should be individualized according to the patient's age, health status,

Clinical Guideline	Recommendation(s)

	previous exposure to opioids, level of pain, comorbidities, potential drug interactions, opioid formulation, level of care, attainment of therapeutic goals, and predicted or observed harms.
	• The daily dose may be increased by 25 to 100% at a time. Smaller increments are appropriate for elderly patients, those with likely low opioid tolerance, and patients experiencing unsatisfactory pain relief in the presence of some adverse effects. Larger increments may be used in patients with severe uncontrolled pain or likely high level of opioid tolerance.
	• To ensure that the full effect from a dosage change has been manifested, and to avoid potential toxicity due to rapid accumulation of a drug, do not increase the dose more frequently than every five half-lives.
	• Methadone dosage titration should not occur more frequently than every seven days or longer (e.g., every one to two months), and only if there is no problem with daytime sedation.
	• If possible, titrate one drug at a time while observing the patient for additive effects. Maintain patients on as few medications as possible to minimize drug interactions and adverse events.
	• Discontinue medications, especially adjuvant medications, which do not add substantially to patient function or comfort.
	• If a medication provides less than satisfactory pain reduction despite increasing the dose as tolerated to a reasonable level (<200 mg/day morphine equivalent), evaluate for potential causes such as nonadherence and drug interactions, and consider changing to an alternate opioid medication.
	• During the titration phase, reasonable supplemental doses of a short acting opioid may be considered.
	• Consider one or more of the following adjustments in therapy when there is an apparent loss of analgesic effect:
	  o Further optimize adjuvant therapies.
	  o Re-titrate the dose.
	  o Rotate to another opioid.
	  o Refer or consult with advanced pain care specialist.
	  o Discontinue opioid therapy.
	
	<u>Maintenance phase</u>
	• Maintain the lowest effective and well-tolerated dose. The optimal opioid dose is the one that achieves the goals of pain reduction and/or improvement in functional status and patient satisfaction with tolerable adverse effects.
	
	<u>Supplemental therapy</u>
	• Supplemental short- acting opioids may be considered in specific situations but their routine use in chronic pain is controversial.
	• This guideline supports the use of long-acting opioids in a scheduled manner for chronic pain, rather than the use of supplemental or as-needed opioids for exacerbations.
	• Evaluate worsening or new pain symptoms to determine the cause and the best treatment approach.
	• Encourage the use of nonpharmacologic treatments.
	• Evaluate the potential benefits, side effects, and risks when considering supplemental opioids. Consider supplemental short-acting opioid, non-opioid, or a combination of both agents on an as needed basis.
	• Avoid the use of rapid-onset opioids as supplemental opioid therapy in chronic pain, unless the time course of action of the preparation matches the temporal pattern of pain intensity fluctuation.
	• Avoid use of long-acting agents for acute pain or on an as-needed basis in an outpatient setting.

Clinical Guideline	Recommendation(s)
	• When using combination products, do not exceed maximum recommended daily doses of acetaminophen, aspirin, or ibuprofen. • Avoid the use of mixed agonist-antagonist opioids, as these agents may precipitate withdrawal in patients who have physical opioid dependence. • Whenever possible, use the same opioid for supplemental therapy as the long-acting opioid to avoid confusion about the cause of any adverse effects that may develop. • When using short-acting pure agonist opioids (alone or in combination with non-opioid analgesics) for supplemental therapy, give opioid doses equivalent to about 10 to 15%, the every four hourly equivalent, or 1/6th of the total daily opioid dose, as needed. • Use rescue short-acting opioids to assist with pain management during the titration process and to help determine the long-term daily opioid dose. • Do not use breakthrough pain therapy routinely for chronic pain. If necessary, use breakthrough pain therapy sparingly. • Consider adjusting the long-acting opioid regimen if pain exacerbations are interfering with patient function due to severity, frequency, or diurnal variations in pain intensity. • Consider providing preemptive analgesia for preventing incident pain.
American Pain Society/ American Academy of Pain Medicine: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[24]	• Consider a trial of chronic opioid therapy if chronic noncancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms. • Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. • There is insufficient evidence to recommend short-acting vs long-acting opioids, or as-needed vs around-the-clock dosing of opioids. • Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously by clinicians familiar with its use and risks. • When repeated dose escalations occur in patients on chronic opioid therapy, evaluate potential causes and reassess benefits relative to harms. • In patients who require relatively high doses of chronic opioid therapy, evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits. • Consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse effects or inadequate benefit despite dose increases. • Taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects. • In patients on around-the-clock chronic opioid therapy with breakthrough pain, consider as-needed opioids based upon an initial and ongoing analysis of therapeutic benefit vs risk.
Veterans Health Administration, Department of Defense: **Clinical Practice Guideline for Management of Substance Use Disorders (2009)**[25]	General considerations • Opioid agonist treatment is the first-line treatment for chronic opioid dependence. • Provide access to opioid agonist treatment for all opioid dependent patients, under appropriate medical supervision and with concurrent addition-focused psychosocial treatment. • Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first-line therapy. Buprenorphine monotherapy is preferred in pregnancy.

Clinical Guideline	Recommendation(s)
	• By administering an opioid to prevent withdrawal, reduce craving, and reduce the effects of illicit opioids, the opioid-dependent patient is able to focus more readily on recovery activities. <u>Opioid agonist treatment program and office-based opioid treatment</u> • Opioid agonist treatment should be administered in an opioid agonist treatment program or office-based opioid treatment. • Doses should be adjusted to maintain a therapeutic range between signs/symptoms of overmedication and opioid withdrawal. • The usual dosage range for optimal effects is 60 to 120 mg/day. • Buprenorphine target dose is generally up to 16 mg/day; doses >32 mg are rarely indicated. • In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. <u>Methadone therapy</u> • Methadone for the treatment of opioid dependence may only be prescribed out of an accredited opioid agonist treatment program as it is a schedule II agent. It is illegal to prescribe methadone for the treatment of opioid dependence out of an office-based practice. • For newly admitted patients, the initial dose of methadone should not exceed 30 mg and the total dose for the first day should not exceed 40 mg, without provider documentation that 40 mg did not suppress opioid withdrawal symptoms. • Under usual practices, a stable, target dose is greater than 60 mg/day and most patients will require considerably higher doses in order to achieve a pharmacological blockade of reinforcing effects of exogenously administered opioids. <u>Buprenorphine therapy</u> • Office-based treatment with sublingual buprenorphine for opioid dependence can only be provided by physicians who have received a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) and have a special Drug Enforcement Agency (DEA) number. • Buprenorphine induction (~1 week) involves helping a patient in the process of switching from the opioids of abuse to buprenorphine. • In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. • The initial dose of buprenorphine/naloxone combination is between 2/0.5 mg to 4/1 mg, which can be repeated after two hours. The amount of buprenorphine administered in the first day should not exceed 8 mg. • The daily buprenorphine/naloxone dose is the equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on day one. Doses may be increased as needed for symptomatic relief, with a target dose of 12/3 mg to 16/4 mg per day to be achieved within the first week.
American Psychiatric Association: **Practice Guideline for Treatment of Patients with Substance Use Disorders (2006)[26]**	<u>Treating dependence and abuse</u> • Goals of therapy are to identify stable maintenance dose of opioid agonist and facilitate rehabilitation. • The choice of treatment for opioid dependence is based on patient preference, past response to treatment, probability of achieving and maintaining abstinence, and assessment of the short- and long-term effects of continued use of illicit opioids on the patient's life adjustment and overall health status. • Maintenance treatment with methadone or buprenorphine is appropriate for patients with ≥ 1 year history of opioid dependence. Maintenance therapy with naltrexone is an alternative strategy.

Clinical Guideline	Recommendation(s)

	• Methadone is a full mu agonist opioid, and is the most thoroughly studied and widely used agent for opioid dependence.
	• Methadone maintenance treatment for opioid-dependent individuals has generally been shown to be effective in:
	  o Decreasing illicit opioid use.
	  o Decreasing psychosocial and medical morbidity.
	  o Improving overall health status.
	  o Decreasing mortality.
	  o Decreasing criminal activity.
	  o Improving social functioning.
	  o Reducing the spread of Human Immunodeficiency Virus infection among intravenous drug users.
	• Maintenance on methadone is generally safe; however, one key issue is determining a dose sufficient to suppress the patient's opioid withdrawal and craving, as no single dose is optimal for all patients.
	• Methadone can be diverted for abuse, as can other opiates that have agonist effects at the mu receptor.
	• Buprenorphine produces a partial agonist effect at the mu receptor and an antagonistic effect at the kappa receptor.
	• Buprenorphine enters the systemic circulation more slowly through the sublingual route than with parenteral administration and has less abuse potential compared to the parenterally delivered form.
	• The combination of buprenorphine and naloxone significantly reduces the risk of diversion because naloxone will exert a potent opioid antagonist effect if the combination tablet is crushed and administered intravenous by an opioid-dependent person. Naloxone has poor sublingual bioavailability.
	• Buprenorphine is generally safe. Overdose with buprenorphine generally does not produce significant respiratory depression
	
	<u>Treating intoxication</u>
	• Mild to moderate opioid intoxication usually does not require specific therapy.
	• Severe opioid toxicity, marked by respiratory depression, is a medical emergency. Naloxone will reverse respiratory depression and other overdose manifestations.
	
	<u>Treating withdrawal</u>
	• Treatment of withdrawal is directed at safely decreasing acute symptoms and easing transition into a long-term treatment program.
	• Effective strategies include:
	  o Substitution of opioid with methadone or buprenorphine.
	  o Abrupt discontinuation of opioids, with use of clonidine to suppress withdrawal symptoms.
	  o Clonidine-naltrexone detoxification.

Center for Substance Abuse Treatment: **Medication-Assisted Treatment For Opioid Addiction in Opioid Treatment Programs (TIP 43) (2005)**[27]	• To be considered for buprenorphine maintenance, patients should have a diagnosis of opioid dependence. • It is recommended that buprenorphine and naloxone be used for induction treatment (and for stabilization and maintenance) for most patients. • The initial induction doses should be administered as observed treatment; further doses may be provided via prescription thereafter. • To minimize the chances of precipitated withdrawal, patients who are transferring from long-acting opioids to buprenorphine should be inducted using buprenorphine monotherapy, but switched to buprenorphine and naloxone soon thereafter. • The longest period that a patient is on buprenorphine is the maintenance

Clinical Guideline	Recommendation(s)
	phase. This period may be indefinite. • Buprenorphine can be used for the medically supervised withdrawal of patients from both self-administered opioids and from opioid agonist treatment with methadone or levo-alpha-acetyl-methadol. • The goal of using buprenorphine for medically supervised withdrawal from opioids is to provide a transition from the state of physical dependence on opioids to an opioid-free state, while minimizing withdrawal symptoms. • It is recommended that patients dependent on short-acting opioids who will be receiving medically supervised withdrawal be inducted directly onto buprenorphine and naloxone tablets. • The use of buprenorphine or buprenorphine and naloxone to taper off long-acting opioids should be considered only for those patients who have evidence of sustained medical and psychosocial stability, and should be undertaken in conjunction and in coordination with patients' opioid treatment programs.

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 moderate to severe pain in patients where an opioid analgesic is appropriate			✔	✔			✔
Management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time						✔ ‖	✔ #
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		✔ †					
Relief of mild to moderate pain	✔						
Relief of moderate to severe pain					✔ ‡§	✔ ‡	
Treatment of pain following major surgery							✔ **
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					✔ ‡		
Support of anesthesia					✔ ‡		
Detoxification/Dependence							
For detoxification treatment of opioid addiction (heroin or other						✔ ¶	

Indication	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine
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.
^Intranasal formulation.
»Sublingual 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 moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time				✔†
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 moderate to severe pain in patients where an opioid analgesic is appropriate	✔	✔		
Relief of moderate to moderately severe pain				✔
Relief of moderate to severe pain			✔	
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	Codeine and Acetaminophen	Codeine, Butalbital, Acetaminophen and Caffeine	Codeine, Butalbital, Aspirin and Caffeine	Dihydrocodeine, Acetaminophen and Caffeine	Dihydrocodeine, Aspirin and Caffeine	Hydrocodone and Acetaminophen	Hydrocodone and Ibuprofen
Analgesia							
Relief of mild to moderate pain	✔						
Relief of moderate to moderately severe pain				✔	✔	✔	
Short-term (≤10 days) management of acute pain							✔
Headache							
Relief of tension or muscle contraction headache		✔	✔				

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

Indication	Opium and Belladonna	Oxycodone and Acetaminophen	Oxycodone and Aspirin	Oxycodone and Ibuprofen	Tramadol and Acetaminophen
Analgesia					
Relief of moderate to moderately severe pain		✔	✔		
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					✔
Short-term (≤7 days) management of acute, moderate to severe pain				✔	

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 individuals 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	Liver (24 to 89)	Renal (11)	2.5 to 3.5
Dihydrocodeine	21	Not reported	Not reported	Not reported	3.3 to 4.5
Fentanyl	Buccal: 50 to 76 SL: 54 TD: 92	80 to 86	Liver	Renal (10)	Buccal: 2.6 to 12.0 Injection: <4 SL: 5 to 13.5 TD: 17
Hydrocodone	Not reported	Not reported	Liver	Renal (6 to 20)	3.8 to 4.5
Hydromorphone	24	8 to 27	Liver (95)	Renal (1 to 13)	2.5
Levorphanol	Rapid	40 to 50	Liver	Not reported	11
Meperidine	Oral: variable	65 to 80	Liver	Renal (0.5 to 2)	3.2 to 3.7
Methadone	Oral: 85	71 to 88	Liver	Renal (21)	23
Morphine	Buccal: 50 Oral: 20 to 40 TD: 75	20 to 36	Liver	Renal (9)	1.5 to 2.0
Oxycodone	60 to 87	45	Liver	Renal (19)	3.2
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
Tramadol	IR: 75 ER: 85 to 95	20	Liver	Renal (30)	IR: 6.3 ER: 7.9
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

V. Drug Interactions

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

Table 8. Significant Drug Interactions with the Opiate Agonists[4]

Generic Name(s)	Significance Level	Interaction	Mechanism
Opiate agonists (fentanyl, methadone, oxycodone)	1	Azole antifungal agents	Pharmacologic effects and adverse reactions of opiates may be increased due to inhibition of CYP3A4 metabolism by azole antifungals.
Opiate agonists (fentanyl, oxycodone)	1	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

Generic Name(s)	Significance Level	Interaction	Mechanism
			cytochrome P450 3A4 isoenzymes by Human immunodeficiency virus protease inhibitors may decrease the metabolic elimination of opiate agonists.
Opiate agonists (codeine, fentanyl, methadone, oxycodone)	1	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.
Acetaminophen	1	Isoniazid	Isoniazid may increase the toxic effects of acetaminophen. The mechanism of this interaction is unknown.
Aspirin	1	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	1	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	1	Methotrexate	Therapeutic and toxic effects (bone marrow depression, 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	1	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	1	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	1	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.
Fentanyl	1	Amiodarone	Profound bradycardia, sinus arrest, and hypotension have occurred.
Fentanyl	1	Diltiazem	Diltiazem may increase plasma concentrations of fentanyl, increasing the potential for enhanced pharmacologic effects and toxicity. Inhibition of

Generic Name(s)	Significance Level	Interaction	Mechanism
			cytochrome P450 3A4 isoenzyme by diltiazem may decrease the metabolic elimination of fentanyl.
Fentanyl	1	Verapamil	Verapamil may increase plasma concentrations of fentanyl, increasing the potential for enhanced pharmacologic effects and toxicity. Inhibition of cytochrome P450 3A4 isoenzyme by verapamil may decrease the metabolic elimination of fentanyl.
Ibuprofen	1	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	1	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	1	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	1	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.
Meperidine	1	Monoamine oxidase inhibitors	A severe and potentially fatal reaction may occur shortly after administering meperidine to patients receiving monoamine oxidase inhibitors.
Methadone	1	Benzodiazepines	The synergistic effects of opioids and benzodiazepines may increase the risk of sedation and life-threatening respiratory depression, especially with overdosage.
Methadone	1	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.

Generic Name(s)	Significance Level	Interaction	Mechanism
Methadone	1	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	1	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	1	Dronedarone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades 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	1	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	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and methadone. QT interval effects of each agent may be additive.
Methadone	1	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.

Generic Name(s)	Significance Level	Interaction	Mechanism
			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.
Tapentadol	1	Monoamine oxidase inhibitors	Toxic effects may be increased with concurrent administration of tapentadol and monoamine oxidase inhibitors. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of tapentadol and monoamine oxidase inhibitors may be additive.
Tramadol	1	Monoamine oxidase inhibitors	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering tramadol to patients receiving monoamine oxidase inhibitors. The seizure threshold may also be reduced.
Tramadol	1	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).
Opiate agonists (codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone, tapentadol)	2	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.
Opiate agonists (codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone)	2	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 (codeine, dihydrocodeine,	2	Rifamycins	Rifamycins may decrease pharmacologic effects and plasma concentrations of opiate agonists. Pain control may be decreased.

Generic Name(s)	Significance Level	Interaction	Mechanism
fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone)			
Opiate agonists (fentanyl, meperidine, oxycodone)	2	Serotonin reuptake inhibitors	Toxic effects of serotonin reuptake inhibitors may be increased, resulting in development of serotonin syndrome.
Opiate agonists (codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone)	2	Sodium oxybate	Concurrent use of sodium oxybate and opiate agonists may result in an increase in sleep duration and central nervous system depression. Pharmacologic effects of sodium oxybate and opiate agonists may be additive.
Opiate agonists (fentanyl, meperidine)	2	Sibutramine	Use of sibutramine with opiate agonists has been reported by the manufacturer of sibutramine to increase the potential risk for serotonin syndrome. The mechanism is unknown.
Opium and belladonna	2	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	2	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	2	Carbonic anhydrase inhibitors	Aspirin may increase the toxic effects of carbonic anhydrase inhibitors; Carbonic anhydrase inhibitors may decrease the pharmacologic effects of aspirin.
Aspirin	2	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	2	Clopidogrel	The risk of life-threatening bleeding such as intracranial or gastrointestinal hemorrhage may be increased in high-risk patients with

Generic Name(s)	Significance Level	Interaction	Mechanism
			transient ischemic attack or ischemic stroke when given the combination of clopidogrel with aspirin.
Aspirin	2	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	2	Meglitinides	Hypoglycemic effects of meglitinides may be increased by aspirin. The mechanism of action in unknown.
Aspirin	2	Probenecid	The uricosuric action of probenecid is decreased. Hyperuricemia with possible exacerbation of gout may occur. The effects of this interaction depend on the dose of aspirin.
Aspirin	2	Serotonin reuptake blockers	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of aspirin and serotonin reuptake blockers. The mechanism of action is unknown.
Aspirin	2	Sulfinpyrazone	The uricosuric effect of sulfinpyrazone may be decreased. Hyperuricemia with possible exacerbation of gout may occur. The effects of this interaction depend on the dose of aspirin.
Butalbital	2	Clozapine	Butalbital may decrease pharmacologic effects and plasma concentrations of clozapine. The mechanism of this interaction is unknown.
Butalbital	2	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	2	Doxycycline	The antimicrobial effectiveness of doxycycline may be decreased. Induction of hepatic microsomal enzymes by butalbital may increase the metabolic elimination of doxycycline.
Butalbital	2	Metronidazole	The antimicrobial effectiveness of metronidazole may be decreased. Induction of hepatic microsomal enzymes by butalbital may increase the metabolic elimination of metronidazole.
Butalbital	2	Tacrolimus	Plasma concentrations and pharmacologic effects of tacrolimus may be decreased. Increased hepatic metabolism via CYP3A4 of tacrolimus by butalbital may occur.
Butalbital	2	Teniposide	The therapeutic and toxic effects of teniposide may be decreased by butalbital. The mechanism of this interaction in unknown.
Butalbital	2	Theophyllines	Pharmacologic effects of theophyllines may be decreased by butalbital. Decreased

Generic Name(s)	Significance Level	Interaction	Mechanism
			theophylline plasma concentrations, possibly with a suboptimal therapeutic response, may occur. Hepatic metabolism of theophyllines may be increased by butalbital.
Codeine	2	Quinidine	Quinidine may decrease pharmacologic effects of codeine. Loss of analgesic effect may occur.
Fentanyl	2	Monoamine oxidase inhibitors	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering fentanyl to patients receiving monoamine oxidase inhibitors. The mechanism is unknown.
Fentanyl	2	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	2	Angiotensin-converting-enzyme inhibitor inhibitors	The antihypertensive effects of Angiotensin-converting-enzyme inhibitor inhibitors may be decreased by ibuprofen. Also, the risk Angiotensin-converting-enzyme inhibitor inhibitors or ibuprofen-related nephrotoxicity, including hyperkalemia, may be increased by this drug combination.
Ibuprofen	2	Bisphosphonates	Gastrointestinal adverse effects may be increased with concurrent administration of bisphosphonates and ibuprofen. The mechanism is unknown.
Ibuprofen	2	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	2	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	2	Loop diuretics	Diuretic effects of loop diuretics may be decreased by ibuprofen. Sodium retention and hypervolemia may occur. Ibuprofen may decrease natriuresis and diuresis of loop diuretics by inhibiting the synthesis of renal prostaglandins.
Ibuprofen	2	Probenecid	Pharmacologic and toxic effects of ibuprofen may be increased by probenecid.
Ibuprofen	2	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

Generic Name(s)	Significance Level	Interaction	Mechanism
			increase the risk of gastrointestinal bleeding compared to ibuprofen alone.
Meperidine	2	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	2	Phenothiazines	Excessive or prolonged central nervous system depression, respiratory depression and hypotension may occur, when phenothiazines and meperidine are used concomitantly.
Meperidine	2	Serotonin reuptake inhibitors	Risk of serotonin syndrome may be increased due to an unknown mechanism. Monitor closely for adverse reactions.
Methadone	2	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	2	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	2	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	2	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	2	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	2	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.
Tramadol	2	Anticoagulants	Tramadol may increase hypoprothrombinemic effects of

Generic Name(s)	Significance Level	Interaction	Mechanism
			anticoagulants. The mechanism of this interaction is unknown.
Tramadol	2	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	2	Carbamazepine	Carbamazepine may decrease the plasma concentrations and pharmacologic effects of tramadol. The mechanism of this interaction is unknown.
Tramadol	2	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	2	Loxapine	Use of tramadol with loxapine may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Molindone	Use of tramadol with molindone may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Phenothiazines	Use of tramadol with phenothiazines may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Thioxanthenes	Use of tramadol with thioxanthenes may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Tiagabine	Use of tramadol with tiagabine may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Tricyclic antidepressants	Use of tramadol with tricyclic antidepressants may increase the risk of seizures. The mechanism of this interaction is unknown.

Significance level 1=major severity, significance level 2=moderate severity.

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 individuals components listed in the tables below. The boxed warnings for the opiate agonists are listed in Tables 12 to 24.

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

Adverse Events	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	-	-	-	-	✔

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Ventricular fibrillation	-	-	-	-	-	-	-	✔
Ventricular tachycardia	-	-	-	-	-	-	-	✔
Central Nervous System								
Abnormal coordination	-	-	≥1	-	-	-	-	-
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	✔	✔	3 to 20	-	✔	-	✔	✔
Hemiplegia	-	-	✔	-	-	-	-	-
Hostility	-	-	✔	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	✔	-	-
Hypertonia	-	-	✔	-	-	-	-	-
Hypesthesia	-	-	✔	-	-	-	-	-
Hypokinesia	-	-	✔	-	-	✔	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Hypotonia	-	-	✔	-	-	-	-	-
Impairment of performance	✔	✔	-	✔	✔	-	-	-
Incoordination	-	-	✔	-	✔	-	✔	-
Increased intracranial pressure	-	-	-	-	✔	-	-	-
Insomnia	✔	-	1 to 10	-	✔	✔	-	✔
Lethargy	✔	-	-	✔	✔	✔	✔	-
Lightheadedness	✔	-	-	✔	✔	-	-	✔
Mental clouding	✔	-	-	✔	✔	-	-	-
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	✔	✔	✔	-	✔

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Skin discoloration	-	-	✔	-	-	-	-	-
Skin ulcer	-	-	✔	-	-	-	-	-
Sweating	✔	-	-	-	✔	✔	✔	✔
Urticaria	-	-	✔	-	✔	✔	-	✔
Vesiculobullous rash	-	-	✔	-	-	-	-	-
Wheal/flare	-	-	-	-	✔	-	-	✔
Endocrine and Metabolic								
Acidosis	-	-	✔	-	-	-	-	-
Antidiuretic effect	-	-	-	-	-	-	-	✔
Amenorrhea	-	-	-	-	-	-	-	✔
Cyanosis	-	-	-	-	-	-	✔	-
Hypercalcemia	-	-	✔	-	-	-	-	-
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	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
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	✔	✔	✔	✔	✔
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	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
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	-	-	-	✔	-	-	-	-
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	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
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	-	-	✔	-	-	-	-	-
Hiccoughs	-	-	✔	-	-	-	-	-
Hyperventilation	-	-	✔	-	-	-	-	-
Laryngospasm	-	-	✔	-	✔	-	-	-
Lung disorder	-	-	✔	-	-	-	-	-
Pharyngitis	-	-	3 to 10	-	-	-	-	-
Pleural effusion	-	-	✔	-	-	-	-	-
Pneumonia	-	-	✔	-	-	-	-	-
Pneumothorax	-	-	✔	-	-	-	-	-
Pulmonary edema	-	-	-	-	-	-	-	✔
Pulmonary embolus	-	-	✔	-	-	-	-	-
Respiratory arrest	✔	-	✔	-	✔	-	✔	✔
Respiratory depression	✔	✔	✔	✔	✔	-	✔	✔
Respiratory disorder	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
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	-	-	✔	-	-	-	-	-
Edema	-	-	✔	-	-	-	-	✔
Eye hemorrhage	-	-	✔	-	-	-	-	-
Fever	-	-	✔	-	-	-	-	-
Flu syndrome	-	-	✔	-	-	-	-	-
Fungal infection	-	-	✔	-	-	-	-	-
Hyperacusis	-	-	✔	-	-	-	-	-
Infection	-	-	✔	-	-	-	-	-
Lacrimation disorder	-	-	✔	-	-	-	-	-
Malaise	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
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
Myocardial infarction	-	-	-	-	<1
Myocardial ischemia	-	-	-	-	<1
Orthostatic hypotension	-	-	-	-	<1
Palpitation	✔	<3	-	-	<1
Pallor	✔	-	-	-	-
Peripheral edema	-	-	-	-	<1
Presyncope	-	-	-	<1	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
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	✔	13	-	24	26 to 33
Drowsiness	✔	-	✔	-	-
Dysphoria	-	✔	-	-	-
Emotional lability	-	<1	-	-	-
Euphoria	✔	1 to 5	✔	<1	1 to 5
Hallucinations	-	<1	✔	<1	<1
Headache	✔	7	✔	<1	18 to 32
Insomnia	✔	1 to 5	-	2	-
Irritability	-	-	-	<1	<1
Lethargy	-	-	-	1	-
Lightheadedness	✔	-	-	-	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
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	-	<1	-
Dermatological					
Cellulitis	-	-	-	-	<1
Dry skin	✔	-	<1	-	-
Exfoliative dermatitis	-	-	<1	-	-
Flushing	-	-	✔	1	-
Hyperhidrosis	-	-	-	3	-
Itching/pruritus	✔	✔	13	-	8 to 11
Pruritus	-	-	-	3 to 5	-
Rash	✔	-	1 to 5	1	1 to 5
Stevens-Johnson Syndrome	-	-	-	-	<1
Sweating	✔	✔	5	-	6 to 9
Toxic epidermal necrolysis	-	-	-	-	<1
Urticaria	✔	-	<3	<1	<1
Vesicles	-	-	-	-	<1
Wheal/flare	✔	-	-	-	1 to 5
Endocrine and Metabolic					
Gout	-	-	<3	-	-
Hyperglycemia	-	-	<3	-	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Menstrual disorder	-	-	-	-	<1
Metabolic acidosis	-	-	-	-	-
Gastrointestinal					
Abdominal distention	-	-	1 to 5	-	-
Abdominal pain	-	✔	-	<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	✔	✔	23	8	24 to 46
Cramps	✔	-	✔	-	-
Diverticulitis	-	-	-	-	<1
Dry mouth	✔	✔	6	4	5 to 10
Diarrhea	✔	-	1 to 5	<1	5 to 10
Dyspepsia	✔	-	1 to 5	2	5 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	✔	-	-	-	-
Nausea	✔	✔	23	30	24 to 40
Rectal disorder	✔	-	-	-	-
Stomatitis	-	-	<1	-	<1
Taste perversion	-	-	-	-	<1
Toxic megacolon	-	✔	-	-	-
Vomiting	✔	✔	12	18	9 to 17
Weight loss	✔	-	-	-	<1

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
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					
Hepatic steatosis	-	-	-	-	-
Hepatitis	-	-	-	-	<1
Hepatocellular injury	-	-	-	-	-
Hepatomegaly	-	-	-	-	-
Jaundice	-	-	-	-	-
Liver dysfunction	-	-	-	-	-
Liver failure	-	-	-	-	<1

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
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	-	-
Bronchospasm	-	-	-	-	<1
Cough	-	-	<3	<1	-
Dyspnea	-	-	1 to 5	<1	<1
Epistaxis	-	-	<3	-	-
Hiccoughs	-	-	1 to 5	-	-
Hypoxia	-	-	<3	-	-
Laryngospasm	✔	-	<3	-	-
Lung disorder	-	-	<3	-	-
Pharyngitis	-	-	-	1	-
Pneumonia	-	-	-	-	<1
Pulmonary edema	-	-	-	-	<1
Pulmonary embolus	-	-	-	-	<1
Respiratory arrest	✔	-	-	-	-
Respiratory depression	✔	✔	-	<1	-
Rhinitis	-	-	<3	-	-
Sinusitis	-	-	<3	-	-
Other					
Abnormal vision	-	-	<1	-	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
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	-	-
Hypersensitivity	-	-	-	<1	<1
Hypoesthesia	-	-	-	<1	-
Infection	✔	-	-	1	-
Joint stiffness	-	-	-	-	<1
Malaise	✔	-	-	-	1 to 5
Miosis	✔	✔	-	-	-
Night sweats	-	-	-	-	<1

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
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 Transmucosal Fentanyl[7]

WARNING
Respiratory Depression: Fatal respiratory depression has occurred in patients treated with transmucosal immediate-release fentanyl, including following use in opioid non-tolerant patients and improper dosing. The substitution of one transmucosal fentanyl product for any other fentanyl product may result in fatal overdose. Due to the risk of respiratory depression, transmucosal immediate-release fentanyl is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. Transmucosal immediate-release fentanyl must be kept out of reach of children. Death has been reported in some children who have ingested transmucosal immediate-release fentanyl formulations. The concomitant use of transmucosal immediate-release fentanyl with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

WARNING
Medication Errors: Substantial differences exist in the pharmacokinetic profile of each transmucosal immediate-release fentanyl product compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose. When prescribing, do not convert patients on a µg per µg basis from any other fentanyl products to a transmucosal immediate-release fentanyl product. When dispensing, do not substitute a transmucosal immediate-release fentanyl prescription for any other fentanyl products. **Abuse Potential:** Transmucosal immediate-release fentanyl products are opioid agonists and Schedule II controlled substances, with an abuse liability similar to other opioid analgesics. Transmucosal immediate-release fentanyl can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing transmucosal immediate-release fentanyl in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Because of the risk for misuse, abuse, addiction, and overdose, transmucosal immediate-release fentanyl products are available only through a restricted program, required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

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 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. **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

WARNING
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.

Table 17. Boxed Warning for Hydromorphone Injection[6]

WARNING
Hydromorphone high potency injection is for use in opioid-tolerant patients only. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer. Hydromorphone high potency injection is a more concentrated solution of hydromorphone than hydromorphone injection, and is for use in opioid-tolerant patients only. Do not confuse hydromorphone high potency injection with standard parenteral formulations of hydromorphone injection or other opioids, as overdose and death could result. Hydromorphone injection and hydromorphone high potency injection are opioid agonists and Schedule II controlled substances with an abuse liability similar to other opioid analgesics. Hydromorphone injection and hydromorphone high potency injection can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing hydromorphone injection and hydromorphone high potency injection in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion. Schedule II opioid agonists, including morphine, oxymorphone, hydromorphone, oxycodone, fentanyl, and methadone, have the highest potential for abuse and risk of producing fatal overdose due to respiratory

depression. Ethanol, other opioids, and other central nervous system depressants (e.g., sedative-hypnotics, skeletal muscle relaxants) can potentiate the respiratory-depressant effects of hydromorphone and increase the risk of adverse outcomes, including death.

Table 18. Boxed Warning for Methadone Injection[6]

WARNING
To treat narcotic addiction in detoxification or maintenance programs, methadone should be dispensed only by hospitals, community pharmacies, and maintenance programs approved by the Food and Drug Administration (FDA) and designated state authorities. Approved maintenance programs shall dispense and use methadone in oral form only and according to treatment requirements stipulated in *Federal Methadone Regulations*. 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. Methadone, used as an analgesic, may be dispensed in any licensed pharmacy. **Cardiac conduction effects:** Laboratory studies, in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (greater than 200 mg/day). 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.

Table 19. Boxed Warning for Oral 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**: Life-threatening, or fatal respiratory depression may occur with use of methadone. Monitor for respiratory depression, especially during initiation of methadone or following a dose increase. **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 during initiation and titration of methadone. **Neonatal opioid withdrawal syndrome**: Prolonged use of methadone 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 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.

Table 20. Boxed Warning for Morphine Injection[6]

WARNING
Risk of overdose (Infumorph): Infumorph is not recommended for single-dose intravenous (IV),

intramuscular (IM), or subcutaneous administration because of the very large amount of morphine in the ampul and the associated risk of overdosage.

Product interchange (Infumorph): Improper or erroneous substitution of **Infumorph** 200 or 500 (10 or 25 mg/mL, respectively) for regular **Duramorph** (0.5 or 1 mg/mL) is likely to result in serious overdosage, leading to seizures, respiratory depression and, possibly, fatal outcome.

Intrathecal use (Duramorph): Intrathecal dosage is usually 1/10 that of epidural dosage.

Appropriate administration (Infumorph, Duramorph):
Because of the risk of severe adverse effects when the epidural or intrathecal route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose. For patients receiving **Infumorph**, monitor, as appropriate, for the first several days after catheter implantation.

Infumorph: Naloxone injection and resuscitative equipment should be immediately available for use in case of case of life-threatening or intolerable side effects and whenever **Infumorph** therapy is being initiated, the reservoir is being refilled or any manipulation of the reservoir system is taking place.

Duramorph: Naloxone injection and resuscitative equipment should be immediately available for administration in case of life-threatening or intolerable side effects and whenever **Duramorph** therapy is being initiated.

Safety and handling (Infumorph, Duramorph):
Infumorph and **Duramorph** are supplied in sealed ampuls. Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water.

Each ampul of **Infumorph** and **Duramorph** contains a large amount of a potent narcotic which has been associated with abuse and dependence among health care providers. Due to the limited indications for this product, the risk of overdosage and the risk of its diversion and abuse, it is recommended that special measures be taken to control this product within the hospital or clinic. **Infumorph** and **Duramorph** should be subject to rigid accounting, rigorous control of wastage, and restricted access.

Parenteral drug products should be inspected for particulate matter before opening the amber ampul and again for color after removing contents from the ampul. Do not use if the solution in the unopened ampul contains a precipitate which does not disappear upon shaking. After removal, do not use unless the solution is colorless or pale yellow.

Table 21. Boxed Warning for Morphine Oral[6]

WARNING
Avinza and Kadian: **Interaction with alcohol**: Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking morphine extended-release (ER) capsules. The co-ingestion of alcohol with morphine may result in increased plasma levels and a potentially fatal overdose of morphine. **Avinza, Kadian, and MS Contin**: **Addiction, abuse, and misuse**: Morphine 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 morphine 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 morphine ER. Monitor for respiratory depression, especially during initiation of morphine or following a dose increase. Instruct patients to swallow morphine ER formulations whole; Avinza capsule contents may be sprinkled on applesauce and swallowed 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

WARNING

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 1 dose of morphine, especially by children, can result in a fatal overdose of morphine.

Oral solution:
Morphine oral solution is available in 10 mg per 5 mL, 20 mg per 5 mL, and 100 mg per 5 mL (20 mg/mL) concentrations.

The 100 mg per 5 mL (20 mg/mL) concentration is indicated for use in opioid-tolerant patients only.

Take care when prescribing and administering morphine oral solution to avoid dosing errors due to confusion between different concentrations and between milligrams and milliliters, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed.

Keep morphine oral solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

Table 22. Boxed Warning for Oxycodone[6]

WARNING

Extended release:
Addiction, abuse, and misuse: Oxycodone 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 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 ER. Monitor for respiratory depression, especially during initiation of oxycodone ER or following a dose increase. Instruct patients to swallow oxycodone ER tablets whole; crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of oxycodone.

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

Neonatal opioid withdrawal syndrome: Prolonged use of oxycodone ER 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 ER 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 ER and any CYP3A4 inhibitor or inducer.

Concentrated (20 mg/mL) oral solution:
Oxycodone concentrated oral solution is available as a 20 mg/mL concentration and is indicated for use in

opioid-tolerant patients only.

Take care when prescribing and administering oxycodone concentrated oral solution to avoid dosing errors due to confusion between milligram and milliliter, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. Keep oxycodone out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

Oral solution (5 mg/5 mL): Take care when prescribing and administering oxycodone oral solution to avoid dosing errors due to confusion between milligram and milliliter, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. Keep oxycodone out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

Table 23. Boxed Warning for Oxymorphone[6]

WARNING
Extended-release tablets: **Addiction, abuse, and misuse**: Oxymorphone 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 oxymorphone ER, 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 ER. Monitor for respiratory depression, especially during initiation of oxymorphone ER or following a dose increase. Instruct patients to swallow oxymorphone 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 ER, especially by children, can result in a fatal overdose of oxymorphone. **Neonatal opioid withdrawal syndrome**: Prolonged use of oxymorphone ER 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 ER. The co-ingestion of alcohol with oxymorphone ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

Table 24. Boxed Warning for Tapentadol Extended-Release[6]

WARNING
Abuse Potential: Tapentadol extended-release is an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing tapentadol extended-release. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving tapentadol extended-release for signs of misuse, abuse, and addiction during treatment. **Life-threatening Respiratory Depression**: Respiratory depression, including fatal cases, may occur with use of tapentadol extended-release, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and tapentadol extended-release should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic

pain. Monitor for respiratory depression, especially during initiation of tapentadol extended-release or following a dose increase. Instruct patients to swallow tapentadol extended-release tablets whole. Crushing, dissolving, or chewing tapentadol extended-release can cause rapid release and absorption of a potentially fatal dose of tapentadol.

Accidental Exposure: Accidental ingestion of tapentadol extended-release, especially in children, can result in a fatal overdose of tapentadol.

Interaction with Alcohol: The co-ingestion of alcohol with tapentadol extended-release may result in an increase of plasma levels and potentially fatal overdose of tapentadol. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on tapentadol extended-release.

VII. Dosing and Administration

The usual dosing regimens for the opiate agonists are listed in Table 25.

Table 25. 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.	Solution: 30 mg/5 mL 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 Nasal spray: initial, 100 µg; if after 30 minutes pain is unrelieved, an alternative rescue medication may be used as directed by the health care provider. Must wait at least two hours before treating another	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 every 72 hours	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 Nasal spray: 100 µg 400 µg Sublingual spray: 100 µg 200 µg 400 µg 600 µg 800 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	episode with fentanyl intranasal. However, for the next pain episode, increase to a higher dose Sublingual spray: initial, 100 µg; titrate to tolerable dose that provides adequate analgesia using a single dose; maximum, two doses per breakthrough pain episode; wait at least four hours before treating another episode Sublingual tablet: initial, 100 µg; titrate to tolerable dose that provides adequate analgesia; maximum, two doses per breakthrough pain episode; wait at least two hours before treating another episode Transdermal patch: 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 every 72 hours		1,200 µg 1,600 µg Sublingual tablet: 100 µg 200 µg 300 µg 400 µg 600 µg 800 µg Transdermal patch: 12 µg/hr 25 µg/hr 37.5 µg/hr 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 slowly over at least two to three minutes. 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 250 mg Liquid: 1 mg/mL Rectal suppository: 3 mg Tablet: 2 mg 4 mg 8 mg
Levorphanol	Analgesia: Tablet: one tablet every three to six hours	Safety and efficacy in children have not been established.	Tablet: 2 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	Injection: 10 mg/mL 25 mg/0.5 mL 25 mg/mL 50 mg/mL 75 mg/mL 75 mg/1.5 mL 100 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		mg/kg (0.5 to 0.8 mg/lb) up to the adult dose, every three to four hours as necessary	100 mg/2 mL Solution: 50 mg/5 mL Tablet: 50 mg 100 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 Solution, tablet: 5 to 30 mg every four hours Rectal suppository: 10 to 20 mg 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 2 mg/mL 4 mg/mL 5 mg/mL 8 mg/mL 10 mg/mL 15 mg/mL 25 mg/mL 30 mg/30 mL 50 mg/mL 100 mg/4 mL 150 mg/30 mL 250 mg/10 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:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			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 Injection: initial, SC or IM, 1 to 1.5 mg every four to six hours; IV, 0.5 mg; titrate to adequate pain relief	Safety and efficacy in children have not been established.	Injection: 1 mg/mL 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 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	Analgesia: Tablet (IR): ≥16 years of age, 50 to 100 mg every four to six hours	Capsule (ER): 100 mg 200 mg 300 mg Tablet (ER): 100 mg 200 mg 300 mg Tablet (IR): 50 mg
Combination Products			
Codeine and acetaminophen	Analgesia: Elixir, suspension: 15 mL every four hours Tablet: 0.5 to two tablets every four hours	Analgesia: Elixir, suspension: ≥12 years of age, 15 mL every four hours; seven to 12 years of age, 10 mL three to four times daily; three to six years of age, 5 mL three to four times daily Tablet: two to 12 years of age, 0.5 to 1 mg	Elixir: 12-120 mg/5 mL Suspension: 12-120 mg/5 mL Tablet: 15-300 mg 30-300 mg 60-300 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		codeine/kg/dose every four to six hours (10 to 15 mg acetaminophen/kg/dose every four hours)	
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
Dihydrocodeine, aspirin, and caffeine	Analgesia: Capsule: one to two capsules every four to six hours	Safety and efficacy in children have not been established.	Capsule: 16-356.4-30 mg
Hydrocodone and acetaminophen	Analgesia: , tablet: one to two e very four to six hours; 7.5-300 and 10-300 mg tablets, 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: Capsule, tablet: ≥15 years of age, one to two every four to six hours Solution: ≥15 years of age, 15 mL every four to six hours; two to 14 years of age, 0.27 ml/kg every four to six hours; 10-300/15 mL solution, >14 years of age, 11.25 mL every four to six hours; two to 13 years of age, 0.20 mL/kg every four to six hours	Solution: 2.5-167 mg/5 mL 5-163 mg/7.5 mL 7.5-325 mg/15 mL 10-300 mg/15 mL 10-325 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: 2.5-200 mg 5-200 mg 7.5-200 mg 10-200 mg
Opium and belladonna	Analgesia: Rectal suppository: one or two suppositories inserted per day	Safety and efficacy in children have not been established.	Rectal suppository: 30-16.2 mg 60-16.2 mg
Oxycodone and acetaminophen	Analgesia: Tablet: one to two capsules or tablets every six hours Solution: 5 to 10 mL every six hours	Safety and efficacy in children have not been established.	Tablet (ER): 7.5-325 mg Solution: 5-325 mg/5 mL 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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			10-650 mg
Oxycodone and aspirin	Analgesia: Tablet: one tablet every six hours	Safety and efficacy in children have not been established.	Tablet: 4.8355-325 mg
Oxycodone and ibuprofen	Analgesia: Tablet: one tablet every six hours	Analgesia: Tablet: ≥14 years of age, one tablet every six hours	Tablet: 5-400 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

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 26.

Table 26. 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.[28] (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.
Rauck et al.[29] (2012) Fentanyl sublingual spray (100 to 1,600 µg) vs placebo Fentanyl sublingual spray was titrated up to	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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).	oral hydromorphone/ day or 25 µg transdermal fentanyl/hour or equivalent			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 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	DB, MC, PC, RCT, XO Patients ≥18 years of age with pain associated with cancer or cancer treatment, receiving 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	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 difference, pain relief, global satisfaction	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.				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 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	PC, RCT, XO Adults with chronic cancer pain receiving 60 to 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	N=123 Duration not reported	Primary: $SPID_{30}$ Secondary: Pain relief and pain 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	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: 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
effective dose of fentanyl buccal tablet, patients received ten doses of study medication (seven contained fentanyl and three were placebo).				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 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	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 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	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 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	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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	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			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).
Zeppetella et al.[33] (2010) Fentanyl buccal tablet vs placebo Combined analysis of patients previously enrolled in Portenoy et al and Slatkin et al.	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	receiving maintenance opioid therapy for ≥1 week prior to screening			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 vs sublingual fentanyl tablet 200 µg vs sublingual fentanyl tablet 400 µg vs placebo	DB, MC, RCT, XO Adult patients with cancer pain that were regularly experiencing at least 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	N=38 Duration unknown	Primary: Pain intensity difference Secondary: Global assessment of treatment (none, mild, moderate or excellent), need for rescue medication	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. 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.				
Rauck et al.[35] (2009) Fentanyl sublingual tablet 100 to 800 µg vs placebo Fentanyl sublingual tablet was titrated up to 800 µg until an effective dose was reached.	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 1,000 mg oral morphine per day, transdermal fentanyl 50 to 300 µg per hour or equivalent	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 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.
Portenoy et al.[36] (2010)	DB, MC, PC, RCT, XO	N=114 10 BTP	Primary: Patient-averaged, $SPID_{30}$	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fentanyl nasal spray 100 to 800 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).	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	episodes	Secondary: 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	difference of 2.12 (±3.91) (95% CI, 1.21 to 3.03; P<0.0001). 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.[37] (2010) Fentanyl nasal spray 100 to 800 µg vs placebo	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	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	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

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. 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.	equivalent to 60 mg of oral morphine		spray, ease of use and convenience of nasal spray	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 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.
Christie et al.[38] (1998) Fentanyl transmucosal lozenge 200 µg vs fentanyl transmucosal lozenge 400 µg	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

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 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 episodes/day. Patients' usual BTP medication included codeine, hydrocodone, hydromorphone, morphine, oxycodone, propoxyphene, tramadol, or no medication.				>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. 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.[39] (1998) Fentanyl transmucosal lozenge 200 µg	DB, MC, PC, RCT, XO Patients ≥18 years of age with cancer who had sufficient pain to require at	N=89 Duration not reported	Primary: Pain intensity, pain relief, and use of rescue medication at 15 minute intervals over a 60 minute period	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 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	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		Secondary: Not reported	(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
take a dose of their usual BTP medication. Patients' usual BTP medication included hydrocodone, hydromorphone, morphine, oxycodone, and other medications.				
Hanks et al.[40] (2004) Fentanyl transmucosal lozenge 200 µg 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	MC, OL Patients stabilized on a long-acting opioid (60 to 1,000 mg/day of oral 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	N=57 Duration not reported	Primary: SPID and TOTPAR up to 60 minutes Secondary: Not reported	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 (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
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 medication was documented in a run-in phase and patients then changed to fentanyl transmucosal lozenge.				
Payne et al.[41] (2001) Fentanyl transmucosal lozenge Patients had participated in a previous short-term titration trial	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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	persistent pain, experiencing ≥1 BTP episode/day, and achieving at least partial relief of BTP by use of an opioid in the past			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
Portenoy et al.[42] (1999) 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	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 morphine/day, experienced ≥1 BTP episode per day between 0700 to 1600 hours on the three days immediately preceding screening, and achieved at least	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 ('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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	partial relief of this BTP by the use of an oral opioid rescue dose			Secondary: Not reported
Davies et al.[43] (2011) Fentanyl nasal spray vs morphine IR Fentanyl nasal spray was titrated up to 800 µg until the patient reached an effective dose that treated two	DB, DD, MC, XO Patients with a diagnosis of cancer, who were receiving fixed-schedule 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	N=110 10 BTP episodes	Primary: Pain intensity score, SPID, pain relief score, TOTPAR, onset of clinically meaningful pain relief (≥2 point reduction in pain intensity score), patient acceptability score (overall satisfaction, satisfaction with speed of relief and	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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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).			satisfaction with reliability), adverse events Secondary: Not reported	Secondary: Not reported
Fallon et al.[44] (2011) Fentanyl nasal spray 100 to 800 µg vs morphine IR 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	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 morphine and experiencing one to four BTP episodes per day	N=110 10 BTP episodes	Primary: Pain intensity difference after 15 minutes Secondary: Patient- and episode-averaged pain intensity difference, SPID, pain intensity 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	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, 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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).			reduction in pain intensity and pain relief or 33% reductions in pain intensity and SPID), need for rescue medication	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.
Webster et al.[45] (2013) Fentanyl buccal tablet vs oxycodone IR OL extension: Fentanyl buccal tablet vs	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
any traditional short-acting opioid (SAO) deemed appropriate by their treating physician	BTP daily with at least partial relief with opioids			satisfaction with fentanyl buccal tablet vs short-acting opioids (P<0.05).
Shear et al.[46] (2010) Fentanyl 100 µg transbuccal vs oxycodone-APAP 5-325 mg	DB, RCT Adult patients who presented to the ED with a chief complain of extremity injury	N=60 1 hour	Primary: Time required to achieve a 2-point drop on a 10-point pain scale Secondary: Maximum pain scale reduction and vital signs	Primary: Treatment with fentanyl was associated with faster pain relief onset than 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.[47] (2001)	DB, DD, RCT, XO	N=89	Primary: Pain intensity	Primary: Mean pain intensity differences across all time points significantly favored

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fentanyl transmucosal lozenge 200 µg vs morphine IR 15 to 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.	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 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	Up to 14 days or 10 BTP episodes	difference at 15, 30, 45 and 60 minutes post dose Secondary: Adverse events	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 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.[48] (2006) Opioid analgesics vs placebo or opioid analgesics All RCTs were concerned with the use 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:*

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
transmucosal fentanyl in the management of BTP. Two trials examined the titration of 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 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. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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, 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.[49] (2007) Fentanyl transmucosal lozenge, dose proportional to basal daily opioid dose vs IV morphine, dose proportional to	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
basal daily opioid dose Patients were planned to receive fentanyl transmucosal lozenge and IV morphine for each couple of BTP episodes between 0700 to 1900 hours. The order of administration was randomized.				(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. 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.[50] (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	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medication was assessed. Patients were then randomized to receive fentanyl nasal spray followed by 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.	500 mg/day of oral morphine for ≥1 month prior to the study			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.
Vissers et al.[51] (2010) Fentanyl nasal spray vs	MA (six RCT) Adult cancer patients suffering from BTP, treated with opioid analgesics for	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fentanyl transmucosal lozenge vs fentanyl buccal tablet vs oral morphine vs placebo	management of background pain			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. Secondary: Not reported
Velázquez Rivera et al.[52] (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.[53] (2013) Fentanyl buccal tablet, sublingual	MA (five studies) Patient population not specified	N=Not available Duration unknown	Primary: Likelihood of more efficacious pain relief (based on pain intensity	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tablet or transmucosal lozenge vs morphine IR vs placebo			difference) Secondary: Not reported	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 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.[54] (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.[55] (2006)	RCT	N=75	Primary: Maximum post-op	Primary: Post-op pain scores in postoperative care unit were significantly lower in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fentanyl 2 to 3 µg/kg IV bolus vs sufentanil 0.2 to 0.3 µg/kg IV bolus vs remifentanil 0.4 to 5 µg/kg IV bolus All trial medications were administered intraoperatively.	Adults scheduled for elective total thyroidectomy	24 hours post-op	pain scores, Secondary: Necessity of morphine injection in both surgical ward and postoperative care unit; incidence of opioid related side effects (nausea/ vomiting, sedation) Secondary: Not reported	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). 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.[56] (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).
Lazaraki et al.[57] (2007) Midazolam 2 to 5 mg IV vs	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:	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fentanyl 25 to 50 µg IV			Adverse effects and recovery time	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.[58] (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.
Sudheer et al.[59] (2007) Morphine PCA (up to 50 mg/4 hours) vs tramadol PCA (up to 200 mg/4 hours) vs codeine 60 mg IM,	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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
then 60 mg after 1 hour if needed, then 60 mg every 4 hours as needed				compared to 20% with morphine and 29% with codeine.
Poonai et al.[60] (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 dose of 15 mg/kg (max 975 mg) for breakthrough pain	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).
Kelly et al.[61] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
needed) All patients were given acetaminophen (10 to 15 mg/kg per dose every four hours as needed)				(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.
Karaman et al.[62] (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.[63] (2015) Oxycodone-APAP 5-325 mg vs cyclobenzaprine 5 mg vs placebo	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
One or two of the randomized 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				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 the same medications during a subsequent ED visit for acute low back pain.
Kleinert et al.[64] (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 placebo	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				that morphine 60 mg provides an analgesic dose comparable to a dose of tapentadol between 100 and 200 mg.
Gimbel et al.[65] (2004) Oxymorphone IR 10, 20, or 30 mg vs oxycodone IR 10 mg vs placebo	DB, DR, MC, PC, PG, RCT Men and nonpregnant, nonlacting 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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				multiple-dose phase compared to the oxymorphone IR groups (61% to 71%). Secondary: Not reported
Özalevli et al.[66] (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.[67] (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: Incidence of adverse events	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). Secondary: Treatment-related adverse events included nausea (13.4%), dizziness (10.2%), vomiting (7.6%) and somnolence (6.4%). In the placebo group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				no treatment-related adverse event was reported by more than 2% of subjects.
Palangio et al.[68] (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 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.[69] (2000) Hydrocodone-ibuprofen 7.5-200 mg (1 tablet) plus	DB, MC, PG, RCT Males and females >18 years of age with a chronic pain condition that	N=469 4 weeks	Primary: Pain relief scores, number of daily doses of study medication, number of daily	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 (CA)	required opioid or opioid-nonopioid combination analgesic therapy		doses of supplemental analgesics, number of patients who discontinued therapy due to an unsatisfactory analgesic response, and global assessment scores Secondary: Not reported	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. 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.[70] (2005) Oxycodone-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	N=73 60 minutes	Primary: Pain score (verbal numeric rating scale) at 30 and 60 minutes Secondary:	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs hydrocodone-APAP as a combination liquid formulation	10 scale		Presence and severity of side effects	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.[71] (2005) Oxycodone-ibuprofen 5-400 mg vs oxycodone-APAP 5-325 mg vs hydrocodone-APAP 7.5-500 mg vs placebo	AC, MC, PC, PG, RCT Men or women >12 years of age who were scheduled to undergo complete removal of >2 ipsilateral, partially or completely impacted third molars	N=249 6 hours	Primary: TOTPAR through six hours after dosing (TOTPAR6), sum 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	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 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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). 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.[72] (2004) Tramadol-APAP 75-650 mg vs codeine-APAP 30-300 mg vs placebo All study meds were administered	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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
as 2 tablets stat, then 1 to 2 tablets every 4 to 6 hours as needed.			one to six; overall rating of study medication by both patients and investigators using a five-point scale; incidence of adverse events	
Hewitt et al.[73] (2007) Tramadol-APAP 75-650 mg vs hydrocodone-APAP 7.5-650 mg vs placebo	RCT Patients 18 to 75 years of age with ankle sprain within previous 48 hours; clinical diagnosis of partial ligament tear, pain on ambulation and ankle swelling.	N=396 5 days	Primary: Pain relief as measured by patient response to two standardized pain relief/pain intensity scales Secondary: Adverse events	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. Secondary: Common adverse events included somnolence, nausea, dizziness, and vomiting.
Zenz et al.[74] (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	DB, PRO, RCT	N=24	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[75] (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	Children 1 to 12 years of age undergoing scheduled surgery	72 hours	Number of patients requiring dose increments Secondary: Sedation, heart rate, blood pressure, and vomiting	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.[76] (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.[77] (1988) Pentazocine 60 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
naloxone 0.4 mg IV vs morphine 8 or 15 mg IV vs naloxone 0.4 mg + morphine 8 mg IV vs naloxone 0.4 mg + pentazocine 60 mg IV vs placebo				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 the group of patients receiving low-dose naloxone plus pentazocine still reported significant analgesia. Secondary: Not reported
Petti[78] (1985) Pentazocine 25 mg and APAP 650 mg vs codeine 30 mg and APAP 300 mg vs propoxyphene	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
napsylate 100 mg and APAP 650 mg vs placebo				
Chronic Pain				
Le Loët et al.[79] (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 moderate/severe pain not adequately controlled with APAP, NSAIDs, COX-2 inhibitors or weak opioids.	N=159 28 days	Primary: Pain control Secondary: Pain assessment; pain intensity; treatment assessment; quality of life; functionality using the WOMAC; adverse events	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. 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%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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.[80] (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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			previous supplemental medication, Global Medication Performance questionnaire, dose changes over time	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.[81] (2010) Fentanyl transdermal patch 12 µg/hour and titrated every 2 to 3 days as necessary Oral morphine at a dose of 5 mg was allowed for BTP.	OL Opioid-naïve patients with advanced cancer and moderate pain	N=46 4 weeks	Primary: Pain intensity, time to dose stabilization, and quality of life Secondary: Not reported	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). 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.[82]	OL, PRO	N=53	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Fentanyl transdermal system 25 to 150 µg/hour replaced every 72 hours	Patients >18 years of age with neuropathic pain persisting for >3 months	16 weeks	Change in pain intensity and daily activity Secondary: Pain relief, cognition, physical function and mood	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 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.[83] (2005) Fentanyl	MC, OL, SA Patients 2 to 16 years of age with	N=199 15 days (with 3 month	Primary: Global assessment of pain treatment; changes in pain	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
transdermal system 12.5 to 100 µg/hour applied every 3 days	moderate to severe chronic pain due to malignant or nonmalignant disease	extension)	level, PPS, and CHQ and safety Secondary: Not reported	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 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.[84] (2011) Fentanyl transdermal patch	OL, PRO Patients ≥19 years of age, with overall good health, and	N=65 12 weeks	Primary: Percentage of change in pain intensity from before the	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12.5 µg/hour, dose could be increased by 12.5 or 25 µg/hour	complaining of chronic pain of the spine and limbs that scored >4 points on a numerical rating scale 72 hours prior to baseline data		administration of the study drug to 12 weeks Secondary: Degree of satisfaction, patient's function/sleep interference, dose, safety	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). 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.[85] (2006) Fentanyl transdermal system 25 to 100 µg/hour every 72 hours vs	MC, PC, RCT Patients ≥40 years of age meeting the ACR diagnostic criteria for hip or knee OA and requiring joint replacement surgery, with	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	moderate to severe pain that was not adequately controlled with weak opioids			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).
Morley et al.[86] (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).	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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).	drug regimens			completed the trial. Secondary: Not reported
Fleishmann et al.[87] (2001) Tramadol up to 400 mg/daily vs placebo	DB, MC, PC, PG, RCT Patients aged 35 to 75 with symptomatic (painful) OA of the knee for ≥1 year and had used NSAIDs for ≥3 months	N=129 3 months	Primary: Efficacy (as measured by pain intensity, relief, patient and investigator overall assessments, discontinuation, time to failure, and WOMAC OA index scores) Secondary: Tolerability and adverse events	Primary: The mean final pain intensity score was not statistically different between 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[88] (2003) Tramadol-APAP 37.5-325 mg up to 8 tablets daily vs placebo	DB, MC, PC, PG, RCT Men and non-pregnant women 25 to 75 years of age, in general good health, ambulatory, and with lower back pain such that daily medication was needed for ≥3 months	N=318 3 months	Primary: PVA score at final visit Secondary: Scores on the PRRS, SF-MPQ, RDQ, SF-36, discontinuation due to insufficient pain relief, and overall assessments of medication by patients and investigators	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[89] (2007) Tramadol ER 200-400 mg/ daily vs tramadol IR 50-100 mg every 4 to 6 hours vs placebo	DB, DD, RCT, XO Men and non-pregnant women aged 18 to 75 years with chronic (>1 month) noncancerous pain	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, 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Allan et al.[90] (2001) Morphine (MS Contin®) 10 to 200 mg for 4 weeks vs fentanyl transdermal system 25 to 100 µg/hour for 4 weeks	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 pain control with a stable dose of oral opioid for seven days before the trial	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. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[91] (2003) Fentanyl 25 µg/hour transdermal every 3 days vs morphine ER 30 mg every 12 hours	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). 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.[92] (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	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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
addition to IR morphine 5 mg every 4 hours as needed for BTP				38 to 68 vs 61%; 95% CI, 47 to 75; P=0.41).
De Conno et al.[93] (2008) Morphine 5 mg IR every 4 hours, if taking Step 1 analgesics 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.	OL Cancer patients ≥18 years of age, never treated with strong opioids, and with pain score of >5 points on a 0 to 11 point standard scale for ≥24 hours	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 Secondary: Adverse events	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. Secondary: The most commonly reported adverse events were somnolence (24% of patients), constipation (22%), vomiting (13%), nausea (10%) and confusion (7%).
Reid et al.[94] (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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[95] (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	DB, PC, PG, RCT 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)	N=395 (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)	Primary: 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	Primary: 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.				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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[96] (2009) Tapentadol 50 to 75 mg every 4 to 6 hours vs oxycodone 10 mg every 4 to 6 hours vs placebo	DB, RCT Patients 18 to 80 years of age who were candidates for primary joint replacement surgery as a result of end-stage degenerative joint disease	N=674 10 days	Primary: 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)	Primary: 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[97] (2010) Tapentadol ER 100 mg BID vs 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	AC, DB, MC, PC, RCT Patients ≥40 years of age with a diagnosis of OA of the knee (per ACR 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	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 Secondary: Change in average pain intensity over the entire 12-week 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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.				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; 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.[98] (2010) Tapentadol ER 100 mg BID	AC, DB, MC, PC, PRO, RCT Patients ≥18 years with a history of	N=981 12 weeks (maintenance phase after a	Primary: Change from baseline in mean pain intensity at week-12 of the	Primary: Throughout the 12-week maintenance period, average pain intensity scores improved in both the tapentadol ER and oxycodone CR groups relative to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxycodone CR 20 mg BID vs placebo 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)	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, if applicable, were equivalent to ≤160 mg of oral morphine	3-week titration phase)	maintenance period Secondary: Change from baseline in mean pain intensity over the entire 12-week maintenance period, proportion of patients with ≥30 and ≥50% reduction in pain intensity at week-12 of maintenance, PGIC score, BPI survey, SF-36 health survey	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. 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
was permitted.				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 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%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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. 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.[99] (2010) Tapentadol 100 to 250 mg BID vs 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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 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	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			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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
consecutive days and no more that 14 out of 30 days) were permitted.				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.[100] Tramadol 50 mg vs. tramadol-APAP 37.5-325 mg vs placebo	DB, PC, RCT Men and women aged 18 to 75 who underwent elective outpatient surgery for extraction of at least two upper or lower impacted third molars	N=456 1 dose	Primary: Efficacy (measured by hourly PAR and pain intensity scores) Secondary: PID and PAR at each time point, time to onset of perceptible/ meaningful PAR, time to rescue analgesia, and adverse events	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 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.[101] (2007)	DB, RCT Patients with	N=177 3 weeks	Primary: Analgesic efficacy	Primary: There was no significant difference in the analgesic efficacy of the three opioids (P=0.69).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Codeine-APAP vs hydrocodone-APAP vs tramadol	persistent moderate or severe cancer-associated pain		Secondary: Adverse effects	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.[102] (2001) 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	AC, DB, DD, PG, RCT Men and non-pregnant women >18 years of age with chronic nonmalignant low back pain, OA pain, or both	N=462 4 weeks	Primary: Efficacy (measured by patient reported pain relief and pain intensity using Likert scales, and overall efficacy as reported by investigators) Secondary: Safety	Primary: Mean TOTPAR scores were comparable between the two groups at each 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fricke et al.[103] (2002) Tramadol-APAP 37.5-325 mg vs tramadol-APAP 75-650 mg vs hydrocodone-APAP 10-650 mg vs placebo	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 associated bone	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 re-medication with a supplemental analgesic agent; and patients' overall assessment of medication	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: 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients' mean overall assessment of study medication was statistically superior in all active-treatment groups compared to placebo (P<0.001).
Furlan et al.[104] (2006) Weak opioids: Tramadol, propoxyphene, codeine Strong opioids: morphine, oxycodone	MA Patients with nociceptive pain (OA, rheumatoid arthritis or back pain), neuropathic pain (postherpetic neuralgia, diabetic neuropathy or phantom limb pain), fibromyalgia, and mixed pain	N=6,019 1 to 16 weeks	Primary: Pain relief; improvement in functional outcome, based upon standardized indices and scoring methods Secondary: Adverse events	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. 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.[105] (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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			number of tablets of supplemental analgesic medication during DB period, and the Oswestry Disability Index at weeks four, eight, and 12	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.[106] (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 OA 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 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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				commonly observed adverse events in the buprenorphine group were nausea (30.4%), constipation (18.8%) and dizziness (15.9%).
Felden et al.[107] (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). Secondary: Not reported.
Opioid Dependence				
Johnson et al.[108] (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%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[109] (1992) Buprenorphine sublingual tablets (flexible dosing schedule) vs methadone (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 use Secondary: Not reported	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). 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.[110] (1994) Buprenorphine sublingual tablets (flexible dosing schedule) vs methadone (flexible dosing	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
schedule)				Secondary: Not reported
Ling et al.[111] (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
Schottenfeld et al.[112] (1997) Buprenorphine 4 mg daily vs buprenorphine 12 mg daily vs methadone 20 mg daily vs methadone 65 mg	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily				
Soyka et al.[113] (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
Gibson et al.[114] (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.[115] (2007)	OL Patients involved in	N=213 12 months	Primary: Opioid use, psychiatric status,	Primary: There were significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for buprenorphine-treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine vs methadone	a long-term treatment program with buprenorphine or methadone		quality of life Secondary: Not reported	and methadone-treated patients. Secondary: Not reported
Jones et al.[116] (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
Cornish et al.[117] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[118] (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 substitution therapy Secondary: Not reported	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 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.[119] (2002) Buprenorphine ≥8 mg daily (high dose vs buprenorphine <8	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily (low dose) vs methadone ≥50 mg daily (high dose) vs methadone <50 mg daily (low dose) vs levo-acetylmethadol				retention than those receiving high doses of methadone (OR, 1.92; 95% CI 1.32 to 2.78). Secondary: Not reported
Mattick et al.[120] (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%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). <u>Medium Dose Buprenorphine vs Medium Dose Methadone</u> 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). <u>Low Dose Buprenorphine Maintenance vs Placebo</u> 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). <u>Medium Dose Buprenorphine Maintenance vs Placebo</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). <u>High Dose Buprenorphine Maintenance vs Placebo</u> 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). Secondary: Not reported
Kakko et al.[121] (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.[122] (2008)	DB, DD, RCT Patients ≥18 years	N=268 17 weeks	Primary: Amount of opioid abstinence	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine-naloxone 8-2 mg daily vs buprenorphine-naloxone 16-4 mg daily vs methadone 45 to 90 mg daily	of age who met criteria for opioid dependence and who were using heroin or prescription opioids or receiving methadone maintenance treatment		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 retention	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 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).
Strain et al.[123] (2000) Buprenorphine 4 mg to 16 mg per day vs buprenorphine-	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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				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, 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 24. Relative Cost of the Opiate Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Alfentanil	injection^	Alfenta®*	$$$	$-$$
Codeine	tablet	N/A	N/A	$
Fentanyl	buccal lozenge, buccal tablet, injection, nasal spray, sublingual spray, sublingual tablet, transdermal patch	Abstral®, Actiq®*, Duragesic®*, Fentora®, Lazanda®, Sublimaze®*, Subsys®	$$$$$	$$$
Hydromorphone	injection, liquid, rectal suppository, tablet	Dilaudid®*	$$-$$$$$	$
Levorphanol	tablet	N/A	N/A	$$$
Meperidine	injection, solution, tablet	Demerol®*	$$$	$
Methadone	injection, oral concentrate, solution, tablet	Dolophine®*, Methadose®*	$$$	$$$
Morphine	epidural, injection, rectal	Astramorph-PF®, Duramorph®, Infumorph®	$$$$-$$$$$	$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
	suppository, solution, tablet			
Oxycodone	capsule, oral concentrate, solution, tablet	Oxecta®, Roxicodone®*	$$$-$$$$$	$$
Oxymorphone	injection, tablet	Opana®*	$$$$$	$$$$$
Remifentanil	injection^	Ultiva®	$$$-$$$$$	N/A
Sufentanil	injection^	Sufenta®*	$$$-$$$$$	
Tapentadol	extended-release tablet, tablet	Nucynta®, Nucynta ER®	$$$$$	N/A
Tramadol	extended-release capsule, extended-release tablet, tablet	Conzip ER®*, Ultram®*, Ultram ER®*	$$$-$$$$$	$
Combination Products				
Codeine and acetaminophen	elixir, suspension, tablet	Capital w/Codeine®, Tylenol-Codeine No.3®*, Tylenol-Codeine No.4®*	$-$$$	$
Codeine, butalbital, acetaminophen, and caffeine	capsule	Fioricet With Codeine®*	$$$$	$$$
Codeine, butalbital, aspirin, and caffeine	capsule	Fiorinal With Codeine®*	$$-$$$	$
Dihydrocodeine, acetaminophen, and caffeine	capsule	N/A	N/A	$$$$
Dihydrocodeine, aspirin, and caffeine	capsule	Synalgos-DC®*	$$$	$$$$
Hydrocodone and acetaminophen	solution, tablet	Hycet®*, Lorcet HD®*, Lorcet Plus®*, Lortab®*, Norco®*, Verdrocet®*, Vicodin®*, Vicodin ES®*, Vicodin HP®*, Xodol®*, Zamicet®*	$$$-$$$$	$
Hydrocodone and ibuprofen	tablet	Ibudone®*, Reprexain®*, Vicoprofen®*, Xylon®*	$$-$$$	$$
Opium and belladonna	rectal suppository	N/A	N/A	$$$$$
Oxycodone and acetaminophen	extended-release tablet, solution, tablet	Percocet®*, Primlev®, Xartemis XR®	$$$$-$$$$$	$
Oxycodone and aspirin	tablet	Percodan®*	$$$	$$
Oxycodone and ibuprofen	tablet	N/A	N/A	$
Tramadol and acetaminophen	tablet	Ultracet®*	$$-$$$$$	$

*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, and ibuprofen. All of the products are available in a generic formulation, with the exception of remifentanil and tapentadol.

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.[18,20]

For the treatment of chronic noncancer pain, guidelines recommend the use of an opiate agonist in patients with moderate to severe pain.[19,21,23,24] 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.[21,23,14] The Veterans Health Administration, Department of Defense guidelines recommend that an opiate agonist with a long duration of action be used in patients experiencing continuous chronic pain.[23] However, the American Pain Society/American Academy of Pain Medicine guidelines state that there is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids.[24] Guidelines do not give preference to one opiate agonist over another for the treatment of noncancer pain, although it is generally agreed that morphine is a reasonable initial agent.[19,21,23,24] The efficacy of the opiate agonists for the acute treatment of noncancer pain has been demonstrated in short-term trials; however, the available evidence is variable for the long-term (>6 months) treatment of chronic noncancer pain.[28-107]

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.[9,25-27] 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.[9,107-123] 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).[124] 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]

Within the past several years, the Food and Drug Administration (FDA) notified healthcare providers about an increased risk of suicide with tramadol.[10] An additional safety communication regarding the risks of using tramadol in children aged 17 years and younger was released in September 2015. The FDA is reviewing available information on the rare but serious risk of slowed or difficult breathing and will communicate final conclusions when the review is complete.[11]They also recommended against the continued prescribing and use of propoxyphene-containing products and asked manufacturers to voluntarily remove these products from the United States market.[12] The FDA has also asked manufacturers to limit the amount of acetaminophen in prescription drug products (which are predominantly combinations of acetaminophen and opioids) to 325 mg per dosage form to make these products safer for patient to use, has asked health care professionals to discontinue prescribing and dispensing prescription combination drug products with over 325 mg of acetaminophen, and has made efforts to reduce the misuse and abuse of extended release/long acting opioids.[13-15]

In September 2013, the FDA announced labeling changes for all extended-release and long-acting opioids, and the changes were finalized in April 2014. Safety labeling across the class now includes an updated indication stating that these agents are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or otherwise inadequate. The FDA requires a new boxed warning regarding the risk of neonatal opioid withdrawal syndrome when these agents are used during pregnancy, and also requires the manufacturers of extended-release and long-acting opioids to conduct postmarket studies further

assessing the known risks of misuse, abuse, hyperalgesia, addiction, overdose, and death. These changes are incorporated into the Risk Evaluation and Mitigation Strategy (REMS) program.[16]

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.

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.

XII. References

1. International Association for the Study of Pain. ISAP Taxonomy 2012 [cited 2015 Nov]. Available at: http://www.iasp-pain.org/Taxonomy.
2. Coghill RC. Individual differences in the subjective experience of pain: New insights into mechanisms and models. Headache. 2010;9:1531-5.
3. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11:S133-S153.
4. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Nov]. Available from: http://online.factsandcomparisons.com.
5. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Nov]. Available from: http://www.thomsonhc.com/.
6. Daily Med [database on the internet]. Bethesda (MD): National Library of Medicine; 2015 [cited 2015 Nov 23]. Available at: http://dailymed.nlm.nih.gov/dailymed/about.cfm.
7. Ballantyne J (ed). Opioids. Massachusetts General Hospital Handbook of Pain Management. 3rd ed. Philadelphia: Lippincott Williams & Wilkins. 2006.
8. Work Group on Substance Use Disorders, Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, Strain EC, Greenfield SF, Ziedonis DM, Kosten TR, Hennessy G, O'Brien CP, Connery HS. Treatment of patients with substance use disorders, second edition. American Psychiatic Association. Am J Psychiatry. 2006;163(8 Suppl):5-82.
9. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004. Available at: http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf. Accessed 2015 Nov 19.
10. FDA Drug Safety Communication: Ultram (tramadol hydrochloride), Ultracet (tramadol hydrochloride/acetaminophen): Label Change. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm213264.htm. Accessed 2013 Sep 12.
11. Tramadol: Drug Safety Communication - FDA Evaluating Risks of Using in Children Aged 17 and Younger. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm463499.htm. Accessed 2015 Nov 19.
12. FDA Drug Safety Communication: FDA recommends against the continued use of propoxyphene. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm234338.htm. Accessed 2013 Sep 12.
13. FDA Drug Safety Communication: Prescription acetaminophen products to be limited to 325 mg per dosage unit; Boxed warning will highlight potential for severe liver failure. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm. Accessed 2013 Sep 12.
14. Acetaminophen Prescription Combination Drug Products with more than 325 mg: FDA Statement - Recommendation to Discontinue Prescribing and Dispensing. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm381650.htm. Accessed 2015 Nov 19.
15. FDA News Release: FDA Introduces new safety measures for extended-release and long-acting opioid medications. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310870.htm. Accessed 2013 Sep 12.
16. FDA News Release: FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm. Accessed 2013 Oct 18.
17. Federal Register [database on the internet]. Washington (DC): US Government Printing Office; 2014 [cited 2014 Aug 22]. Available from: http://www.gpo.gov/fdsys/pkg/FR-2014-08-22/pdf/2014-19922.pdf.
18. National Comprehensive Cancer Network (NCCN). Practice guidelines in oncology: adult cancer pain. National Comprehensive Cancer Network (NCCN), 2015 [cited 2015 Nov 19]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
19. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2 – guidance. Pain Physician. 2012;15:S67-S116.
20. Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F, on behalf of the ESMO Guidelines Working Group Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23(suppl 7): vii39-vii154.

21. National Opioid Use Guideline Group (NOUGG). Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. National Opioid Use Guideline Group (NOUGG), 2010. Available at: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf. Accessed 2013 Sep 13.
22. American Society of Anesthesiologists Task Force on Chronic Pain Management, American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2010;112:810-33.
23. Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain. Washington (DC): Veterans Health Administration, Department of Defense; 2010 May. Available at: http://www.healthquality.va.gov/Chronic_Opioid_Therapy_COT.asp. Accessed 2013 Sep 13.
24. Chou R, Fanciullo GJ, Fine PG, et al. American Pain Society: Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10:113-30.
25. Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of substance use disorders (SUD). Washington (DC): Veterans Health Administration, Department of Defense; 2009 Aug. Available at: http://www.guideline.gov/summary/summary.aspx?doc_id=4812&nbr=3474. Accessed 2013 Sep 13.
26. Work Group on Substance Use Disorders, Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, Strain EC, Greenfield SF, Ziedonis DM, Kosten TR, Hennessy G, O'Brien CP, Connery HS. Treatment of patients with substance use disorders, second edition. American Psychiatic Association. Am J Psychiatry. 2006;163(8 Suppl):5-82.
27. Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. DHHS Publication No. (SMA) 05-4048. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005. Available at: http://www.naabt.org/documents/TIP43-buprenorphine-methadone-suboxone-opiate.pdf. Accessed 2013 Sep 12.
28. Drendel AL, Gorelick MH, Weisman SJ, et al. A randomized clinical trial of ibuprofen vs acetaminophen with codeine for acute pediatric arm fracture pain. Ann Emerg Med. 2009;54:553-60.
29. Rauck R, Reynolds L, Geach J, Bull J, Stearns L, Scherlis M, et al. Efficacy and safety of fentanyl sublingual spray for the treatment of breakthrough cancer pain: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin 2012; 28(5):859-70.
30. Rauck R, North J, Gever LN, Tagarro I, Finn AL. Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. Ann Oncol. 2010;21:1308-14.
31. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. The Clinical Journal of Pain (abstract). 2006;22(9):805-11.
32. Slatkin NE, Xie F, Messina J, Segal TJ. A double-blind, randomized, placebo-controlled study: fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. J Support Oncol. 2007;5:327-34.
33. Zeppetella G, Messina J, Xie F, Slatkin N. Consistent and clinically relevant effects of fentanyl buccal tablet in the treatment of patients receiving maintenance opioid therapy and experiencing cancer-related breakthrough pain. Pain Practice. 2010 Mar 3. Epub 2009 Dec 13.
34. Lennernäs B, Frank-Lissbrant I, Lennernäs H, Kälkner KM, Derrick R, Howell J. Sublingual administration of fentanyl to cancer patients is an effective treatment for breakthrough pain: results from a randomized phase II study. Palliat Med. 2010 Apr;24(3):286-93
35. Rauck RL, Tark M, Reyes E, Hayes TG, Bartkowiak AJ, Hassman D, et al. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. Curr Med Res Opin 2009;25(12):2877-85.
36. Portenoy RK, Burton AW, Gabrail N, Taylor D; Fentanyl Pectin Nasal Spray 043 Study Group. A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain. Pain. 2010 Dec;151(3):617-24.
37. Taylor D, Galan V, Weinstein SM, Reyes E, Pupo-Araya AR, Rauck R, et al. Fentanyl pectin nasal spray in breakthrough cancer pain. J Support Oncol. 2010 Jul-Aug;8(4):184-90.
38. Christie JM, Simmonds M, Patt R, Coluzzi P, Busch MA, Nordbrock E, et al. Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. J Clin Oncol. 1998;16:3238-45.

39. Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. J Natl Cancer Inst. 1998;90(15):611-6.
40. Hanks GW, Nugent M, Higgs CMB, Busch MA. Oral transmucosal fentanyl citrate in the management of breakthrough pain in cancer, an open, multicentre, dose-titration and long-term use study. Palliat Med. 2004;18:698-704.
41. Payne R, Coluzzi P, Hart L, Simmonds M, Lyss A, Rauck R, et al. Long-term safety of oral transmucosal fentanyl citrate for breakthrough cancer pain. J Pain Symptom Manage. 2001;22:575-83.
42. Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain. 1999;79:3003-12.
43. Davies A, Sitte T, Elsner F, Reale C, Espinosa J, Brooks D, et al. Consistency of efficacy, patient acceptability and nasal tolerability of fentanyl pectin nasal spray compared to immediate-release morphine sulfate in breakthrough cancer pain. J Pain Symptom Manage. 2011;41:358-66.
44. Fallon M, Reale C, Davies A, Lux AE, Kumar K, Stachowiak A, et al. Efficacy and safety of fentanyl pectin nasal spray compared to immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: a multicenter, randomized, controlled, double-blind, double-dummy multiple-crossover study. J Support Oncol. 2011 Nov-Dec;9(6):224-31.
45. Webster LR, Slevin KA, Narayana A, Earl CQ, Yang R. Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic cancer and noncancer pain: a randomized, double-blind, crossover study followed by a 12-week open-label phase to evaluate patient outcomes. Pain Med. 2013 Sep;14(9):1332-45.
46. Shear ML, Adler JN, Shewakramani S, et al. Transbuccal fentanyl for rapid relief of orthopedic pain in the emergency department. Am J Emerg Med. 2010;28:847-52.
47. Coluzzi PH, Schwartzberg L, Conroy JD Jr., Charapata S, Gay M, Busch MA, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate and morphine sulfate immediate release. Pain. 2001;91:123-30.
48. Zeppetella G, Ribeiro MDC. Opioids for the management of breakthrough (episodic) pain in cancer patients. Cochrane Database of Systematic Reviews. 2006;1: Art. No.: CD004311. DOI:10.1002/14561858.CD004311.pub2.
49. Mercadante S, Villari P, Ferrera P, Casuccio, Mangionie S, Intravaia G. Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. Br J Cancer. 2007;96:1828-33.
50. Mercadante S, Radbruch L, Davies A, Poulain P, Sitte T, Perkins P, et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomized, crossover trial. Curr Med Res & Opin. 2009;25(11):2805-15.
51. Vissers D, Stam W, Nolte T, Lenre M, Jansen J. Efficacy of intranasal fentanyl spray vs other opioids for breakthrough pain in cancer. Curr Med Res Opin. 2010;26(5):1037-45.
52. Velázquez Rivera I, Muñoz Garrido JC, García Velasco P, et al. Efficacy of sublingual fentanyl vs. oral morphine for cancer-related breakthrough pain. Adv Ther. 2014 Jan;31(1):107-17.
53. Jandhyala R, Fullarton JR, Bennett MI. Efficacy of rapid-onset oral fentanyl formations vs oral morphine for cancer-related breakthrough pain: a meta-analysis of comparative trials. J Pain Symptom Manage. 2013 Feb 1.
54. Joshi VS, Chauhan S, Kiran U et al. Comparison of analgesic efficacy of fentanyl and sufentanil for chest tube removal after cardiac surgery. Ann Card Anaesth. 2007;10:42-45.
55. Motamed C, Merle JC, Yakhou L et al. Postoperative pain scores and analgesic requirements after thyroid surgery: comparison of three intraoperative opioid regimens. Int J Med Sci. 2006;3:11-3.
56. Chang AK, Bijur PE, Meyer RH et al. Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. Ann Emerg Med. 2006;48:164-72.
57. Lazaraki G, Kountouras J, Metallidis S et al. Single use of fentanyl in colonoscopy is safe and effective and significantly shortens recovery time. Surg Endosc. 2007;21:1631-6.
58. Plummer JL, Owen H, Ilsley AH, Inglis S. Morphine patient-controlled analgesia is more efficacious to meperidine patient-controlled analgesia for postoperative pain. Anesth Analg. 1997;84:794-9.
59. Sudheer PS, Logan SW, Terblanche C et al. Comparison of the analgesic efficacy and respiratory effects of morphine, tramadol and codeine after craniotomy. Anaesthesia. 2007;62:555-60.
60. Poonai N, Bhullar G, Lin K, et al. Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial. CMAJ. 2014 Dec 9;186(18):1358-63.

61. Kelly LE, Sommer DD, Ramakrishna J, et al. Morphine or Ibuprofen for post-tonsillectomy analgesia: a randomized trial. Pediatrics. 2015 Feb;135(2):307-13.
62. Karaman S, Kocabas S, Uyar M et al. The effects of sufentanil or morphine added to hyperbaric bupivacaine in spinal anesthesia for caesarean section. Eur J Anaesthesiol. 2006;23:285-91.
63. Friedman BW, Dym AA, Davitt M, et al. Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial. JAMA. 2015 Oct 20;314(15):1572-80.
64. Kleinert R, Lange C, Steup A, et al. Single dose analgesic efficacy of tapentadol in postsurgical dental pain: the results of a randomized, double-blind, placebo-controlled study. Anesth Analg. 2008;107:2048-55.
65. Gimbel J, Ahdieh H. The efficacy and safety of oral immediate-release oxymorphone for postsurgical pain. Anesth Analog. 2004; 99:1472-7.
66. Özalevli M, Ünlügenç H, Tuncer U et al. Comparison of morphine and tramadol by patient-controlled analgesia for postoperative analgesia after tonsillectomy in children. Paediatr Anaesth. 2005;15:979-84.
67. Silberstein SD, Freitag FG, Rozen TD et al. Tramadol/acetaminophen for the treatment of acute migraine pain: findings of a randomized, placebo-controlled trial. Headache. 2005;45:1317-27.
68. Palangio M, Wideman GL, Keffer M, Landau CJ, Morris E, Doyle RT, et al. Combination hydrocodone and ibuprofen vs combination oxycodone and acetaminophen in the treatment of postoperative obstetric or gynecologic pain. Clin Ther. 2000; 22:600-12.
69. Palangio M, Damask MJ, Morris E, Doyle RT, Jiang JG, Landau CJ, et al. Combination hydrocodone and ibuprofen vs combination codeine and acetaminophen for treatment of chronic pain. Clin Ther. 2000; 22:879-92.
70. Marco CA, Plewa MC, Buderer N, Black C, Roberts A. Comparison of oxycodone and hydrocodone for the treatment of acute pain associated with fractures; A double-blind, randomized, controlled trial. Academic Emergency Medicine. 2005; 12:282-8.
71. Litkowski LJ, Christensen SE, Adamson DN, VanDyke T, Han S, Newman KB. Analgesic efficacy and tolerability of oxycodone 5 mg/Ibuprofen 400 mg compared to those of oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 7.5 mg/acetaminophen 500 mg in patients with moderate to severe postoperative pain: A randomized, double-blind, placebo-controlled, single-dose, parallel-group study in a dental pain model. Clin Ther. 2005; 27:418-29.
72. Smith AB, Ravikumar TS, Kamin M et al. Combination tramadol plus acetaminophen for postsurgical pain. Am J Surg. 2004;187:521-7.
73. Hewitt DJ, Todd KH, Xiang J et al. Tramadol/acetaminophen or hydrocodone/acetaminophen for the treatment of ankle sprain: a randomized, placebo-controlled trial. *Ann Emerg Med.* 2007;49:468-80.
74. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage. 1992;7:69-77.
75. Moyao-Garcia D, Hernandez-Palacios JC, Ramirez-Mora JC, et al. A pilot study of nalbuphine vs tramadol administered through continuous intravenous infusion for postoperative pain control in children. Acta Biomed. 2009;80:124-30.
76. Yeh YC, Lin TF, Chang HC, et al. Combination of low-dose nalbuphine and morphine in patient-controlled analgesia decreases incidence of opioid-related side effects. J Formos Med Assoc. 2009;108:548-53.
77. Levine J, Gordon N, Taiwo Y, et al. Potentiation of pentazocine analgesia by low-dose naloxone. J Clin Invest. 1988;82:1574-7.
78. Petti A. Postoperative pain relief with pentazocine and acetaminophen: comparison with other analgesic combinations and placebo. Clin Ther. 1985;8:126-33.
79. Le Loët X; Pavelka K; Richarz U et al. Transdermal fentanyl for the treatment of pain caused by osteoarthritis of the knee or hip: an open, multicentre study. BMC Musculoskelet Disord. 2005;6:31.
80. Weinstein SM, Messina J, Xie F. Fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic cancer pain. A long-term, open-label study. Cancer. 2009;115:2571-9.
81. Mercadante S, Porzio G, Ferrera P, et al. Low doses of transdermal fentanyl in opioid-naïve patients with cancer pain. Curr Med Res Opin. 2010;12:2765-8.
82. Agarwal A., Polydefkis M., Block B., Haythornthwaite J., Raja S. Transdermal fentanyl reduces pain and improves functional activity in neuropathic pain states. Pain Medicine. 2007;8(7):554-62.
83. Finkel JC., Finley A., Greco C., Weisman SJ., Zeltzer L. Transdermal fentanyl in the management of children with chronic severe pain. Results from an international study. Cancer. 2005;104:2847-57.
84. Park JH, Kim JH, Yun SC, Roh SW, Rhim SC, Kim CJ, et al. Evaluation of efficacy and safety of fentanyl transdermal patch (Durogesic® D-TRANS) in chronic pain. Acta Neurochir. 2011;153:181-90.

85. Langford R., McKenna F., Ratcliffe S., Vojtassak J., Richarz U. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis. Arthritis & Rheumatism 2006;54(6):1829-37.
86. Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliative Medicine. 2003;17:576-87.
87. Fleischmann RM, et al. Tramadol for the treatment of joint pain associated with osteoarthritis: A randomized, double-blind, placebo-controlled trial. Curr Ther Res Clin Exp. 2001;62:113-8.
88. Ruoff GE, et al. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: A multicenter, randomized, double-blind, placebo-controlled outpatient study. Clin Ter. 2003;25:1123-41.
89. Beaulieu AD, et al. A randomized, double-blind, 8-week crossover study of once-daily controlled-release tramadol versus immediate-release tramadol taken as needed for chronic noncancer pain. Clin Ther. 2007;29:49-60.
90. Allan L. Hays H. et al. Randomized crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ. 2001;322:1-7.
91. van Seventer R, Smit JM, Schipper et al. Comparison of TTS-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain. Curr Med Res Opin. 2003;19:457-69.
92. Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C et al. Methadone vs morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. Clin Oncol. 2004;22:185-92.
93. De Conno F, Ripamonti C, Fagnoni E et al. The MERITO Study: a multicentre trial of the analgesic effect and tolerability of normal-release oral morphine during 'titration phase' in patients with cancer pain. Palliat Med. 2008;22:214-21.
94. Reid CM, Martin RM, Sterne JA et al. Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166:837-43.
95. Schwartz S, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin. 2011 Jan;27(1):151-62.
96. Hartrick C, Van Hove I, Stegmann J, et al. Efficacy and tolerability of tapentadol immediate release and oxycodone HCI immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. Clin Ther. 2009;31:260-71.
97. Afilalo M, Etropolski MS, Kuperwasser B, Kelly K, Okamoto A, Van Hove I, et al. Efficacy and safety of tapentadol extended release compared to oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clin Drug Investig. 2010;30(8):489-505.
98. Buynak R, Shapiro DY, Okamoto A, Van Hove I, Rauschkolb C, Steup A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. Expert Opin Pharmacother. 2010 Aug;11(11):1787-804.
99. Wild JE, Grond S, Kuperwasser B, Gilbert J, McCann B, Lange B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Pract. 2010 Sept-Oct;10(5):416-27.
100. Fricke JR, Hewitt DJ, Jordan D, Fisher A, Rosenthal NR. A double-blind placebo controlled comparison of tramadol/acetaminophen and tramadol in patients with postoperative dental pain. Pain. 2004;109:250-7.
101. Rodriguez RF, Bravo LE, Castro F et al. Incidence of weak opioids adverse events in the management of cancer pain: a double-blind comparative trial. J Palliat Med. 2007;10:56-60.
102. Mullican WS, Lacy JR. Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: A comparative trial. Clin Ther. 2001;23:1429-45.
103. Fricke JR, Karim R, Jordan D, Rosenthal N. A double-blind, single-dose comparison of the analgesic efficacy of tramadol/acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery. Clin Ther. 2002;24:953-68.
104. Furlan AD, Sandoval JA, Mailis-Gagnon A et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ. 2006;174:1589-94.
105. Steiner D, Munera C, Hale M, Ripa S, Landau C. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study. J Pain. 2011;12(11):1163-73.
106. Karlsson M, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) vs prolonged-release tramadol tablets (75, 100, 150 and 200 mg) in patients with chronic

osteoarthritis pain: a 12-week, randomized, open-label, controlled, paralled-group noninferiority study. Clin Ther. 2009;31(3):503-13.
107. Felden L, Walter C, Harder S, Treede RD, Kayser H, Drover D, Geisslinger G, Lötsch J. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. Br J Anaesth. 2011 Sep;107(3):319-28.
108. Johnson RE, Jaffe JH, Fudala PJ: A controlled trial of buprenorphine treatment for opioid dependence. JAMA. 1992;267:2750–5.
109. Petitjean S, Stohler R, Deglon J, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. Drug Alcohol Depend. 2001;62:97-104.
110. Strain E, Stitzer M, Liebson I, Bigelow G. Comparison of buprenorphine and methadone in the treatment of opioid dependence. Am J Psychiatry. 1994;151:1025-30.
111. Ling W, Wesson D, Charuvastra C, Klett C. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry. 1996;53:401-7.
112. Schottenfeld R, Pakes J, Oliveto A, et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiatry. 1997;54:713-20.
113. Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. Int J Neuropsychopharmacol. 2008;11:641-53.
114. Gibson A, Degenhardt L, Mattick R, et al. Exposure to opioid maintenance treatment reduces long-term mortality. Addiction. 2008;103:462-8.
115. Maremmani I, Pani P, Pacini M, et al. Substance use and quality of life over 12 months among buprenorphine maintenance-treated and methadone maintenance-treated heroin-addicted patients. J Subst Abuse Treat. 2007 Jul;33(1):91-8.
116. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. NEJM. 2010;363:2320-31.
117. Cornish R, Macleod J, Strang J, et al. Risk of death during and after opiate substitution in primary care: prospective observational study in UK General Practice Research Database. BMJ 2010;341:c5475.
118. Pinto H, Maskrey V, Swift L, et all. The SUMMIT trial: a field comparison of buprenorphine vs methadone maintenance treatment. J Subst Abuse Treat. 2010;394:340-52.
119. Farré M, Mas A, Torrens M, et al. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. Drug Alcohol Depend. 2002;65:283-90.
120. Mattick R, Kimber J, Breen C, Davoli M. Buprenorphine maintenance vs placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2008, Issue 2. Art.No.: CD002207. DOI: 10.1002/14651858.CD002207.pub3.
121. Kakko J, Grönbladh L, Svanborg K, et al. A stepped care strategy using buprenorphine and methadone vs conventional methadone maintenance in heroin dependence: a randomized controlled trial. Am J Psychiatry. 2007;164:797-803.
122. Kamien J, Branstetter S, Amass L. Buprenorphine-naloxone vs methadone maintenance therapy: a randomized double-blind trial with opioid-dependent patients. Heroin Addict Relat Clin Probl. 2008;10:5-18.
123. Strain E, Stoller K, Walsh S, et al. Effects of buprenorphine vs buprenorphine/naloxone tablets in non-dependent opioid abusers. Psychopharmacology. 2000;148:374-83.
124. FDA Drug Safety Communication: Death, Narcotic Overdose, and Serious Cardiac Arrhythmias. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142841.htm. Accessed 2013 Sep 13.more efficacious.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Opiate Partial Agonists
AHFS Class 280812
February 10, 2016

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.[8-14] 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.[6-12]

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.[15] Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence.[6-12] 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.[15,16] 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.[16]

Butrans® (buprenorphine transdermal system) is an FDA-approved partial agonist for the management of moderate to severe chronic pain.[9] Another noteworthy event impacting this class was the notification to the FDA in September 2012, that Reckitt Benckiser Pharmaceuticals was voluntarily discontinuing production of Suboxone® (buprenorphine and naloxone) sublingual tablets as a result of increasing concerns over accidental or unsupervised pediatric exposure with the tablets compared to the film formulation which is available in a child-resistant, unit dose packaging. Distribution of Suboxone® (buprenorphine and naloxone) sublingual tablets was discontinued in March 2013; however, the generic formulation remains available.[17] Newly approved buprenorphine-naloxone formulations include Bunavail®, a buccal film, and Zubsolv®, a sublingual tablet with enhanced bioavailability as compared to Suboxone®, thus requiring a lower dosage.[8,10,11]

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 with the exception of pentazocine. This class was last reviewed in November 2013.

Table 1. Opiate Partial Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Buprenorphine	injection, sublingual tablet, transdermal patch	Buprenex®*, Butrans®	none†
Butorphanol	injection, nasal spray	N/A	butorphanol
Nalbuphine	injection	N/A	nalbuphine
Pentazocine	injection	Talwin®	none
Combination Products			
Buprenorphine and naloxone	buccal film, sublingual film, sublingual tablet*	Bunavail®, Suboxone®, Zubsolv®	none†
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.
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 (2015)**[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 (7 to 10), moderate pain (4 to 6) and mild pain (1 to 3). • Pain associated with oncology emergency should be addressed while treating the underlying condition. <u>General principles of opioid treatment</u> • The appropriate dose is that which relieves the patient's pain throughout the dosing interval without causing unmanageable adverse effects. • 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. • 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 provide adequate pain relief while avoiding the toxicities of the non-opioid component. • Monitor for aberrant drug-taking behaviors. • Risk Evaluation and Mitigation Strategies (REMS) programs are currently in place for all transmucosal fentanyl products; long-acting, extended-release formulations of opioids (e.g. hydrocodone ER, hydromorphone ER, morphine ER, oxycodone ER, oxymorphone ER, tapentadol ER); methadone tablets and solutions indicated for use as analgesics; and fentanyl or buprenorphine-containing transdermal systems. <u>Principles of maintenance opioid therapy</u>

Clinical Guideline	Recommendation(s)
	• 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. • When possible, use the same opioid for short-acting and extended-release forms. • Increase the dose of extended-release 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. • 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 one hour as needed. <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 severe pain should receive rapid titration of short-acting opioids. • For opioid-naïve patients whose pain intensity is moderate at presentation, the pathways are quite similar to those for severe pain, with slower titration of short-acting opioids. • Opioid-naïve patients experiencing mild pain intensity should receive nonopioid analgesics, such as NSAIDs or acetaminophen, or treatment with consideration of slower titration of short-acting opioids. • Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended-release or long-acting formulations of opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain. Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment. <u>Management of pain in opioid-tolerant patients</u> • Opioid-tolerant patients are those chronically taking opioids for pain relief. 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." • In order to achieve adequate analgesia in opioid-tolerant patients who are experiencing breakthrough pain of intensity greater than or equal to 4, or a pain intensity less than 4 without meeting goals for pain control and function, the previous 24-hour total oral or intravenous opioid requirement must be calculated and the new "rescue" dose must be increased by an opioid dose equivalent to 10 to 20% of the total opioid taken in the previous 24 hours. • Efficacy and adverse effects should be assessed every 60 minutes for orally administered opioids and every 15 minutes for intravenous opioids to determine a subsequent dose. Upon assessment, if the pain score remains unchanged or is increased, administration of 50 to 100% of the previous rescue dose is recommended. <u>Selecting an appropriate opioid</u> • Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). An individual

Clinical Guideline	Recommendation(s)
	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. • In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice. • Morphine and hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. • Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone. • 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. • The methods of administering analgesics that are widely accepted within clinical practice include “around the clock”, “as needed”, and “patient-controlled analgesia.” • “Around the clock” dosing is provided to chronic pain patients for continuous pain relief. A “rescue dose” should also be provided as a subsequent treatment for patients receiving “around the clock” doses. Rescue doses of short acting opioids should be provided for pain that is not relieved by regularly scheduled, “around the clock” doses. Opioids administered on an “as needed” basis are for patients who have intermittent pain with pain-free intervals. The “as needed” method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows a patient to control a device that delivers a bolus of analgesic “on demand”. • No single opioid is optimal for all patients. When considering opioid rotation, defined as changing to an equivalent dose of an alternative opioid to avoid adverse effects, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. • Subsequent treatment is based upon the patient’s continued pain rating score. All approaches for all pain intensity levels must include administering regular doses of opioids with rescue doses as needed, management of constipation,

Clinical Guideline	Recommendation(s)
	and psychosocial support and education for patients and their families. • Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's goals of comfort and function is mandated at each contact. • If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patients should be converted to an extended-release oral medication (if feasible) or another extended-release formulation (i.e., transdermal fentanyl) or long-acting agent (i.e., methadone). The subsequent treatment is based upon the patients' continued pain rating score. Rescue doses of the short acting formulation of the same long acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by extended-release opioids. • Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety. • Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, other individual characteristics of the patient such as age, and physical condition. • Opioids alone may not provide the optimal therapy, but when used in conjunction with nonopioid analgesics, such as an NSAID or adjuvant, and psychological and physical approaches, they can help to improve patient outcomes. • Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or, in some cases, to counter the adverse events associated with opioids. • The term adjuvant refers to medications that are coadministered to manage an adverse event of an opioid or to adjuvant analgesics that are added to enhance analgesia. Adjuvant may also include drugs for neuropathic pain. Clinically, adjuvant analgesics consist of anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch). • Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, visceral pain, and to reduce systemic opioid requirement, and are particularly important in treating neuropathic pain that is resistant to opioids. • Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain. Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic interventions. Attentions should be focused on psychosocial support and providing education to patients and families.
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

Clinical Guideline	Recommendation(s)
	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 (2012)**[20]	• Treatment of mild pain (WHO Step 1 analgesics):
	  o Acetaminophen or NSAIDs.
	• Treatment of moderate pain (WHO Step 2 analgesics):
	  o Acetaminophen, aspirin or an NSAID plus a weak immediate-release opioid such as codeine, dihydrocodeine, tramadol or propoxyphene or a strong opioid at low doses such as morphine or oxycodone.
	  o New opioid formulations may improve drug administration for patients with moderate pain. These include controlled release formulations of codeine, dihydrocodeine, tramadol, morphine and oxycodone in dosages appropriate for moderate pain.
	  o Additional options include low-dose formulations of transdermal fentanyl and of transdermal buprenorphine.
	• Treatment of severe pain (WHO Step III analgesics):
	  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 Methadone is an alternative treatment option, but may be more complicated to use because of its pharmacokinetic parameters. Methadone should be initiated by physicians with experience and expertise in its use.
	  o Strong opioids may be combined with a nonopioid analgesic (step 1).
	  o Patients with severe pain that need urgent relief should be treated with parenteral opioids
	• Opioid doses should be titrated to effect as rapidly as possible, with around-the-clock dosing and an as-needed 'breakthrough dose' (usually=10% of total daily dose) to manage transient pain exacerbations. If more than four 'breakthrough doses' per day are necessary, opioid treatment with a slow-release formulation should be initiated.
	• Reduction in opioid dose may be achieved by using a co-analgesic, such an antidepressant, neuroleptic psychoactive drug or anticonvulsant. Such combinations may also alleviate refractory side effects such as constipation, nausea, vomiting and central nervous system toxicity. Other strategies include the continued use of anti-emetics, laxatives, major tranquilizers, and psychostimulants; also, switching to another opioid agonist and/or another route may allow titration to adequate analgesia without the same disabling effects.
	• Neuropathic pain may not be adequately controlled by opioids alone; combination with co-analgesics may improve pain control. Steroids should be considered in case of nerve compression. There is sufficient evidence for use of bisphosphonates for refractory bone pain, but not for general use as first-line therapy of bone pain.

Clinical Guideline	Recommendation(s)

National Opioid Use Guideline Group: **Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain (2010)**[21]	<u>Conducting an opioid trial</u>
	• During an opioid trial, select the most appropriate opioid for trial therapy using a stepped approach, and consider safety.
	• Mild-to-moderate pain:
	  o First-line therapy: codeine or tramadol. There is a lower risk of overdose and addiction with these agents than stronger opioids. Tramadol is associated with seizures in patients at high seizure risk, or when combined with medications that increase serotonin levels (e.g., selective serotonin reuptake inhibitors).
	  o Second-line therapy: morphine, oxycodone or hydromorphone.
	• Severe pain:
	  o First-line therapy: morphine, oxycodone or hydromorphone. Oxycodone, hydromorphone and hydrocodone may have a higher abuse liability than morphine.
	  o Second-line therapy: fentanyl. Before starting fentanyl, ensure the patient is fully opioid tolerant.
	  o Third-line therapy: methadone. Titration of methadone is hazardous due to its very long half life leading to drug accumulation.
	• Start with a low dosage, increase dosage gradually and monitor opioid effectiveness until optimal dose is attained.
	• Chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200 mg/day of morphine or equivalent.
	• When initiating opioid therapy for patients at higher risk for misuse, prescribe only for well-defined somatic or neuropathic pain conditions, start with lower doses and titrate in small-dose increments, and monitor closely for signs of drug-related behaviors.
	• Meperidine is not recommended for use in chronic non-cancer pain. Oral meperidine has poor bioavailability and is less effective than codeine. Normeperidine can accumulate with frequent use of parenteral doses of meperidine, causing seizures and delirium.
	• Use acetaminophen-opioid combinations with caution to avoid acetaminophen toxicity.
	• Titrate controlled-release formulations with caution to avoid overdose and misuse. Each controlled-release tablet can contain a much higher opioid dose than immediate-release formulations, and can easily be converted to immediate release by biting or crushing the tablet.
	• Parenteral opioids are not recommended for use in chronic non-cancer pain. The parenteral route has higher risk of overdose, abuse and addiction, and infection.
	
	<u>Monitoring long-term opioid therapy</u>
	• For patients experiencing unacceptable adverse effects or insufficient opioid effectiveness from one particular opioid, try prescribing a different opioid or discontinuing therapy.
	• For patients receiving opioids for a prolonged period who may not have had an appropriate trial of therapy, take steps to ensure that long-term therapy is warranted and dose is optimal.
	
	<u>Treating specific populations with long-term opioid therapy</u>
	• Opioid therapy in elderly patients can be safe and effective. They cause less organ toxicity than NSAIDs and appear to cause less cognitive impairment than benzodiazepines. Among strong opioids, oxycodone and hydromorphone may be preferred over oral morphine because they are less likely to cause constipation and sedation. Controlled-release formulations are recommended due to compliance. There is no evidence controlled-release formulations are

Clinical Guideline	Recommendation(s)

	more effective than immediate-release formulations. For breakthrough pain or activity-related pain, immediate release formulations can be used.
	• A trial of opioid therapy may be considered for adolescent patients with well-defined somatic or neuropathic pain conditions when non-opioid alternatives have failed, risk of opioid misuse is assessed as low, close monitoring is available, and consultation, if feasible, is included in the treatment plan.
	• Pregnant patients taking long-term opioid therapy should be tapered to the lowest effective dose slowly enough to avoid withdrawal symptoms, and then therapy should be discontinued if possible.
	• Patients with a psychiatric diagnosis are at greater risk for adverse effects from opioid treatment. Usually in these patients, opioids should be reserved for well-defined somatic or neuropathic pain conditions. Titrate more slowly and monitor closely; seek consultation where feasible.
	
	<u>Managing opioid misuse and addiction in chronic non-cancer pain patients</u>
	• For patients with chronic non-cancer pain who are addicted to opioids, three treatment options should be considered: methadone or buprenorphine treatment, structured opioid therapy, or abstinence-based treatment.
	• Indications for methadone treatment are any of the following:
	  o Failed trial of structured opioid therapy.
	  o Using opioids by injection, snorting, or crushing tablets.
	  o Accessing opioids from multiple physicians or from the "street".
	  o Addiction to opioids and to other drugs/substances.
	• Indications for buprenorphine treatment are similar to those for methadone treatment. Buprenorphine could be preferred over methadone for:
	  o Patients who are at higher risk of methadone toxicity.
	  o Adolescents and young adults.
	  o Patients in communities where methadone treatment is unavailable.
	• An ideal candidate for a structured opioid therapy trial would be an opioid-addicted patient with chronic non-cancer pain who:
	  o Has a well-defined somatic or neuropathic pain condition for which opioids have been shown to be effective.
	  o Is well-known to the physician.
	  o Is not currently addicted to cocaine, alcohol or other drugs.
	  o Is not accessing opioids.
	• Abstinence-based treatment can be a patient preference or used when methadone or buprenorphine treatment is not available.

American Society of Anesthesiologists/ American Society of Regional Anesthesia and Pain Medicine: **Practice Guidelines for Chronic Pain Management (2010)**[22]	• Pharmacologic management of chronic pain includes anticonvulsants, antidepressants, benzodiazepines, N-methyl-D-aspartate (NMDA) receptor antagonists, NSAIDs, opioid therapy, skeletal muscle relaxants, and topical agents. • Anticonvulsants should be used as part of a multimodal strategy for patients with neuropathic pain. • Tricyclic antidepressants should be used as part of a multimodal strategy for patients with chronic pain. • Serotonin–norepinephrine reuptake inhibitors should be used as part of a multimodal strategy for a variety of chronic pain patients. • Selective serotonin reuptake inhibitors may be considered specifically for patients with diabetic neuropathy. • As part of a multimodal pain management strategy, extended-release oral opioids should be used for neuropathic or back pain patients, and transdermal, sublingual, and immediate-release oral opioids may be used. • For selected patients, NMDA receptor antagonists (e.g., neuropathic pain), NSAIDs (e.g., back pain), and topical agents (e.g., peripheral neuropathic pain) may be used; benzodiazepines and skeletal muscle relaxants may be

Clinical Guideline	Recommendation(s)
	considered. • A strategy for monitoring and managing side effects, adverse effects, and compliance should be considered for all patients undergoing any long-term pharmacologic therapy.

Veterans Health Administration, Department of Defense: **Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (2010)**[23]	<u>General considerations</u>
	• A trial of opioid therapy is indicated for a patient with chronic pain who meets all of the following criteria:
	  o Moderate to severe pain that has failed to adequately respond to non-opioid and non-drug therapeutic interventions.
	  o The potential benefits of opioid therapy are likely to outweigh the risks.
	  o The patient is fully informed and consents to the therapy.
	  o Clear and measurable treatment goals are established.
	
	<u>Initiation phase</u>
	• There is no evidence to recommend for or against the selection of any specific opioid:
	  o Select a specific opioid formulation that matches the individual's needs and specific medical conditions.
	  o Consider patient preference, and agent that allows administration by the least in visual analogue scale route.
	  o Consider the ease of drug administration, patient's prior experience with, and level of tolerance to opioid medications, potential risk for misuse, and abuse patterns.
	  o Transdermal fentanyl should be avoided in opioid naïve patients.
	• Start the opioid therapy trial with a low dose and with one medication at a time.
	• For continuous chronic pain, an agent with a long duration of action, such as controlled-release morphine or methadone is recommended. Short-acting opioids can be started, and later converted to long acting opioids.
	• Treatment of continuous chronic pain should be initiated with opioids on a defined and scheduled basis.
	• For episodic chronic pain, consider short-acting opioids (such as morphine, oxycodone, or hydrocodone), trying one medication at a time on an as needed basis. Long-acting opioids should not be used on an as needed basis.
	
	<u>Titration phase</u>
	• Titration should be individualized according to the patient's age, health status, previous exposure to opioids, level of pain, comorbidities, potential drug interactions, opioid formulation, level of care, attainment of therapeutic goals, and predicted or observed harms.
	• The daily dose may be increased by 25 to 100% at a time. Smaller increments are appropriate for elderly patients, those with likely low opioid tolerance, and patients experiencing unsatisfactory pain relief in the presence of some adverse effects. Larger increments may be used in patients with severe uncontrolled pain or likely high level of opioid tolerance.
	• To ensure that the full effect from a dosage change has been manifested, and to avoid potential toxicity due to rapid accumulation of a drug, do not increase the dose more frequently than every five half-lives.
	• Methadone dosage titration should not occur more frequently than every seven days or longer (e.g., every one to two months), and only if there is no problem with daytime sedation.
	• If possible, titrate one drug at a time while observing the patient for additive effects. Maintain patients on as few medications as possible to minimize drug interactions and adverse events.

Clinical Guideline	Recommendation(s)

	• Discontinue medications, especially adjuvant medications, which do not add substantially to patient function or comfort.
	• If a medication provides less than satisfactory pain reduction despite increasing the dose as tolerated to a reasonable level (<200 mg/day morphine equivalent), evaluate for potential causes such as nonadherence and drug interactions, and consider changing to an alternate opioid medication.
	• During the titration phase, reasonable supplemental doses of a short acting opioid may be considered.
	• Consider one or more of the following adjustments in therapy when there is an apparent loss of analgesic effect:
	  o Further optimize adjuvant therapies.
	  o Re-titrate the dose.
	  o Rotate to another opioid.
	  o Refer or consult with advanced pain care specialist.
	  o Discontinue opioid therapy.
	
	<u>Maintenance phase</u>
	• Maintain the lowest effective and well-tolerated dose. The optimal opioid dose is the one that achieves the goals of pain reduction and/or improvement in functional status and patient satisfaction with tolerable adverse effects.
	
	<u>Supplemental therapy</u>
	• Supplemental short- acting opioids may be considered in specific situations but their routine use in chronic pain is controversial.
	• This guideline supports the use of long-acting opioids in a scheduled manner for chronic pain, rather than the use of supplemental or as-needed opioids for exacerbations.
	• Evaluate worsening or new pain symptoms to determine the cause and the best treatment approach.
	• Encourage the use of nonpharmacologic treatments.
	• Evaluate the potential benefits, side effects, and risks when considering supplemental opioids. Consider supplemental short-acting opioid, non-opioid, or a combination of both agents on an as needed basis.
	• Avoid the use of rapid-onset opioids as supplemental opioid therapy in chronic pain, unless the time course of action of the preparation matches the temporal pattern of pain intensity fluctuation.
	• Avoid use of long-acting agents for acute pain or on an as-needed basis in an outpatient setting.
	• When using combination products, do not exceed maximum recommended daily doses of acetaminophen, aspirin, or ibuprofen.
	• Avoid the use of mixed agonist-antagonist opioids, as these agents may precipitate withdrawal in patients who have physical opioid dependence.
	• Whenever possible, use the same opioid for supplemental therapy as the long-acting opioid to avoid confusion about the cause of any adverse effects that may develop.
	• When using short-acting pure agonist opioids (alone or in combination with non-opioid analgesics) for supplemental therapy, give opioid doses equivalent to about 10 to 15%, the every four hourly equivalent, or 1/6th of the total daily opioid dose, as needed.
	• Use rescue short-acting opioids to assist with pain management during the titration process and to help determine the long-term daily opioid dose.
	• Do not use breakthrough pain therapy routinely for chronic pain. If necessary, use breakthrough pain therapy sparingly.
	• Consider adjusting the long-acting opioid regimen if pain exacerbations are interfering with patient function due to severity, frequency, or diurnal

Clinical Guideline	Recommendation(s)
	variations in pain intensity. • Consider providing preemptive analgesia for preventing incident pain.
American Pain Society/ American Academy of Pain Medicine: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[24]	• Consider a trial of chronic opioid therapy if chronic noncancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms. • Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. • There is insufficient evidence to recommend short-acting vs long-acting opioids, or as-needed vs around-the-clock dosing of opioids. • Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously by clinicians familiar with its use and risks. • When repeated dose escalations occur in patients on chronic opioid therapy, evaluate potential causes and reassess benefits relative to harms. • In patients who require relatively high doses of chronic opioid therapy, evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits. • Consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse effects or inadequate benefit despite dose increases. • Taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects. • In patients on around-the-clock chronic opioid therapy with breakthrough pain, consider as-needed opioids based upon an initial and ongoing analysis of therapeutic benefit vs risk.
Veterans Health Administration, Department of Defense: **Clinical Practice Guideline for Management of Substance Use Disorders (2009)**[25]	General considerations • Opioid agonist treatment is the first-line treatment for chronic opioid dependence. • Provide access to opioid agonist treatment for all opioid dependent patients, under appropriate medical supervision and with concurrent addition-focused psychosocial treatment. • Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first-line therapy. Buprenorphine monotherapy is preferred in pregnancy. • By administering an opioid to prevent withdrawal, reduce craving, and reduce the effects of illicit opioids, the opioid-dependent patient is able to focus more readily on recovery activities. Opioid agonist treatment program and office-based opioid treatment • Opioid agonist treatment should be administered in an opioid agonist treatment program or office-based opioid treatment. • Doses should be adjusted to maintain a therapeutic range between signs/symptoms of overmedication and opioid withdrawal. • The usual dosage range for optimal effects is 60 to 120 mg/day. • Buprenorphine target dose is generally up to 16 mg/day; doses >32 mg are rarely indicated. • In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. Methadone therapy • Methadone for the treatment of opioid dependence may only be prescribed

Clinical Guideline	Recommendation(s)
	out of an accredited opioid agonist treatment program as it is a schedule II agent. It is illegal to prescribe methadone for the treatment of opioid dependence out of an office-based practice. • For newly admitted patients, the initial dose of methadone should not exceed 30 mg and the total dose for the first day should not exceed 40 mg, without provider documentation that 40 mg did not suppress opioid withdrawal symptoms. • Under usual practices, a stable, target dose is greater than 60 mg/day and most patients will require considerably higher doses in order to achieve a pharmacological blockade of reinforcing effects of exogenously administered opioids. <u>Buprenorphine therapy</u> • Office-based treatment with sublingual buprenorphine for opioid dependence can only be provided by physicians who have received a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) and have a special Drug Enforcement Agency (DEA) number. • Buprenorphine induction (~1 week) involves helping a patient in the process of switching from the opioids of abuse to buprenorphine. • In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. • The initial dose of buprenorphine/naloxone combination is between 2/0.5 mg to 4/1 mg, which can be repeated after two hours. The amount of buprenorphine administered in the first day should not exceed 8 mg. • The daily buprenorphine/naloxone dose is the equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on day one. Doses may be increased as needed for symptomatic relief, with a target dose of 12/3 mg to 16/4 mg per day to be achieved within the first week.

American Psychiatric Association:
Practice Guideline for Treatment of Patients with Substance Use Disorders (2006)[15]
	<u>Treating dependence and abuse</u>
	• Goals of therapy are to identify stable maintenance dose of opioid agonist and facilitate rehabilitation.
	• The choice of treatment for opioid dependence is based on patient preference, past response to treatment, probability of achieving and maintaining abstinence, and assessment of the short- and long-term effects of continued use of illicit opioids on the patient's life adjustment and overall health status.
	• Maintenance treatment with methadone or buprenorphine is appropriate for patients with ≥ 1 year history of opioid dependence. Maintenance therapy with naltrexone is an alternative strategy.
	• Methadone is a full mu agonist opioid, and is the most thoroughly studied and widely used agent for opioid dependence.
	• Methadone maintenance treatment for opioid-dependent individuals has generally been shown to be effective in:
	  o Decreasing illicit opioid use.
	  o Decreasing psychosocial and medical morbidity.
	  o Improving overall health status.
	  o Decreasing mortality.
	  o Decreasing criminal activity.
	  o Improving social functioning.
	  o Reducing the spread of Human Immunodeficiency Virus infection among intravenous drug users.
	• Maintenance on methadone is generally safe; however, one key issue is determining a dose sufficient to suppress the patient's opioid withdrawal and craving, as no single dose is optimal for all patients.
	• Methadone can be diverted for abuse, as can other opiates that have agonist effects at the mu receptor.

Clinical Guideline	Recommendation(s)

	• Buprenorphine produces a partial agonist effect at the mu receptor and an antagonistic effect at the kappa receptor.
	• Buprenorphine enters the systemic circulation more slowly through the sublingual route than with parenteral administration and has less abuse potential compared to the parenterally delivered form.
	• The combination of buprenorphine and naloxone significantly reduces the risk of diversion because naloxone will exert a potent opioid antagonist effect if the combination tablet is crushed and administered intravenous by an opioid-dependent person. Naloxone has poor sublingual bioavailability.
	• Buprenorphine is generally safe. Overdose with buprenorphine generally does not produce significant respiratory depression
	
	<u>Treating intoxication</u>
	• Mild to moderate opioid intoxication usually does not require specific therapy.
	• Severe opioid toxicity, marked by respiratory depression, is a medical emergency. Naloxone will reverse respiratory depression and other overdose manifestations.
	
	<u>Treating withdrawal</u>
	• Treatment of withdrawal is directed at safely decreasing acute symptoms and easing transition into a long-term treatment program.
	• Effective strategies include:
	  o Substitution of opioid with methadone or buprenorphine.
	  o Abrupt discontinuation of opioids, with use of clonidine to suppress withdrawal symptoms.
	  o Clonidine-naltrexone detoxification.

Center for Substance Abuse Treatment: **Medication-Assisted Treatment For Opioid Addiction in Opioid Treatment Programs (TIP 43) (2005)**[26]	• To be considered for buprenorphine maintenance, patients should have a diagnosis of opioid dependence. • It is recommended that buprenorphine and naloxone be used for induction treatment (and for stabilization and maintenance) for most patients. • The initial induction doses should be administered as observed treatment; further doses may be provided via prescription thereafter. • To minimize the chances of precipitated withdrawal, patients who are transferring from long-acting opioids to buprenorphine should be inducted using buprenorphine monotherapy, but switched to buprenorphine and naloxone soon thereafter. • The longest period that a patient is on buprenorphine is the maintenance phase. This period may be indefinite. • Buprenorphine can be used for the medically supervised withdrawal of patients from both self-administered opioids and from opioid agonist treatment with methadone or levo-alpha-acetyl-methadol. • The goal of using buprenorphine for medically supervised withdrawal from opioids is to provide a transition from the state of physical dependence on opioids to an opioid-free state, while minimizing withdrawal symptoms. • It is recommended that patients dependent on short-acting opioids who will be receiving medically supervised withdrawal be inducted directly onto buprenorphine and naloxone tablets. • The use of buprenorphine or buprenorphine and naloxone to taper off long-acting opioids should be considered only for those patients who have evidence of sustained medical and psychosocial stability, and should be undertaken in conjunction and in coordination with patients' opioid treatment programs.
Center for Substance Abuse Treatment:	<u>Considerations of maintenance treatment</u> • Maintenance treatment with buprenorphine for opioid addiction consists of

Clinical Guideline	Recommendation(s)
Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40) (2004)[16]	induction, stabilization, and maintenance phases. • The goal of the induction phase is to find the minimum dose of buprenorphine at which the patient discontinues or markedly diminishes use of other opioids and experiences no withdrawal symptoms, minimal or no side effects, and no craving for the drug of abuse. • Buprenorphine and naloxone can be used for induction treatment (and for stabilization and maintenance) for most patients. • Patients who are transferring from long-acting opioids to buprenorphine should be inducted using buprenorphine monotherapy, but switched to buprenorphine and naloxone soon thereafter. • Pregnant women should be inducted and maintained on buprenorphine monotherapy. • The stabilization phase has begun when a patient is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has uncontrollable cravings for opioid agonists. The goal is to reduce self-reported cravings and self-reported use of illicit opioids with the minimum dose of medication. • Maintenance can be relatively short-term (<12 months) or a lifetime process. • Factors to be considered when determining suitability for long-term medication-free status include stable housing and income, adequate psychosocial support, and the absence of legal problems. • Data suggest that longer duration of medication treatment is associated with less illicit drug use and fewer complications. <u>Induction phase (day 1)</u> • Patients who are experiencing objective signs of opioid withdrawal and whose last use of a short-acting opioid was more than 12 to 24 hours prior to the initiation of induction can receive a first dose of buprenorphine and naloxone 4/1–8/2 mg. • If the initial dose of the buprenorphine/naloxone is 4/1 mg and opioid withdrawal symptoms subside but then return (or are still present) after two hours, a second dose of 4/1 mg can be administered. • The total amount of buprenorphine administered in the first day should not exceed 8 mg. • Patients who are not physically dependent on opioids should receive the lowest possible dose (2/0.5 mg) of buprenorphine and naloxone for induction treatment. <u>Induction phase (day 2 and forward)</u> • If buprenorphine monotherapy was administered on day 1, switch to buprenorphine and naloxone on day 2. • The daily buprenorphine and naloxone dose is the equivalent of the total amount of buprenorphine and naloxone (or buprenorphine) that was administered on day 1. • Doses may be increased in 2/0.5 to 4/1 mg increments each day for symptomatic relief. The target dose of 12/3 to 16/4 mg per day to be achieved within the first week. • The total dose on day 2 should not exceed 16/4 mg. • Continue dose increases on subsequent days up to a maximum of 32/8 mg per day. <u>Considerations for medically supervised withdrawal (detoxification)</u> • The goal of using buprenorphine for medically supervised withdrawal from opioids is to transition to an opioid-free state, while minimizing withdrawal symptoms.

Clinical Guideline	Recommendation(s)
	• Medically supervised withdrawal with buprenorphine consists of an induction phase and a dose-reduction phase. • The goal of induction should be to stabilize the patient as rapidly as possible, to minimize any withdrawal symptoms, and to eliminate further use of illicit opioids. • It is recommended that patients dependent on short-acting opioids be inducted directly onto buprenorphine and naloxone tablets. <u>Induction phase</u> • Patients should have discontinued the use of illicit opioids and should be exhibiting the early symptoms of withdrawal. • An initial recommended dose of buprenorphine and naloxone is 4/1 mg. This dose can be followed in two to four hours with a second dose of 4/1 mg. • Over the next 2 days, the dose of buprenorphine and naloxone should be increased to 12/3 to 16/4 mg per day. <u>Dose reduction phase: long-period reduction</u> • The use of buprenorphine for gradual detoxification over long periods is probably more effective than its use for rapid detoxification over short or moderate periods. <u>Dose reduction phase: moderate-period reduction.</u> • Patients without a compelling need to undergo short-term detoxification, but with a desire to become opioid free and to engage in rehabilitation aimed at an opioid-free lifestyle, can be detoxified over a 10- to 14-day (or longer) period by gradually decreasing the initial stabilization dose of buprenorphine (usually 8 to 16 mg per day) by 2 mg every two to three days. <u>Dose reduction phase: short-period reduction</u> • Patients with a compelling reason to achieve an opioid-free state quickly (e.g., impending incarceration, foreign travel, job requirement) may have their buprenorphine dose reduced over three days and then discontinued. • When compared to clonidine for the treatment of short-term opioid withdrawal, buprenorphine is better accepted by patients and more effective in relieving withdrawal symptoms. <u>Buprenorphine for discontinuation of opioid agonist treatment</u> • The use of buprenorphine or buprenorphine and naloxone to taper off opioid agonist treatment with methadone or levo-alpha-acetyl-methadol should be considered only for those patients who have evidence of sustained medical and psychosocial stability. <u>Methadone discontinuation</u> • Patients who are clinically stable and are being slowly tapered off methadone maintenance treatment generally experience little difficulty until the daily methadone dose reaches ≤30 mg. • As the daily dose of methadone drops below 30 mg, opioid withdrawal symptoms often emerge. The euphoria-blocking and anti-craving effects of methadone are diminished as well. <u>Discontinuation of buprenorphine and naloxone</u> • When discontinuing buprenorphine and naloxone, the daily dose should be decreased gradually over a predetermined period or at a rate negotiated by the patient and the physician together. • Withdrawal symptoms may emerge as the buprenorphine/naloxone dose is

Clinical Guideline	Recommendation(s)

	decreased and the taper may be temporarily suspended.
	• Discontinuation of buprenorphine/naloxone may be performed over short periods (e.g., three days), but should only be used when there is a compelling urgency to discontinue therapy quickly. Discontinuation over a longer period is preferred.
	
	<u>Determining appropriateness for buprenorphine treatment</u>
	• A candidate for buprenorphine treatment for opioid addiction should have a diagnosis of opioid addiction as well as:
	  o Be interested in treatment for opioid addiction.
	  o Have no contraindication to buprenorphine or to naloxone.
	  o Be expected to be reasonably compliant with treatment.
	  o Understand the risks and benefits of treatment.
	  o Be willing to follow safety precautions.
	  o Agree to buprenorphine treatment after a review of other treatment options.
	• Conditions and circumstances that may preclude a patient as a candidate for office-based buprenorphine treatment:
	  o Comorbid dependence on high doses of benzodiazepines or other central nervous system depressants.
	  o Significant untreated psychiatric comorbidity.
	  o Active or chronic suicidal or homicidal ideation or attempts.
	  o Multiple previous treatments for drug abuse with frequent relapses.
	  o Poor response to previous well-conducted attempts at buprenorphine treatment.
	  o Significant medical complications.
	  o Conditions that are outside the area of the treating physician's expertise.

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[6-12]

Indication	Single Entity Agents				Combination Products	
	Buprenorphine*	Butorphanol	Nalbuphine	Pentazocine	Buprenorphine and Naloxone*	Pentazocine and Naloxone
Analgesia						
Management of pain when the use of an opioid analgesic is appropriate		✔				
Relief of mild to moderate pain						
Relief of moderate to severe pain	✔ †		✔	✔		✔
Relief of pain during labor		✔ †	✔			
Management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time	✔ ‡					
Anesthesia						
Preoperative or preanesthetic medication		✔ †	✔	✔		
Supplement to surgical anesthesia		✔ †	✔	✔		
Opioid Dependence						
Treatment of opioid dependence	✔ §				✔ §‖^	

*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.

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Opiate Partial Agonists[6-12]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Buprenorphine	Injection: 90 to 100 SL: 31 TD: 15	96	Liver	Renal (30) Feces (70)	Injection: 2 SL: 37 TD: 26
Butorphanol	Oral: 17 Intranasal: 70	80 to 83	Liver	Renal (75) Feces (15)	4 to 7
Nalbuphine	Not reported	Not reported	Liver	Renal (7) Feces (not reported)	2.2 to 2.6
Pentazocine	Not reported	60	Liver	Renal (60 to 70) Feces (<2)	2 to 10
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

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

Table 5. Significant Drug Interactions with the Opiate Partial Agonists[6]

Generic Name(s)	Significance Level	Interaction	Mechanism
Buprenorphine	1	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.
Buprenorphine	1	Benzodiazepines	Synergistic effects of opioids and benzodiazepines increase the risk of sedation and life-threatening respiratory depression, especially with overdosage.
Buprenorphine	1	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.
Buprenorphine	1	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

Generic Name(s)	Significance Level	Interaction	Mechanism
			metabolism (CYP3A4) in the gut wall and liver.
Opiate partial agonists (buprenorphine,)	2	Rifamycins	Rifamycins may decrease pharmacologic effects and plasma concentrations of opiate partial agonists. Pain control may be decreased.
Opiate partial agonists (buprenorphine, butorphanol, nalbuphine, pentazocine)	2	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)	2	Methadone	Narcotic antagonists and agonist-antagonists may decrease or attenuate the pharmacologic effects of methadone. Precipitation of withdrawal symptoms in those dependent on morphine-like drugs may occur.

Significance level 1=major severity, significance level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the opiate partial agonists are listed in Table 6. The boxed warning for buprenorphine transdermal is listed in Table 7. The boxed warning for pentazocine-naloxone is listed in Table 8.

Table 6. Adverse Drug Events (%) Reported with the Opiate Partial Agonists[6-12]

Adverse Events	Single Entity Agents				Combination Products	
	Buprenorphine	Butorphanol	Nalbuphine	Pentazocine	Buprenorphine and Naloxone	Pentazocine and Naloxone
Cardiovascular						
Bradycardia	-	-	≤1	-	-	-
Circulatory depression/collapse	-	-	-	✔	-	✔
Flushing	-	-	-	✔	-	✔
Hypertension	<1	-	≤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	12	>1	<1	-	✔	-
Asthenia	5 to 7	>1	-	-	✔	-
Chills	-	-	-	✔	-	✔
Coma	<1	-	-	-	<1	-
Confusion	<1	>1	≤1	✔	<1	✔
Depersonalization	<1	-	-	-	<1	-
Depression	11	-	≤1	✔	<1	✔
Disorientation	-	-	-	✔	-	✔
Dizziness	4	19	5	✔	✔	✔
Drowsiness	-	-	-	-	✔	✔
Dysphoria	-	<1	≤1	-	-	-
Euphoria	<1	>1	≤1	✔	>1	✔
Fatigue	<1	-	-	-	-	-
Foot drop	-	<1	-	-	<1	-
Hallucinations	<1	-	≤1	✔	-	✔
Headache	30 to 36	>1	3	✔	>1	✔

Adverse Events	Single Entity Agents				Combination Products	
	Buprenorphine	Butorphanol	Nalbuphine	Pentazocine	Buprenorphine and Naloxone	Pentazocine and Naloxone
Hostility/irritability	-	<1	≤1	✔	<1	✔
Impairment of performance	-	-	-	✔	-	✔
Insomnia	15 to 22	-	-	✔	✔	✔
Nervousness	6	>1	≤1	-	<1	-
Nightmares	-	-	-	✔	-	✔
Paresthesia	<1	>1	-	✔	<1	✔
Psychosis	<1	-	-	-	<1	-
Restlessness	-	-	≤1	-	✔	-
Sedation	✔	43	✔	✔	-	✔
Seizures	<1	-	-	-	<1	✔
Tremor	<1	>1	-	✔	<1	✔
Weakness	<1	-	-	✔	<1	✔
Withdrawal syndrome	19 to 27	<1	-	-	✔	-
Dermatological						
Erythema multiforme	-	-	-	✔	-	✔
Localized reactions	-	-	-	✔	-	-
Pruritus	<1	>1	≤1	✔	<1	✔
Rash	<1	-	-	✔	<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	✔	-	-	-	12	✔
Cramps	8 to 13	>1	-	✔	✔	✔
Dry mouth	<1	-	4	✔	<1	✔
Diarrhea	<1	-	4	✔	✔	✔
Dyspepsia	4 to 5	-	-	-	✔	-
Dysphagia	-	-	≤1	-	-	-

Adverse Events	Single Entity Agents				Combination Products	
	Buprenorphine	Butorphanol	Nalbuphine	Pentazocine	Buprenorphine and Naloxone	Pentazocine and Naloxone
Flatulence	<1	-	-	-	<1	-
Hepatitis	-	-	-	-	✔	-
Nausea	✔	-	6	✔	15	✔
Oral moniliasis	14 to 16	13	6	✔	-	✔
Vomiting	✔	-	6	-	7	✔
Weight loss	8	13	6	✔	-	✔
Genitourinary						
Urinary retention	<1	-	-	✔	<1	✔
Urinary urgency	-	<1	-	✔	-	✔
Urinary tract infection	-	-	≤1	-	-	-
Respiratory						
Apnea	<1	-	-	-	<1	-
Bronchitis	-	-	≤1	-	-	-
Bronchospasm	-	-	-	-	✔	-
Cough	-	>1	-	-	-	-
Dyspnea	<	-	-	✔	<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	-	-	✔	✔	✔	✔
Bone pain	4 to 8	-	-	-	-	-
Blurred vision	<1	-	-	-	<1	-
Carcinoma	>1	>1	≤1	✔	-	✔

Adverse Events	Single Entity Agents				Combination Products	
	Buprenorphine	Butorphanol	Nalbuphine	Pentazocine	Buprenorphine and Naloxone	Pentazocine and Naloxone
Chills	-	-	-	-	✔	-
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	-	-	-	-	✔	-
Flu syndrome	-	-	-	-	✔	-
Flushing	<1	-	-	-	<1	-
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.

Table 7. Boxed Warning for buprenorphine transdermal[9]

WARNING
Addiction, Abuse, and Misuse Buprenorphine transdermal 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 transdermal, 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 transdermal. Monitor for respiratory depression, especially during initiation of buprenorphine transdermal or following a dose increase. Misuse or abuse of buprenorphine transdermal by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal 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 transdermal, especially by children, can result in a fatal overdose of buprenorphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of buprenorphine transdermal 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.

Table 8. Boxed Warning for Pentazocine and Naloxone[12]

WARNING
Pentazocine and naloxone combination is intended for oral use only. Severe, potentially lethal reactions (e.g., pulmonary emboli, vascular occlusion, ulceration, and abscesses, withdrawal symptoms in narcotic-dependent individuals) may result from misuse of this drug by injection or in combination with other substances.

VII. Dosing and Administration

The usual dosing regimens for the opiate partial agonists are listed in Table 9.

Table 9. Usual Dosing Regimens for the Opiate Partial Agonists[6-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Buprenorphine	Opioid dependence: 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	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	Injection: 0.3 mg/mL Sublingual tablet: 2 mg 8 mg Transdermal patch: 5 µ/hr 7.5 µ/hr 10 µ/hr 15 µ/hr 20 µ/hr

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	as day two; maintenance, 12 to 16 mg as a single dose Moderate to severe pain: 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	buprenorphine and naloxone at the same buprenorphine dose as day two; maintenance, 12 to 16 mg as a single dose 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)	
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 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.	Safety and efficacy in children have not been established.	Injection: 1 mg/mL 2 mg/mL Nasal spray: 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	Safety and efficacy in children have not been established.	Injection: 10 mg/mL 20 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	over a 10 to 15 minute period initially, then 0.25 mg to 0.5 mg/kg as a single IV administration for maintenance		
Pentazocine	Analgesia: Injection: 30 mg IM, SC, or IV every three to four hours Labor pain: Injection: 30 mg as a single IM dose Preoperative supplement to anesthesia: Injection: 30 mg IV or 60 mg IM or SC; may be repeated every three to four hours	Premedication for Sedation: Injection: ≥1 year of age: 0.5 mg/kg as a single IM dose	Injection: 30 mg/mL
Combination Products			
Buprenorphine and naloxone	Opioid dependence: Buccal film: the film is applied to the buccal mucosa as a single daily dose and is for use in patients who have already been initially inducted using buprenorphine sublingual tablets. For maintenance treatment, the recommended dose is 8.4-1.4 mg per day as a single dose; the dose should be adjusted in increments of 2.1-0.3 mg; the usual dose range is 2.1-0.3 to 12.6-2.1 mg per day 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	Opioid dependence: Patients ≥16 years of age: dosing same as adult use	Buccal film: 2.1-0.3 mg 4.2-0.7 mg 6.3-1 mg Sublingual film: 2-0.5 mg 4-1 mg 8-2 mg 12-3 mg Sublingual tablet (Suboxone®, generic): 2-0.5 mg8-2 mg Sublingual tablet (Zubsolv®): 1.4-0.36 mg 5.7-1.4 mg 8.6-2.1 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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 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

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the opiate partial agonists are summarized in Table 10.

Table 10. 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				
Zenz et al.[27] (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
Steiner et al.[28] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			number of tablets of supplemental analgesic medication during DB period, and the Oswestry Disability Index at weeks four, eight, and 12	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.[29] (2010) Buprenorphine transdermal system 5, 10, or 20 µg/hr every 7 days vs placebo	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with low back pain of at least moderate severity, not adequately controlled with non-opioid analgesic medications for ≥6 weeks	N=79 DB: 8 weeks (XO at the end of week 4) ES: 6 weeks	Primary: Average pain score over the last week on a five-point pain intensity scale ranging from 0 (no 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	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). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			preference and safety	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 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.[30] (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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	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: 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.[31] (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-	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			investigator-rated and global assessment of pain relief, patient preference and safety	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.[32] (2011) 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	AC, MC, OL, PG, RCT 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)	N=220 10 weeks of titration period followed by 12 weeks of assessment period	Primary: Average pain score over the last 24 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	Primary: In the intent-to-treat analysis, the treatment difference between buprenorphine plus paracetamol and codeine-paracetamol with regard to 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			rate during the titration period and safety	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). 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.
Desjardins et al.[33] (2000) Butorphanol 0.25 mg	DB, MC, PG, RCT Patients with pain after the removal of impacted third	N=151 Single dose intranasal formulation	Primary: Patient-rated pain intensity, pain relief, pain half gone, adverse	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs butorphanol 0.5 mg vs butorphanol 1 mg vs butorphanol 2 mg vs placebo	molars		events at 0.25, 0.5, one, two, three, four, five, and six hours after treatment; global evaluation Secondary: Not reported	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
Wermeling et al.[34] (2005) Butorphanol 1 mg vs butorphanol 2 mg vs placebo	DB, PC, PG, RCT Patients receiving standard anesthesia with moderate to severe pain after dental impaction surgery	N=30 Single dose intranasal formulation	Primary: Summed pain intensity difference at two, four, and six hours after administration of study medication and total pain relief at six hours Secondary: Not reported	Primary: A dose response was observed in summed pain intensity differences scores, with the 2 mg dose of butorphanol providing the greatest response 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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. 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	DB, PRO, RCT	N=24	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	Children 1 to 12 years of age undergoing scheduled surgery	72 hours	Number of patients requiring dose increments Secondary: Sedation, heart rate, blood pressure, and vomiting	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) 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	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.[39]	DB, RCT	N=105	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(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 vs naloxone 0.4 mg + pentazocine 60 mg intravenous vs placebo	Patients undergoing surgery for the removal of impacted third molars	Single dose	Pain intensity using a visual-analogue scale Secondary: Not reported	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 the group of patients receiving low-dose naloxone plus pentazocine still reported significant analgesia.
Petti[40] (1985) Pentazocine 25 mg and acetaminophen 650 mg	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs codeine 30 mg and acetaminophen 300 mg vs propoxyphene napsylate 100 mg and acetaminophen 650 mg vs placebo				Secondary: Not reported
Opioid Dependence				
Kornor et al.[41] (2007) Buprenorphine flexible daily dosing to a maximum dose of 16 mg daily	OL Patients ≥22 years of age with opioid dependence who were willing to enroll in a nine-month buprenorphine program	N=75 9 months	Primary: Self reported opioid abstinence 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,	Primary: More program completers compared to non-completers reported abstinence from opioids during the 30 days prior to the follow-up, a 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			polysubstance and intravenous use, employment, illegal activities, psychiatric problems and medical problems	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).
Fareed et al.[42] (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.[43] (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.[44] (1999) Buprenorphine maintenance dose	DB, PC Patients ≥18 years of age who were in good health and met	N=16 80 days	Primary: Self-report measures (i.e., VAS and adjective rating scales) and	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 not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(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.	DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment		observer measures Secondary: 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.[45] (1999) Buprenorphine maintenance dose (ranged from 4 to 8 mg/70 kg) SL every 24 hours vs double maintenance dose	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
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.[46] (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 There was a three-	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
day buprenorphine induction phase prior to randomization.				Secondary: Not reported
Gibson et al.[47] (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 patients (95% CI, 2 to 19) than younger participants who were randomized to methadone.
Johnson et al.[48] (1992)	DB, PG, RCT Adults seeking	N=162 17-week	Primary: Retention time in treatment, urine	Primary: During the maintenance phase, the retention rates were significantly greater for buprenorphine (42%) than for methadone 20 mg/day (20%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine 8 mg daily vs methadone 60 mg daily vs methadone 20 mg daily	treatment for opioid dependence	maintenance phase, followed by a 8-week detoxification phase	samples negative for opioids, and failure to maintain abstinence Secondary: Not reported	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.[49] (1992) Buprenorphine SL tablets (flexible dosing schedule) vs methadone (flexible dosing	DB, RCT Patients seeking treatment for opioid dependence	N=58 6 weeks	Primary: Treatment retention rate, urine samples positive for opiates, substance use Secondary: Not reported	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). The proportion of cocaine-positive toxicology results did not differ between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
schedule)				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.[50] (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.[51] (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
Schottenfeld et al.[52]	DB, RCT	N=116	Primary: Retention in	Primary: There were significant effects of maintenance treatment on rates of illicit

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1997) Buprenorphine 4 mg daily vs buprenorphine 12 mg daily vs methadone 20 mg daily vs methadone 65 mg daily	Patients seeking treatment for opioid dependence	24 weeks	treatment and illicit opioid and cocaine use Secondary: Not reported	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.[53] (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
Maremmani et al.[54] (2007)	OL Patients involved in	N=213 12 months	Primary: Opioid use, psychiatric status,	Primary: There were significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for buprenorphine-treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine vs methadone	a long-term treatment program with buprenorphine or methadone		quality of life Secondary: Not reported	and methadone-treated patients. Secondary: Not reported
Jones et al.[55] (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.[56] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Older patients on buprenorphine had significantly improved survival. Secondary: Not reported
Cornish et al.[57] (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.[58] (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 substitution therapy Secondary:	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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	A total of 28% of patients selecting buprenorphine reported they would not have accessed treatment with methadone therapy. Secondary: Not reported
Farré et al.[59] (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
Mattick et al.[60] (2008) Buprenorphine	MA Patients dependent on heroin or other	N=4,497 (24 trials) Variable	Primary: Treatment retention, suppression of	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs methadone vs placebo	opioids	duration	opioid use, use of other substances Secondary: Not reported	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). <u>Medium Dose Buprenorphine vs Medium Dose Methadone</u> 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). <u>Low Dose Buprenorphine Maintenance vs Placebo</u> 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). <u>Medium Dose Buprenorphine Maintenance vs Placebo</u> 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). <u>High Dose Buprenorphine Maintenance vs Placebo</u> 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). Secondary: Not reported
Daulouede et al.[61]	MC, OL, PRO, XO	N=53	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Buprenorphine at patient's current dosage SL vs buprenorphine-naloxone at the same buprenorphine dose SL	Patients ≥18 years of age who were receiving stable, maintenance treatment with buprenorphine 2 to 16 mg/day for at least six months	5 days	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	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.[62] (2011) Buprenorphine soluble film 16 mg SL daily vs buprenorphine-naloxone soluble	RCT Patients 25 to 56 years of age with opioid dependence	N=34 5 days	Primary: Change in COWS scores Secondary: Pupillometry, VAS and subjective adjective rating scales and adverse events	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
film 16 mg SL daily				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.[63] (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)* 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.[64]	DB, DD, PC	N=7	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(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	Adults with active opioid abuse, but not physically dependent		Peak drug effect; physiologic and psychomotor measures Secondary: Not reported	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.[65] (2003) <u>RCT</u> Buprenorphine-naloxone SL tablets 16-4 mg daily vs buprenorphine SL	DB, MC, PC, RCT, followed by OL phase Patients 18 to 59 years of age who met the diagnostic criteria for opiate dependence and were seeking opiate-substitution pharmacotherapy	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 Secondary: Impressions of overall status since enrollment in	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tablets 16 mg daily vs placebo OL Phase Buprenorphine-naloxone up to 24-6 mg daily			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	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). OL Phase 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.
Woody et al.[66] (2008) Buprenorphine-naloxone 24 mg/day for 9	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	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-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks, then tapered to week 12 (extended) vs buprenorphine-naloxone up to 14 mg/day, then tapered to day 14 (detox)			Secondary: Proportion of patients remaining in treatment; reported opioid use, injection use, non-study addiction treatments	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 addiction treatment (P<0.001) compared to the detox group.
Weiss et al.[67] 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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 randomized to receive standard medical management or standard medical management plus opioid dependence counseling prior to entering each study phase.				depression leading to hospitalization (N=5), were the most common serious adverse events, all of which occurred soon after completion of treatment taper.
Bell et al.[68] (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.[69] (2008)	OS	N=166	Primary: Retention in	Primary: During the follow-up period, 40 patients left treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine-naloxone	Patients meeting criteria for opioid dependence	2 to 5 years	treatment; percentage of opioid-negative urine specimens Secondary: Percentage of cocaine-negative urine specimens; buprenorphine dose; patient satisfaction; serum transaminases; adverse events	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. 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.
Kakko et al.[70] (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.[71] (2014) Buprenorphine-	OL, RCT Opioid-dependent individuals	N=1267 24 weeks	Primary: Treatment completion (the participant	Primary: Fewer buprenorphine-naloxone participants (46%) than methadone participants (74%) completed treatment (P<0.01) at 24 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
naloxone vs methadone Doses were titrated as determined by the local study physician			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	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.[72] (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).

*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.[73] 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 11. Relative Cost of the Opiate Partial Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Buprenorphine†	injection, sublingual tablet, transdermal patch	Buprenex®*, Butrans®	$$$$$	$$$$
Butorphanol	injection, nasal spray	N/A	N/A	$$
Nalbuphine	injection	N/A	N/A	$$$
Pentazocine	injection	Talwin®	$$$	N/A
Combination Products				
Buprenorphine and naloxone†	buccal film, sublingual film, sublingual tablet*	Bunavail®, 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]

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.[19,21-24] 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.[22,23] According to the Veterans Health Administration, 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.[23] 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.[26-39]

Interventions for opioid-related conditions (dependence, abuse, intoxication, and withdrawal) include psychosocial therapy and pharmacotherapy with long-acting opioids.[15] 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.[15] For the maintenance treatment of opioid dependence, guidelines recommend the use of methadone or buprenorphine and naloxone as first-line therapy.[15,16,25,26] 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.[15] Buprenorphine monotherapy is the 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.[41-72] 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.[48-54,57-59,69-71] 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.

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 dependence. 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.

Buprenorphine and buprenorphine-naloxone should not be placed in preferred status regardless of cost.

XII. References

1. International Association for the Study of Pain. ISAP Taxonomy 2012 [cited 2015 Nov]. Available at: http://www.iasp-pain.org/Taxonomy.
2. Coghill RC. Individual differences in the subjective experience of pain: New insights into mechanisms and models. Headache. 2010;9:1531-5.
3. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11:S133-53.
4. Yaksh TL, Wallace MS. Chapter 18. Opioids, Analgesia, and Pain Management. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2011. http://www.accesspharmacy.com/content.aspx?aID=16663974. Accessed December 3, 2015.
5. Baumann TJ, Herndon CM, Strickland JM. Chapter 44. Pain Management. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York: McGraw-Hill; 2014. http://www.accesspharmacy.com/content.aspx?aID=7986332. Accessed December 2, 2015.
6. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Nov]. Available from: http://online.factsandcomparisons.com.
7. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Nov]. Available from: http://www.thomsonhc.com/.
8. Suboxone® sublingual film [package insert]. Richmond, VA: Indivior, Inc.; 2015 Aug.
9. Butrans® [package insert]. Stamford (CT): Purdue Pharma L.P.; 2014 Jun.
10. Bunavail® [package insert]. Raleigh (NC): BioDelivery Sciences International, Inc.; 2014 Jun.
11. Zubsolv® [package insert]. Morristown, (NJ): Orexo US, Inc.; 2015 Aug.
12. Daily Med [database on the internet]. Bethesda (MD): National Library of Medicine; 2015 [cited 2015 Dec 3]. Available at: http://dailymed.nlm.nih.gov/dailymed/about.cfm.
13. Wesson D and Smith D. Buprenorphine in the treatment of opiate dependence. J Psychoactive Drugs. 2010;42:161-75.
14. Orman JS and Keating GM. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. Drugs 2009;69:577-607.
15. Work Group on Substance Use Disorders, Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, Strain EC, Greenfield SF, Ziedonis DM, Kosten TR, Hennessy G, O'Brien CP, Connery HS. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry. 2006;163(8 Suppl):5-82.
16. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004 [cited 2013 Sep 9]. Available from: http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf.
17. Questions and answers about the discontinuation of SUBOXONE® (buprenorphine and naloxone) sublingual tablet (CIII) [press release on the Internet]. Parsippany (NJ): Reckitt Benckiser (North America) Inc.; 2013 Jan 10 [cited 2013 Sep 16]. Available from: http://www.suboxone.com/hcp/Default.aspx.
18. National Comprehensive Cancer Network (NCCN). Practice guidelines in oncology: adult cancer pain. National Comprehensive Cancer Network (NCCN), 2015 [cited 2015 Nov 19]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
19. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2 – guidance. Pain Physician. 2012;15:S67-S116.
20. Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F, on behalf of the ESMO Guidelines Working Group Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23(suppl 7): vii39-vii154.
21. National Opioid Use Guideline Group (NOUGG). Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. National Opioid Use Guideline Group (NOUGG), 2010 [cited 2013 Sep 9]. Available at: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf
22. American Society of Anesthesiologists Task Force on Chronic Pain Management, American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2010;112:810-33.
23. Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain. Washington (DC): Veterans Health Administration, Department of Defense; 2010 May [cited 2013 Sep 7]. Available at: http://www.healthquality.va.gov/Chronic_Opioid_Therapy_COT.asp.

24. Chou R, Fanciullo GJ, Fine PG, et al. American Pain Society: Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10:113-30.
25. Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of substance use disorders (SUD). Washington (DC): Veterans Health Administration, Department of Defense; 2009 Aug [cited 2013 Sep 7]. Available at: http://www.guideline.gov/summary/summary.aspx?doc_id=4812&nbr=3474.
26. Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. DHHS Publication No. (SMA) 05-4048. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005 [cited 2013 Sep 7]. Available at: http://www.naabt.org/documents/TIP43-buprenorphine-methadone-suboxone-opiate.pdf.
27. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage. 1992;7:69-77.
28. Steiner D, Munera C, Hale M, Ripa S, Landau C. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study. J Pain. 2011;12(11):1163-73.
29. Gordon A, Rashiq S, Moulin DE, Clark AJ, Beaulieu AD, Eisenhoffer J, et al. Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. Pain Res Manag. 2010;15(3):169-78.
30. Gordon A, Callaghan D, Spink D, Cloutier C, Dzongowski P, O'Mahony W, et al. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clin Ther. 2010;32(5):844-60.
31. Karlsson M, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) vs prolonged-release tramadol tablets (75, 100, 150 and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, paralled-group noninferiority study. Clin Ther. 2009;31(3):503-13.
32. Conaghan PG, O'Brien CM, Wilson M, Schofield JP. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomized trial. Osteoarthritis Cartilage. 2011;19(8):930-8.
33. Desjardins P, Norris L, Cooper S, et al. Analgesic efficacy of intranasal butorphanol (Stadol NS) in the treatment of pain after dental impaction surgery. J Oral Maxillofac Surg. 2000;58(Suppl 2):19-26.
34. Wermeling D, Grant G, Lee A, et al. Analgesic effects of intranasal butorphanol tartrate administered via a unit-dose device in the dental impaction pain model: a randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2005;27:430-40.
35. Scott J, Smith M, Sanford S, et al. Effectiveness of transnasal butorphanol for the treatment of musculoskeletal pain. Am J Emerg Med. 1994;12:469-71.
36. Olsen J, McGrath N Schwarz D, et al. A double-blind randomized clinical trial evaluating the analgesic efficacy of ketorolac vs butorphanol for patients with suspected biliary colic in the emergency department. Acad Emerg Med. 2008;15:718-22.
37. Moyao-Garcia D, Hernandez-Palacios JC, Ramirez-Mora JC, et al. A pilot study of nalbuphine vs tramadol administered through continuous intravenous infusion for postoperative pain control in children. Acta Biomed. 2009;80:124-30.
38. Yeh YC, Lin TF, Chang HC, et al. Combination of low-dose nalbuphine and morphine in patient-controlled analgesia decreases incidence of opioid-related side effects. J Formos Med Assoc. 2009;108:548-53.
39. Levine J, Gordon N, Taiwo Y, et al. Potentiation of pentazocine analgesia by low-dose naloxone. J Clin Invest. 1988;82:1574-7.
40. Petti A. Postoperative pain relief with pentazocine and acetaminophen: comparison with other analgesic combinations and placebo. Clin Ther. 1985;8:126-33.
41. Kornor H, Waal H, Sandvik L. Time-limited buprenorphine replacement therapy for opioid dependence: two-year follow-up outcomes in relation to program completion and current agonist therapy status. Drug Alcohol Rev. 2007 Mar;26(2):135-41.
42. Fareed A, Vayalapalli S, Casarella J, Drexler K. Treatment outcome for flexible dosing buprenorphine maintenance treatment. Am J Drug Alcohol Abuse. 2012 Mar;38(2):155-60.
43. Fareed A, Vayalapalli S, Casarella J, Drexler K. Effect of buprenorphine dose on treatment outcome. J Addict Dis. 2012;31(1):8-18.
44. Bickel WK, Amass L, Crean JP, Badger GJ. Buprenorphine dosing every one, two or three days in opioid-dependant patients. Psychopharmacology (Berl). 1999 Sep;146(2):111-8.
45. Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. Clin Pharmacol Ther. 1999 Sep;66(3):306-14.

46. Schottenfeld RS, Pakes J, O'Connor P, Chawarski M, Oliveto A, Kosten TR. Thrice-weekly vs daily buprenorphine maintenance. Biol Psychiatry. 2000 Jun;47(12):1072-9.
47. Gibson A, Degemhardt L, Mattick RP, Ali R, White J O'Brien S. Exposure to opioid maintenance treatment reduces long term mortality. Addiction. 2008;103(3):462-8.
48. Johnson RE, Jaffe JH, Fudala PJ: A controlled trial of buprenorphine treatment for opioid dependence. JAMA. 1992;267:2750–5.
49. Petitjean S, Stohler R, Deglon J, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. Drug Alcohol Depend. 2001;62:97-104.
50. Strain E, Stitzer M, Liebson I, Bigelow G. Comparison of buprenorphine and methadone in the treatment of opioid dependence. Am J Psychiatry. 1994;151:1025-30.
51. Ling W, Wesson D, Charuvastra C, Klett C. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry. 1996;53:401-7.
52. Schottenfeld R, Pakes J, Oliveto A, et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiatry. 1997;54:713-20.
53. Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. Int J Neuropsychopharmacol. 2008;11:641-53.
54. Maremmani I, Pani P, Pacini M, et al. Substance use and quality of life over 12 months among buprenorphine maintenance-treated and methadone maintenance-treated heroin-addicted patients. J Subst Abuse Treat. 2007 Jul;33(1):91-8.
55. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. NEJM. 2010;363:2320-31.
56. Gibson A, Degenhardt L, Mattick R, et al. Exposure to opioid maintenance treatment reduces long-term mortality. Addiction. 2008;103:462-8.
57. Cornish R, Macleod J, Strang J, et al. Risk of death during and after opiate substitution in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010;341:c5475.
58. Pinto H, Maskrey V, Swift L, et all. The SUMMIT trial: a field comparison of buprenorphine vs methadone maintenance treatment. J Subst Abuse Treat. 2010;394:340-52.
59. Farré M, Mas A, Torrens M, et al. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. Drug Alcohol Depend. 2002;65:283-90.
60. Mattick R, Kimber J, Breen C, Davoli M. Buprenorphine maintenance vs placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2008, Issue 2. Art.No.: CD002207. DOI: 10.1002/14651858.CD002207.pub3.
61. Daulouède JP, Caer Y, Galland P, Villeger P, Brunelle E, Bachellier J, et al. Preference for buprenorphine/naloxone and buprenorphine among patients receiving buprenorphine maintenance therapy in France: a prospective, multicenter study. J Subst Abuse Treat. 2010 Jan;38(1):83-9.
62. Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. Clin Pharmacol Ther. 2011 Mar;89(3):443-9.
63. Minozzi S, Amato L, Davoli M. Detoxification treatments for opiate dependent adolescents. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006749.
64. Strain E, Stoller K, Walsh S, et al. Effects of buprenorphine vs buprenorphine/naloxone tablets in non-dependent opioid abusers. Psychopharmacology. 2000;148:374-83.
65. Fudala P, Bridge T, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003;349:949-58.
66. Woody G, Poole S, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA. 2008;300:2003-11.
67. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a two-phase randomized controlled trial. Arch Gen Psychiatry. 2011 Dec;68(12):1238-46.
68. Bell J, Shanahan M, Mutch C, et al. A randomized trial of effectiveness and cost-effectiveness of observed vs unobserved administration of buprenorphine-naloxone for heroin dependence. Addiction. 2007;102:1899-907.
69. Fiellin D, Moore B, Sullivan L, et al. Long-term treatment with buprenorphine/naloxone in primary care: results at 2-5 years. Am J Addict. 2008;17:116-20.
70. Kakko J, Grönbladh L, Svanborg K, et al. A stepped care strategy using buprenorphine and methadone vs conventional methadone maintenance in heroin dependence: a randomized controlled trial. Am J Psychiatry. 2007;164:797-803.

71. Hser YI, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014 Jan;109(1):79-87.
72. Kamien J, Branstetter S, Amass L. Buprenorphine-naloxone vs methadone maintenance therapy: a randomized double-blind trial with opioid-dependent patients. Heroin Addict Relat Clin. Probl 2008;10:5-18.
73. Simojoki K, Vorma H, Alho H. A retrospective evaluation of patients switched from buprenorphine (Subutex) to the buprenorphine/naloxone combination (Suboxone). Subst Abuse Treat Prev Policy 2008;3:16.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Selective Serotonin Agonists
AHFS Class 283228
February 10, 2016

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) 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 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.[7-17]

The selective serotonin agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Almotriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan are available in a generic formulation. This class was last reviewed in November 2013.

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	Axert®*	none
Eletriptan	tablet	Relpax®	none
Frovatriptan	tablet	Frova®	none
Naratriptan	tablet	Amerge®*	naratriptan
Rizatriptan	orally disintegrating tablet, tablet	Maxalt®*, Maxalt MLT®*	rizatriptan
Sumatriptan	nasal spray, subcutaneous injection, tablet	Imitrex®*, Sumavel DosePro®, Alsuma®*	sumatriptan
Zolmitriptan	nasal spray, orally disintegrating tablet, tablet	Zomig®*, Zomig ZMT®*	zolmitriptan
Combination Products			
Sumatriptan and naproxen	tablet	Treximet®	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 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]	• 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.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of**	<u>Migraine headaches</u> • Mild headaches can be treated with over the counter analgesics, including

Clinical Guideline	Recommendation(s)
Headache (2013)[2]	nonsteroidal anti-inflammatory drugs (NSAIDs). • Triptans are more effective at halting migraine pain at mild levels than if the headache is more severe. • Moderate headaches can be treated with triptans. Opioids and barbiturates should be avoided, particularly meperidine. • Use of drugs for acute treatment of headache for more than nine days per month is associated with an increased risk of chronic daily headache. • Second doses of triptans have not been shown to relieve headache more if the first dose has been ineffective. • Combination sumatriptan and naproxen may be more effective than either drug alone however there is no data suggesting the combination product is more efficacious to taking each together. A dose of 100 mg of sumatriptan and a dose of 550 mg naproxen taken at the same time is recommended. • Dihydroergotamine is effective in halting intractable migraine attacks or migraine status. It is also effective in halting the acute cycle of cluster headaches. <u>Cluster headaches</u> • Subcutaneous sumatriptan and intranasal zolmitriptan are the most effective self-administered medications for the relief of cluster headaches. Sumatriptan is not effective when used before the actual attack nor is it useful as a prophylactic medication. <u>Menstrual-associated migraines</u> • NSAIDs are first-line therapy for the prophylaxis of menstrual migraines. • There are good placebo studies supporting the use of triptans for cyclic prophylaxis.
European Federation of Neurological Societies: **European Federation of Neurological Societies Guideline on the Drug Treatment of Migraine-Revised Report of an European Federation of Neurological Societies Task Force (2009)[3]**	<u>Acute treatment</u> • Drugs of first choice for mild or moderate migraine attacks are analgesics. In order to prevent drug overuse headache, the intake of simple analgesics should be restricted to 15 days per month and the intake of combined analgesic to 10 days per month. • The use of antiemetics in acute migraine attacks is recommended to treat nausea and potential emesis and because it is assumed that these drugs improve the resorption of analgesics. Of note, there is no evidence to support this. Metoclopramide is recommended for adults and adolescents, and domperidone for children. • There are very few randomized, placebo-controlled trials on the efficacy of ergot alkaloids in acute migraine treatment. The advantage of these agents is a lower recurrence rate in some patients. The ergot alkaloids should be restricted to patients with very long migraine attacks or with regular recurrence. Use must be limited to 10 days per month. • Triptans are migraine medications and should not be applied in other headache disorders except cluster headache. The efficacy of all available triptans has been proven in large, placebo-controlled trials. Evidence suggests that the earlier the triptans are taken the better their efficacy; however, there is evidence to support that triptans can be effective at any time during a migraine attack. The use of triptans is restricted to maximum nine days per month by the International Headache Society criteria. A second dose of the triptan is effective in most cases; if the first dose of a triptan is not effective, the second dose is useless. Combining a nonsteroidal anti-inflammatory drug (NSAID) with a triptan reduces headache recurrence. • A triptan can be efficacious even if another triptan was not. Subcutaneous sumatriptan has the fastest onset of efficacy (10 minutes). There is no

Clinical Guideline	Recommendation(s)
	evidence that different oral formulations, such as rapidly dissolving tablets, wafer forms or rapid release forms act earlier than others. • The highest recurrence rate is observed after subcutaneous sumatriptan. Naratriptan and frovatriptan show the lowest recurrence rates but have poor initial response rates. • There is weak evidence to suggest that intravenous valproic acid or flunarizine are efficacious in acute migraine attacks. Tramadol plus paracetamol has also shown efficacy in acute migraine attacks. • Opioids offer minor efficacy, and these agents, along with tranquilizers, should not be used in the acute treatment of migraine. <u>Specific situations</u> • First-line treatment of a severe migraine attack in an emergency situation consists of intravenous aspirin, with or without metoclopramide. Subcutaneous sumatriptan can be administered as an alternative. • Steroids are recommended for the treatment of status migrainosus. • Dihydroergotamine nasal spray may also be used for the treatment of severe migraine attacks. • Triptans, naproxen and oestrogen therapy have all been evaluated for the treatment of menstrual migraines. • There are no specific clinical trials evaluating drug treatment of migraine during pregnancy. Most of the drugs are contraindicated in pregnancy. If migraine occurs, only paracetamol is allowed during the whole period, while NSAIDs can be administered during the second trimester. • The only analgesics with evidence of efficacy for the acute migraine treatment in childhood and adolescents are ibuprofen and paracetamol. There is evidence supporting the use of triptans. Ergotamine should not be used.
American Academy of Neurology/ Child Neurology Society: **Practice Parameter: Pharmacological Treatment of Migraine Headache in Children and Adolescents (2004)[4]**	• Ibuprofen should be considered first-line therapy. Acetaminophen may also be used as an alternative option. • Sumatriptan nasal spray may also be used when the above analgesics fail; there is no data to support or contest the use of oral triptans in this population and inadequate data to draw conclusions on the efficacy of subcutaneous sumatriptan.
American Academy of Family Physicians/American College of Physicians-American Society of Internal Medicine: **Pharmacologic Management of Acute Attacks of Migraine and Prevention of Migraine Headaches (2002)[5]**	• NSAIDs are considered first-line therapy. • In patients whose migraines fail to respond to NSAIDs, use migraine-specific agents. Recommended agents include dihydroergotamine nasal spray, naratriptan, rizatriptan, subcutaneous or oral sumatriptan and zolmitriptan. • Select a non-oral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex. Treat nausea with an antiemetic. • Acute therapies should be limited to no more than two times per week to guard against medication overuse headache, or drug-induced headache, per expert opinion.
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[7-17]

Indication	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Acute treatment of cluster headache episodes						✔ *		
Acute treatment of migraine attacks with or without aura in adults 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[7-17]

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)	N-deoxidation	4 to 5	1	18
Frovatriptan	24 to 30	Feces (62) Renal (10 to 32)	None	25	2	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	24 to 25 (IN)	Feces (38) Renal (57)	None	2	1 (IN)	Not reported (IN)
	14 to 15 (PO)				1 to 2 (PO)	3 (PO)
	97 (SC)				0.2 to 1.0 (SC)	Not reported (SC)
Zolmitriptan	102 (IN)*	Feces (20 to 30) Renal (60)	N-desmethyl zolmitriptan	2.5 to 3.0	1	Not reported
	39 to 48 (PO)					
Combination Products						
Sumatriptan and naproxen	14 to 15/95	Feces (40/not reported) Renal (57/95)	None	2/19	Not reported	Not reported

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

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Selective Serotonin Agonists[7]

Generic Name(s)	Significance Level	Interaction	Mechanism
Selective serotonin agonists (, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)	1	Ergot alkaloids	The risk of vasospastic reactions may be increased. Possibly additive vasospastic effects. Use of 5-HT_1 agonists within 24 hours of treatment with an ergot-containing medication is contraindicated.
Selective serotonin agonists (rizatriptan, sumatriptan, zolmitriptan)	1	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

Generic Name(s)	Significance Level	Interaction	Mechanism
			necessary to use such agents together, naratriptan appears to be less likely to interact with monoamine oxidase inhibitors.
Selective serotonin agonists (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)	1	Linezolid	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 (naratriptan, rizatriptan, sumatriptan, zolmitriptan)	1	Sibutramine	Serotonin syndrome, including central nervous system irritability, motor weakness, shivering, myoclonus, and altered consciousness may occur. The serotonergic effects of these agents may be additive.
Naproxen	1	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	1	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	1	Warfarin	Risk of hemorrhagic adverse reactions may be increased and gastric erosion. Monitor warfarin levels.
Selective serotonin agonists (almotriptan, eletriptan)	2	Azole antifungals	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.
Rizatriptan	2	Propranolol	Rizatriptan concentrations may be elevated, increasing the pharmacologic effects and adverse reaction. Inhibition of rizatriptan metabolism by propranolol is suspected.
Naproxen	2	Angiotensin-converting-enzyme inhibitors	Naproxen may reduce the antihypertensive effect of angiotensin-converting-enzyme inhibitors and may potentiate renal disease states.

Generic Name(s)	Significance Level	Interaction	Mechanism
Naproxen	2	Bisphosphonates	Gastrointestinal adverse effects may be increased with concurrent administration of bisphosphonates and naproxen. The mechanism is unknown.
Naproxen	2	Cyclosporine	The nephrotoxicity of cyclosporine and naproxen may both be increased. Monitor renal function frequently.
Naproxen	2	Diuretics	Naproxen may reduce the natriuretic effect of furosemide and thiazides. Monitor blood pressure, weight, and signs of renal failure if co administer.
Naproxen	2	Lithium	Naproxen may reduce renal lithium clearance and cause increase in plasma lithium plasma levels by up to 20%. Monitor for lithium toxicity.
Naproxen	2	Probenecid	The pharmacologic toxic effects may be increased by probenecid; however, the clinical significance is unknown.
Naproxen	2	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	2	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	2	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.

Significance level 1=major severity, significance level 2=moderate severity.

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[7-17]

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Cardiovascular								
Acute coronary syndrome	-	-	-	-	-	-	-	≤1
Angina	-	<1	-	-	-	-	<1	-
Arrhythmia	-	<1	-	-	-	<1	<1	-
Atrial fibrillation	-	<1	-	<1	-	<1	-	-
Atrial flutter	-	-	-	<1	-	-	-	≤1
Atrial-ventricular block	-	<1	-	-	-	-	-	-
Bradycardia	-	<1	<1	-	<1	-	-	-
Chest tightness/pain	<1	1 to 4	2	-	<2 to 9	1 to 2[‡]/2 to 3[§]	2 to 4	3
Congestive heart failure	-	-	-	-	-	-	-	≤1
Coronary artery vasospasm	-	-	-	<1	-	-	<1	-
Cyanosis	-	<1	-	-	-	-	<1	-
Electrocardiogram changes	-	-	<1	-	-	<1	-	-
Flushing	-	-	4	-	✔	-	-	≤1
Heart block	-	-	-	-	-	<1	-	-
Hypertension	<1	<1	-	-	-	1[‡§]	<1	≤1
Hypertensive crisis	-	-	-	-	-	-	<1	-
Hypotension	-	<1	-	-	-	1[‡§]	-	-
Myocardial infarction	-	-	-	<1	-	-	<1	-
Myocardial ischemia	-	-	-	-	-	<1	<1	-
Myocarditis, viral	-	-	-	-	-	-	-	≤1
Palpitation	<1	✔	1	-	✔	-	≤2	>1
Peripheral vascular disease	-	<1	-	-	-	-	-	-
PR prolongation	-	-	-	<1	-	-	-	-
Premature ventricle contractions	-	-	-	<1	-	-	-	-
Prinzmetal angina	-	-	-	-	-	<1	-	-
Pulmonary embolism	-	-	-	-	-	<1	-	-
QTc prolongation	-	-	-	<1	-	-	<1	-
Tachycardia	<1	<1	<1	-	<1	-	-	≤1
Thrombophlebitis	-	-	-	-	-	<1	-	-
Thrombosis	-	-	-	-	-	<1	-	-
Vasospasm	-	<1	-	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Ventricular arrhythmia	-	<1	-	-	-	-	-	-
Ventricular extrasystoles	-	-	-	-	-	-	-	≤1
Ventricular failure, right	-	-	-	-	-	-	-	≤1
Ventricular fibrillation	-	-	-	<1	-	-	-	-
Ventricular tachycardia	-	-	-	<1	-	-	-	-
Central Nervous System								
Abnormal dreams	-	<1	-	-	-	-	-	-
Abnormal thinking	-	<1	-	-	-	-	-	-
Agitation	-	<1	<1	-	<1	<1	-	-
Amnesia	-	<1	<1	-	-	1[§]	-	-
Anxiety	<1	<1	1	-	-	1[§]	-	≤1
Apathy	-	<1	-	-	-	-	-	-
Aphasia	-	<1	-	-	-	-	-	≤1
Ataxia	-	<1	-	-	-	-	<1	-
Attention disturbances	-	-	-	-	<1[†]	-	-	≤1
Back pain	<1	✔	<1	-	-	-	-	-
Burning	-	-	-	-	-	1[‡]/7[§]	-	≤1
Catatonic reaction	-	<1	-	-	-	-	-	-
Central nervous system	<1	-	-	-	-	-	-	-
Cerebral ischemia	-	-	-	-	-	<1	<1	-
Cerebrovascular accident	-	-	-	-	-	<1	-	-
Cerebrovascular disorder	-	<1	-	-	-	-	-	-
Change in dreams	<1	-	-	-	-	-	-	-
Cold extremities	-	-	-	-	-	-	-	-
Cold sensation	-	-	-	-	-	1[§]	-	≤1
Confusion	-	<1	<1	-	<1	-	-	-
Convulsions	-	-	-	-	-	<1	-	-
Dementia	-	<1	-	-	-	-	-	-
Depersonalization	-	<1	<1	-	-	-	-	-
Depression	<1	<1	<1	-	-	-	-	≤1
Disorientation	-	-	-	-	-	-	-	≤1
Dizziness	3 to 4*	3 to 7	8	1 to 10	4 to 9	1 to 2[‖]/>1[‡]/12[§]	6 to 10	4
Drowsiness	-	-	-	1 to 10	-	>1[‡]/3[§]	-	-
Dysesthesia	-	-	1	-	-	-	-	-
Emotional lability	-	<1	<1	-	-	-	-	-
Euphoria	<1	<1	<1	-	✔	-	-	-
Fatigue	<1	-	5	1 to 10	4 to 7, ✔[†]	2 to 3[‡]/1[§]	-	≥1
Feeling strange	-	-	-	-	-	2[§]	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Hallucination	-	<1	-	<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	-	-	-	-	-
Hyperkinesia	-	<1	-	-	-	-	-	-
Hyperreflexia	<1	-	-	-	-	-	-	-
Hypertonia	<1	✔	<1	-	-	-	-	-
Hypoesthesia	<1	✔	1	-	✔	-	1 to 2	-
Hypokinesia	-	<1	-	-	-	-	-	-
Hypotonia	-	-	<1	-	-	-	-	-
Hysteria	-	<1	-	-	-	-	-	-
Impaired concentration	<1	-	<1	-	-	-	-	-
Incoordination	<1	<1	-	-	<1†	-	-	-
Insomnia	<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
Neuropathy	<1	<1	-	-	-	-	-	-
Neurosis	-	<1	-	-	-	-	-	-
Nightmares	<1	-	-	-	-	-	-	-
Nystagmus	<1	-	-	-	-	-	-	-
Oculogyric crisis	-	<1	-	-	-	-	-	-
Optic neuropathy	-	-	-	-	-	<1	-	-
Pain	-	✔	1	-	-	1 to 2§	2 to 3	-
Paralysis	-	<1	-	-	-	-	-	-
Paresthesia	1, <1 to 1	3 to 4	4	1 to 10	3 to 4	<1‖/3 to 5‡/14§	5 to 9	2
Personality disorder	-	-	<1	-	-	-	-	-
Psychomotor disorders	-	-	-	-	-	<1	-	≤1
Psychotic depression	-	<1	-	-	-	-	-	-
Restlessness	<1	-	-	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Shakiness	<1	-	-	-	-	-	-	-
Sleep disorder	-	<1	-	-	-	-	-	-
Somnolence	<1 to 5*	3 to 7	-	-	4 to 8	-	5 to 8	3
Stupor	-	<1	-	-	-	-	-	-
Subarachnoid hemorrhage	-	-	-	-	-	<1	-	-
Twitching	-	<1	-	-	-	-	-	-
Vertigo	<1	✔	<1	-	<1	<1 to 2‡	≤2	≤1
Warm/cold sensation	-	-	-	-	-	2 to 3‡	5 to 7	-
Warm/hot sensation	-	-	-	-	✔	11§	-	>1
Weakness	-	-	-	-	-	5§	3 to 9	≥1
Dermatological								
Alopecia	-	<1	-	-	-	-	-	-
Bullous eruption	-	-	<1	-	-	-	-	-
Cheilitis	-	-	<1	-	-	-	-	-
Dermatitis	<1	<1	-	-	-	-	-	-
Dry skin	-	<1	-	-	-	-	-	-
Eczema	-	<1	-	-	-	-	-	-
Erythema	<1	-	-	-	<1	-	-	-
Flushing	-	2	-	-	-	<1‡‖/7§	-	-
Itching	-	-	<1	-	-	<1	-	-
Photosensitivity	<1	-	-	-	-	<1	<1	-
Pruritus	<1	<1	-	-	<1	-	-	≤1
Psoriasis	-	<1	-	-	-	-	-	-
Rash	<1	<1	-	-	<1	<1	<1	≤1
Skin discoloration	-	<1	-	-	-	-	-	-
Skin hypertrophy	-	<1	-	-	-	-	-	-
Sweating	<1	✔	1	-	<1	2§	<3	-
Urticaria	-	<1	-	-	<1	-	<1	≤1
Vasculitis	-	-	-	-	-	<1	-	-
Endocrine and Metabolic								
Alkaline phosphatase increased	-	<1	-	-	-	-	-	-
Bilirubin	-	<1	-	-	-	-	-	-
Diabetes mellitus	-	-	-	-	-	-	-	≤1
Edema	-	<1	-	-	<1	<1	-	-
Goiter	-	<1	-	-	-	-	-	≤1
Growth hormone increase (mild)	-	-	-	-	1 to 10	-	-	-
Hot flashes	-	-	<1	-	<1	-	-	-
Hypercholesterolemia	<1	-	-	-	-	-	-	-
Hyperglycemia	<1	<1	-	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Hypocalcemia	-	-	<1	-	-	-	-	-
Hypoglycemia	-	-	<1	-	-	-	-	≤1
Hypothyroidism	-	-	-	-	-	-	-	≤1
Increased gamma glutamyl transpeptidase	<1	-	-	-	-	-	-	-
Liver function tests abnormal or elevated	-	<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
Anorexia	-	<1	-	-	-	-	-	-
Bad taste	-	-	-	-	-	13 to 24[‖]	-	-
Biliary colic	-	-	-	-	-	-	-	≤1
Colitis	<1	-	-	-	-	<1	<1	≤1
Constipation	-	<1	<1	-	-	-	-	≤1
Diarrhea	<1	<1	1	-	✔	<1[§][‖]/1[‡]	-	≤1
Diverticulitis	-	-	-	-	-	-	-	≤1
Dysgeusia	-	-	-	-	-	-	-	≤1
Dyspepsia	<1	1 to 2	2	-	<1	<1	1 to 3	2
Dysphagia	-	1 to 2	<1	-	-	<1[‡][‖]/1[§]	<2	≤1
Eructation	-	<1	<1	-	-	-	-	-
Esophagitis	-	<1	-	-	-	-	-	-
Flatulence	-	<1	-	-	-	-	-	≤1
Gastric ulcer	-	-	-	-	-	-	-	≤1
Gastritis	<1	<1	-	-	-	-	-	≤1
Gastroenteritis	<1	-	-	-	-	-	-	-
Gastroesophageal reflux	<1	-	<1	-	-	-	-	≤1
Gastrointestinal disorder	-	<1	-	-	-	-	-	-
Gastrointestinal pain	-	-	-	-	-	<1	-	-
Glossitis	-	<1	-	-	-	-	-	-
Hematemesis	-	<1	-	-	-	-	<1	-
Hiccup	-	-	<1	-	-	-	-	-
Hypersalivation	<1	<1	<1	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Hyposalivation	-	-	3	-	-	>1‡	-	-
Intestinal obstruction	-	-	-	-	-	<1	-	-
Irritable bowel syndrome	-	-	-	-	-	-	-	≤1
Melena	-	-	-	-	-	-	<1	-
Nausea	1 to 2, 1 to 3*	4 to 8	-	1 to 10	4 to 6	11 to 13‖/>1‡	4 to 9	3
Pancreatitis	-	-	-	-	-	-	<1	-
Peptic ulcer disease	-	-	<1	-	-	-	<1	-
Rectal disorder	-	<1	-	-	-	-	-	-
Splenic infarction	-	-	-	-	-	-	<1	-
Swallowing disorders	-	-	-	-	-	<1	-	-
Taste alteration	<1	<1	<1	-	-	-	-	-
Vomiting	<1, 2*	-	1	1 to 10	✔	11 to 13‖/>1‡	-	≤1
Genitourinary								
Acute renal failure	-	-	-	-	-	<1	-	-
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
Urinary tract disorder	-	<1	-	-	-	-	-	-
Vaginitis	-	<1	-	-	-	-	-	-
Hematologic								
Anemia	-	<1	-	-	-	-	-	≤1
Eosinophilia	-	-	-	-	-	-	<1	-
Hemolytic anemia	-	-	-	-	-	<1§‖/1‡	-	-
Monocytosis	-	<1	-	-	-	-	-	-
Pancytopenia	-	-	-	-	-	<1	-	-
Purpura	-	<1	<1	-	-	-	-	-
Thrombocytopenia	-	-	-	-	-	<1	<1	-
Musculoskeletal								
Abnormal gait	-	<1	<1	-	<1	-	-	≤1
Abnormal reflexes	-	-	<1	-	-	-	-	-
Arthralgia	<1	<1	<1	-	-	-	-	≤1

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Arthritis	<1	<1	-	-	-	-	-	-
Arthrosis	-	<1	<1	-	-	-	-	-
Asthenia	<1	4 to 10	<1	-	-	-	-	-
Ataxia	-	-	<1	-	-	-	-	-
Back pain	-	-	-	-	-	-	-	≤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	-	-
Joint disorder	-	<1	-	-	-	-	-	-
Muscle cramps	-	-	<1	-	<1	1[§]	-	-
Muscle tightness	-	-	-	-	-	-	-	>1
Muscle stiffness	-	-	-	-	<1	<1	-	-
Muscle weakness	<1	-	<1	-	<1	1[§]	-	≥1
Myalgia	<1	<1	<1	-	<1	1[‡]/2[§]	1 to 2	≤1
Myasthenia	-	<1	-	-	-	-	<2	-
Myopathy	<1	<1	-	-	-	-	-	-
Numbness	-	-	-	-	-	1[‡]/5[§]	-	-
Rigid neck	<1	-	-	-	-	-	-	-
Rigors	-	-	<1	-	-	-	-	-
Skeletal pain	-	-	3	-	-	-	-	-
Tenosynovitis	-	<1	-	-	-	-	-	-
Tetany	-	-	-	-	-	-	<1	-
Tremor	<1	<1	<1	-	✔	-	-	≤1
Respiratory								
Asthma	-	<1	-	-	-	-	-	≤1
Bronchitis	<1	<1	-	-	-	-	-	-
Bronchospasm	-	-	-	-	-	<1	<1	-
Choking sensation	-	<1	-	-	-	-	-	-
Dyspnea	<1	<1	<1	-	✔	1[§]	-	≤1
Esophagitis	-	<1	-	-	-	-	<1	-
Hyperventilation	<1	<1	<1	-	-	-	-	-
Laryngitis	<1	<1	<1	-	-	-	-	-
Nasal disorder/discomfort	-	-	-	-	-	2 to 4[‖]/2[§]	-	-
Nose/throat hemorrhage	-	-	-	-	-	<1[§‖]/1[‡]	-	-
Pharyngeal edema	-	-	-	-	<1	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Pharyngitis	<1	✔	<1	-	-	-	-	-
Pleurisy	-	-	-	-	-	-	-	≤1
Respiratory disorder	-	<1	-	-	-	-	-	-
Respiratory tract infection	-	<1	-	-	-	-	-	-
Rhinitis	<1	<1	1	-	-	1[‡]	-	-
Sinusitis	<1	<1	1	-	-	1[‡]	-	-
Sneezing	<1	-	-	-	-	-	-	-
Sputum	-	<1	-	-	-	-	-	-
Throat discomfort	-	-	-	-	-	1 to 2[‖]/3[§]	-	-
Throat or neck pain/pressure	<1	-	-	1 to 10	-	-	-	-
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	-
Anaphylaxis	-	-	-	-	-	<1	<1	-
Angioneurotic edema	-	-	-	-	-	<1	-	-
Breast pain	-	<1	-	-	-	-	-	-
Bruising	-	-	-	-	-	-	-	≤1
Cataract	-	-	-	-	-	-	-	≤1
Chills	<1	✔	-	-	-	-	-	-
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	-	-	-
Earache	<1	<1	<1	-	-	-	-	≤1
Ear hemorrhage	-	<1	-	-	-	-	-	-
Epistaxis	<1	<1	<1	-	-	-	-	≤1
Eye irritation	<1	-	-	-	-	-	-	-
Eye pain	<1	<1	<1	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Eye swelling	-	-	-	-	<1	-	-	-
Facial edema	-	-	-	-	<1	-	-	≤1
Fever	<1	<1	<1	-	-	-	-	≤1
Flu syndrome	-	<1	-	-	-	-	-	-
Gingivitis	-	<1	-	-	-	-	-	-
Halitosis	-	<1	-	-	-	-	-	-
Heaviness sensation	-	-	-	-	-	-	-	≤1
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	-	-	-	-	-	-	-	≤1
Leukopenia	-	<1	-	-	-	-	-	≤1
Lymphadenopathy	-	<1	-	-	-	-	-	≤1
Malaise	-	<1	-	-	-	-	-	≤1
Miscarriage	-	-	-	-	-	-	<1	-
Moniliasis	-	<1	-	-	-	-	-	-
Motion sickness	-	-	-	-	-	-	-	≤1
Mouth/tongue discomfort	-	-	-	-	-	5§	-	-
Neck/throat/jaw pain/ tightness/Pressure	-	-	-	-	<2 to 2	2 to 5§/2 to 3‡	4 to 10	3
Numbness of tongue	-	-	-	-	-	<1	-	-
Optic neuropathy (ischemic)	-	-	-	-	-	<1	-	-
Oral mucosal blistering	-	-	-	-	-	-	-	≤1
Oropharyngeal edema	-	-	-	-	-	-	-	≤1
Otitis media	<1	<1	-	-	-	-	-	-
Pain at injection site	-	-	-	-	-	59§	-	-
Parosmia	<1	<1	-	-	-	-	-	-
Peripheral edema	-	<1	-	-	-	-	-	≤1
Photophobia	-	<1	-	-	-	-	-	-
Pressure sensation	-	-	-	-	-	7§/1 to 3‡	-	-
Presyncope	-	-	-	-	<1†	-	-	-
Ptosis	-	<1	-	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan and Naproxen
Raynaud's syndrome	-	-	-	-	-	<1	-	-
Rheumatoid arthritis	-	<1	-	-	-	-	-	-
Scotoma	<1	-	-	-	-	-	-	-
Sedation	-	-	-	-	-	-	-	≤1
Seizure	-	-	-	<1	-	-	-	-
Shock	-	<1	-	-	-	<1	-	-
Speech disorder	-	<1	<1	-	-	-	-	-
Stomatitis	-	<1	<1	-	-	-	-	-
Stroke	-	-	-	-	-	-	-	-
Syncope	<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[‡]	<1	≤1
Tooth disorder	-	<1	-	-	-	-	-	-
Tongue edema	-	<1	-	-	<1	-	-	≤1
Vision abnormalities	-	<1	1	-	-	1[§]	-	≤1
Vision loss	-	-	-	-	<1	<1	-	-
Xerostomia	-	-	-	-	-	<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[7]

WARNING
Cardiovascular risk: Sumatriptan and naproxen may cause an increased risk of serious cardiovascular thrombotic reactions, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Gastrointestinal risk: Sumatriptan and naproxen contains a nonsteroidal anti-inflammatory drug (NSAID). NSAID-containing products cause an increased risk of serious gastrointestinal adverse reactions, including bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These reactions can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal reactions.

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[7-17]

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
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 returns; maximum, 30 mg/day	Acute treatment of migraine with or without aura in pediatric patients six to 17 years of age: Orally disintegrating tablet, tablet: 5 mg for patients <40 kg, 10 mg for patients ≥40 kg	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Sumatriptan	Acute treatment of migraine attacks with or without aura: Nasal spray: initial, 5, 10, or 20 mg, may repeat after two hours if headache returns; maximum, 40 mg/day Subcutaneous injection: initial, 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 spray: 5 mg 20 mg Subcutaneous injection: 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.[18] (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.[19] (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.[20] (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.[21] (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.[22] (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.[23] (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.[24] (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.[25] (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.[26] (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.[27] (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.[28] (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.[29] (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.[30] (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.[31] (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.[32] (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.[33] (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.[34] (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.[35] (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.[36] (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.[37] (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.[38] (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.[39] (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.[40] (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.[41] (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.[42] (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.[43] (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.[44] (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.[45] (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.[46] (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.[47] (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.[48] (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.[49] (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.[50] (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.[51] (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.[52] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Stark et al.[53] (2000) Naratriptan 2.5 mg vs sumatriptan 50 mg vs placebo	DB, PC, PG, RCT Self-described poor sumatriptan responders with a history of migraine for more than one year	N=347 2 migraine attacks	Primary: Conversion from 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	Primary: Naratriptan was significantly more efficacious compared to placebo for the 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.[54] (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.[55] (2004)	MA Patients with	N=449 Single	Primary: Response rate ratios for pain-free	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Naratriptan 1 to 2.5 mg vs rizatriptan 10 mg vs sumatriptan 100 mg vs placebo	moderate or severe migraine attacks	migraine attack	response Secondary: Adverse events	(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 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.[56] (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.[57] (2001)	MA (DB, RCTs) Outpatients with a	N=4,816 Single	Primary: Pain relief, associated	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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rizatriptan 5 to 10 mg vs placebo	history of migraine for at least six months	migraine attack	migraine symptoms and functional disability and headache recurrence Secondary: Not reported	nausea, photophobia, phonophobia and functional disability (P values not reported). The benefit was maintained over 24 hours; 37% of patients had 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.[58] (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.[59] (2006)	DB, MC, PC, PG, RCT	N=1,030 Single dose	Primary: Pain freedom at two hours post-	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rizatriptan 10 mg vs placebo	Patients ≥18 years of age with at least a 6-month history of 1 to 4 migraine attacks per month that were typically mild at onset		dose Secondary: Sustained pain freedom at 24 hours post-dose	rizatriptan vs placebo, respectively. (P<0.001 for both). 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.[60] (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.[61] (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.[62] (2009) Rizatriptan 10 mg	MC, OL, PRO, XO Patients ≥18 years of age with more than one migraines	N=79 2 migraine attacks	Primary: Mean time to onset of pain relief and pain freedom using a stopwatch	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs almotriptan 12.5 mg	per month who were rizatriptan naïve		Secondary: Not reported	dosing with rizatriptan (55.7%) or almotriptan (45.6%; P=0.10). 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.[63] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: More patients indicated they were very satisfied when treating a migraine 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.[64] (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.[65] (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,	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			24-hour quality of life and safety	compared to patients receiving naratriptan at two hours (means scores, 3.55 vs 4.21; P<0.001). 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.[66] (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.[67] (2001) Rizatriptan 10 mg vs sumatriptan 25 to 100 mg vs	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),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
naratriptan 2.5 mg vs zolmitriptan 2.5 mg vs placebo				sumatriptan 50 mg (P=0.001) and naratriptan 2.5 mg (P=0.015). 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.[68] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: 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.[69] (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.[70] (2009) Rizatriptan 10 mg ODT	DB, MC, PC, PG, RCT Patients ≥18 years of age with a history of migraine with or	N=207 Single migraine attack	Primary: Proportion of patients free of pain at two hours and determination of whether	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Patients within each treatment group were also R to receive migraine education or to receive no migraine education.	without aura for at least one year and a history of one to four migraine attacks per month with attacks that were typically mild at onset and recognizable as migraine		treatment effects were consistent 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	A nonsignificant greater proportion of patients receiving rizatriptan plus 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.[71] (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[72] (1991)	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sumatriptan 6 to 8 mg SC vs placebo			Secondary: Not reported	Compared to placebo, 47 and 54% more patients receiving sumatriptan 6 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.[73] (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[74] (1991) Sumatriptan 100 mg vs placebo One tablet at onset of headache, one tablet 2 hours later if migraine, and	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
one tablet if the headache came back within 24 hours.				
Cutler et al.[75] (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.[76] (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.[77] (2006) Sumatriptan 25 to	MA (16 PC, RCTs) Adult patients with history of migraine	N=16,200 Single migraine	Primary: Pain-free response at two hours, headache relief/	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 mg vs placebo	with or without aura	attack	headache intensity, functional disability, headache recurrence, adverse events Secondary: Not reported	(P values 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.[78] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
second study.				
Djupesland et al.[79] (2010) Sumatriptan 10 or 20 mg IN vs placebo	DB, MC, PC, PG, 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	N=117 Single migraine attack	Primary: 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	Primary: 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.[80] (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	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
divided dose in the second trial.				
Cady et al.[81] (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.[82](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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	Satisfaction domain of the PPMQ-R, and a baseline Migraine-ACT scores ≤2 (reflecting the need for a chance in acute migraine therapy)			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 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.[83] (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	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	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
reported.			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/or presence at two hours)	*Sumatriptan 25 mg vs rizatriptan 5 mg* The proportion of participants pain-free at two hours with sumatriptan 25 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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); 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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; 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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; 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				pain intensity. The proportion of participants requiring rescue medication with sumatriptan 50 mg was 20% (167/851; range, 19 to 21%) compared 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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.[84] (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	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,

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)	respectively. The proportion of participants with headache relief at two hours after treating with sumatriptan was 89%, compared to 65, 75, 83, 94, 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.[85] (2012) Sumatriptan IN vs placebo vs	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
active control Results from the pooled analysis of PC trials have been reported.			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 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)	(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 occurred more frequently with sumatriptan than placebo.
Gershovich et al.[86] (2006) Sumatriptan vs rizatriptan ODT	RETRO Patients ≥18 years of age	N=457 (n=315 randomly sampled for a satisfaction questionnaire) 180 day	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
		medication conversion period (plus an 180 day follow up period)		to sumatriptan; whereas 8.5% of patients who failed conversion rated rizatriptan as their preferred medication (P<0.001). 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.[87] (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.[88] (2000) Sumatriptan 25 to 100 mg vs ergotamine 2 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,	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and caffeine 200 mg vs aspirin 900 mg and metoclopramide 10 mg vs placebo			clinical disability, migraine-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	Secondary: Early intervention also resulted in less re-dosing with mild pain compared 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.[89] (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.[90] (2007) Sumatriptan-	MC, OL Patients 18 to 35 years of age with	N=562 12 months	Primary: Clinical adverse events and clinical chemical analysis	Primary: For overall safety data, 66% of patients reported at least one treatment emergent adverse event.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
naproxen 85-500 mg Administered at the onset of a moderate to severe migraine attack.	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		Secondary: Not reported	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 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.[91] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lipton et al.[92] (2009) Sumatriptan-naproxen 85-500 mg vs placebo	2 DB, PC, RCT, XO 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	N=4,145 Four migraine attacks	Primary: Pain-free response at two hours and 24-hour sustained pain-free response Secondary: Migraine-free response at two and four hours	Primary: Across attacks in both trials, pain-free response at two hours was reported in significantly more attacks treated with combination therapy compared 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.[93] (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;	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			nausea, photophobia and phonophobia rates at two and four hours; neck pain/discomfort and sinus pain/pressure at two and four hours	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 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.[94] (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,	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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			photophobia, phonophobia at two, four and eight hours and recurrence	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 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.[95] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				lower at two hours following sumatriptan-naproxen vs placebo (P<0.001). Frequencies and types of adverse events reported did not differ between treatment groups, with dizziness and somnolence being the most common.
Brandes et al.[96] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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.[97] (2007) Sumatriptan-naproxen 85-500 mg vs sumatriptan 85 mg vs naproxen 500 mg vs	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;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				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). 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.[98] (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.[99] (2004) Zolmitriptan 5 mg ODT vs	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with at least two migraine headaches per month of moderate	N=656 6 weeks	Primary: Migraine response at 30 minutes Secondary: Speed of onset of headache response, duration of	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo One dose was used to treat migraine headache; if there was inadequate relief or if the headache returned, a second dose was allowed 2 to 24 hours later.	to severe intensity, in addition to <10 days of non migraine headaches per month for the three months prior to enrollment		response	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). 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.[100] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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.[101] (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.[102] (2003) Zolmitriptan 5.0 mg administered	DB, PG, RCT, XO Patients 18 to 65 years of age with migraine with or	N=1,093 (n=783 entered the post XO phase)	Primary: Tolerability Secondary: Headache response	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IN	without aura, previous participation in a 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	1 year	at two hours, pain-free response rate	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 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.[103] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). 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).
Geraud et al.[104] (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.[105] (2005) Zolmitriptan 2.5 mg ODT vs	PC, RCT (vs placebo); OL, RCT, XO Patients with migraines	N=470 (vs placebo) N=168 (vs sumatriptan) N=171	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sumatriptan 50 mg tablet or rizatriptan 10 mg ODT or placebo		(vs rizatriptan ODT) 12 weeks (vs sumatriptan)		sumatriptan (76.7 vs 63.4%; P=0.006). Patient preference for zolmitriptan ODT was greater than that of rizatriptan ODT (70 vs 27%; P<0.001). Secondary: Not reported
Chen et al.[106] (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	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 rizatriptan 10 mg vs placebo				
Sun et al.[107] (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.[108] (2013) Patients were taking NSAIDs and/or triptans	Longitudinal, OS, population-based Adult patients with EM or CM surveyed in the American	N=9031 (537 CM onsets occurring in 507 distinct individuals)	Primary: NSAID and triptan combined use exposure, medication use and association with	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	Migraine Prevalence and Prevention study with data for at least two consecutive survey years	5 years	chronic migraine onset Secondary: Not reported	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 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
Menstrual Migraine				
Allais et al.[109] (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; recurrence within 24 hours of treatment; level of functional impairment before intake and after one-half, one, one and one-half and two hours	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Tolerability	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.[110] (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.[111] (2011) Frovatriptan 2.5 mg vs almotriptan 12.5 mg	DB, MC, RCT, XO Women suffering from menstrual-related migraine for at least six months	N=114 Six months or six migraine attacks	Primary: Proportion of pain-relief episodes and pain-free episodes at two, four and 24 hours and proportion of patients with migraine recurrence within 24 or 48 hours	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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				recurrences at 48 hours with frovatriptan compared to almotriptan (9 vs 24%; P<0.05).
Silberstein et al.[112] (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.[113] (2009) Frovatriptan 2.5 mg once daily vs frovatriptan 2.5 mg twice daily vs placebo Therapy started 2 days prior to expected menstruation and continued for 6 days.	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 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	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). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	minimum of 2 cycles) were included			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.[114] (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 treatment sequentially over separate 6-day perimenstrual periods.	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 (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Individually there were only significantly lower instances of photosensitivity, photosensitivity and nausea in the frovatriptan twice daily group.
MacGregor et al.[115] (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 estimated start of a menstrual migraine headache and continued dosing for a total of 6 days.	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 2, 3% of patients reported chest pain and <1% reported tightness. Secondary: Not reported
Mannix et al.[116] (2007)	DB, MC, PC, PG, RCT	N=633 4 to 6 months	Primary: Mean percentage of treated	Primary: Mean percentage of PMPs without menstrual-related migraines per patient was 38 and 34% in naratriptan groups, significantly higher than 29 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Naratriptan 1 mg twice a day vs placebo	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		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	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.[117] (2009) Sumatriptan-naproxen 85-500 mg vs placebo	2 replicate studies: DB, MC, PC, R 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	N=621 1 menstrual cycle	Primary: Two hour pain-free response Secondary: 24-hour and 48-hour pain-free period	Primary: A significantly greater percentage of patients receiving sumatriptan-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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	periods prior to screening			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.[118] (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 menstrual cycles before the screening visit	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.
Tuchman et al.[119] (2008) Zolmitriptan 2.5 mg three times daily	DB, MC, PC, PG, R Women ≥18 years of age with a diagnosis of menstrual-related	N=253 3 menstrual cycles	Primary: Proportion of patients with a ≥50% reduction in the frequency of menstrual migraine	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	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		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	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.[120] (2013) Triptan (frovatriptan, naratriptan, zolmitriptan) vs placebo	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 38 years, and all were women	N=1,999 6 trials 5 to 7 days	Primary: Proportion of patients free from menstrual migraine during the treated perimenstrual period Secondary: Menstrual migraine severity, need for rescue medication, adverse events	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. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[121] (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 migraines per month	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 Secondary: Not reported	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). 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.[122] (2002)	DB, R, 3-way, XO Patients with mild-	N=20 Single dose	Primary: Assess cardiovascular	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Almotriptan 12.5 mg vs almotriptan 25 mg vs placebo	to-moderate hypertension controlled by medications		effects of almotriptan in patients with mild-to-moderate hypertension controlled by antihypertensive medication Secondary: Plasma concentrations and cardiovascular effects	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	Axert®*	$$$$-$$$$	$$$$$
Eletriptan	tablet	Relpax®	$$$$$	N/A
Frovatriptan	tablet	Frova®	$$$$$	N/A
Naratriptan	tablet	Amerge®*	$$$$$	$$
Rizatriptan	orally disintegrating tablet, tablet	Maxalt®*, Maxalt MLT®*	$$$$$	$
Sumatriptan	nasal spray, subcutaneous injection, tablet	Imitrex®*, Sumavel DosePro®, Alsuma®*	$$$$-$$$$$	$
Zolmitriptan	nasal spray, orally disintegrating tablet, tablet	Zomig®*, Zomig ZMT®*	$$$$-$$$$$	$$$
Combination Products				
Sumatriptan and naproxen	tablet	Treximet®	$$$$$	N/A

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

X. Conclusions

The selective serotonin agonists (triptans) are approved for the treatment of acute treatment of migraine attacks with or without aura.[7-17] The subcutaneous formulation of sumatriptan is also approved for the treatment of cluster headaches.[7,8,14] Almotriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan 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.[19-122] 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.[89-97,117] 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.

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

1. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology and American Headache Society. Neurology. 2012;78:1337-45.
2. Institute for Clinical Systems Improvement (ICSI). Diagnosis and Treatment of Headache. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); January 2013. Available at: http://www.icsi.org/guidelines_and_more/gl_os_prot/other_health_care_conditions/headache/headache__diagnosis_and_treatment_of__guideline_.html. Accessed September 2013.
3. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. EFNS guideline on the drug treatment of migraine - revised report of an EFNS task force. Eur J Neurol. 2009;16:968-81.
4. Lewis D, Ashwal S, Hershey A et al. Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004:63;2215-24.
5. Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med. 2002 Nov 19;137(10):840-9.
6. Francis GJ, Becker WJ, Pringsheim TM. Acute and preventative pharmacologic treatment of cluster headache. Neurology. 2010;75:463-73
7. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Oct]. Available from: http://online.factsandcomparisons.com.
8. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Oct]. Available from: http://www.thomsonhc.com/.
9. Axert® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2014.
10. Relpax® [package insert]. New York, NY: Pfizer, Inc.; September 2013.
11. Frova® [package insert]. Chadds Ford, PA: Endo Pharmaceuticals Inc.; October 2013.
12. Amerge® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; October 2013.
13. Maxalt® and Maxalt-MLT® [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; December 2011.
14. Imitrex® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; November 2013.
15. Treximet® [package insert]. Morristown, NJ: Pernix Therapeutics, LLC; May 2015.
16. Zomig® and Zomig-ZMT® [package insert]. Wilmington, DE: AstraZeneca; September 2012.
17. Zomig® Nasal Spray [package insert]. Wilmington, DE: AstraZeneca; June 2015.
18. Siow HC, Pozo-Rosich P and Silberstein SD. Frovatriptan for the treatment of cluster headaches. Cephalagia. 2004;24:1045-8.
19. Gobel H, Linder V, Heinze A, Ribbat M, Deushl G. Acute therapy for cluster headache with sumatriptan: Findings of a one-year long-term study. Neurology. 1998;51(3):908-11.
20. Ekbom K, Monstad I, Prusinski A, Cole JA, Pilgrim AJ, Noronha D. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. The Sumatriptan Cluster Headache Study Group. Acta Neurol Scand. 1993;88(1):63-9.
21. Rapoport AM, Mathew NT, Silberstein SD et al. Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. Neurology 2007. Aug 28;69(9):821-6.
22. Cabarrocas X, Esbri R, Peris F, Ferrer P. Long-term efficacy and safety of oral almotriptan: interim analysis of a 1-year open study. Headache. 2001;41:57-62.
23. Berenson F, Vasconcellos E, Pakalnis A, Mao L, Biondi M, Armstrong RB. Long-term, open-label safety study of oral almotriptan 12.5 mg for acute treatment of migraine in adolescents. Headache. 2010;50:795-807.
24. Cabarrocas X, Esbri R, Peris F, Ferrer P. Long-term efficacy and safety of oral almotriptan: interim analysis of a one-year open study. Headache. 2001;41:57-62.
25. Diener HC, Gendolla A, Gerbert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. Headache. 2005;45:874-82.
26. Pascual J, Falk R, Docekal R, Prusinski A, Jelencsik J, Cabarrocas X, Segarra X, et al. Tolerability and efficacy of almotriptan in the long-term treatment of migraine. Eur J Neurol. 2001;45:206-13.
27. Dowson AJ, Massiou H, Lainez JM, Cabarrocas X. Almotriptan is an effective and well-tolerated treatment for migraine pain: results of a randomized, double-blind, placebo-controlled clinical trial. Cephalagia. 2002; 22(6):453-61.
28. Dahlof CG, Tfelt-Hansen P, Massiou H, Fazekas A. Dose finding, placebo-controlled study of oral almotriptan in the acute treatment of migraine. Neurology. 2001;57(10):1811-7.

29. Dahlof C, Pascual J, Dodick DW, Dowson AJ. Efficacy, speed of action and tolerability of almotriptan in the acute treatment of migraine: pooled individual patient data from four randomized, double-blind, placebo-controlled clinical trials. Cephalagia. 2006;26:400-8.
30. Mathew NT, Finlayson G, Smith TR et al. Early intervention with almotriptan: results of the AEGIS trial (AXERT Early Migraine Intervention Study). Headache. 2007 Feb;47 (2):189-98.
31. Colman SS, Brod MI, Krishnamurthy A, Rowland CR, Jirgens KJ, Gomez-Mancilla B. Treatment satisfaction, functional status, and health related quality of life of migrating patients treated with almotriptan or sumatriptan. Clin Ther. 2001;23(1):127-45.
32. Spierings EL, Gomez-Mancilla B, Grosz DE, Rowland CR, Whaley FS, Jirgens KJ. Oral almotriptan vs oral sumatriptan in the abortive treatment of migraine: a double-blind, randomized, parallel-group, optimum-dose comparison. Arch Neurol. 2001;58(6):944-50.
33. Goadsby PJ, Massiou H, Pascual J et al. Almotriptan and zolmitriptan in the acute treatment of migraine. Acta Neurol Scand. 2007 Jan; 115(1):34-40.
34. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalagia. 2002;22:633-58.
35. Olesen J, Diener HC, Schoenen J, Hettiarachchi J. No effect of eletriptan administration during the aura phase of migraine. Eur J Neurol. 2004;11:671-7.
36. Farkkila M, Olesen J, Daholf C, Stovner LJ, ter Bruggen JP, Rasmussen S, Muirhead N, Sikes C. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to sumatriptan. Cephalagia. 2003;23:463-71.
37. Sheftell F, Ryan R, Pitman V. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. Headache. 2003;43:202-13.
38. Winner P, Linder SL, Lipton RB et al. Eletriptan for the acute treatment of migraine in adolescents: results of a double-blind, placebo-controlled trial. Headache 2007 Apr; 47(4):511-8.
39. Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot®) in the treatment of migraine: A multicentre, randomized, double-blind, placebo-controlled comparison. Eur Neurol. 2002;47:99-107.
40. Garcia-Ramos G, MacGregor EA, Hilliard B, Bordini CA, Leston J, Hettiarachchi J. Comparative efficacy of eletriptan vs naratriptan in the acute treatment of migraine. Cephalalgia. 2003;23:869–76.
41. Goadsby PJ, Ferrari MD, Olesen J, Stovner LJ, Senard JM, Jackson JC, and Poole PH. Eletriptan in acute migraine: a double blind, placebo-controlled comparison to sumatriptan. Neurology. 2000;54(1):156-61.
42. Mandema JW, Cox E, and Alderman J. Therapeutic benefit of eletriptan compared to sumatriptan for the acute relief of migraine pain—results of a model-based meta-analysis that accounts for encapsulation. Cephalalgia.2005;25:715-25.
43. Mathew NT, Schoenen J, Winner P, Muirhead N, and Sikes CR. Comparative efficacy of eletriptan 40 mg vs sumatriptan 100 mg. Headache. 2003;43:214-22.
44. Schoenen J, Pascual J, Rasmussen S, Sun W, Sikes C, Hettiarachchi J. Patient preference for eletriptan 80 mg vs subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. Eur J Neurol. 2005;25:108-17.
45. Sandrini G, Farkkila M, Burgess G, Forster E, and Haughie S. Eletriptan vs sumatriptan a double-blind, placebo-controlled, multiple migraine attack study. Neurol. 2002;59:1210–7.
46. Steiner TJ, Diener HC, MacGregor EA, Schoenen J, Muirhead N, Sikes CR. Comparative efficacy of eletriptan and zolmitriptan in the acute treatment of migraine. Cephalalgia. 2003;23:942-52.
47. Ryan R. Geraud G, Goldstein J, Cady R, Keywood C. Clinical efficacy of frovatriptan: placebo-controlled studies. Headache. 2002;(42 Suppl 2):S84-92.
48. Cady R, Elkind A, Goldstein J, Keywood C. Randomized, placebo-controlled comparison of early use of frovatriptan in a migraine attack vs dosing after the headache has become moderate or severe. Curr Med Res Opin. 2004;20:1465-72.
49. Gobel H, Heinze A. The Migraine Intervention Score – a tool to improve efficacy of triptans in acute migraine therapy: the ALADIN study. Int J Clin Pract. 2011 Aug;65(8):879-86.
50. Bartolini M, Giamberardino MA, Lisotto C, Martelletti P, Moscato D, Panascia B, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan vs almotriptan for the acute treatment of migraine. J Headache Pain. 2011;12:361-8.
51. Tullo V, Allais G, Ferrari MD, et al. Frovatriptan vs zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. Neurol Sci 2010;31 (Suppl 1):S51-54.

52. Klassen A, Elkind A, Asgharnejad M, Webster C, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine: results of a double-blind, placebo-controlled, parallel-group study. Headache. 1997;37:640-45.
53. Stark S, Spierings EL, McNeal S, Putnam GP, Bolden-Watson CP, O'Quinn S. Naratriptan efficacy in migraineurs who respond poorly to oral sumatriptan. Headache. 2000;40:513-20.
54. Gobel H, Winter P, Boswell D, et al. Comparison of naratriptan and sumatriptan in recurrence-prone migraine patients. Clin Ther. 2000;22(8):981-9.
55. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomized controlled trials. Pharmacoepidemiol Drug Saf. 2004;13(2):73-82.
56. Mathew NT, Kailasam J, Meadors L. Early treatment of migraine with rizatriptan: a placebo-controlled study. Headache. 2004;44:669-73.
57. Ferrari MD, Loder E, McCarroll KA, Lines CR. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. Cephalalgia. 2001;21:129-36.
58. Oldman AD. Smith, LA. McQuay, HJ. Moore RA. Rizatriptan for acute migraine. Cochrane Pain, Palliative and Supportive Care Group Cochrane Database of Systematic Reviews. 4, 2006.
59. Cady R, Martin V, Mauskop A et al. Efficacy of Rizatriptan 10 mg administered early in a migraine attack. Headache 2006 Jun;46 (6):914-24.
60. Martin V, Cady R, Mauskop A, et al. Efficacy of rizatriptan for menstrual migraine in an early intervention model: a prospective subgroup analysis of the rizatriptan TAME (Treat A Migraine Early) studies. Headache. 2008;48:226-35.
61. Nett R, Mannix LK, Mueller L, et al. Rizatriptan efficacy in ICHD-II pure menstrual migraine and menstrually related migraine. Headache. 2008;48:1194-201.
62. Ng-Mak DS, Hu XH, Bigal M. Migraine treatment with rizatriptan and almotriptan: a crossover study. Headache. 2009;49:655-62.
63. Klassen A, Elkind A, Asgharnejad M, Webster C, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine: results of a double-blind, placebo-controlled, parallel-group study. Headache. 1997;37:640-5.
64. Láinez MJA, Evers S, Kinge E, Allais G, Allen C, Rao NA, Massaad R, Lis K. Preference for rizatriptan 10-mg wafer vs eletriptan 40-mg tablet for acute treatment of migraine. Cephalalgia. 2006;26:246–56.
65. Bomhof M, Paz J, Legg N, Allen C, Vandermael K, Patel K, and the Rizatriptan-Naratriptan Study Group. Comparison of rizatriptan 10 mg vs naratriptan 2.5 in migraine. Euro Neurol. 1999;42:173-9.
66. Kolodny A, Polis A, Battisti WP, Johnson-Pratt L, Skobieranda F. Comparison of rizatriptan 5 mg and 10 mg tablets and sumatriptan 25 mg and 50 mg tablets. Cephalagia. 2004;24:540-6.
67. Lipton RB, Pascual J, Goadsby PJ, Massiou H, McCarroll KA, Vandormael K, Jiang K, Lines CR. Effect of rizatriptan and other triptans on the nausea symptom of migraine: a post hoc analysis. Headache. 2001;41(8):754-63.
68. Adelman JU, Lipton RB, Ferrari MD, Diener HC, McCarrol KA, Vandormael K, Lines CR. Comparison of rizatriptan and other triptans on stringent measures of efficacy. Neurology. 2001;57:1377-83.
69. Seeburger JL, Cady RK, Winner P, MacGregor A, Valade D, Zhang Y, et al. Rizatriptan for treatment of acute migraine in patients taking topiramate for migraine prophylaxis. Headache. 2012;52:57-67.
70. Cady RK, Martin VT, Geraud G, Rodgers A, Zhang Y, Ho AP, et al. Rizatriptan 10-mg ODT for early treatment of migraine and impact of migraine education on treatment response. Headache. 2009 May;49(5):687-96.
71. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous sumatriptan. JAMA. 1991;265(21):2831-5.
72. Treatment of migraine attacks with sumatriptan. The Subcutaneous Sumatriptan International Study Group. The Subcutaneous Sumatriptan International Study Group. New England Journal of Medicine. 1991;325(5):316-21.
73. Winner P, Adelman J, Aurora S et al. Efficacy and tolerability of sumatriptan injection for the treatment of morning migraine: two multicenter, prospective, randomized, double-blind, controlled studies in adults. Clin Ther 2006 Oct 01;28(10):1582-91.
74. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. Sumatriptan Auto-Injector Study Group. Eur Neurol. 1991;31:323-31.
75. Cutler N, Mushet GR, Davis R, Clements B, Whitcher L. Oral sumatriptan for the acute treatment of migraine: evaluation of three dosage strengths. Neurology. 1995;45(suppl 7):S5-9.
76. Winner P, Landy S, Richardson M, Ames M. Early intervention in migraine with sumatriptan tablets 50 mg verses 100 mg: a pooled analysis of data from six clinical trials. Clin Ther. 2005;27:1785-94.

77. McCrory, DC. Gray, RN. Oral sumatriptan for acute migraine. Cochrane Database of Systematic Reviews. 4, 2006.
78. Salonen R, Ashford E, Dahlöf C, et al. Intranasal sumatriptan for the acute treatment of migraine. J Neurol. 1994;241:463-9.
79. Djupesland PG, Docekal P. Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: a randomized, placebo-controlled study. Cephalagia. 2010;30(8):933-42.
80. Salonen R, Ashford E, Dahlöf C, Dawson R, Gilhus NE, Luben V, et al. Intranasal sumatriptan for the acute treatment of migraine. J Neurol. 1994;241:463-9.
81. Cady RK, Aurora SK, Brandes JL, Rothrock JF, Myers JA, Fox AW, et al. Satisfaction with and confidence in needle-fee subcutaneous sumatriptan in patients currently treated with triptans. Headache. 2011;51:1202-11.
82. Rothrock JF, Cady RK, Aurora SK, Brandes JL, Myers JA, Fox AW, et al. Needle-free subcutaneous sumatriptan for triptan users requiring a change in migraine therapy: efficacy and impact on patient-rated functionality, satisfaction, and confidence. Curr Med Res Opin. 2011 Nov;27(11):2185-91.
83. Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD008615.
84. Derry CJ, Derry S, Moore RA. Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD009665.
85. Derry CJ, Derry S, Moore RA. Sumatriptan (intranasal route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD009663.
86. Gershovich OE, Billups SJ, Delate T, et al. Assessment of clinical, service, and cost outcomes of a conversion program of sumatriptan to rizatriptan ODT in primary care patients with migraine headaches. J Manag Care Pharm. 2006;12:246-53.
87. Loder E, Brandes JL, Silberstein S, et al. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. Headache. 2001;41(8):745-53.
88. Cady RK, Sheftell F, Lipton RB, Quinn S, Jones M, Putnam G, Crisp A, Metz A, NcNeal S. Effect of early intervention with sumatriptan on migraine pain: Retrospective analyses of data from 3 clinical trials. Clin Ther. 2000;22:1035-48.
89. Smith T, Blumenthal H, Diamond M et al. Sumatriptan/Naproxen sodium for migraine: efficacy, health related quality of life, and satisfaction outcomes. Headache. 2007 May; 47 (5):683-92.
90. Winner P, Cady R, Ruoff G, Frishberg B, Alexander WJ, Zhang Y, et al. Twelve-month tolerability and safety of sumatriptan-naproxen sodium for the treatment of acute migraine. Mayo Clin Proc. 2007 Jan;82(1):61-8.
91. Landy S, Hoagland R, Hoagland NA. Sumatriptan-naproxen migraine efficacy in allodynic patients: early intervention. Headache. 2012;52:133-9.
92. Lipton RB, Dodick DW, Adelman JU, Kaniecki RG, Lener SE, White JD, et al. Consistency of response to sumatriptan/naproxen sodium in a placebo-controlled, crossover study. Cephalagia. 2009;29:826-36.
93. Silberstein SD, Mannix LK, Goldstein J et al. Multimechanistic (sumatriptan-naproxen) early intervention for the acute treatment of migraine. Neurology. 2008 Jul 08;71(2):114-21.
94. Mathew NT, Landy S, Stark S, et al. Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. Headache. 2009;49:971-82.
95. Smith TR, Sunshine A, Stark SR et al. Sumatriptan and naproxen sodium for the acute treatment of migraine. Headache. 2005 Sep;45(8):983-91.
96. Brandes J, Kudrow D, Stark S et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. JAMA. 2007 Apr 04;297:1443-54.
97. Landy S, DeRossett S, Rapoport A et al. Two Double-Blind, Multicenter, Randomized, Placebo-Controlled, Single-Dose Studies of Sumatriptan/Naproxen Sodium in the Acute Treatment of Migraine: Function, Productivity, and Satisfaction Outcomes. MedGenMed. 2007;9(2):53.
98. Diener H, Gendolla A. Part IV: Effects of zolmitriptan orally disintegrating tablet on migraine symptoms and ability to perform normal activities: a post-marketing surveillance study in Germany. Curr Med Res Opin. 2005;21 Suppl 3:S18-S24.
99. Spierings ELH, Rapoport AM, Dodick DW, et al. Acute treatment of migraine with zolmitriptan 5 mg orally disintegrating tablet. CNS Drugs. 2004;18:1133-41.
100. Loder EW, Dowson AJ, Spierings ELH. Part II: Clinical efficacy and tolerability of zolmitriptan orally disintegrating tablet in the acute treatment of migraine. Curr Med Res Opin. 2005;21 Suppl 3:S8-S12.

101. Charlesworth BR, Dowson AJ, Purdy A, Becker WJ, Boes-Hansen S, Farkkila M. Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomized, double-blind, placebo-controlled, dose-ranging study vs zolmitriptan tablet. CNS Drugs. 2003;17:653-67.
102. Dowson AJ, Charlesworth BR, Prudy A, Becker WJ, Boes-Hansen S, Farkkila M. Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. CNS Drugs. 2003; 17:839-51.
103. Loder EW, Dowson AJ, Spierings ELH. Part II: Clinical efficacy and tolerability of zolmitriptan orally disintegrating tablet in the acute treatment of migraine. Curr Med Res Opin. 2005;21(Suppl 3):S8-12.
104. Geraud G, Olsen J, Pfaffenrath V, Tfelt-Hansen P, Zupping R, Diener HC, Sweet R. Comparison of the efficacy of zolmitriptan and sumatriptan: issues in migraine trial design. Cephalagia. 2000;20:30-8.
105. Dowson AJ, Almquist P. Part III: The convenience of, and patient preference for, zolmitriptan orally disintegrating tablet. Curr Med Res Opin. 2005;21 Suppl 3:S13-S17.
106. Chen LC, Ashcroft DM. Meta-analysis of the efficacy and safety of zolmitriptan in the acute treatment of migraine. Headache. 2008;48:236-47.
107. Sun H, Bastings E, Temeck J, Smith B, Men A, Tandon V, Murphy D, Rodriguez W. Migraine therapeutics in adolescents A systematic analysis and historic perspectives of triptan trials in adolescents. JAMA Pediatr. 2013;167(3):243-9.
108. Lipton RB, Serrano D, Nicholson RA, Buse DC, Runken MC, Reed ML. Impact of NSAID and Triptan use on developing chronic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache. 2013 Nov-Dec;53(10):1548-63.
109. Allais G, Acuto G, Cabarrocas X, Esbri R, Benedetto G, Bussone G. Efficacy and tolerability of almotriptan vs zolmitriptan for the acute treatment of menstrual migraine. Neurol Sci. 2006;27:S193-7.
110. Marcus DA, Bernstein CD, Sullivan EA, et al. Perimenstrual eletriptan prevents menstrual migraine: an open-label study. Headache. 2010;50:551-62.
111. Bartolini M, Giamberardino MA, Lisotto C, Martelletti P, Moscato D, Panascia B, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan vs almotriptan for the acute treatment of migraine. J Headache Pain. 2011;12:361-8.
112. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. Neurology. 2004;63:261-9.
113. Brandes JL, Poole A, Kallela M, et al. Short-term frovatriptan for the prevention of difficult-to-treat menstrual migraine attacks. Cephalalgia. 2009;29:1133-48.
114. Silberstein SD, Berner T, Tobin J, et a. Scheduled short-term prevention with frovatriptan for migraine occurring exclusively in association with menstruation. Headache. 2009;49:1283-97.
115. MacGregor EA, Brandes JL, Silberstein S, et al. Safety and tolerability of short-term preventive frovatriptan: a combined analysis. Headache. 2009;49:1298-314.
116. Mannix LK, Savani N, Landy S et al. Efficacy and tolerability of naratriptan for short-term prevention of menstrually related migraine: data from two randomized, double-blind, placebo-controlled studies. Headache 2007 Jul-Aug; 47 (7):1037-49.
117. Mannix LK, Martin VT, Cady RK, et al. Combination treatment for menstrual migraine and dysmenorrhea using sumatriptan-naproxen: two randomized controlled trials. Obstet Gynecol. 2009;114:106-13.
118. Mannix LK; Loder E; Nett R et al. Rizatriptan for the acute treatment of ICHD-II proposed menstrual migraine: two prospective, randomized, placebo-controlled, double-blind studies. Cephalalgia. 2007 May; 27 (5):414-21.
119. Tuchman MM, Hee A, Emeribe U, et al. Oral zolmitriptan in the short-term prevention of menstrual migraine: a randomized, placebo-controlled study. CNS Drugs. 2008;22:877-86.
120. Hu Y, Guan X, Fan L, Jin L. Triptans in prevention of menstrual migraine: a systematic review with meta-analysis. The Journal of Headache and Pain. 2013;14:7.
121. Elkind AH, Satin LZ, Nila A, Keywood C. Frovatriptan use in migraineurs with or at high risk of coronary artery disease. Headache. 2004;44:403-10.
122. Fleishaker JC, McEnroe JD, Azie NE, Francom SF, Carel BJ. Cardiovascular effect of almotriptan in treated hypertensive patients. Clin Pharmacol Ther. 2002;71;169-75.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, Antihistamines
AHFS Class 562208
February 10, 2016

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.[3-10] Prochlorperazine is also approved for the treatment of schizophrenia, as well as for the short-term treatment of generalized non-psychotic anxiety.[3,4,7,8] Conversely, doxylamine succinate and pyridoxine is currently indicated for the treatment of nausea and vomiting in pregnancy.[10] 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 November 2013.

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	tablet	N/A	meclizine
Prochlorperazine	injection, rectal suppository, tablet	N/A	prochlorperazine
Trimethobenzamide	capsule, injection	Tigan®*	trimethobenzamide
Combination Products			
Doxylamine succinate and pyridoxine	delayed-release tablet	Diclegis®	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 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 Guidelines in Oncology:**	For high emetic risk intravenous chemotherapy the following is recommended: • Combination of a neurokinin 1 ($NK-_1$) receptor antagonist, dexamethasone, and any serotonin (5-HT_3) antagonist. • Lorazepam, a histamine (H_2) receptor blocker, or proton pump inhibitor (PPI)

Clinical Guideline	Recommendation(s)
Antiemesis (2015)[11]	may be given. **OR** • Combination of olanzapine, palonosetron, and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. **OR** • Combination of netupitant and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. • The regimen and doses for each therapy are modified on days two to four after chemotherapy. For moderate emetic risk chemotherapy the following is recommended for *Day 1*: • Combination of dexamethasone and a 5-HT_3 antagonist (palonosetron preferred) with or without a NK-$_1$ receptor antagonist. • Lorazepam, an H_2 receptor blocker, or PPI may be given. **OR** • Combination of olanzapine, palonosetron, and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. **OR** • Combination of netupitant and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. For moderate emetic risk chemotherapy the following is recommended for *Days 2 and 3*: • A 5-HT_3 antagonist as monotherapy (unless palonosetron or granisetron patch used on Day 1); **OR** • Dexamethasone as monotherapy; **OR** • A NK-$_1$ receptor antagonist with or without a steroid; **OR** • Olanzapine given days two through four (if given Day 1). • Lorazepam may be added on to the regimen. • An H_2 receptor blocker or PPI may be given. For low and minimal emetic risk chemotherapy the following is recommended: • Dexamethasone; **OR** • Metoclopramide as needed (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. For oral chemotherapy with moderate to high emetic risk the following is recommended: • A 5-HT_3 antagonist (dolasetron, granisetron, or ondansetron). • Lorazepam may be given. • An H_2 receptor blocker or PPI may be given. For oral chemotherapy with low emetic risk the following is recommended: • Metoclopramide PRN; **OR** • Prochlorperazine PRN (maximum 40 mg/day); **OR** • Haloperidol PRN; **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

Clinical Guideline	Recommendation(s)
	since acute and delayed emesis may overlap after the initial day of chemotherapy until the last day. • Corticosteroids: 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. o Side effects associated with prolonged dexamethasone administration should be carefully considered. • 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 Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis, but appear to be less effective for delayed emesis. IV palonosetron is effective for preventing both delayed and acute emesis. However, repeat dosing of palonosetron in the days after chemotherapy (that is, days two or three) is not supported by the scientific literature. • NK-$_1$ receptor antagonists: o Aprepitant or fosaprepitant may be used for multiday chemotherapy regimens likely to be highly emetogenic associated with significant risk for delayed nausea and emesis. <u>Principles for managing breakthrough emesis</u> • 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: **Guideline Update for Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology in the Prevention of Chemotherapy- and Radiotherapy-induced Nausea and Vomiting (2010)**[12]	<u>Prevention of acute nausea and vomiting induced by highly emetogenic chemotherapy</u> • A three-drug regimen including single doses of a 5-HT$_3$ receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended to prevent acute nausea and vomiting following chemotherapy of high emetic risk. • The principles for use of 5-HT$_3$ receptor antagonists are as follows: o Use the lowest tested fully effective dose. o No schedule better than a single dose beginning before chemotherapy. o The adverse effects of these agents are comparable. o Intravenous and oral formulations are equally effective and safe. o Give with dexamethasone and an NK1 receptor antagonist beginning before chemotherapy. <u>Prevention of delayed nausea and vomiting induced by highly emetogenic chemotherapy</u> • In patients receiving cisplatin treated with a combination of aprepitant, a 5-HT$_3$ receptor antagonist and dexamethasone to prevent acute vomiting and nausea, the combination of dexamethasone and aprepitant is suggested to

Clinical Guideline	Recommendation(s)
	prevent delayed nausea and vomiting, on the basis of its greater efficacy compared with dexamethasone alone. <u>Prevention of acute nausea and vomiting induced by moderately emetogenic chemotherapy</u> • A combination of palonosetron plus dexamethasone is recommended as standard prophylaxis for non-anthracycline/cyclophosphamide MEC regimens. • To prevent acute nausea and vomiting in women receiving a combination of anthracycline plus cyclophosphamide, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended. • If aprepitant is not available, women receiving a combination of anthracycline plus cyclophosphamide should receive a combination of palonosetron plus dexamethasone. • There are no differences in tolerability between the 5-HT_3 receptor antagonists used for the prophylaxis of acute emesis induced by moderately emetogenic chemotherapy. • There is no difference in the efficacy of oral or intravenous administration of a 5-HT_3 receptor antagonist. <u>Prevention of delayed nausea and vomiting induced by moderately emetogenic chemotherapy</u> • Patients who receive moderately emetogenic chemotherapy known to be associated with a significant incidence of delayed nausea and vomiting should receive antiemetic prophylaxis for delayed emesis. • In patients receiving chemotherapy of moderate emetic risk that does not include a combination of anthracycline plus cyclophosphamide and in which palonosetron is recommended, multiday oral dexamethasone treatment is the preferred treatment for the prevention of delayed nausea and vomiting. • Aprepitant should be used for the prevention of delayed emesis induced by moderately emetogenic chemotherapy in breast cancer patients receiving a combination of anthracycline plus cyclophosphamide. <u>Prevention of acute and delayed nausea and vomiting induced by chemotherapy with low and minimal emetogenic potential</u> • Patients with no prior history of nausea and vomiting who receive chemotherapy of low emetic potential as an intermittent schedule should be treated with a single antiemetic agent such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, as prophylaxis. • For patients receiving minimally emetogenic chemotherapy, no antiemetic treatment should be routinely administered before chemotherapy in patients without a history of nausea and vomiting. • No prophylactic treatment should be administered for the prevention of delayed emesis induced by low or minimally emetogenic 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: prophylaxis or rescue with a 5-HT_3 receptor antagonist is recommended. • Minimal emetic risk: rescue with dopamine receptor antagonists or 5-HT_3 receptor antagonists.

Clinical Guideline	Recommendation(s)
Society for Ambulatory Anesthesia: **Consensus Guidelines for the Management of Postoperative Nausea and Vomiting (2014)**[13]	Prevention of postoperative nausea and vomiting (PONV) in adults • The efficacy of dexamethasone 4 mg intravenous, ondansetron 4 mg intravenous and droperidol 1.25 mg intravenous for the prevention of postoperative nausea and vomiting appears to be similar. • Ondansetron, dolasetron, granisetron, and tropisetron are most effective in the prophylaxis of PONV when given at the end of surgery, although; some data on dolasetron suggest timing may have little effect on efficacy. Palonosetron is typically given at the start of surgery. • Aprepitant is similar to ondansetron in achieving complete response (no vomiting and no use of rescue antiemetic) for 24 hours after surgery. However, aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 and 48 hours after surgery and in reducing nausea severity in the first 48 hours after surgery. It also has a greater antiemetic effect compared with ondansetron. • Systematic reviews have demonstrated that 5-HT_3 receptor antagonists in combination with dexamethasone or droperidol are more effective than monotherapy with any of the agents. • Droperidol in combination with dexamethasone is more effective than either agent as monotherapy. • Combinations that include metoclopramide have not been shown to be more effective than monotherapy. Prevention of postoperative nausea and vomiting in children • Children are at increased risk of postoperative nausea and vomiting compared to adults. • Children at moderate to high risk for postoperative nausea and vomiting should receive combination therapy with two to three prophylactic agents from different classes. • Ondansetron has been studied extensively in pediatric patients and is approved for patients as young one month of age. • There is now good evidence to suggest that 5-HT_3 antagonists and dexamethasone are the most effective antiemetics in the prophylaxis of pediatric postoperative nausea Treatment of PONV in patients who failed or did not receive prophylaxis • If prophylactic therapy fails, an agent from a different pharmacologic class should be selected for treatment. • If no prophylactic therapy was given, first-line treatment should include a low-dose 5-HT_3 antagonist.
American Society of Clinical Oncology: **Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update (2011)**[14]	High emetic risk • The three-drug combination of an NK1 receptor antagonist (days one to three for aprepitant; day one only for fosaprepitant), a 5-HT_3 receptor antagonist (day one only), and dexamethasone (days one to three or one to four) is recommended for patients receiving highly emetogenic chemotherapy. Moderate emetic risk • The two-drug combination of palonosetron (day one only) and dexamethasone (days one to three) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT_3 serotonin receptor antagonist, preferably granisetron or ondansetron. Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT_3 antagonists is appropriate.

Clinical Guideline	Recommendation(s)
	Low emetic risk • A single 8-mg dose of dexamethasone before chemotherapy is suggested. No routine preventive use of antiemetics for delayed emesis is suggested. Minimal emetic risk • No antiemetic should be administered routinely before or after chemotherapy. • Prochlorperazine may be used in patients receiving minimal emetic risk radiation therapy on an as needed basis. Combination chemotherapy • Patients should be administered antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk. Adjunctive drugs • Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics. Pediatric patients • The combination of a 5-HT_3 antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Because of variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT_3 antagonists than those used in adults may be required for antiemetic protection. Multiple consecutive days of chemotherapy • It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy and for two days after, if appropriate. • To prevent vomiting caused by chemotherapy of high or moderate emetic risk, there is no group of patients for whom cannabinoids are appropriate as first-choice antiemetics. These agents should be reserved for patients intolerant of or refractory to 5-HT3 serotonin receptor antagonists, dexamethasone, and aprepitant. Special emetic problems: • For radiation-induced emesis, patients should receive a 5-HT_3 antagonist before each fraction and for at least 24 hours after completion of radiotherapy. Patients should also receive a 5-day course of dexamethasone during fractions one to five. • For patients with emesis or nausea despite optimal prophylaxis, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT_3 antagonist or adding a dopamine antagonist to the regimen. • For anticipatory nausea and vomiting, use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested.
American Gastroenterological Association: **Medical Position Statement of the Use of Gastrointestinal**	Nausea and vomiting • Metoclopramide, prochlorperazine, promethazine, trimethobenzamide, and ondansetron are considered low-risk drugs based on studies in pregnant women and can be used for nausea and vomiting and for hyperemesis gravidarum. • Granisetron and dolasetron have not been studied in human pregnancies.

Clinical Guideline	Recommendation(s)
Medications in Pregnancy (2006)[15]	
American College of Obstetricians and Gynecologists: **Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy (2015)[16]**	General considerations • Taking a multivitamin at the time of conception may decrease the severity of nausea and vomiting of pregnancy. • The standard recommendation to take prenatal vitamins for three months before conception may reduce the incidence and severity of nausea and vomiting of pregnancy. • Treatment of nausea and vomiting of pregnancy with vitamin B_6 or vitamin B_6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy. • In patients with hyperemesis gravidarum who also have suppressed thyroid-stimulating hormone levels, treatment of hyperthyroidism should not be undertaken without evidence (such as goiter, thyroid autoantibodies, or both) of intrinsic thyroid disease. • Treatment of nausea and vomiting of pregnancy with ginger has shown beneficial effects and can be considered as a nonpharmacologic option. • Early treatment of nausea and vomiting of pregnancy is recommended to prevent progression to hyperemesis gravidarum. • 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 treatment of last resort. • 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, especially thiamine, should be included in the therapy when prolonged vomiting is present. • Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as 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. Evidence is limited on the safety or efficacy of the 5-HT_3 receptor inhibitors (e.g., ondansetron) for nausea and vomiting of pregnancy; however, because of their effectiveness in reducing chemotherapy-induced emesis, their use appears to be increasing.
Society of Obstetricians and Gynaecologists of Canada: **Clinical Practice Guideline: Management of Nausea and Vomiting of Pregnancy (2002)[17]** According to The Society of Obstetricians and Gynaecologists of Canada, this guideline has recently been reviewed and an updated version will be soon be published - this version should be used with discretion as some information has been deemed to be	General considerations • Dietary and lifestyle changes should be liberally encouraged, and women should be counseled to eat whatever appeals to them. • Alternative therapies, such as ginger supplementation, acupuncture, and acupressure, may be beneficial. • A doxylamine and pyridoxine combination should be the standard of care, since it has the greatest evidence to support its efficacy and safety. • H_1 receptor antagonists should be considered in the management of acute or breakthrough episodes of nausea and vomiting of pregnancy. • Pyridoxine monotherapy supplementation may be considered as an adjuvant measure. • Phenothiazines are safe and effective for severe nausea and vomiting of pregnancy. • Metoclopramide is safe to be used for management of nausea and vomiting of pregnancy, although evidence for efficacy is more limited. • Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. • Limited evidence is available on the effectiveness of ondansetron for the

Clinical Guideline	Recommendation(s)

outdated	treatment of nausea and vomiting of pregnancy. Intravenous ondansetron did not demonstrate a therapeutic benefit over promethazine in one trial for the treatment of hyperemesis gravidarum.
	• In general, 5-HT_3 antagonists may be safe to use during the first trimester, but the data are scant. Because of their limited effectiveness, they should not be advocated for first-line use until agents with established safety and effectiveness have been tried and have failed.
	
	<u>Algorithm for the treatment of nausea and vomiting of pregnancy</u>
	• Step 1: Give 10 mg of doxylamine combined with 10 mg of pyridoxine, up to four tablets per day.
	• Step 2: Add dimenhydrinate 50 to 100 mg every four to six hours (orally or rectally) or promethazine 5 to 10 mg every six to eight hours (orally or rectally).
	• Step 3 (no dehydration): Add any of the following (in order of proven fetal safety):
	  o Chlorpromazine 10 to 25 mg every four to six hours (orally or intramuscularly) or 50 to 100 mg every four to six hours (rectally).
	  o Prochlorperazine 5 to10 mg every six to eight hours (intramuscularly, orally or rectally).
	  o Promethazine 12.5 to 25 mg every four to six hours (intramuscularly or orally).
	  o Metoclopramide 5 to 10 mg every eight hours (intramuscularly or orally).
	  o Ondansetron 8 mg every 12 hours orally.
	• Step 4 (dehydration): Start rehydration treatment:
	  o Intravenous fluid replacement.
	  o Multivitamin intravenous supplementation.
	  o Dimenhydrinate 50 mg intravenous every four to six hours.
	• Step 5: Add any of the following (in order of proven fetal safety):
	  o Chlorpromazine 25 to 50 mg every four to six hours (intravenous).
	  o Prochlorperazine 5 to 10 mg every six to eight hours (intravenous).
	  o Promethazine 12.5 to 25 mg every four to six hours (intravenous).
	  o Metoclopramide 5 to 10 mg every eight hours (intravenous).
	• Step 6: Add methylprednisolone 15 to 20 mg every eight hours (intravenous) or ondansetron 8 mg every 12 hours (intravenous) or 1 mg/hour continuously up to 24 hours.
	• At any time, add any or all of the following:
	  o Pyridoxine 25 mg every eight hours.
	  o Ginger 250 mg every six hours.
	  o P6 acupressure/acupuncture.
	• At any step, consider parenteral nutrition when indicated.

American Gastroenterological Association: **Technical Review: Nausea and Vomiting (2001)**[18]	• In clinical studies, dimenhydrinate and meclizine, among others, have shown efficacy in the prevention and treatment of motion sickness. • Prochlorperazine may be used to treat more severe nausea and vomiting due to vertigo or motion sickness. • Trimethobenzamide has been used in the treatment of moderate to severe nausea and vomiting in a variety of clinical contexts. • Scopolamine is used principally for prophylaxis and treatment of motion sickness. • In pregnant patients with more severe symptoms and hyperemesis, hospitalization, fluid and electrolyte replacement, thiamine supplementation, and administration of antiemetics including antihistamines, such as meclizine may be used. For more severe cases of hyperemesis gravidarum, parenteral prochlorperazine may be used.

Clinical Guideline	Recommendation(s)
	• For the prevention of acute post chemotherapy- and radiation-related nausea and vomiting, the combination of a 5-HT_3 receptor antagonist and dexamethasone is the preferred option. • Scopolamine has been shown to have mild efficacy against cytotoxic chemotherapy-related nausea and vomiting and may have a role as adjunctive therapy in this context. • 5-HT_3 antagonists have been shown to be more effective than either placebo or other agents such as prochlorperazine in the prevention of radiotherapy-induced nausea and vomiting, as well as in the treatment of nausea and vomiting that is unrelated to chemotherapy and radiation therapy in cancer patients. • The various 5-HT_3 antagonists appear to be of similar efficacy and have a comparable incidence of side effects. • For postoperative nausea and vomiting, the use of a 5-HT_3 receptor antagonist and droperidol have been proven to be the most effective compared to placebo and with other agents in large randomized trials. Comparisons between the various 5-HT_3 antagonists or between members of this class of compounds and droperidol have generally found similar efficacies for all. • Dronabinol is available for use in the United States and is indicated for anorexia resulting in weight loss among patients with the acquired immunodeficiency syndrome and for refractory chemotherapy-related nausea and vomiting.
American Gastroenterological Association: **American Gastroenterological Association Medical Position Statement: Nausea and Vomiting (2001)**[19]	• Severe intractable nausea and vomiting episodes require parenteral administration of such agents as phenothiazines • Motion sickness and related disorders are treated primarily with histamine H1 and cholinergic receptor antagonists (e.g., scopolamine). • The prevention and treatment of both acute cancer chemotherapy-related and postoperative nausea and vomiting have come to be based largely on the use of 5-HT_3 receptor antagonists.

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[3-10]

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[3-10]

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

Significant drug interactions with the antihistamine antiemetics are listed in Table 5.

Table 5. Significant Drug Interactions with the Antihistamine Antiemetics[3]

Generic Name(s)	Significance Level	Interaction	Mechanism
Prochlorperazine	1	Cisapride	Concomitant use of prochlorperazine and cisapride may result in additive prolongation of the QT interval.
Prochlorperazine	1	Dofetilide	Prochlorperazine may decrease renal elimination of dofetilide, elevating plasma concentrations, which may increase the risk of ventricular arrhythmias.
Doxylamine succinate and pyridoxine	2	Levodopa	Pyridoxine increases the peripheral metabolism of levodopa, resulting in lower levels available for penetration into the central nervous system.
Prochlorperazine	2	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	2	Guanethidine	Concurrent use may inhibit the uptake of guanethidine into nerve endings where it exhibits its effects, resulting in decreased hypotensive effects.

Significance level 1=major severity, significance level 2=moderate severity.

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[3-10]

Adverse Events	Single Entity Agents				Combination Products
	Dimen-hydrinate	Meclizine	Prochlor-perazine	Trimetho-benzamide	Doxylamine Succinate and Pyridoxine
Cardiovascular					

Adverse Events	Single Entity Agents				Combination Products
	Dimen-hydrinate	Meclizine	Prochlor-perazine	Trimetho-benzamide	Doxylamine Succinate and Pyridoxine
Cardiac arrest	-	-	✔	-	-
Hypertension	✔	-	-	-	-
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 to10	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					

Adverse Events	Single Entity Agents				Combination Products
	Dimen-hydrinate	Meclizine	Prochlor-perazine	Trimetho-benzamide	Doxylamine Succinate and Pyridoxine
Amenorrhea	-	-	✔	-	-
Breast enlargement	-	-	✔	-	-
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	-	-	✔	-	-

Adverse Events	Single Entity Agents				Combination Products
	Dimen-hydrinate	Meclizine	Prochlor-perazine	Trimetho-benzamide	Doxylamine Succinate and Pyridoxine
Bronchospasm	-	<1	-	-	-
Laryngeal edema	-	-	✔	-	-
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[3,7,8]

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[3-10]

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:	Motion sickness in children ≥12 years of age: Tablet: 25 to 50 mg one hour prior to travel; may repeat every 24 hours	Tablet: 12.5 mg 25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: 25 to 100 mg daily in divided doses	Vertigo in children ≥12 years 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: Tablet: 20-20 mg as a single dose at bedtime; maximum, 40-40 mg daily in divided doses	Safety and efficacy in children have not been established.	Delayed-release tablet: 10-10 mg

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.[20] (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.[21] (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.[22] (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.[23] (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.[24] (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.[25] (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.[26] (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.[27] (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.[28] (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.[29] (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.[30] (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.[31] (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.[32] (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.[33] (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[34] (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.[35] (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.[36] (2010)	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
Sullivan et al.[37] (1996) Ondansetron 10 mg IV for one dose (mandatory), then every eight hours as needed (optional) vs promethazine 50 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 medication or hospitalization who required hospital admission	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 hydration), antiemetic usage, severity of nausea, weight gain, and adverse events Secondary: Not reported	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). 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.[38] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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).
Turner et al.[39] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Eberhart et al.[40] (2000) Dimenhydrinate 1 mg/kg vs 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.	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 of vomiting, retching, nausea; need for additional antiemetics Secondary: Side effects	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). Secondary: The incidence of side effects was the same in all four groups.
Kothari et al.[41] (2000) Dimenhydrinate 50 mg IV vs ondansetron 4 mg IV	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All medications administered before induction of anesthesia.			discharge Secondary: Not reported	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: Not reported
McCall et al.[42] (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.[43] (1998) Dimenhydrinate 0.5 mg/kg vs ondansetron 0.1	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg IV vs placebo All given at induction of anesthesia				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
Bopp et al.[44] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				groups. Secondary: Not reported
Layeeque et al.[45] (2006) Dronabinol 5 mg as prophylaxis and prochlorperazine 25 mg rectal suppository after anesthesia vs standard preoperative care (which excludes prophylactic use of antiemetics)	RETRO Patients undergoing surgery	N=242 Variable duration	Primary: Rate and severity of PONV Secondary: Not reported	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 standard preoperative care. Secondary: Not reported
Jamil et al.[46] (2005) Prochlorperazine 0.1 to 0.2 mg/kg IM vs metoclopramide 0.1 to 0.2 mg/kg IV vs placebo	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All treatments were injected 10 minutes before the induction of general anesthesia.				Secondary: Not reported
Chen et al.[47] (1998) Prochlorperazine maleate 10 mg IM vs ondansetron 4 mg IV All administered at end of surgical procedure.	DB, RCT Patients ≥18 years of age undergoing elective, primary or revisionary total hip or total knee replacement procedures	N=78 48 hours post-operatively	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).
Van den Berg et al.[48] (1996) Prochlorperazine 0.2 mg/kg IM vs ondansetron 0.06 mg/kg IV vs prochlorperazine	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.2 mg/kg IV vs placebo All given with induction of anesthesia				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 (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.[49] (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.

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.[47] 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	tablet	N/A	N/A	$
Prochlorperazine	injection, rectal suppository, tablet	N/A	N/A	$
Trimethobenzamide	capsule, injection	Tigan®*	$$$	$$$
Combination Products				
Doxylamine succinate and pyridoxine	delayed-release tablet	Diclegis®	$$$$$	N/A

*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.[3-10] Doxylamine succinate and pyridoxine is approved for nausea and vomiting associated with pregnancy.[10] Prochlorperazine is also approved for the treatment of schizophrenia, as well as for the short-term treatment of generalized non-psychotic anxiety.[7,8] All of the products are available in a generic formulation with the exception of Diclegis® (doxylamine succinate and pyridoxine).

The antihistamine antiemetics are effective for the treatment of nausea and vomiting associated with motion sickness, vertigo, and other related disorders.[18,19] They may also be considered in the management of acute or breakthrough episodes of nausea and vomiting of pregnancy.[15-17] For nausea and vomiting associated with chemotherapy and radiation, the selection of therapy depends on the relative emetogenic potential of the regimen.[11,14] Prochlorperazine is recommended as one of several options to treat acute nausea and vomiting induced by low or minimal emetogenic chemotherapy.[11,14] It may also be useful as rescue therapy in patients receiving minimal or intermediate emetic risk radiation therapy.[13,14] 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

1. Longstreth GF, Hesketh PJ. Characteristics of antiemetic drugs. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2015 [cited 2015 Sep 30]. Available from: http://www.utdol.com/utd/index.do.
2. Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. Am Fam Physician. 2004;1169-74.
3. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Sep]. Available from: http://online.factsandcomparisons.com.
4. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Sep]. Available from: http://www.thomsonhc.com/.
5. Dimenhydrinate [package insert]. Shaumburg, IL: APP Pharmaceuticals, LLC; April 2008.
6. Meclizine [package insert]. Hauppauge, NY: Contract Pharmacal Corp; December 2011.
7. Prochlorperazine tablet [package insert]. Morgantown, WV: Mylan Pharmaceuticals Inc.; September 2010.
8. Prochlorperazine suppository [package insert]. Charlottesville, VA: PBM Pharmaceuticals Inc.; August 2013.
9. Tigan® [package insert]. Bristol, TN: Monarch Pharmaceuticals, Inc.; April 2008.
10. Diclegis® [package insert]. Bryn Mawr (PA): Duchesnay USA, Inc; April 2013.
11. National Comprehensive Cancer Network (NCCN): Clinical Practice Guidelines in Oncology: Antiemesis [guideline on the Internet]. 2015 Feb [cited 2015 Sep 29]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
12. Roila F, Herrstedt J, Aapro M, et al.; ESMO/MASCC Guidelines Working Group. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010;21(Suppl 5):v232-43.
13. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014 Jan;118(1):85-113.
14. Basch E, Prestrund AA, Hesketh PJ, Kris MG, Feyr PC, Somerfield MR, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2011 Nov 1;29(31):4189-98.
15. Mahadevan U, Kane S. American gastroenterological association institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology. 2006;131:278-82.
16. Nausea and vomiting of pregnancy. Practice Bulletin No. 153. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015; 126:e12–24.
17. Arsenault M, Lane C, MacKinnon C, et al. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2002;24:817-31.
18. Quigley EMM, Hasler WL, Parkman HP. American Gastroenterological Association (AGA) technical review: nausea and vomiting. Gastroenterology. 2001;120:263-86.
19. American Gastroenterological Association Medical Position Statement: Nausea and Vomiting. Gastroenterology. 2001 Jan;120(1):261-2.
20. Friedman BW, Esses D, Solorzano C, et al. A randomized controlled trial of prochlorperazine vs metoclopramide for treatment of acute migraine. Ann Emerg Med. 2008;52:399-406.
21. Miller MA, Levsky ME, Enslow W, et al. Randomized evaluation of octreotide vs prochlorperazine for ED treatment of migraine headache. Am J Emerg Med 2009;27:160-4.
22. Lane M, Vogel CL, Ferguson J. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. J Pain Symptom Manage. 1991;6(6):352-9.
23. Machado Rocha FC, Stéfano SC, De Cássia Haiek R, et al. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer Care (Engl). 2008;17:431-43.
24. Niiranen A, Mattson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. Am J Clin Oncol. 1985;8:336-40.
25. Einhorn L, Nagy C, Furnas B, et al. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. J Clin Pharmacol. 1981;21:64S-69S.
26. Tramer MR, Carroll D, Campbell FA, et al. Cannabinoids for control of chemotherapy-induced nausea and vomiting: quantitative systematic review. BMJ. 2001 Jul 7;323(7303):16-21.
27. Lindley C, Goodin S, McCune J, et al. Prevention of delayed chemotherapy-induced nausea and vomiting after moderately high to highly emetogenic chemotherapy: comparison of ondansetron, prochlorperazine, and dexamethasone. Am J Clin Oncol. 2005;28(3):270-6.
28. Hickok JT, Roscoe JA, Marrow GR, et al. 5-Hydroxytryptamine-receptor antagonists vs prochlorperazine for control of delayed nausea caused by doxorubicin: a URCC CCOP randomized controlled trial. Lancet Oncol. 2005;6(10):765-72.

29. Friedman CJ, Burris HA, Yocom K, et al. Oral granisetron for the prevention of acute late onset nausea and vomiting in patients treated with moderately emetogenic chemotherapy. Oncologist. 2000;5:136-43.
30. Braude D, Soliz T, Crandall C, et al. Antiemetics in the ED: a randomized controlled trial comparing 3 common agents. Am J Emerg Med. 2006;24(2):177-82.
31. Callan JE, Kostic MA, Bachrach EA, et al. Prochlorperazine vs promethazine for headache treatment in the emergency department: a randomized controlled trial. J Emerg Med. 2008;35:247-53.
32. Uhlig U, Pfeil N, Gelbrich G, et al. Dimenhydrinate in children with infectious gastroenteritis: a prospective, RCT. Pediatrics 2009;124:e622-32.
33. Paul MA, MacLellan M, Gray G. Motion-sickness medications for aircrew: impact on psychomotor performance. Aviat Space Environ Med. 2005;76(6):560-5.
34. Spinks AB, Wasiak J, Villanueva EV, Bernath V. Scopolamine (hyoscine) for preventing and treating motion sickness. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD002851.
35. Dahle E, Offer-Ohlsen D, Lillevold PE, et al. Transdermal scopolamine, oral meclizine, and placebo in motion sickness. Clin Pharmacol Ther. 1984;36:116-20.
36. Koren G, Clark, S, Hankins GD, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. American Journal of Obstetrics and Gynecology. 2010 Dec;2013:571.e1-7.
37. Turner KE, Parlow JL, Avery ND, et al. Prophylaxis of postoperative nausea and vomiting with oral, long-acting dimenhydrinate in gynecologic outpatient laparoscopy. Anesth Analg. 2004;98(6):1660-4.
38. Loewen PS, Marra CA, Zed PJ. 5-HT_3 receptor antagonists vs traditional agents for the prophylaxis of postoperative nausea and vomiting. Can J Anesth. 2000;47:1008-18.
39. Sullivan CA, Johnson CA, Roach H, et al. A pilot study of intravenous ondansetron for hyperemesis gravidarum. Am J Obstet Gynecol 1996;174:1565-8.
40. Eberhart LH, Seeling W, Ulrich B, et al. Dimenhydrinate and metoclopramide alone or in combination for prophylaxis of PONV. Can J Anaesth. 2000;47(8):780-5.
41. Kothari SN, Boyd WC, Bottcher PJ. Antiemetic efficacy of prophylactic dimenhydrinate (Dramamine®) vs ondansetron (Zofran®). Surg Endosc. 2000;14:926-9.
42. McCall JE, Stubbs K, Saylors S, et al. The search for cost-effective prevention of postoperative nausea and vomiting in the child undergoing reconstructive burn surgery: ondansetron vs dimenhydrinate. J Burn Care Rehabil. 1999;20(4):309-15.
43. Hamid SK, Selby IR, Sikich N, et al. Vomiting after adenotonsillectomy in children: A comparison of ondansetron, dimenhydrinate, and placebo. Anesth Analg. 1998;86:496-500.
44. Bopp EJ, Estrada TJ, Kilday JM, et al. Biphasic dosing regimen of meclizine for prevention of postoperative nausea and vomiting in a high-risk population. AANA J 2010;78:55-62.
45. Layeeque R, Siegel E, et al. Prevention of nausea and vomiting following breast surgery. The American Journal of Surgery. 2006;(191):767-72.
46. Jamil M, Gilani SM, Khan SA. Comparison of metoclopramide, prochlorperazine and placebo in prevention of postoperative nausea and vomiting (PONV) following tonsillectomy in young adults. J Ayub Med Coll Abbottabad. 2005;17:40-4.
47. Chen JJ, Frame DG, White TJ. Efficacy of ondansetron and prochlorperazine for the prevention of postoperative nausea and vomiting after total hip replacement or total knee replacement procedures; a randomized, double blind, comparative trial. Arch Intern Med. 1998;158(19):2124-8.
48. Van den Berg AA. A comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after tympanoplasty. Can J Anaesth. 1996;43(9):939-45.
49. Schmitt LG, Shaw JE. Alleviation of induced vertigo. Therapy with transdermal scopolamine and oral meclizine. Arch Otolaryngol Head Neck Surg. 1986;112(1):88-91.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, 5-HT_3 Receptor Antagonists
AHFS Class 562220
February 10, 2016

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 miscellaneous antiemetic, aprepitant.[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.[3-11] 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.[12-14]

In December 2010, the Food and Drug Administration notified healthcare providers that the injectable formulation of dolasetron should no longer be used to prevent nausea and vomiting associated with chemotherapy.[15] Dolasetron causes a dose-dependent prolongation in the QT, PR, and QRS intervals.[5,6,15] There have been postmarketing reports of Torsades de Pointes, as well as second or third degree atrioventricular block, cardiac arrest, and serious ventricular arrhythmias (including fatalities) in adult and pediatric patients.[5,6] Patients at risk are those with underlying structural heart disease and preexisting conduction system abnormalities, elderly, patients with sick sinus syndrome, patients with atrial fibrillation with slow ventricular response, patients with myocardial ischemia, or patients receiving drugs known to prolong the PR and QRS intervals.[5,6]

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. Granisetron and ondansetron are available in a generic formulation. This class was last reviewed in November 2013.

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	injection, tablet	Anzemet®	none
Granisetron	injection*, tablet*, transdermal patch	Kytril®*, Sancuso®	granisetron
Ondansetron	film, injection*, orally disintegrating tablet*, solution*, tablet*	Zofran®*, Zofran ODT®*, Zuplenz®	ondansetron
Palonosetron	injection	Aloxi®	none

*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**	For high emetic risk intravenous chemotherapy the following is recommended: • Combination of a neurokinin 1 (NK_1) receptor antagonist, dexamethasone, and any serotonin (5-HT_3) antagonist.

Clinical Guideline	Recommendation(s)
Guidelines in Oncology: Antiemesis (2015)[16]	• Lorazepam, a histamine (H_2) receptor blocker, or proton pump inhibitor (PPI) may be given. **OR** • Combination of olanzapine, palonosetron, and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. **OR** • Combination of netupitant and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. • The regimen and doses for each therapy are modified on days two to four after chemotherapy. For moderate emetic risk chemotherapy the following is recommended for *Day 1*: • Combination of dexamethasone and a 5-HT_3 antagonist (palonosetron preferred) with or without a NK-$_1$ receptor antagonist. • Lorazepam, an H_2 receptor blocker, or PPI may be given. **OR** • Combination of olanzapine, palonosetron, and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. **OR** • Combination of netupitant and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. For moderate emetic risk chemotherapy the following is recommended for *Days 2 and 3*: • A 5-HT_3 antagonist as monotherapy (unless palonosetron or granisetron patch used on Day 1); **OR** • Dexamethasone as monotherapy; **OR** • A NK-$_1$ receptor antagonist with or without a steroid; **OR** • Olanzapine given days two through four (if given Day 1). • Lorazepam may be added on to the regimen. • An H_2 receptor blocker or PPI may be given. For low and minimal emetic risk chemotherapy the following is recommended: • Dexamethasone; **OR** • Metoclopramide as needed (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. For oral chemotherapy with moderate to high emetic risk the following is recommended: • A 5-HT_3 antagonist (dolasetron, granisetron, or ondansetron). • Lorazepam may be given. • An H_2 receptor blocker or PPI may be given. For oral chemotherapy with low emetic risk the following is recommended: • Metoclopramide PRN; **OR** • Prochlorperazine PRN (maximum 40 mg/day); **OR** • Haloperidol PRN; **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

Clinical Guideline	Recommendation(s)
	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. • Corticosteroids: 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. o Side effects associated with prolonged dexamethasone administration should be carefully considered. • 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 Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis, but appear to be less effective for delayed emesis. IV palonosetron is effective for preventing both delayed and acute emesis. However, repeat dosing of palonosetron in the days after chemotherapy (that is, days two or three) is not supported by the scientific literature. • $NK-_1$ receptor antagonists: o Aprepitant or fosaprepitant may be used for multiday chemotherapy regimens likely to be highly emetogenic associated with significant risk for delayed nausea and emesis. <u>Principles for managing breakthrough emesis</u> • 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: **Guideline Update for Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology in the Prevention of Chemotherapy- and Radiotherapy-induced Nausea and Vomiting (2010)**[17]	<u>Prevention of acute nausea and vomiting induced by highly emetogenic chemotherapy</u> • A three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended to prevent acute nausea and vomiting following chemotherapy of high emetic risk. • The principles for use of 5-HT_3 receptor antagonists are as follows: o Use the lowest tested fully effective dose. o No schedule better than a single dose beginning before chemotherapy. o The adverse effects of these agents are comparable. o Intravenous and oral formulations are equally effective and safe. o Give with dexamethasone and an NK1 receptor antagonist beginning before chemotherapy. <u>Prevention of delayed nausea and vomiting induced by highly emetogenic chemotherapy</u> • In patients receiving cisplatin treated with a combination of aprepitant, a 5-HT_3 receptor antagonist and dexamethasone to prevent acute vomiting and nausea,

Clinical Guideline	Recommendation(s)
	the combination of dexamethasone and aprepitant is suggested to prevent delayed nausea and vomiting, on the basis of its greater efficacy compared with dexamethasone alone. <u>Prevention of acute nausea and vomiting induced by moderately emetogenic chemotherapy</u> • A combination of palonosetron plus dexamethasone is recommended as standard prophylaxis for non-anthracycline/cyclophosphamide MEC regimens. • To prevent acute nausea and vomiting in women receiving a combination of anthracycline plus cyclophosphamide, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended. • If aprepitant is not available, women receiving a combination of anthracycline plus cyclophosphamide should receive a combination of palonosetron plus dexamethasone. • There are no differences in tolerability between the 5-HT_3 receptor antagonists used for the prophylaxis of acute emesis induced by moderately emetogenic chemotherapy. • There is no difference in the efficacy of oral or intravenous administration of a 5-HT_3 receptor antagonist. <u>Prevention of delayed nausea and vomiting induced by moderately emetogenic chemotherapy</u> • Patients who receive moderately emetogenic chemotherapy known to be associated with a significant incidence of delayed nausea and vomiting should receive antiemetic prophylaxis for delayed emesis. • In patients receiving chemotherapy of moderate emetic risk that does not include a combination of anthracycline plus cyclophosphamide and in which palonosetron is recommended, multiday oral dexamethasone treatment is the preferred treatment for the prevention of delayed nausea and vomiting. • Aprepitant should be used for the prevention of delayed emesis induced by moderately emetogenic chemotherapy in breast cancer patients receiving a combination of anthracycline plus cyclophosphamide. <u>Prevention of acute and delayed nausea and vomiting induced by chemotherapy with low and minimal emetogenic potential</u> • Patients with no prior history of nausea and vomiting who receive chemotherapy of low emetic potential as an intermittent schedule should be treated with a single antiemetic agent such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, as prophylaxis. • For patients receiving minimally emetogenic chemotherapy, no antiemetic treatment should be routinely administered before chemotherapy in patients without a history of nausea and vomiting. • No prophylactic treatment should be administered for the prevention of delayed emesis induced by low or minimally emetogenic 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: prophylaxis or rescue with a 5-HT_3 receptor antagonist is recommended. • Minimal emetic risk: rescue with dopamine receptor antagonists or 5-HT_3 receptor antagonists.

Clinical Guideline	Recommendation(s)
Society for Ambulatory Anesthesia: **Consensus Guidelines for the Management of Postoperative Nausea and Vomiting (2014)**[18]	Prevention of postoperative nausea and vomiting (PONV) in adults • The efficacy of dexamethasone 4 mg intravenous, ondansetron 4 mg intravenous and droperidol 1.25 mg intravenous for the prevention of postoperative nausea and vomiting appears to be similar. • Ondansetron, dolasetron, granisetron, and tropisetron are most effective in the prophylaxis of PONV when given at the end of surgery, although; some data on dolasetron suggest timing may have little effect on efficacy. Palonosetron is typically given at the start of surgery. • Aprepitant is similar to ondansetron in achieving complete response (no vomiting and no use of rescue antiemetic) for 24 hours after surgery. However, aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 and 48 hours after surgery and in reducing nausea severity in the first 48 hours after surgery. It also has a greater antiemetic effect compared with ondansetron. • Systematic reviews have demonstrated that 5-HT_3 receptor antagonists in combination with dexamethasone or droperidol are more effective than monotherapy with any of the agents. • Droperidol in combination with dexamethasone is more effective than either agent as monotherapy. • Combinations that include metoclopramide have not been shown to be more effective than monotherapy. Prevention of postoperative nausea and vomiting in children • Children are at increased risk of postoperative nausea and vomiting compared to adults. • Children at moderate to high risk for postoperative nausea and vomiting should receive combination therapy with two to three prophylactic agents from different classes. • Ondansetron has been studied extensively in pediatric patients and is approved for patients as young one month of age. • There is now good evidence to suggest that 5-HT_3 antagonists and dexamethasone are the most effective antiemetics in the prophylaxis of pediatric postoperative nausea Treatment of PONV in patients who failed or did not receive prophylaxis • If prophylactic therapy fails, an agent from a different pharmacologic class should be selected for treatment. • If no prophylactic therapy was given, first-line treatment should include a low-dose 5-HT_3 antagonist.
American Society of Clinical Oncology: **Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update (2011)**[13]	High emetic risk • The three-drug combination of an NK1 receptor antagonist (days one to three for aprepitant; day one only for fosaprepitant), a 5-HT_3 receptor antagonist (day one only), and dexamethasone (days one to three or one to four) is recommended for patients receiving highly emetogenic chemotherapy. Moderate emetic risk • The two-drug combination of palonosetron (day one only) and dexamethasone (days one to three) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT_3 serotonin receptor antagonist, preferably granisetron or ondansetron. Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT_3 antagonists is appropriate. Low emetic risk

Clinical Guideline	Recommendation(s)
	• A single 8-mg dose of dexamethasone before chemotherapy is suggested. No routine preventive use of antiemetics for delayed emesis is suggested. Minimal emetic risk • No antiemetic should be administered routinely before or after chemotherapy. • Prochlorperazine may be used in patients receiving minimal emetic risk radiation therapy on an as needed basis. Combination chemotherapy • Patients should be administered antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk. Adjunctive drugs • Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics. Pediatric patients • The combination of a 5-HT_3 antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Because of variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT_3 antagonists than those used in adults may be required for antiemetic protection. Multiple consecutive days of chemotherapy • It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy and for two days after, if appropriate. • To prevent vomiting caused by chemotherapy of high or moderate emetic risk, there is no group of patients for whom cannabinoids are appropriate as first-choice antiemetics. These agents should be reserved for patients intolerant of or refractory to 5-HT3 serotonin receptor antagonists, dexamethasone, and aprepitant. Special emetic problems: • For radiation-induced emesis, patients should receive a 5-HT_3 antagonist before each fraction and for at least 24 hours after completion of radiotherapy. Patients should also receive a 5-day course of dexamethasone during fractions one to five. • For patients with emesis or nausea despite optimal prophylaxis, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT_3 antagonist or adding a dopamine antagonist to the regimen. • For anticipatory nausea and vomiting, use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested.
American Gastroenterological Association: **Medical Position Statement of the Use of Gastrointestinal Medications in**	Nausea and vomiting • Metoclopramide, prochlorperazine, promethazine, trimethobenzamide, and ondansetron are considered low-risk drugs based on studies in pregnant women and can be used for nausea and vomiting and for hyperemesis gravidarum. • Granisetron and dolasetron have not been studied in human pregnancies.

Clinical Guideline	Recommendation(s)
Pregnancy (2006)[19]	
American College of Obstetricians and Gynecologists: **Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy (2015)[20]**	General considerations • Taking a multivitamin at the time of conception may decrease the severity of nausea and vomiting of pregnancy. • The standard recommendation to take prenatal vitamins for three months before conception may reduce the incidence and severity of nausea and vomiting of pregnancy. • Treatment of nausea and vomiting of pregnancy with vitamin B_6 or vitamin B_6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy. • In patients with hyperemesis gravidarum who also have suppressed thyroid-stimulating hormone levels, treatment of hyperthyroidism should not be undertaken without evidence (such as goiter, thyroid autoantibodies, or both) of intrinsic thyroid disease. • Treatment of nausea and vomiting of pregnancy with ginger has shown beneficial effects and can be considered as a nonpharmacologic option. • Early treatment of nausea and vomiting of pregnancy is recommended to prevent progression to hyperemesis gravidarum. • 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 treatment of last resort. • 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, especially thiamine, should be included in the therapy when prolonged vomiting is present. • Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as 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. Evidence is limited on the safety or efficacy of the 5-HT_3 receptor inhibitors (e.g., ondansetron) for nausea and vomiting of pregnancy; however, because of their effectiveness in reducing chemotherapy-induced emesis, their use appears to be increasing.
Society of Obstetricians and Gynaecologists of Canada: **Clinical Practice Guideline: Management of Nausea and Vomiting of Pregnancy (2002)[21]** According to The Society of Obstetricians and Gynaecologists of Canada, this guideline has recently been reviewed and an updated version will be soon be published - this version should be used with discretion as some information has been	General considerations • Dietary and lifestyle changes should be liberally encouraged, and women should be counseled to eat whatever appeals to them. • Alternative therapies, such as ginger supplementation, acupuncture, and acupressure, may be beneficial. • A doxylamine and pyridoxine combination should be the standard of care, since it has the greatest evidence to support its efficacy and safety. • H_1 receptor antagonists should be considered in the management of acute or breakthrough episodes of nausea and vomiting of pregnancy. • Pyridoxine monotherapy supplementation may be considered as an adjuvant measure. • Phenothiazines are safe and effective for severe nausea and vomiting of pregnancy. • Metoclopramide is safe to be used for management of nausea and vomiting of pregnancy, although evidence for efficacy is more limited. • Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. • Limited evidence is available on the effectiveness of ondansetron for the treatment of nausea and vomiting of pregnancy. Intravenous ondansetron did not demonstrate a therapeutic benefit over promethazine in one trial for the

Clinical Guideline	Recommendation(s)

deemed to be outdated	treatment of hyperemesis gravidarum.
	• In general, 5-HT_3 antagonists may be safe to use during the first trimester, but the data are scant. Because of their limited effectiveness, they should not be advocated for first-line use until agents with established safety and effectiveness have been tried and have failed.
	
	<u>Algorithm for the treatment of nausea and vomiting of pregnancy</u>
	• Step 1: Give 10 mg of doxylamine combined with 10 mg of pyridoxine, up to four tablets per day.
	• Step 2: Add dimenhydrinate 50 to 100 mg every four to six hours (orally or rectally) or promethazine 5 to 10 mg every six to eight hours (orally or rectally).
	• Step 3 (no dehydration): Add any of the following (in order of proven fetal safety):
	  o Chlorpromazine 10 to 25 mg every four to six hours (orally or intramuscularly) or 50 to 100 mg every four to six hours (rectally).
	  o Prochlorperazine 5 to10 mg every six to eight hours (intramuscularly, orally or rectally).
	  o Promethazine 12.5 to 25 mg every four to six hours (intramuscularly or orally).
	  o Metoclopramide 5 to 10 mg every eight hours (intramuscularly or orally).
	  o Ondansetron 8 mg every 12 hours orally.
	• Step 4 (dehydration): Start rehydration treatment:
	  o Intravenous fluid replacement.
	  o Multivitamin intravenous supplementation.
	  o Dimenhydrinate 50 mg intravenous every four to six hours.
	• Step 5: Add any of the following (in order of proven fetal safety):
	  o Chlorpromazine 25 to 50 mg every four to six hours (intravenous).
	  o Prochlorperazine 5 to 10 mg every six to eight hours (intravenous).
	  o Promethazine 12.5 to 25 mg every four to six hours (intravenous).
	  o Metoclopramide 5 to 10 mg every eight hours (intravenous).
	• Step 6: Add methylprednisolone 15 to 20 mg every eight hours (intravenous) or ondansetron 8 mg every 12 hours (intravenous) or 1 mg/hour continuously up to 24 hours.
	• At any time, add any or all of the following:
	  o Pyridoxine 25 mg every eight hours.
	  o Ginger 250 mg every six hours.
	  o P6 acupressure/acupuncture.
	• At any step, consider parenteral nutrition when indicated.

American Gastroenterological Association: **Technical Review: Nausea and Vomiting (2001)**[14]	• In clinical studies, dimenhydrinate and meclizine, among others, have shown efficacy in the prevention and treatment of motion sickness. • Prochlorperazine may be used to treat more severe nausea and vomiting due to vertigo or motion sickness. • Trimethobenzamide has been used in the treatment of moderate to severe nausea and vomiting in a variety of clinical contexts. • Scopolamine is used principally for prophylaxis and treatment of motion sickness. • In pregnant patients with more severe symptoms and hyperemesis, hospitalization, fluid and electrolyte replacement, thiamine supplementation, and administration of antiemetics including antihistamines, such as meclizine may be used. For more severe cases of hyperemesis gravidarum, parenteral prochlorperazine may be used. • For the prevention of acute post chemotherapy- and radiation-related nausea and vomiting, the combination of a 5-HT_3 receptor antagonist and

Clinical Guideline	Recommendation(s)
	dexamethasone is the preferred option. • Scopolamine has been shown to have mild efficacy against cytotoxic chemotherapy-related nausea and vomiting and may have a role as adjunctive therapy in this context. • 5-HT_3 antagonists have been shown to be more effective than either placebo or other agents such as prochlorperazine in the prevention of radiotherapy-induced nausea and vomiting, as well as in the treatment of nausea and vomiting that is unrelated to chemotherapy and radiation therapy in cancer patients. • The various 5-HT_3 antagonists appear to be of similar efficacy and have a comparable incidence of side effects. • For postoperative nausea and vomiting, the use of a 5-HT_3 receptor antagonist and droperidol have been proven to be the most effective compared to placebo and with other agents in large randomized trials. Comparisons between the various 5-HT_3 antagonists or between members of this class of compounds and droperidol have generally found similar efficacies for all. • Dronabinol is available for use in the United States and is indicated for anorexia resulting in weight loss among patients with the acquired immunodeficiency syndrome and for refractory chemotherapy-related nausea and vomiting.
American Gastroenterological Association: **American Gastroenterological Association Medical Position Statement: Nausea and Vomiting (2001)**[22]	• Severe intractable nausea and vomiting episodes require parenteral administration of such agents as phenothiazines • Motion sickness and related disorders are treated primarily with histamine H1 and cholinergic receptor antagonists (e.g., scopolamine). • The prevention and treatment of both acute cancer chemotherapy-related and postoperative nausea and vomiting have come to be based largely on the use of 5-HT_3 receptor antagonists.

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[3-11]

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 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				✔

Indication	Dolasetron	Granisetron	Ondansetron	Palonosetron
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				
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.

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	Liver (100)	Renal (45 to 68)	8
Granisetron	PO: 60 TD: 66	65	Liver (89)	Renal (12)	IV: 5 to 9 PO: 6.23
Ondansetron	56 to 71	70 to 76	Liver (90 to 95)	Renal (44 to 60)	3 to 6
Palonosetron	Not reported	62	Liver (50 to 60)	Renal (80)	37 to 48

IV=intravenous, PO=oral, TD=transdermal

V. Drug Interactions

Significant drug interactions with the 5-HT$_3$ receptor antagonists are listed in Table 5.

Table 5. Significant Drug Interactions with the 5-HT$_3$ Receptor Antagonists[3]

Generic Name(s)	Significance Level	Interaction	Mechanism
Dolasetron, granisetron	1	Vandetanib	Concomitant administration of vandetanib with dolasetron may result in synergistic or additive prolongation of the QT interval.
Dolasetron	1	Ziprasidone	Concomitant administration of ziprasidone with dolasetron may result in synergistic or additive prolongation of the QT interval.

Generic Name(s)	Significance Level	Interaction	Mechanism
5-HT$_3$ receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron)	2	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.
Ondansetron	2	Rifamycins	Induction of hepatic metabolism (CYP3A4) of ondansetron by rifamycins is suspected. Plasma concentrations of ondansetron may be reduced, decreasing its antiemetic effect.

Significance level 1=major severity, significance level 2=moderate severity.

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[3-11]

Adverse Events	Dolasetron	Granisetron	Ondansetron	Palonosetron
Cardiovascular				
Angina	<1	<1	<1	-
Arrhythmia	<1	<1	<1	<1
Atrial fibrillation	<1	<1	<1	-
Atrial flutter	<1	-	-	-
Atrioventricular block	<1	-	<1	-
Bradycardia	4 to 5	-	<1	1 to 4
Bundle branch block	<1	-	-	-
Cardiopulmonary arrest	<1	-	<1	-
Chest discomfort	-	-	<1	-
ECG changes	<1	<1	<1	<1
Extrasystole	<1	-	-	<1
Hypertension	2 to 3	1 to 2	2	<1
Hypotension	5	<1	3 to 5	<1
Myocardial ischemia	<1	-	-	<1
Orthostatic hypotension	<1	-	-	-
Palpitation	<1	-	<1	-
PR prolongation	<1	-	-	-
Premature ventricular contractions	-	-	<1	-
QRS prolongation	<1	-	-	-
QT prolongation	<1	2 to 3	<1	1 to 5
Shock	-	-	<1	-
ST-T wave change	<1	-	-	-
Supraventricular extrasystoles	-	-	-	<1
Supraventricular tachycardia	-	-	<1	-
Syncope	<1	-	<1	-
T wave change	<1	-	-	-
Tachycardia	2 to 3	-	<1	<1
Torsades de pointes	<1	-	<1	-
U wave change	<1	-	-	-
Ventricular arrhythmia	<1	-	<1	-
Ventricular fibrillation	<1	-	<1	-
Ventricular tachycardia	<1	-	<1	-
Central Nervous System				

Adverse Events	Dolasetron	Granisetron	Ondansetron	Palonosetron
Abnormal dreams	<1	-	-	-
Agitation	<1	<2	-	-
Anxiety	<1	2	6	1
Chills	1 to 2	5	7	<1
Central nervous system stimulation	-	<2	-	-
Cold sensation	-	-	2	-
Confusion	<1	-	-	-
Depersonalization	<1	-	-	-
Dizziness	2 to 4	4 to 5	4 to 7	<1
Drowsiness	1 to 2	-	8	-
Euphoria	-	-	-	<1
Extrapyramidal symptoms	-	<1	<1	-
Fatigue	-	-	-	<1
Fever	3 to 4	3 to 9	2 to 8	<1
Headache	7 to 24	3 to 21	9 to 27	3 to 9
Hypersomnia	-	-	-	<1
Insomnia	-	<2 to 5	-	<1
Malaise/fatigue	2 to 5	-	9 to 13	<1
Motion sickness	-	-	-	<1
Paresthesia	<1	-	2	<1
Seizure	-	-	<1	<1
Sleep disorder	<1	-	-	-
Somnolence	-	1 to 4	-	<1
Syncope	-	<1	-	-
Tremor	<1	-	-	-
Vertigo	<1	-	-	-
Dermatological				
Allergic dermatitis	-	-	-	<1
Erythema	-	-	-	<1
Hyperhidrosis	<1	-	<1	-
Pruritus	3	-	2 to 5	<1
Rash	<1	1	1	<1
Urticaria	<1	-	<1	-
Gastrointestinal				
Abdominal pain	3	4 to 6	3	<1
Anorexia	<1	-	-	<1
Appetite decreased	-	-	-	<1
Constipation	<1	3 to 18	6 to 11	2 to 5
Diarrhea	2 to 12	3 to 9	2 to 7	<1
Dyspepsia	2	3 to 6	-	<1
Flatulence	-	-	-	<1
Hiccups	-	-	<1	<1
Pancreatitis	<1	-	-	-
Taste perversion	<1	2	-	-
Xerostomia	-	-	2	<1
Genitourinary				
Acute renal failure	<1	-	-	-
Dysuria	<1	-	-	-
Glycosuria	-	-	-	<1
Gynecological disorder	-	-	7	-
Hematuria	<1	-	-	-
Oliguria	2	2	-	-
Polyuria	<1	-	-	-
Urinary retention	2	-	5	<1

Adverse Events	Dolasetron	Granisetron	Ondansetron	Palonosetron
Hematologic				
Metabolic acidosis	-	-	-	<1
Partial thromboplastin time prolonged	<1	-	-	-
Thrombocytopenia	<1	-	-	<1
Hepatic				
Alanine aminotransferase increased	3	5 to 6	1 to 5	<1
Aspartate aminotransferase increased	3	5 to 6	1 to 5	<1
Hepatic failure	-	-	<1	-
Hepatic necrosis	-	-	<1	-
Hepatitis	-	-	<1	-
Jaundice	-	-	<1	-
Laboratory Test Abnormalities				
Alkaline phosphatase increased	<1	-	-	-
Bilirubin increased	-	-	-	<1
Hyperglycemia	-	-	-	<1
Hyperkalemia	-	-	-	<1
Hypokalemia	-	-	<1	<1
Musculoskeletal				
Arthralgia	<1	-	<1	<1
Asthenia	-	14	-	-
Myalgia	<1	-	-	-
Respiratory				
Bronchospasm	<1	-	<1	-
Cough	-	2	-	-
Dyspnea	<1	-	<1	-
Hypoventilation	-	-	-	<1
Hypoxia	-	-	9	-
Laryngeal edema	-	-	<1	-
Laryngospasm	-	-	<1	<1
Stridor	-	-	<1	-
Other				
Abnormal vision	<1	-	-	-
Allergic reaction	-	<1	-	-
Amblyopia	-	-	-	<1
Anaphylaxis	<1	<1	<1	-
Anemia	<1	-	-	<1
Angioedema	-	-	<1	-
Application site reaction (patch)	-	<1	-	-
Ataxia	<1	-	-	-
Blurred vision	-	-	<1	-
Dystonic reaction	-	-	<1	-
Edema	<1	-	-	<1
Epistaxis	<1	-	-	<1
Eye irritation	-	-	-	<1
Facial edema	<1	-	-	-
Flu-like syndrome	-	-	-	<1
Flushing	<1	-	<1	-
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

Adverse Events	Dolasetron	Granisetron	Ondansetron	Palonosetron
Photophobia	<1	-	-	-
Tinnitus	<1	-	-	<1
Twitching	<1	-	-	-
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[3-11]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Dolasetron	Chemotherapy induced nausea and vomiting: Injection: 1.8 mg/kg or 100 mg intravenously 30 minutes before chemotherapy Tablet: 100 mg within one hour before chemotherapy Postoperative nausea and vomiting: Injection: 12.5 mg intravenously 15 minutes before cessation of anesthesia or as soon as nausea or vomiting presents	Chemotherapy induced nausea and vomiting in children two to 16 years of age: Injection: 1.8 mg/kg up to 100 mg intravenously 30 minutes before chemotherapy Tablet: 1.8 mg/kg up to 100 mg within one hour before chemotherapy Postoperative nausea and vomiting in children two to 16 years of age: Injection: 0.35 mg/kg up to 12.5 mg intravenously 15 minutes before cessation of anesthesia or as soon as nausea or vomiting presents	Injection: 12.5 mg/0.625 mL 20 mg/mL 100 mg/5 mL Tablet: 50 mg 100 mg
Granisetron	Chemotherapy induced nausea and vomiting: 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	Chemotherapy induced nausea and vomiting in children two to 16 years of age: Injection: 10 µg/kg intravenously	Injection: 100 µg/mL 1 mg/mL Tablet: 1 mg Transdermal patch: 3.1 mg/24 hours

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	before induction of anesthesia or immediately before reversal of anesthesia Radiation induced nausea and vomiting Tablet: 2 mg within one hour of radiation		
Ondansetron	Chemotherapy induced nausea and vomiting: 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: Oral soluble film: 24 mg given successively as three 8 mg films 30 minutes before the start of 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: Oral soluble film: 8 mg film 30 minutes before chemotherapy followed by an 8 mg dose eight hours later; administer one 8 mg film twice daily for one to two days after completion of chemotherapy Orally disintegrating tablet: 8 mg orally twice daily Solution: 8 mg orally twice daily Tablet: 8 mg orally twice	Chemotherapy induced nausea and vomiting in children six 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: Oral soluble film: 4 mg film three times daily; administer the first dose 30 minutes before chemotherapy, with subsequent doses four and eight hours later; administer one 4 mg film three times daily for one to two days after completion of chemotherapy 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: Oral soluble film: 8 mg film 30 minutes before chemotherapy followed by an 8 mg dose eight hours later; administer one 8 mg film twice daily for one to two days after completion of chemotherapy. Orally disintegrating tablet: 8 mg twice daily Solution: 8 mg twice daily Tablet: 8 mg twice daily	Injection: 2 mg/mL 4 mg/2 mL Oral soluble film: 4 mg 8 mg 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
	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 Oral soluble film: 16 mg given successively as two 8 mg films one hour before anesthesia 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: Oral soluble film: 8 mg film three times daily Orally disintegrating tablet: 8 mg three times daily Solution: 8 mg three times daily Tablet: 8 mg three times 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	
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/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.[23] (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.[24] (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.[25] (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.[26] (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.[27] (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.[28] (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.[29] (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.[30] (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.[31] (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.[32] (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.[33] (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.[34] (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.[35] (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.[36] (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.[37] (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.[38] (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.[39] (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.[40] (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.[41] (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.[42] (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
Days three to five (flexible dose) 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.[43] (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.[44] (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.[45] (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.[46] (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.[47] (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.[48] (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.[49] (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
Saito et al.[50] (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,	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
			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	
Jordan et al.[51] (2007) Granisetron vs ondansetron granisetron vs tropisetron ondansetron vs tropisetron ondansetron vs dolasetron	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 chemotherapy Secondary: Not reported	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-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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Abali et al.[52] (2007) Ondansetron 8 mg IV vs granisetron 3 mg IV vs tropisetron 5 mg IV Dexamethasone 8 mg IV was coadministered with all treatments.	OL, PRO Patients receiving highly and moderately emetogenic chemotherapy	N=158 5 days	Primary: Emesis control and nausea control in acute (within 24 hours of chemotherapy) and 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	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%), 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gralla et al.[53] (2003) Ondansetron 32 mg IV vs palonosetron 0.25 mg IV vs palonosetron 0.75 mg IV	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 after chemotherapy (acute period) Secondary: Efficacy in treatment of delayed CINV (≤5 days post chemotherapy), overall tolerability	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). 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.[54] (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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chemotherapy, daily from day one of high-dose cytarabine up to day five vs palonosetron 0.25 mg IV 30 minutes before high-dose cytarabine on days one, three and five				Secondary: Not reported
Davidson et al.[55] (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.[56] (2009) Palonosetron 0.25 mg IV as a single dose	DB, MC, PG, RCT Chinese patients undergoing highly emetogenic chemotherapy	N=240 120 hours	Primary: Complete response rate (defined as no emetic episodes and no rescue medication) during	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs granisetron 3 mg IV as a single dose Rescue medication was permitted.	regimens		the first 24 hours after chemotherapy Secondary: Complete response rates during successive 24 hour time periods (24 to 48, 48 to 72, 72 to 96 and 96 to 120); safety	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). There were no clinically relevant differences between groups with regard to overall incidence of adverse events.
Tian et al.[57] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Saito et al.[58] (2009) Palonosetron 0.75 mg IV as a single 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	DB, DD, MC, PG, RCT Patients ≥20 years of age who were scheduled to receive a single dose of highly emetogenic chemotherapy on day one (cisplatin >50 mg/m^2, doxorubicin-cyclophosphamide, or epirubicin-cyclophosphamide)	N=1,114 120 hours	Primary: Proportion of patients with a complete response during the acute 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	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). 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chemotherapy).				
Aapro et al.[59] (2006) Palonosetron 0.25 mg IV vs palonosetron 0.75 mg IV vs ondansetron 32 mg IV	DB, DD, MC, PG, RCT Patients ≥18 years 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	N=673 5 days	Primary: Complete response (no emetic episodes and no 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	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). 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.[60] (2005) Palonosetron 0.25 mg IV vs ondansetron 32 mg	RETRO post hoc analysis of studies by Eisenberg et al.[37] and Gralla et al.[46] Patients ≥65 years receiving moderately emetogenic	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV or dolasetron 100 mg IV	chemotherapy		to 120 hours) with significance P<0.025 Secondary: Not reported	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: Not reported
Botrel et al.[61] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV vs ondansetron 32 mg IV				
Likun et al.[62] (2011) 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	MA, SR (8 DB, RCTs including 6 NI and 2 XO) Adults with cancer receiving chemotherapy	N=3,592 5 days	Primary: Complete response 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	Primary: Treatment with palonosetron reduced the risk of acute CINV by 24% (OR, 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%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cisplatin chemotherapy on days two and three and 4 mg orally for anthracycline plus 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				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). 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 16 mg IV vs ondansetron 32 mg IV vs ondansetron 32 mg IV plus dexamethasone 20 mg before chemotherapy				
Schwartzberg et al.[63] (2014) Palonosetron 0.25 or 0.75 mg vs other 5-HT_3 antagonists (ondansetron 32 mg, dolasetron 100 mg, or granisetron 40 µg/kg)	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 antiemetics, and no more than mild nausea), number of emetic episodes, nausea severity	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 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.[64]	MC, PRO	N=220	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(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	Chemotherapy-naïve patients with histologically or cytologically proven solid or blood tumors	5 days	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 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	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
			period, safety	
Choi et al.[65] (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.[66] (2005) Prochlorperazine sustained release 15 mg two times a day vs dexamethasone 8 mg two times a day vs ondansetron 8 mg two times a day	MC, RCT Chemotherapy-naïve patients scheduled to receive moderately high to highly emetogenic chemotherapy	N=232 5 days	Primary: Number of vomiting episodes, average nausea score reported on days two through five Secondary: Not reported	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received ondansetron 24 mg and dexamethasone 20 mg orally before chemotherapy.				
Friedman et al.[67] (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 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.[68]	DB, RCT	N=36	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2014) Ondansetron 4 mg plus placebo tablet every eight hours vs pyridoxine 25 mg plus doxylamine 12.5 mg every eight hours	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	5 days	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	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.[69] (1996) Ondansetron 10 mg IV for one dose (mandatory), then every eight hours as needed (optional) vs promethazine 50 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 medication or hospitalization who required hospital admission	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 hydration), antiemetic usage, severity of nausea, weight gain, and adverse events Secondary: Not reported	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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Einarson et al.[70] (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.[71] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prochlorperazine 5 mg				
Diemunsch et al.[72] (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.[73] (2007) Aprepitant 40 mg by mouth vs aprepitant 125 mg by mouth vs ondansetron 4 mg IV	DB, MC, PC, RCT Patients ≥18 years of age (ASA I or III status) scheduled to undergo open abdominal surgery requiring an overnight hospital stay and who 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 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 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.[74] (2014) Aprepitant 40 mg by mouth	DB, RCT Patients 20 to 60 years of age who were scheduled to	N=93 48 hours	Primary: Complete response (visual analogue scale nausea score <4 and no use of	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs palonosetron 0.075 mg IV	undergo laparoscopic gynecologic surgery under general anaesthesia		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	(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[75] (2012) Dolasetron, granisetron, ondansetron or tropisetron vs a different 5-HT_3 receptor antagonist (dolasetron, granisetron, ondansetron or tropisetron) or placebo	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. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Birmingham et al.[76] (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.[77] (2003) Dolasetron 45 µg/kg IV vs dolasetron 175 µg/kg IV vs dolasetron 350 µg/kg IV vs	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: Not reported	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 µg/kg (P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dolasetron 700 µg/kg IV vs ondansetron 100 µg/kg IV				
Meyer et al.[78] (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[79] (2001) Dolasetron 12.5 mg IV vs ondansetron 4 mg IV	RETRO Patients who underwent total abdominal hysterectomy or laparoscopic cholecystectomy	N=59 24 hours	Primary: Number of recorded episodes of PONV in 24 hours after surgery; time to occurrence of PONV Secondary: Not reported	Primary: PONV occurred in 44% patients receiving dolasetron and 53% patients 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.[80] (2003)	DB, PRO, RCT Children	N=150 24 hours	Primary: Total nausea and vomiting scores	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%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	undergoing elective strabismus surgery, middle ear surgery, adenotonsillectomy or orchiopexy		Secondary: Not reported	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.[81] (2004) Dolasetron 12.5 mg IV vs droperidol 10 µg/kg IV vs dolasetron 12.5 mg and droperidol 10 µg/kg IV vs placebo	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). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bhatnagar et al.[82] (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.[83] (2011) Granisetron 3 mg IV vs ondansetron 4 mg IV vs tropisetron 5 mg IV vs placebo	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 cm) requiring rescue medication, incidence of vomiting episodes among four treatment groups Secondary: Not reported	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were premedicated with midazolam 0.07 mg/kg IM 1 to 1.5 hours before surgery.				
Oksuz et al.[84] (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.[85] (2007) Granisetron 0.1 mg IV vs granisetron 1 mg IV vs ondansetron 4 mg IV	DB, RCT Patients 18 to 64 years of age with 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	N=88 24 hours	Primary: Complete response (no further PONV and no requests for further medication) Secondary: Not reported	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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
White et al.[86] (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.[87] (2009) Granisetron 10 µg/kg IV vs ondansetron 50 µg/kg IV vs midazolam 50 µg/kg IV vs placebo	DB, PC, RCT Patients 4 to 12 years of age (ASA class I) who were undergoing elective strabismus surgery using general anesthesia	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). Secondary: No major respiratory or hemodynamic adverse effects were observed in the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All three treatment regimens included dexamethasone 0.5 mg/kg.				
Dabbous et al.[88] (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.[89] (2005) Granisetron 0.1 mg IV and dexamethasone 8 mg IV vs ondansetron 4 mg IV and dexamethasone 8 mg IV	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 Secondary: Proportion of patients with no vomiting during 0 to six hours and overall 0 to 24 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). 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.[90]	DB, PC, RCT	N=60	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Ondansetron orally disintegrating tablet 8 mg before discharge and 12 hours later vs placebo	Patients undergoing outpatient gynecological laparoscopy	24 hours	Incidence of PONV, severity of nausea, rescue antiemetic, side effects, satisfaction PONV management assessed at two and 24 hours post surgery Secondary: Not reported	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.[91] (2009) Ondansetron 4 mg IV vs ondansetron 8 mg orally disintegrating tablet vs placebo	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. 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.[92] (2009)	DB, PC, RCT Patients (ASA I or	N=90 24 hours	Primary: Episodes of PONV within 24 hours	Primary: The overall incidence of emesis within 24 hours after surgery was significantly lower in the ondansetron group (14.8%) and granisetron

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ondansetron 4 mg IV vs granisetron 1 mg IV vs placebo	II status) scheduled for supratentorial craniotomy for intracranial tumor excision		Secondary: Requirement of rescue antiemetic	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.[93] (2008) Ondansetron 4 mg IV vs granisetron 3 mg IV vs dexamethasone 8 mg IV vs placebo	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%. <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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Hamid et al.[94] (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.[95] (2000) Ondansetron 4 mg IV vs dimenhydrinate 50 mg IV	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 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). 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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
McCall et al.[96] (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.[97] (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). Secondary: Not reported
Van den Berg[98] (1996) Ondansetron 0.06 mg/kg IV vs prochlorperazine 0.2 mg/kg IM	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:	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs prochlorperazine 0.2 mg/kg IV vs placebo			Postoperative headache	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 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.[99] (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.[100] (2007)	DB, PC, RCT	N=77	Primary: PONV or retching;	Primary: There were no differences between the transdermal scopolamine and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ondansetron 4 mg vs scopolamine 1.5 mg transdermal patch	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	72 hours	need for rescue antiemetics, complete response rates (i.e., absence of protracted nausea or repeated episodes of emesis requiring antiemetic rescue medication) Secondary: Not reported	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: Not reported
Gan et al.[101] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[102] (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
Loewen et al.[103] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[104] (2008) palonosetron 0.025 mg IV vs palonosetron 0.050 mg IV vs palonosetron 0.075 mg IV vs placebo	DB, MC, PC, PRO, 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	N=544 Monitored over 72 hour time period	Primary: 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	Primary: 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[105] (2008) Palonosetron 0.025 mg IV vs palonosetron 0.05 mg IV vs palonosetron 0.075 mg IV vs placebo	DB, MC, PC, PRO, 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	N=546 Monitored over 72 hour time period	Primary: 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	Primary: 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Only values of palonosetron 0.075 mg group were reported for the secondary end points.
Chun et al.[106] (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 operation, severity of nausea, use of rescue medication, patient satisfaction	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 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.
Radiation-Induced Nausea and Vomiting (RINV)				
Spitzer et al.[107] (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).

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	injection, tablet	Anzemet®	$$$$$	N/A
Granisetron	injection*, tablet*, transdermal patch	Kytril®*, Sancuso®	$$$$$	$$$$
Ondansetron	film, injection*, orally disintegrating tablet*, solution*, tablet*	Zofran®*, Zofran ODT®*, Zuplenz®	$$$$-$$$$$	$
Palonosetron	injection	Aloxi®	$$$$-$$$$$	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).[3-11] Granisetron and ondansetron are both 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 5-HT$_3$ receptor antagonists to prevent acute nausea and vomiting associated with moderately or highly emetogenic chemotherapy (in combination with aprepitant and/or dexamethasone).[13,16,17] 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.[16] Clinical trials have demonstrated similar efficacy and safety with the 5-HT_3 receptor antagonists for the prevention of CINV.[16,17,39,41,43,44,47-51,53,56,58,59] Intravenous and oral formulations are equally effective when used at the appropriate dose.[13,16,17] 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.[1,41,53,63] Guidelines do not give preference to one 5-HT_3 receptor antagonist over another. However, the European Society of Medical Oncology/Multinational Association of Supportive Care in Cancer guidelines specifically recommend the combination of palonosetron and dexamethasone to prevent acute nausea and vomiting in patients receiving non-anthracycline/cyclophosphamide chemotherapy regimens (moderate emetogenic risk).[17] For the prevention of RINV, guidelines recommend the use of a 5-HT_3 receptor antagonist (with or without dexamethasone) before each fraction.[13,16,17]

According to the Society for Ambulatory Anesthesia guidelines, not all surgical patients will benefit from prophylactic antiemetic therapy.[18] Prophylaxis is only recommended for patients who are at moderate or high-risk for PONV. These patients should receive treatment with two or three antiemetic agents from different classes.[18] 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.[18] 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.[18] Clinical trials have demonstrated similar efficacy and safety among the 5-HT_3 receptor antagonists for the prevention and treatment of PONV.[76-77,79-80,86-89,92-93]

Nausea and vomiting of pregnancy is a common condition that can significantly impact a woman's quality of life.[20] 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 of pregnancy.[19,20] 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 nausea and vomiting of pregnancy.[20,21] If there is no improvement, the addition of promethazine, dimenhydrinate, metoclopramide, or trimethobenzamide is recommended.[21] 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.[68,69] One randomized trial demonstrated that intravenous ondansetron was as effective as intravenous promethazine for the treatment of hyperemesis gravidarum.[68] Another demonstrated a greater reduction in nausea in women using ondansetron as compared to pyridoxine plus doxylamine as reported on a visual analog scale.[68]

Dolasetron has been shown to cause a dose-dependent prolongation in the QT, PR, and QRS intervals. There have been postmarketing reports of Torsades de Pointes, as well as second or third degree atrioventricular block, cardiac arrest, and serious ventricular arrhythmias (including fatalities) in adult and pediatric patients.[5,6] The injectable formulation is no longer approved for the prevention of CINV; however, it continues to be approved for the prevention and treatment of PONV because the lower doses are less likely to affect the electrical activity of the heart.[6]

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.

XII. References

1. Longstreth GF, Hesketh PJ. Characteristics of antiemetic drugs. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2015 [cited 2015 Sep 30]. Available from: http://www.utdol.com/utd/index.do.
2. Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. Am Fam Physician. 2004;1169-74.
3. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Sep]. Available from: http://online.factsandcomparisons.com.
4. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Sep]. Available from: http://www.thomsonhc.com/.
5. Anzemet® tablets [package insert]. Bridgewater, NJ: Sanofi-Aventis Pharmaceuticals; September 2014.
6. Anzemet® injection [package insert]. Bridgewater, NJ: Sanofi-Aventis Pharmaceuticals; September 2014.
7. Granisetron Hydrochloride Tablets [package insert]. Columbus, OH: Roxane Laboratories, Inc.; August 2014.
8. Sancuso® [package insert]. Bedminster, NJ: ProStrakan, Inc.; September 2015.
9. Zofran® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; September 2014.
10. Zuplenz® [package insert]. Warren, NJ: Monosol Rx, LLC; September 2014.
11. Aloxi® [package insert]. Woodcliff Lake, NJ: Eisai Inc.; September 2014.
12. Mannix K. Palliation of nausea and vomiting in malignancy. Clin Med. 2006;6:144-7.
13. American Society of Clinical Oncology; Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol. 2006;24(18):2932-2947.
14. Quigley EMM, Hasler WL, Parkman HP. American Gastroenterological Association (AGA) technical review: nausea and vomiting. Gastroenterology 2001;120:263-86.
15. FDA Drug Safety Communication: Abnormal heart rhythms associated with use of Anzemet (dolasetron mesylate). Available from: http://www.fda.gov/drugs/drugsafety/ucm237081.htm. Accessed September 2015.
16. National Comprehensive Cancer Network (NCCN): Clinical Practice Guidelines in Oncology: Antiemesis [guideline on the Internet]. 2015 Feb [cited 2015 Sep 29]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
17. Roila F, Herrstedt J, Aapro M, et al.; ESMO/MASCC Guidelines Working Group. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 2010;21 (Suppl 5):v232-43.
18. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014 Jan;118(1):85-113.
19. Mahadevan U, Kane S. American gastroenterological association institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology 2006;131:278-82.
20. Nausea and vomiting of pregnancy. Practice Bulletin No. 153. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015; 126:e12–24.
21. Arsenault M, Lane C, MacKinnon C, et al. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can 2002;24:817-31.
22. American Gastroenterological Association medical position statement: nausea and vomiting. Gastroenterology. 2001;120:261-2.
23. Billio A, Morello E, Clarke MJ. Serotonin receptor antagonists for highly emetogenic chemotherapy in adults. Cochrane Database of Systematic Reviews. 2010; Issue 1. Art No.: CD006272.
24. Hickok JT, Roscoe JA, Morrow GR, et al. 5-hydroxytryptamine-receptor antagonists vs prochlorperazine for control of delayed nausea caused by doxorubicin: a URCC CCOP randomized controlled trial. Lancet Oncol. 2005;6:765-72.
25. Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer. 2010;18:423-31.
26. Yeo W, Mo FK, Suen JJ, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. Breast Cancer Res Treat. 2009;113:529-35.
27. Herrstedt J, Muss H, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. Cancer. 2005; 104(7):1548-55.
28. Warr DG, Hesketh PJ, Gralla R. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol. 2005; 23 (12):2822-30.

29. Gralla R, de Wit R, Herrstedt J, et al. Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5HT3 antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of combined data from two Phase III randomized clinical trials. Cancer. 2005;104(4):864-8.
30. De Wit R, Herrstedt J, Rapoport B. The oral NK (1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomized, placebo-controlled phase III clinical trials. Eur J Cancer. 2004; 40(3):403-10.
31. Poli-Bigelli S, Rodrigues-Pereira J, et al. Addition of the neurokinin 1 receptor aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Cancer. 2003; 97(12):3090-8.
32. Hesketh PJ, Grunberg SM, Gralla RJ. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. J Clin Oncol. 2003; 21 (22):4112-9.
33. Martin A, Carides A. Functional relevance of antiemetic control. Experience using the FLIE questionnaire in a randomized study of the NK-1 antagonist aprepitant. Eur J Cancer. 2003;39(10):1395-401.
34. Gore L, Chawla S, Petrilli A, et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. Pediatr Blood Cancer. 2009;52:242-7.
35. Jordan K, Kinitz I, Voigt W, et al. Safety and efficacy of a triple antiemetic combination with the NK-1 antagonist aprepitant in highly and moderately emetogenic multiple-day chemotherapy. Eur J Cancer. 2009;45:1184-7.
36. Grunberg SM, Dugan M, Muss H, et al. Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. Support Care Cancer. 2009;17:589-94.
37. Gao HF, Liang Y, Zhou, Zhang DS, and Wu HY. Aprepitant plus palonosetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy. Internal medicine Journal. 2013;43(1):73-6.
38. Hesketh PJ and Sanz-Altamira P. Aprepitant, dexamethasone, and palonosetron in the prevention of doxorubicin/cyclophosphamide-induced nausea and vomiting. Support Care Cancer. 2012;20:653–6.
39. Mandanas R, Beveridge R, Rifkin R, et al. A randomized, multicenter, open-label comparison of the antiemetic efficacy of dolasetron vs ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy. Support Cancer Therapy. 2005;2:114-21.
40. Lofters WS, Pater JL, Zee B, et al. Phase III double-blind comparison of dolasetron mesylate and ondansetron and an evaluation of the additive role of dexamethasone in the prevention of acute and delayed nausea and vomiting due to moderately emetogenic chemotherapy. J Clin Oncol. 1997;15:2966-73.
41. Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT_3 receptor antagonist. Cancer. 2003;98:2473-82.
42. Meiri E, Jhangiani H, Vredenburgh J, et al. Efficacy of dronabinol alone and in combination with ondansetron vs ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin. 2007; 23:533-43.
43. Jaing T, Tsay P, Hung I, et al. Single-dose oral granisetron vs multidose intravenous ondansetron for moderately emetogenic cyclophosphamide-based chemotherapy in pediatric outpatients with acute lymphoblastic leukemia. Pediatr Hemato Onc. 2004;21:227-35.
44. Kalaycio M, Mendez Z, Pohlman B, et al. Continuous-infusion granisetron compared to ondansetron for the prevention of nausea and vomiting after high-dose chemotherapy. J Cancer Res Clin Oncol. 1998;124:265-9.
45. Dempsey CL, Coop AJ, Shillington A, et al. Antiemetic effectiveness of ondansetron and granisetron in patients with breast cancer treated with cyclophosphamide. Am J Health-Syst Pharm. 2004;61:781-6.
46. Lacerda JF, Martins C, Carmo JA, et al. Randomized trial of ondansetron, granisetron, and tropisetron in the prevention of acute nausea and vomiting. Transplantation Proc. 2000;32:2680-1.
47. Walsh T, Morris AK, Holle LM, et al. Granisetron vs ondansetron for prevention of nausea and vomiting in hematopoietic stem cell transplant patients: results of a prospective, double-blind, randomized trial. Bone Marrow Transplantation. 2004;34:963-8.
48. Orchard PJ, Rogosheske J, Burns L, et al. A prospective randomized trial of the antiemetic efficacy of ondansetron and granisetron during bone marrow transplantation. DBMT. 1999;386-93.

49. del Giglio A, Soares HP, Caparroz C, et al. Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced nausea and vomiting. Results of a meta-analysis of randomized controlled trials. Cancer. 2000;89:2301-8.
50. Saito H, Yoshizawa H, Yoshimori K, Katakami N, Katsumata N, Kawahara M, and Eguchi K. Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose cisplatin: a multicentre, randomized, double-blind, placebo-controlled phase 3 trial. Annals of Oncology. 2013;24:1067–73.
51. Jordan K, Hinke A, Grothey A, et al. A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis. Support Care Cancer 2007;15:1023-33.
52. Abali H, Celik I. Tropisetron, ondansetron, and granisetron for control of chemotherapy-induced emesis in Turkish cancer patients: a comparison of efficacy, side-effect profile, and cost. Cancer Investigation 2007;25:135-9.
53. Gralla R, Lichinitser M, Van der Vegt S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncology. 2003;14:1570-7.
54. Mattiuzzi GN, Cortes JE, Blamble DA, Bekele BN, Xiao L, Cabanillas M, et al. Daily palonosetron is more efficacious to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia. Cancer. 2010;116:5659-66.
55. Davidson N, Rapoport B, Erikstein B, et al. Comparison of an orally disintegrating ondansetron tablet with the conventional ondansetron tablet for cyclophosphamide-induced emesis in cancer patients: a multicenter, double-masked study. Clin Ther. 1999;21(3):492-502.
56. Yu Z, Liu W, Wang L, et al. The efficacy and safety of palonosetron compared to granisetron in preventing highly emetogenic chemotherapy-induced vomiting in the Chinese cancer patients: a phase II, multicenter, randomized, double-blind, parallel, comparative clinical trial. Support Care Cancer. 2009;17:99-102.
57. Tian W, Wang Z, Zhou J, Zhang S, Wang J, Chen Q, et al. Randomized, double-blind, crossover study of palonosetron compared to granisetron for the prevention of chemotherapy-induced nausea and vomiting in a Chinese population. Med Oncol. 2011.28:71-8.
58. Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone vs granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomized, comparative phase III trial. Lancet Oncol. 2009;10:115-24.
59. Aapro M, Grunberg S, Manikhas G, et al. A phase III, double-blind, randomized trial of palonosetron compared to ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Annals of Oncology. 2006;17:1441-9.
60. Aapro MA, Macciocchi A, Gridelli C. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting in elderly patients. J Supp Oncology. 2005:3(5):369-74.
61. Botrel TEA, Clark OAC, Clark L, Paladini L, Faleiros E, Pegoretti B. Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT_3R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis. Support Care Cancer. 2011;19:823-32.
62. Likun Z, Xiang J, Yi B, Xin D, Tao ZL. A systematic review and meta-analysis of intravenous palonosetron in the prevention of chemotherapy-induced nausea and vomiting in adults. The Oncologist. 2011;16:207-16.
63. Schwartzberg L, Barbour SY, Morrow GR, Ballinari G, Thorn MD, Cox D. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). Support Care Cancer. 2014 Feb;22(2):469-77.
64. Longo F, Mansueto G, Lapadula V, De Sanctis R, Quadrini S, Grande R, et al. Palonosetron plus 3-day aprepitant and dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer. 2011;19:1159–64.
65. Choi BS, Borsaru GP, Ballinari G, Voisin D, Di Renzo N. Multicenter phase IV study of palonosetron in the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with non-Hodgkin lymphomas undergoing repeated cycles of moderately emetogenic chemotherapy. Leuk Lymphoma. 2014 Mar;55(3):544-50.
66. Lindley C, Goodin S, McCune J, et al. Prevention of delayed chemotherapy-induced nausea and vomiting after moderately high to highly emetogenic chemotherapy: comparison of ondansetron, prochlorperazine, and dexamethasone. Am J Clin Oncol. 2005;28(3):270-6.
67. Friedman CJ, Burris HA, Yocom K, et al. Oral granisetron for the prevention of acute late onset nausea and vomiting in patients treated with moderately emetogenic chemotherapy. Oncologist. 2000;5:136-43.

68. Oliveira LG, Capp SM, You WB, Riffenburgh RH, Carstairs SD. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. Obstet Gynecol. 2014 Oct;124(4):735-42.
69. Sullivan CA, Johnson CA, Roach H, et al. A pilot study of intravenous ondansetron for hyperemesis gravidarum. Am J Obstet Gynecol. 1996;174:1565-8.
70. Einarson A, Maltepe C, Navioz Y, et al. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG. 2004;111:940-3.
71. Hartrick CT, Tang YS, Hunstad D, et al. Aprepitant vs multimodal prophylaxis in the prevention of nausea and vomiting following extended-release epidural morphine. Pain Pract. 2010;10:245-8.
72. Diemunsch P, Gan T, Philip B, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. Br J Anaesth. 2007;99:202-11.
73. Gan T, Apfel C, Kovac A, et al. A randomized, double-blind comparison of the NK_1 antagonist, aprepitant, vs ondansetron for the prevention of postoperative nausea and vomiting. Anesth Analg. 2007;104:1082-9.
74. Moon HY, Baek CW, Choi GJ, et al. Palonosetron and aprepitant for the prevention of postoperative nausea and vomiting in patients indicated for laparoscopic gynaecologic surgery: a double-blind randomised trial. BMC Anesthesiol. 2014 Aug 10;14:68.
75. Tang DH, Malone DC. A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for postoperative nausea and vomiting prophylaxis. Clin Ther. 2012;34:282-94.
76. Birmingham S, Mecklenburg B, Lujan E, et al. Dolasetron vs ondansetron as single-agent prophylaxis for patients at increased risk for postoperative nausea and vomiting: a prospective, double-blind, randomized trial. Military Medicine. 2006;171:913-16.
77. Olutoye O, Jantzen EC, Alexis R, et al. A comparison of the costs and efficacy of ondansetron and dolasetron in the prophylaxis of postoperative vomiting in pediatric patients undergoing ambulatory surgery. Anesth Analg. 2003;97:390-6.
78. Meyer TA, Roberson CR, Rajab MH, et al. Dolasetron vs ondansetron for the treatment of postoperative nausea and vomiting. Anesth Analg. 2005;100:373-7.
79. Walker JB. Efficacy of single-dose intravenous dolasetron vs ondansetron in the prevention of postoperative nausea and vomiting. Clin Ther. 2001;23(6):932-8.
80. Karamanlioglu B, Turan A, Memis D, Sut N. Comparison of oral dolasetron and ondansetron in the prophylaxis of postoperative nausea and vomiting in children. Eur J Anesth. 2003;20:831-5.
81. Eberhart LH, Morin AM, Hoerle S, et al. Droperidol and dolasetron alone or in combination for prevention of postoperative nausea and vomiting after vitrectomy. Ophthalmology. 2004;111:1569-75.
82. Bhatnagar S, Gupta D, Mishra S, et al. Preemptive antiemesis in patients undergoing modified radical mastectomy: oral granisetron vs oral ondansetron in a double-blind, randomized, controlled study. J Clin Anesth. 2007;19:512-6.
83. Metaxari M, Papioannou A, Petrou A, Chatzimichali A, Pharmakalidou E, Askitopoulou H. Antiemetic prophylaxis in thyroid surgery: a randomized, double-blind comparison of three 5-HT_3 agents. J Anesth. 2011;25:356-62.
84. Oksuz H, Zencirci B, Ezberci M. Comparison of the effectiveness of metoclopramide, ondansetron, and granisetron on the prevention of nausea and vomiting after laparoscopic cholescystectomy. J Laparoendosc Adv Surg. 2007;17:803-8.
85. Candiotti K, Nhuch F, Kamat A, et al. Granisetron vs ondansetron treatment for breakthrough postoperative nausea and vomiting after prophylactic ondansetron failure: a pilot study. Anesth Analg. 2007;104:1370-3.
86. White PF, Tang J, Hamza MA, et al. The use of oral granisetron vs intravenous ondansetron for antiemetic prophylaxis in patients undergoing laparoscopic surgery: the effect on emetic symptoms and quality of recovery. Anesth Analg. 2006;102:1387-93.
87. Riad W, Marouf H. Combination therapy in the prevention of PONV after strabismus surgery in children: granisetron, ondansetron, midazolam with dexamethasone. Middle East J Anesthesiol. 2009;20:431-6.
88. Dabbous AS, Jabbour-Khoury SI, Nasr VG, et al. Dexamethasone with either granisetron or ondansetron for postoperative nausea and vomiting in laparoscopic surgery. Middle East J Anesthesiol. 2010;20:565-70.
89. Gan TJ, Coop A, Philip BK, et al. A randomized, double-blind study of granisetron plus dexamethasone vs ondansetron plus dexamethasone to prevent postoperative nausea and vomiting in patients undergoing abdominal hysterectomy. Anesth Analg. 2005;101:1323-9.
90. Gan TJ, Franiak R, Reeves J. Ondansetron orally disintegrating tablet vs placebo for the prevention of post-discharge nausea and vomiting after ambulatory surgery. Anesth Anal. 2002;94:1199-200.

91. Grover VK, Mathew PJ, Hegde H, et al. Efficacy of orally disintegrating ondansetron in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: a randomized, double-blind placebo controlled study. Anaesthesia. 2009;64:595-600.
92. Jain V, Mitra JK, Rath GP, et al. A randomized, double-blinded comparison of ondansetron, granisetron, and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy. J Neurosurg Anesthesiol. 2009;21:226-30.
93. Erhan Y, Erhan E, Aydede H, et al. Ondansetron, granisetron, and dexamethasone compared for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2008;22:1487-92.
94. Hamid SK, Selby IR, Sikich N, et al. Vomiting after adenotonsillectomy in children: A comparison of ondansetron, dimenhydrinate, and placebo. Anesth Analg. 1998;86:496-500.
95. Kothari SN, Boyd WC, Bottcher PJ. Antiemetic efficacy of prophylactic dimenhydrinate (Dramamine®) vs ondansetron (Zofran®). Surg Endosc. 2000;14:926-9.
96. McCall JE, Stubbs K, Saylors S, et al. The search for cost-effective prevention of postoperative nausea and vomiting in the child undergoing reconstructive burn surgery: ondansetron vs dimenhydrinate. J Burn Care Rehabil. 1999;20(4):309-15.
97. Tsutsumi YM, Kakuta N, Soga T, et al. The effects of intravenous fosaprepitant and ondansetron for the prevention of postoperative nausea and vomiting in neurosurgery patients: a prospective, randomized, double-blinded study. Biomed Res Int. 2014;2014:307025
98. Van den Berg AA. A comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after tympanoplasty. Can J Anaesth. 1996;43(9):939-45.
99. Chen JJ, Frame DG, White TJ. Efficacy of ondansetron and prochlorperazine for the prevention of postoperative nausea and vomiting after total hip replacement or total knee replacement procedures; a randomized, double blind, comparative trial. Arch Intern Med. 1998;158(19):2124-8.
100. White P, Tang J, Song D, et al. Transdermal scopolamine: an alternative to ondansetron and droperidol for the prevention of postoperative and postdischarge emetic symptoms. Anesth Analg. 2007;104:92-6.
101. Gan TJ, Sinha AC, Kovac AL, et al. A randomized, double-blind, multicenter trial comparing transdermal scopolamine plus ondansetron to ondansetron alone for the prevention of postoperative nausea and vomiting in the outpatient setting. Anesth Analg. 2009;108:1498-504.
102. Sah N, Ramesh V, Kaul B, et al. Transdermal scopolamine patch in addition to ondansetron for postoperative nausea and vomiting prophylaxis in patients undergoing ambulatory cosmetic surgery. J Clin Anesth. 2009;21:249-52.
103. Loewen PS, Marra CA, Zed PJ. 5-HT_3 receptor antagonists vs traditional agents for the prophylaxis of postoperative nausea and vomiting. Can J Anesth. 2000;47:1008-18.
104. Kovac AL, Eberhart L, Kotarski J, et al. A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo in preventing postoperative nausea and vomiting over a 72-hour period. Anesth Analg. 2008;107(2):439-44.
105. Candiotti K A, Kovac A L, Melson T I, et al. A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo for preventing postoperative nausea and vomiting. Anesth Analog. 2008;107(2):445-4.
106. Chun HR, Jeon IS, Park SY, Lee SJ, Kang SH, Kim SI. Efficacy of palonosetron for the prevention of postoperative nausea and vomiting: a randomized, double-blinded, placebo-controlled trial. Br J Anaesth. 2014 Mar;112(3):485-90.
107. Spitzer TR, Friedman CJ, Bushnell W, et al. Double-blind, randomized, parallel-group study on the efficacy and safety of oral granisetron and oral ondansetron in the prophylaxis of nausea and vomiting in patients receiving hyperfractionated total body irradiation. Bone Marrow Transplantation. 2000;26:203-10.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, Miscellaneous
AHFS Class 562292
February 10, 2016

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.[1-10]

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.[1-10] Aprepitant is a substance P/neurokinin 1 (NK_1) receptor antagonist and has little or no affinity for serotonin, dopamine, or corticosteroid receptors.[4,5] Fosaprepitant, a prodrug of aprepitant, is rapidly converted to aprepitant when administered intravenously. A combination product containing netupitant and palonosetron was Food and Drug Administration (FDA)- approved in October 2014. Netupitant is a NK_1 antagonist and palonosetron is a 5-HT_3 antagonist; Palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.[9] Dronabinol and nabilone are orally active cannabinoids, which have complex effects on the central nervous system.[5-7] Nabilone is classified as a Schedule II controlled substance and dronabinol is classified as a Schedule III controlled substance by federal regulation. 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.[8]

The miscellaneous antiemetics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Dronabinol is the only agent that is available in a generic formulation. This class was last reviewed in November 2013.

Table 1. Miscellaneous Antiemetics 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	Emend®	none
Dronabinol	capsule	Marinol®*	dronabinol
Fosaprepitant	injection	Emend®	none
Nabilone	capsule	Cesamet®	none
Scopolamine	transdermal patch	Transderm-Scop®	none
Combination Products			
Netupitant and palonosetron	capsule	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 miscellaneous antiemetics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Miscellaneous Antiemetics

Clinical Guideline	Recommendation(s)
National Comprehensive Cancer Network:	For high emetic risk intravenous chemotherapy the following is recommended: • Combination of a neurokinin 1 (NK-$_1$) receptor antagonist, dexamethasone,

Clinical Guideline	Recommendation(s)
Clinical Practice Guidelines in Oncology: Antiemesis (2015)[11]	and any serotonin (5-HT_3) antagonist. • Lorazepam, a histamine (H_2) receptor blocker, or proton pump inhibitor (PPI) may be given. **OR** • Combination of olanzapine, palonosetron, and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. **OR** • Combination of netupitant and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. • The regimen and doses for each therapy are modified on days two to four after chemotherapy. For moderate emetic risk chemotherapy the following is recommended for *Day 1*: • Combination of dexamethasone and a 5-HT_3 antagonist (palonosetron preferred) with or without a NK-$_1$ receptor antagonist. • Lorazepam, an H_2 receptor blocker, or PPI may be given. **OR** • Combination of olanzapine, palonosetron, and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. **OR** • Combination of netupitant and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker, or a PPI. For moderate emetic risk chemotherapy the following is recommended for *Days 2 and 3*: • A 5-HT_3 antagonist as monotherapy (unless palonosetron or granisetron patch used on Day 1); **OR** • Dexamethasone as monotherapy; **OR** • A NK-$_1$ receptor antagonist with or without a steroid; **OR** • Olanzapine given days two through four (if given Day 1). • Lorazepam may be added on to the regimen. • An H_2 receptor blocker or PPI may be given. For low and minimal emetic risk chemotherapy the following is recommended: • Dexamethasone; **OR** • Metoclopramide as needed (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. For oral chemotherapy with moderate to high emetic risk the following is recommended: • A 5-HT_3 antagonist (dolasetron, granisetron, or ondansetron). • Lorazepam may be given. • An H_2 receptor blocker or PPI may be given. For oral chemotherapy with low emetic risk the following is recommended: • Metoclopramide PRN; **OR** • Prochlorperazine PRN (maximum 40 mg/day); **OR** • Haloperidol PRN; **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

Clinical Guideline	Recommendation(s)
	• 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. • Corticosteroids: 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. o Side effects associated with prolonged dexamethasone administration should be carefully considered. • 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 Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis, but appear to be less effective for delayed emesis. IV palonosetron is effective for preventing both delayed and acute emesis. However, repeat dosing of palonosetron in the days after chemotherapy (that is, days two or three) is not supported by the scientific literature. • NK-$_1$ receptor antagonists: o Aprepitant or fosaprepitant may be used for multiday chemotherapy regimens likely to be highly emetogenic associated with significant risk for delayed nausea and emesis. <u>Principles for managing breakthrough emesis</u> • 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: **Guideline Update for Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology in the Prevention of Chemotherapy- and Radiotherapy-induced Nausea and Vomiting (2010)[12]**	<u>Prevention of acute nausea and vomiting induced by highly emetogenic chemotherapy</u> • A three-drug regimen including single doses of a 5-HT$_3$ receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended to prevent acute nausea and vomiting following chemotherapy of high emetic risk. • The principles for use of 5-HT$_3$ receptor antagonists are as follows: o Use the lowest tested fully effective dose. o No schedule better than a single dose beginning before chemotherapy. o The adverse effects of these agents are comparable. o Intravenous and oral formulations are equally effective and safe. o Give with dexamethasone and an NK1 receptor antagonist beginning before chemotherapy. <u>Prevention of delayed nausea and vomiting induced by highly emetogenic chemotherapy</u> • In patients receiving cisplatin treated with a combination of aprepitant, a 5-HT$_3$

Clinical Guideline	Recommendation(s)
	receptor antagonist and dexamethasone to prevent acute vomiting and nausea, the combination of dexamethasone and aprepitant is suggested to prevent delayed nausea and vomiting, on the basis of its greater efficacy compared with dexamethasone alone. <u>Prevention of acute nausea and vomiting induced by moderately emetogenic chemotherapy</u> • A combination of palonosetron plus dexamethasone is recommended as standard prophylaxis for non-anthracycline/cyclophosphamide MEC regimens. • To prevent acute nausea and vomiting in women receiving a combination of anthracycline plus cyclophosphamide, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended. • If aprepitant is not available, women receiving a combination of anthracycline plus cyclophosphamide should receive a combination of palonosetron plus dexamethasone. • There are no differences in tolerability between the 5-HT_3 receptor antagonists used for the prophylaxis of acute emesis induced by moderately emetogenic chemotherapy. • There is no difference in the efficacy of oral or intravenous administration of a 5-HT_3 receptor antagonist. <u>Prevention of delayed nausea and vomiting induced by moderately emetogenic chemotherapy</u> • Patients who receive moderately emetogenic chemotherapy known to be associated with a significant incidence of delayed nausea and vomiting should receive antiemetic prophylaxis for delayed emesis. • In patients receiving chemotherapy of moderate emetic risk that does not include a combination of anthracycline plus cyclophosphamide and in which palonosetron is recommended, multiday oral dexamethasone treatment is the preferred treatment for the prevention of delayed nausea and vomiting. • Aprepitant should be used for the prevention of delayed emesis induced by moderately emetogenic chemotherapy in breast cancer patients receiving a combination of anthracycline plus cyclophosphamide. <u>Prevention of acute and delayed nausea and vomiting induced by chemotherapy with low and minimal emetogenic potential</u> • Patients with no prior history of nausea and vomiting who receive chemotherapy of low emetic potential as an intermittent schedule should be treated with a single antiemetic agent such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, as prophylaxis. • For patients receiving minimally emetogenic chemotherapy, no antiemetic treatment should be routinely administered before chemotherapy in patients without a history of nausea and vomiting. • No prophylactic treatment should be administered for the prevention of delayed emesis induced by low or minimally emetogenic 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: prophylaxis or rescue with a 5-HT_3 receptor antagonist is recommended. • Minimal emetic risk: rescue with dopamine receptor antagonists or 5-HT_3

Clinical Guideline	Recommendation(s)
	receptor antagonists.
Society for Ambulatory Anesthesia: **Consensus Guidelines for the Management of Postoperative Nausea and Vomiting (2014)**[13] .	Prevention of postoperative nausea and vomiting (PONV) in adults • The efficacy of dexamethasone 4 mg intravenous, ondansetron 4 mg intravenous and droperidol 1.25 mg intravenous for the prevention of postoperative nausea and vomiting appears to be similar. • Ondansetron, dolasetron, granisetron, and tropisetron are most effective in the prophylaxis of PONV when given at the end of surgery, although; some data on dolasetron suggest timing may have little effect on efficacy. Palonosetron is typically given at the start of surgery. • Aprepitant is similar to ondansetron in achieving complete response (no vomiting and no use of rescue antiemetic) for 24 hours after surgery. However, aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 and 48 hours after surgery and in reducing nausea severity in the first 48 hours after surgery. It also has a greater antiemetic effect compared with ondansetron. • Systematic reviews have demonstrated that 5-HT_3 receptor antagonists in combination with dexamethasone or droperidol are more effective than monotherapy with any of the agents. • Droperidol in combination with dexamethasone is more effective than either agent as monotherapy. • Combinations that include metoclopramide have not been shown to be more effective than monotherapy. Prevention of postoperative nausea and vomiting in children • Children are at increased risk of postoperative nausea and vomiting compared to adults. • Children at moderate to high risk for postoperative nausea and vomiting should receive combination therapy with two to three prophylactic agents from different classes. • Ondansetron has been studied extensively in pediatric patients and is approved for patients as young one month of age. • There is now good evidence to suggest that 5-HT_3 antagonists and dexamethasone are the most effective antiemetics in the prophylaxis of pediatric postoperative nausea Treatment of PONV in patients who failed or did not receive prophylaxis • If prophylactic therapy fails, an agent from a different pharmacologic class should be selected for treatment. • If no prophylactic therapy was given, first-line treatment should include a low-dose 5-HT_3 antagonist.
American Society of Clinical Oncology: **Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update (2011)**[14] .	High emetic risk The three-drug combination of an NK1 receptor antagonist (days one to three for aprepitant; day one only for fosaprepitant), a 5-HT_3 receptor antagonist (day one only), and dexamethasone (days one to three or one to four) is recommended for patients receiving highly emetogenic chemotherapy. Moderate emetic risk The two-drug combination of palonosetron (day one only) and dexamethasone (days one to three) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT_3 serotonin receptor antagonist, preferably granisetron or ondansetron. Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT_3 antagonists is appropriate.

Clinical Guideline	Recommendation(s)
	Low emetic risk • A single 8-mg dose of dexamethasone before chemotherapy is suggested. No routine preventive use of antiemetics for delayed emesis is suggested. Minimal emetic risk • No antiemetic should be administered routinely before or after chemotherapy. • Prochlorperazine may be used in patients receiving minimal emetic risk radiation therapy on an as needed basis. Combination chemotherapy • Patients should be administered antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk. Adjunctive drugs • Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics. Pediatric patients • The combination of a 5-HT_3 antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Because of variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT_3 antagonists than those used in adults may be required for antiemetic protection. Multiple consecutive days of chemotherapy • It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy and for two days after, if appropriate. • To prevent vomiting caused by chemotherapy of high or moderate emetic risk, there is no group of patients for whom cannabinoids are appropriate as first-choice antiemetics. These agents should be reserved for patients intolerant of or refractory to 5-HT3 serotonin receptor antagonists, dexamethasone, and aprepitant. Special emetic problems: • For radiation-induced emesis, patients should receive a 5-HT_3 antagonist before each fraction and for at least 24 hours after completion of radiotherapy. Patients should also receive a 5-day course of dexamethasone during fractions one to five. • For patients with emesis or nausea despite optimal prophylaxis, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT_3 antagonist or adding a dopamine antagonist to the regimen. • For anticipatory nausea and vomiting, use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested.
American Gastroenterological Association: **Medical Position Statement of the Use of Gastrointestinal**	Nausea and vomiting • Metoclopramide, prochlorperazine, promethazine, trimethobenzamide, and ondansetron are considered low-risk drugs based on studies in pregnant women and can be used for nausea and vomiting and for hyperemesis gravidarum. • Granisetron and dolasetron have not been studied in human pregnancies.

Clinical Guideline	Recommendation(s)
Medications in Pregnancy (2006)[15]	
American College of Obstetricians and Gynecologists: **Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy (2015)[16]**	General considerations • Taking a multivitamin at the time of conception may decrease the severity of nausea and vomiting of pregnancy. • The standard recommendation to take prenatal vitamins for three months before conception may reduce the incidence and severity of nausea and vomiting of pregnancy. • Treatment of nausea and vomiting of pregnancy with vitamin B_6 or vitamin B_6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy. • In patients with hyperemesis gravidarum who also have suppressed thyroid-stimulating hormone levels, treatment of hyperthyroidism should not be undertaken without evidence (such as goiter, thyroid autoantibodies, or both) of intrinsic thyroid disease. • Treatment of nausea and vomiting of pregnancy with ginger has shown beneficial effects and can be considered as a nonpharmacologic option. • Early treatment of nausea and vomiting of pregnancy is recommended to prevent progression to hyperemesis gravidarum. • 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 treatment of last resort. • 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, especially thiamine, should be included in the therapy when prolonged vomiting is present. Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as 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. Evidence is limited on the safety or efficacy of the 5-HT_3 receptor inhibitors (e.g., ondansetron) for nausea and vomiting of pregnancy; however, because of their effectiveness in reducing chemotherapy-induced emesis, their use appears to be increasing.
Society of Obstetricians and Gynaecologists of Canada: **Clinical Practice Guideline: Management of Nausea and Vomiting of Pregnancy (2002)[17]** According to The Society of Obstetricians and Gynaecologists of Canada, this guideline has recently been reviewed and an updated version will be soon be published - this version should be used with discretion as some	General considerations • Dietary and lifestyle changes should be liberally encouraged, and women should be counseled to eat whatever appeals to them. • Alternative therapies, such as ginger supplementation, acupuncture, and acupressure, may be beneficial. • A doxylamine and pyridoxine combination should be the standard of care, since it has the greatest evidence to support its efficacy and safety. • H_1 receptor antagonists should be considered in the management of acute or breakthrough episodes of nausea and vomiting of pregnancy. • Pyridoxine monotherapy supplementation may be considered as an adjuvant measure. • Phenothiazines are safe and effective for severe nausea and vomiting of pregnancy. • Metoclopramide is safe to be used for management of nausea and vomiting of pregnancy, although evidence for efficacy is more limited. • Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. • Limited evidence is available on the effectiveness of ondansetron for the treatment of nausea and vomiting of pregnancy. Intravenous ondansetron did

Clinical Guideline	Recommendation(s)

information has been deemed to be outdated	not demonstrate a therapeutic benefit over promethazine in one trial for the treatment of hyperemesis gravidarum.
	• In general, 5-HT_3 antagonists may be safe to use during the first trimester, but the data are scant. Because of their limited effectiveness, they should not be advocated for first-line use until agents with established safety and effectiveness have been tried and have failed.
	
	<u>Algorithm for the treatment of nausea and vomiting of pregnancy</u>
	• Step 1: Give 10 mg of doxylamine combined with 10 mg of pyridoxine, up to four tablets per day.
	• Step 2: Add dimenhydrinate 50 to 100 mg every four to six hours (orally or rectally) or promethazine 5 to 10 mg every six to eight hours (orally or rectally).
	• Step 3 (no dehydration): Add any of the following (in order of proven fetal safety):
	  o Chlorpromazine 10 to 25 mg every four to six hours (orally or intramuscularly) or 50 to 100 mg every four to six hours (rectally).
	  o Prochlorperazine 5 to10 mg every six to eight hours (intramuscularly, orally or rectally).
	  o Promethazine 12.5 to 25 mg every four to six hours (intramuscularly or orally).
	  o Metoclopramide 5 to 10 mg every eight hours (intramuscularly or orally).
	  o Ondansetron 8 mg every 12 hours orally.
	• Step 4 (dehydration): Start rehydration treatment:
	  o Intravenous fluid replacement.
	  o Multivitamin intravenous supplementation.
	  o Dimenhydrinate 50 mg intravenous every four to six hours.
	• Step 5: Add any of the following (in order of proven fetal safety):
	  o Chlorpromazine 25 to 50 mg every four to six hours (intravenous).
	  o Prochlorperazine 5 to 10 mg every six to eight hours (intravenous).
	  o Promethazine 12.5 to 25 mg every four to six hours (intravenous).
	  o Metoclopramide 5 to 10 mg every eight hours (intravenous).
	• Step 6: Add methylprednisolone 15 to 20 mg every eight hours (intravenous) or ondansetron 8 mg every 12 hours (intravenous) or 1 mg/hour continuously up to 24 hours.
	• At any time, add any or all of the following:
	  o Pyridoxine 25 mg every eight hours.
	  o Ginger 250 mg every six hours.
	  o P6 acupressure/acupuncture.
	• At any step, consider parenteral nutrition when indicated.

American Gastroenterological Association: **Technical Review: Nausea and Vomiting (2001)**[18]	• In clinical studies, dimenhydrinate and meclizine, among others, have shown efficacy in the prevention and treatment of motion sickness. • Prochlorperazine may be used to treat more severe nausea and vomiting due to vertigo or motion sickness. • Trimethobenzamide has been used in the treatment of moderate to severe nausea and vomiting in a variety of clinical contexts. • Scopolamine is used principally for prophylaxis and treatment of motion sickness. • In pregnant patients with more severe symptoms and hyperemesis, hospitalization, fluid and electrolyte replacement, thiamine supplementation, and administration of antiemetics including antihistamines, such as meclizine may be used. For more severe cases of hyperemesis gravidarum, parenteral prochlorperazine may be used. • For the prevention of acute post chemotherapy- and radiation-related nausea

Clinical Guideline	Recommendation(s)
	and vomiting, the combination of a 5-HT_3 receptor antagonist and dexamethasone is the preferred option. • Scopolamine has been shown to have mild efficacy against cytotoxic chemotherapy-related nausea and vomiting and may have a role as adjunctive therapy in this context. • 5-HT_3 antagonists have been shown to be more effective than either placebo or other agents such as prochlorperazine in the prevention of radiotherapy-induced nausea and vomiting, as well as in the treatment of nausea and vomiting that is unrelated to chemotherapy and radiation therapy in cancer patients. • The various 5-HT_3 antagonists appear to be of similar efficacy and have a comparable incidence of side effects. • For postoperative nausea and vomiting, the use of a 5-HT_3 receptor antagonist and droperidol have been proven to be the most effective compared to placebo and with other agents in large randomized trials. Comparisons between the various 5-HT_3 antagonists or between members of this class of compounds and droperidol have generally found similar efficacies for all. • Dronabinol is available for use in the United States and is indicated for anorexia resulting in weight loss among patients with the acquired immunodeficiency syndrome and for refractory chemotherapy-related nausea and vomiting.
American Gastroenterological Association: **American Gastroenterological Association Medical Position Statement: Nausea and Vomiting (2001)**[19]	• Severe intractable nausea and vomiting episodes require parenteral administration of such agents as phenothiazines • Motion sickness and related disorders are treated primarily with histamine H1 and cholinergic receptor antagonists (e.g., scopolamine). • The prevention and treatment of both acute cancer chemotherapy-related and postoperative nausea and vomiting have come to be based largely on the use of 5-HT_3 receptor antagonists.

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 Single Entity Miscellaneous Antiemetics[1-9]

Indication	Aprepitant	Dronabinol	Fosaprepitant	Nabilone	Scopolamine
Anorexia					
Anorexia associated with weight loss in patients with acquired immunodeficiency syndrome		✔			
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, when used in combination with other antiemetic agents	✔		✔		
Prevention of nausea and vomiting	✔		✔		

Indication	Aprepitant	Dronabinol	Fosaprepitant	Nabilone	Scopolamine
associated with initial and repeat courses of moderately emetogenic cancer chemotherapy when used in combination with other antiemetic agents					
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	✔				✔ †
Miscellaneous					
Anticholinergic central-nervous system depressant					✔ ‡
Symptomatic treatment of postencephalitic parkinsonism and paralysis agitans					✔ ‡
Spastic states					✔ ‡
Substitute for atropine in ophthalmology					✔ ‡

‡Oral formulation.
†Transdermal formulation.

Table 4. FDA-Approved Indications for the Combination Miscellaneous Antiemetics[1-9]

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	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antiemetics are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Miscellaneous Antiemetics[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Aprepitant	60 to 65	≥95	Liver (extensive)	Feces	9 to 13
Dronabinol	10 to 20	97	Liver (extensive)	Renal (10 to 15) Feces (50)	25 to 36
Fosaprepitant	100	≥95	Liver (extensive)	Renal (57) Feces (45)	9 to 13
Nabilone	100	Not reported	Liver (extensive)	Renal (22 to 24) Feces (60 to 67)	2
Scopolamine	Not reported	Not reported	Liver	Renal (<5)	9.5
Combination Products					
Netupitant and Palonosetron	N: not reported P: 97	N >99.5 P: 62	N: Liver (extensive);	N: Renal (4.7), Feces (86.5);	N: 80 P: 48

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
			P: Liver (partial)	P: Renal (85 to 93), Feces (5 to 8)	

N= Netupitant, P= Palonosetron

V. Drug Interactions

Significant drug interactions with the miscellaneous antiemetics are listed in Table 6.

Table 6. Significant Drug Interactions with the Miscellaneous Antiemetics[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Aprepitant, fosaprepitant	1	Cisapride	Aprepitant may inhibit the metabolism of cisapride, increasing the risk of life-threatening cardiac arrhythmias.
Aprepitant	1	Ibrutinib	Aprepitant may inhibit the CYP3A4 metabolism of ibrutinib, increasing the pharmacologic effects and risk of toxicity (e.g., hemorrhage, renal toxicity) of ibrutinib.
Aprepitant, fosaprepitant	1	Pimozide	Aprepitant may inhibit the metabolism of pimozide, increasing the risk of life-threatening cardiac arrhythmias.
Aprepitant	1	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.
5-HT_3 receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron)	2	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.
Aprepitant	2	Corticosteroids	Aprepitant may inhibit the 3A4 isoenzyme and result in elevated plasma levels of dexamethasone, hydrocortisone, and methylprednisolone.
Aprepitant	2	Ranolazine	Aprepitant may inhibit the 3A4 isoenzyme, decreasing the metabolism of ranolazine. Ranolazine toxicity may occur, including QT-interval prolongation.
Scopolamine	2	Phenothiazines	Therapeutic effects of phenothiazines may be decreased by centrally-acting anticholinergics. Anticholinergics likely antagonize phenothiazines by direct CNS pathways involving cholinergic mechanisms.
Scopolamine	2	Haloperidol	Worsening of schizophrenic symptoms, decreased serum concentration of haloperidol, and development of tardive dyskinesia were reported when anticholinergic agents were used with haloperidol. The mechanism is unknown.
Scopolamine	2	Potassium	Anticholinergics may slow GI motility,

Generic Name(s)	Significance Level	Interaction	Mechanism
		chloride	delaying potassium chloride tablet passage through the GI tract

Significance level 1=major severity, significance level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antiemetics are listed in Tables 7 and 8.

Table 7. Adverse Drug Events (%) Reported with the Single Entity Miscellaneous Antiemetics[1-9]

Adverse Events	Aprepitant	Dronabinol	Fosaprepitant	Nabilone	Scopolamine
Cardiovascular					
Arrhythmia	-	-	-	<1	-
Bradycardia	≤4	-	<1	-	-
Chest discomfort/pain	-	-	<1	<1	-
Hypertension	>0.5	-	-	<1	-
Hypotension	≤6	✔	<1	8	-
Myocardial infarction	>0.5	-	-	-	-
Orthostatic hypotension	-	-	-	<1	✔ †
Palpitation	>0.5	>1	<1	<1	✔ †
Syncope	-	-	-	<1	-
Tachycardia	>0.5	>1	-	<1	✔ †
Central Nervous System					
Amnesia	-	>1	-	-	-
Anxiety	>0.5	>1	<1	<1	-
Apathy	-	-	-	<1	-
Ataxia	-	>1	-	13 to 14	✔ †
Cerebrovascular accident	-	-	-	<1	-
Chills	-	-	<1	-	-
Cognitive disorder	-	-	<1	-	-
Concentration decreased	-	-	-	12	-
Confusion	>0.5	✔	-	-	✔ †
Delusional disorder	-	-	-	-	✔ †
Depersonalization	-	>1	-	2	-
Depression	>0.5	✔	-	14	-
Disorientation	>0.5	-	<1	2	✔ †
Dizziness	≤7	3 to 10	<1	59	✔ †
Dream abnormality	-	-	<1	-	-
Drowsiness	-	-	-	52 to 66	✔ †, 67‡
Dysphoric mood	-	-	-	9	-
Emotional disorder	-	-	-	<1	-
Euphoria	-	8 to 24	<1	11 to 38	-
Fever	-	-	-	<1	-
Gait disturbance	-	-	<1	-	-
Hallucinations	-	>1	-	<1	✔ †
Headache	-	-	2	6 to 7	✔ †
Hyperactivity	-	-	-	<1	-
Insomnia	-	-	-	11	-
Irritation	-	-	-	<1	-
Lethargy	-	-	<1	-	-
Lightheadedness	-	-	-	<1	-
Malaise/fatigue	≤18	✔	1 to 3	<1	✔ †
Memory lapse	-	-	-	<1	✔ †

Adverse Events	Aprepitant	Dronabinol	Fosaprepitant	Nabilone	Scopolamine
Mood swings	-	-	-	<1	-
Nervousness	-	-	-	<1	-
Neurosis	-	-	-	<1	-
Nightmares	-	✔	-	-	-
Numbness	-	-	-	<1	-
Panic	-	-	-	<1	-
Paranoia	-	3 to 10	-	<1	✔ †
Paresthesia	-	-	-	<1	-
Peripheral neuropathy	>0.5	-	-	-	-
Psychotic disorder	-	-	-	<1	✔ †
Sedation	-	-	-	<1	-
Seizure	-	✔	-	<1	-
Somnolence	-	3 to 10	<1	-	-
Speech disorder	-	-	-	<1	-
Stupor	-	-	-	<1	-
Syncope	>0.5	-	-	-	-
Tremor	>0.5	-	-	<1	-
Vertigo	-	-	-	52 to 59	-
Dermatological					
Acne	>0.5	-	<1	-	-
Angioedema	-	-	<1	-	-
Contact dermatitis	-	-	-	-	✔ ‡
Erythema	-	-	<1	-	-
Flushing	-	>1	<1	-	✔ †
Hyperhidrosis	-	-	<1	-	-
Injection site induration	-	-	<1	-	-
Injection site pain	-	-	3	-	-
Oily skin	-	-	<1	-	-
Photosensitivity	-	-	<1	<1	-
Pruritus	>0.5	-	<1	<1	-
Rash	>0.5	-	<1	-	-
Skin lesion	-	-	<1	-	-
Stevens-Johnson Syndrome	>0.5	-	<1	-	-
Urticaria	>0.5	-	<1	-	-
Gastrointestinal					
Abdominal pain/discomfort	≤5	3 to 10	<1	<1	-
Abdominal distention	-	-	<1	-	-
Acid reflux	>0.5	-	<1	-	-
Anorexia	-	-	2	8	-
Appetite decreased	>0.5	-	-	-	-
Constipation	9 to 10	-	2	<1	✔ †
Diarrhea	≤10	✔	1	<1	-
Duodenal ulcer	>0.5	-	<1	-	-
Dyspepsia	≤6	-	2	<1	-
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	3 to 10	<1	4	✔ †
Neutropenic colitis	-	-	<1	-	-

Adverse Events	Aprepitant	Dronabinol	Fosaprepitant	Nabilone	Scopolamine
Obstipation	>0.5	-	<1	-	-
Stomatitis	3	-	<1	-	-
Taste disturbance	>0.5	-	<1	<1	-
Vomiting	-	3 to 10	<1	-	✔ †
Xerostomia	>0.5	-	<1	22 to 36	✔ †‡
Genitourinary					
Dysuria	>0.5	-	<1	-	-
Erythrocyturia	>0.5	-	-	-	-
Glucosuria	>0.5	-	-	-	-
Hematuria	-	-	<1	-	-
Leukocyturia	>0.5	-	-	-	-
Pelvic pain	>0.5	-	-	-	-
Pollakiuria	-	-	<1	-	-
Polyuria	-	-	<1	<1	-
Proteinuria	7	-	-	-	-
Renal insufficiency	>0.5	-	-	-	-
Urinary retention	-	-	-	<1	✔ †
Urinary tract infection	>0.5	-	-	-	-
Hematologic					
Anemia	>0.5	-	<1	<1	-
Hemoglobin decreased	-	-	✔	<1	-
Leukocytosis	>0.5	-	-	-	-
Leukopenia	-	-	-	<1	-
Neutropenia	>0.5	-	<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					
Akathisia	-	-	-	<1	-
Arthralgia	>0.5	-	-	-	-
Back pain	>0.5	-	-	-	-
Dysarthria	>0.5	-	-	-	-
Dystonia	-	-	-	<1	-
Muscle cramp	-	-	<1	-	-
Musculoskeletal pain	>0.5	-	-	-	-
Myalgia	>0.5	✔	<1	-	-
Weakness	≤18	>1	3	8	✔ †
Respiratory					
Cough	>0.5	-	<1	<1	-
Dyspnea	>0.5	-	-	<1	-
Hypoxia	>0.5	-	-	-	-
Pharyngitis	>0.5	-	<1	<1	-
Pharyngolaryngeal pain	>0.5	-	-	-	-
Pneumonia	>0.5	-	-	-	-

Adverse Events	Aprepitant	Dronabinol	Fosaprepitant	Nabilone	Scopolamine
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	-	-	<1	-
Special Senses					
Amblyopia	-	-	-	<1	-
Blurred vision	-	-	-	-	✔ †
Conjunctivitis	>0.5	✔	<1	-	-
Miosis	>0.5	-	-	-	-
Mydriasis	-	-	-	-	✔ †
Pupil dilation	-	-	-	<1	-
Tinnitus	-	✔	<1	<1	-
Visual acuity decreased	>0.5	-	-	-	-
Visual disturbance	-	✔	-	13	-
Other					
Allergic reaction	-	-	-	<1	-
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	-	-	<1	✔ †
Edema	>0.5	-	<1	-	-
Epistaxis	-	-	-	<1	-
Flushing	>0.5	-	<1	<1	-
Herpes simplex	>0.5	-	-	-	-
Hot flash	-	-	<1	<1	-
Hypersensitivity	>0.5	-	<1	-	-
Hypoesthesia	>0.5	-	-	-	-
Hypothermia	>0.5	-	-	-	-
Hypovolemia	>0.5	-	-	-	-
Infection	-	-	-	<1	-
Pain	>0.5	-	-	<1	-
Polydipsia	-	-	<1	-	-
Septic shock	>0.5	-	-	-	-
Thrombophlebitis	-	-	<1	-	-
Vocal disturbance	>0.5	-	-	-	-
Weight gain	-	-	<1	-	-
Weight loss	>0.5	-	<1	-	-

†Oral formulation.
‡Transdermal formulation.
✔ Percent not specified.
- Event not reported.

Table 8. Adverse Drug Events (%) Reported with the Combination Miscellaneous Antiemetics[1-9]

Adverse Events	Netupitant and Palonosetron
Central Nervous System	
Fatigue	4 to 7

Adverse Events	Netupitant and Palonosetron
Headache	9
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 miscellaneous antiemetics are listed in Table 9.

Table 9. Usual Dosing Regimens for the Miscellaneous Antiemetics[1-9]

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 PONV: Capsule: 40 mg orally within three hours prior to induction of anesthesia	CINV in patients 12 years of age and older and patients <12 years of age who weigh ≥30 kg: Capsule: the pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults.	Capsule: 40 mg 80 mg 125 mg Capsule dose pack: 125-80 mg
Dronabinol	Anorexia: 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	CINV: The pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults.	Capsule: 2.5 mg 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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		
Fosaprepitant	CINV: Injection: highly emetogenic chemotherapy: one day therapy, 150 mg administered intravenously on day one only as an infusion over 20 to 30 minutes initiated approximately 30 minutes prior to chemotherapy with no aprepitant capsules administered on days two and three; three day therapy, 115 mg administered on day one only as an infusion over 15 minutes initiated 30 minutes prior to chemotherapy with aprepitant 80 mg capsules administered on days two and three; moderate and highly emetogenic chemotherapy, three day therapy, 115 mg administered on day one only as an infusion over 15 minutes initiated 30 minutes prior to chemotherapy with aprepitant 80 mg capsules administered on days two and three Should be administered in conjunction with a corticosteroid and a 5-HT3 antagonist as specified in the package labeling.	Safety and efficacy in children have not been established.	Injection: 150 mg
Nabilone	CINV: Capsule: usual adult dosage is 1 or 2 mg two times a day, on the day of chemotherapy, the initial dose should be given one to three hours before the chemotherapeutic agent is administered, to minimize side effects, it is recommended that the lower starting dose be used and that the dose be increased as necessary, a dose of 1 or 2 mg the night before may be useful, the maximum	Safety and effectiveness have not been established in patients younger than 18 years of age.	Capsule: 1 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	recommended daily dose is 6 mg given in divided doses three times a day, may be administered two or three times a day during the entire course of each cycle of chemotherapy and, if needed, for 48 hours after the last dose of each cycle of chemotherapy		
Scopolamine	Anticholinergic central nervous system depressant; postencephalitic parkinsonism; spastic states; ophthalmology: Tablet: 0.4 to 0.8 mg Motion sickness: Transdermal patch: apply one patch behind one ear at least four hours before antiemetic effect is required 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.	Tablet: 0.4 mg Transdermal patch: 1.5 mg-72 hours
Combination Products			
Netupitant and palonosetron	CINV: Capsule: one capsule approximately one hour prior to initiation of chemotherapy on day one 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

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 10.

Table 10. 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.[20] (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.[21] (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.[22] (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.[23] (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)				
Rapoport et al.[24] (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 chemotherapy	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%.
Yeo et al.[25] (2009) Aprepitant 125 mg	DB, PC, RCT Breast cancer patients ≥18 years	N=127 120 hours	Primary: Complete response (no vomiting and no rescue therapy	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%,

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	of age who were naïve to chemotherapy and were receiving a moderately emetogenic regimen (doxorubicin and cyclophosphamide)		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	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.[26] (2005) Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus	DB, MC, PG, RCT Patients with breast carcinoma who were naïve to emetogenic chemotherapy and treated with cyclophosphamide	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-	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

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 or in combination with doxorubicin or epirubicin		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	chemotherapy over multiple chemotherapy cycles. Secondary: Not reported
Warr et al.[27] (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,	DB, PG, RCT Patients with breast cancer who were naïve to emetogenic chemotherapy and who were treated with a regimen of cyclophosphamide alone, cyclophosphamide plus doxorubicin, or cyclophosphamide plus epirubicin	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 chemotherapy in cycle one Secondary: Proportion 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. The aprepitant regimen was more effective than the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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			patients with an average item score higher than 6 of 7 on the Functional Living Index-Emesis questionnaire	
Gralla et al.[28] (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 mg on day four vs ondansetron 32 mg	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
IV and dexamethasone 20 mg orally on day one; dexamethasone 8 mg twice daily on days two to four				
De Wit et al.[29] (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
Poli-Bigelli et al.[30] (2003) Aprepitant 125 mg, ondansetron	DB, MC, PG, RCT Patients with cancer who were scheduled to receive treatment	N=1,091 120 hours	Primary: Complete response (no emesis and no rescue therapy) during the five-day	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	with high-dose cisplatin chemotherapy		period post cisplatin therapy Secondary: Not reported	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.[31] (2003) Aprepitant plus ondansetron and dexamethasone on day one; aprepitant and dexamethasone on days two to three; dexamethasone on day four vs	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: Not reported	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. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron and dexamethasone on day one; dexamethasone on days two to four				
Martin et al.[32] (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.[33] (2015) Aprepitant (125 mg for ages 12 to 17 years; 3.0 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on	AC, DB, PG, RCT Patients 6 months to 17 years of age with documented malignancy scheduled to receive at least moderately emetic chemotherapy	N=302 Up to 5 cycles	Primary: Complete response (defined as no vomiting, no retching, and no use of rescue medication) during the delayed phase Secondary: Complete response	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: 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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)			during the acute and overall phases, safety	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.[34] (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	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	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
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			Secondary: Not reported	
Schmitt et al.[35] (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	DB, PC, PG, RCT Patients ≥18 yearsof 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg orally on day one and 4 mg orally on days two to three)				
Nishimura et al.[36] (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.[37] (2009) Aprepitant 125 mg prior to chemotherapy,	PRO Adult patients undergoing multiple-day chemotherapy of	N=78 Variable duration	Primary: Complete response (no vomiting or use of rescue therapy) at the end of the treatment	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
then 80 mg on days two to three, plus granisetron 1 mg on day one, plus dexamethasone 8 mg on days one to three	moderate or high emetogenic potential		cycle Secondary: Complete response in the acute and delayed phase of the treatment cycle	During the acute and delayed phases, the complete response in patients 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.[38] (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.[39] (2013) Aprepitant 125 mg 1 hour before chemotherapy on day 1, and 80 mg	OS, PRO Patients were consecutively included if they received 3-day cisplatin-based (25	N=41 8 days	Primary: Complete response in the overall phase of CINV Secondary: Complete response	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily on the 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	mg/m^2/day) chemotherapy and had never treated with aprepitant before		in the acute and delayed phases, safety and the severity of nausea	achieved in 63.4, 78.0 and 58.5% of patients respectively. 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.[40] (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–	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
			120 following chemotherapy); delayed complete control (no emesis, no nausea, no rescue antiemetics during hours 24–120 following chemotherapy); and safety	
Longo et al.[41] (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	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
			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	
Herrington et al.[42] (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.[43] (2011)	AC, DB, RCT	N=2,322	Primary: Complete response	Primary: In the overall phase, 71.9% (95% CI, 69.1 to 74.5) of patients in the

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	Male and female 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	Single dose or 3 day regimen	in the overall 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	fosaprepitant group reported Complete response compared to 72.3% (95% 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).
Jin et al.[44] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Roila et al.[45] (2014) Aprepitant 80 mg once per day on days two and three vs dexamethasone 4 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.	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 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	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).
Moon et al.[46] (2014)	DB, RCT	N=93	Primary: Complete response	Primary: Aprepitant was non-inferior to palonosetron in terms of complete response

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aprepitant 40 mg by mouth vs palonosetron 0.075 mg IV	Patients 20 to 60 years of age who were scheduled to undergo laparoscopic gynecologic surgery under general anaesthesia	48 hours	(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 pain, consumption of intravenous patient-controlled analgesia, and use of rescue analgesics	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 differences were observed in the incidence and number of additional fentanyl administrations between the two groups.
Saito et al.[47] (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	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg) on day 2, and dexamethasone (8 mg) on day 3			(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	significantly higher in the fosaprepitant group. The percentages of patients with no rescue therapy in the overall phase also did not differ significantly.
Tsutsumi et al.[48] (2014) Fosaprepitant 150 mg IV vs ondansetron 4 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; 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 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
Meiri et al.[49] (2007) <u>Day two (fixed dose)</u> Dronabinol 2.5 mg by mouth four times daily	DB, PC, PG, RCT Patients ≥18 years of age with malignancy that did not involve the bone marrow and be undergoing	N=64 5 days	Primary: Total response two to five days after moderately to highly emetogenic chemotherapy (no vomiting and/or retching, intensity	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 ondansetron 4 to 8 mg by mouth twice daily vs dronabinol 2.5 to 5 mg by mouth four times daily plus	chemotherapy including a moderately to highly emetogenic regimen		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	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 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
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.				
Lane et al.[50] (1991) Dronabinol 10 mg every 6 hours (group 1) vs prochlorperazine 10 mg every 6 hours (group 2) vs	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 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 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
dronabinol and prochlorperazine, each 10 mg every 6 hours (group 3)				
Machado et al.[51] (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.[52] (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.[53] (1981)	DB, PRO, RCT Patients receiving	N=80 Two	Primary: Relief of nausea and vomiting;	Primary: Sixty patients (75%) reported nabilone to be more effective than prochlorperazine for relief of nausea and vomiting. Forty-six patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nabilone vs prochlorperazine	chemotherapy	consecutive chemotherapy cycles	adverse events Secondary: Not reported	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
Tramer et al.[54] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aapro et al.[55] (2014) NEPA 08-18 Netupitant-palonosetron (300 mg-0.5 mg) plus dexamethasone 12 mg for one dose vs palonosetron 0.5 mg plus dexamethasone 20 mg for one dose	DB, DD, MC, PG, RCT Patients ≥18 years of age who were chemotherapy naïve 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	N=1455 One cycle	Primary: Complete response (no emetic episode and no rescue medication) in preventing nausea 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	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: 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.[56] (2014) NEPA 07-07	DB, DD, PG, MC, RCT	N=694 Multiple	Primary: Compelte response during the overall	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Netupitant-palonosetron 100 mg-0.5 mg for one dose vs 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	Patients ≥18 years of age with histologically or cytologically confirmed malignant disease featuring solid tumor(s), 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	cycles	phase period Secondary: Complete response during the acute and delayed phases; 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	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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doses based on study drug assigned)				
Gralla et al.[57] (2014) NEPA 10-29 Netupitant-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)	DB, DD, MC, PG, RCT Patients ≥18 years of age who were 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	N=413 Multiple cycles (total of 1961)	Primary: Safety (adverse events, vital sign measurements, laboratory tests 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	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%). 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).
Motion Sickness				
Spinks et al.[58] (2011)	MA Patients with	N=1,025 (14 trials)	Primary: Prevention and treatment of	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Scopolamine transdermal patch, tablet, capsule, oral solution or IV vs placebo, antihistamines (cinnarizine, dimenhydrinate, meclizine, promethazine) and other drugs (calcium channel antagonists, lorazepam, methscopolamine) vs combination of scopolamine with cyclizine, ephedrine or placebo	motion sickness	Duration varied	clinically defined motion sickness Secondary: Task ability, psychological tests and adverse effects	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 (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				scopolamine in the management of established symptoms of motion sickness.
Dahl et al.[59] (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
Postoperative Nausea and Vomiting (PONV)				
Sinha et al.[60] (2014) Aprepitant 80 mg vs placebo All patients received intravenous ondansetron (4 mg) intraoperatively.	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.
Green et al.[61] (2012) Aprepitant 40 mg	DB, RCT Patients >18 years of age, ASA I–III,	N=120 24 hours	Primary: Complete response Secondary:	Primary: The aprepitant alone and aprepitant with scopolamine did not differ in complete responses (63 vs 57%; P=0.57).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aprepitant 40 mg and scopolamine transdermal patch	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		Incidences of nausea, vomiting, their composite, and the need for rescue medication	Secondary: Incidences of nausea, vomiting, their composite, and the need for rescue medication, all showed no statistical difference.
Hartrick et al.[62] (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.[63] (2007) Aprepitant 40 mg by mouth vs aprepitant 125 mg mouth	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-	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	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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ondansetron 4 mg IV	agent-based general anesthesia including nitrous oxide		Secondary: No vomiting in the first 48 hours after surgery	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.[64] (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).
Layeeque et al.[65] (2006) Dronabinol 5 mg as prophylaxis and prochlorperazine 25 mg rectal suppository after anesthesia vs standard preoperative care (which excludes prophylactic use of	RETRO Patients undergoing surgery	N=242 Variable duration	Primary: Rate and severity of PONV Secondary: Not reported	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 standard preoperative care. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
antiemetics)				
Jones et al.[66] (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.[67] (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: Not reported	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: Not reported
Gan et al.[68] (2009) Scopolamine 1.5 mg transdermal patch applied two	DB, MC, RCT Adult female patients (ASA I or III status) at high risk for PONV who	N=620 24 hours	Primary: Complete antiemetic response through 24 hours postoperatively	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	were undergoing outpatient gynecological laparoscopy, laparoscopic cholecystectomy, or breast augmentation surgery with an anticipated duration of one to three hours		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	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.[69] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron 4 mg 30 minutes prior to the end of surgery				placebo group. Secondary: Not reported
Tarkkila et al.[70] (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.[71] (1986) Meclizine by mouth for one week vs scopolamine transdermal for one week vs	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				

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
Single Entity Agents				
Aprepitant	capsule, capsule dose pack	Emend®	$$$$$	N/A
Dronabinol	capsule	Marinol®*	$$$$$	$$$$$
Fosaprepitant	injection	Emend®	$$$$$	N/A
Nabilone	capsule	Cesamet®	$$$$$	N/A
Scopolamine	transdermal patch	Transderm-Scop®	$$$$$	N/A
Combination Products				
Netupitant and palonosetron	capsule	Akynzeo®	$$$$$	N/A

*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.[1-10] Dronabinol is the only agent that is 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 NK_1 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 NK_1 antagonists to prevent delayed nausea and vomiting when administering highly emetogenic or anthracycline/cyclophosphamide chemotherapy regimens.[11,12,14]

Dronabinol and nabilone are approved for the treatment of the nausea and vomiting associated with chemotherapy in patients who have failed to respond to conventional antiemetic treatments.[5-7] They are recommended as one of several options for the treatment of breakthrough nausea and vomiting.[11] Patients treated with nabilone can be expected to experience disturbing psychotomimetic reactions that are not observed with other antiemetic agents.[7] Nabilone is not intended to be used on as needed basis or as first-line therapy.[7] It is a Schedule II controlled substance that has a high potential for abuse. Prescriptions for nabilone should be limited to the amount necessary for a single cycle of chemotherapy (i.e., a few days).[7] Psychological and physiological dependence have occurred in patients receiving dronabinol, but addiction is uncommon and has only been seen after prolonged high dose administration.[5,6] 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.[6]

Aprepitant and scopolamine are approved for the treatment of PONV. Although there are no studies directly comparing the miscellaneous antiemetics for this indication, scopolamine and aprepitant have demonstrated similar efficacy compared to ondansetron.[62-63,66]

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.[51-52]

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.[20,23] Megestrol acetate, which is available in a generic formulation, was shown to be more effective than dronabinol for improving appetite and producing weight gain.[22-23] Adding dronabinol to megestrol acetate produced no additional clinical benefits.

There is insufficient evidence to support that one brand miscellaneous antiemetic is safer or more efficacious than another. NK_1 antagonists are considered a component of first-line therapy in certain clinical settings, such as in patients receiving moderately or highly emetogenic chemotherapy. Patients with a cancer diagnosis should be allowed approval for an oral NK_1 antagonist 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.

References

1. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Sep]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Sep]. Available from: http://www.thomsonhc.com/.
3. Emend® capsules [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; August 2015.
4. Emend® injection [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; August 2014.
5. Marinol® [package insert]. North Chicago, IL: AbbVie Inc.; August 2015.
6. Dronabinol [package insert]. Parsippany, NJ: Watson Pharma, Inc. January 2014.
7. Cesamet® [package insert]. Somerset, NJ: Meda Pharmaceuticals, Inc.; May 2015.
8. Transderm Scop® [package insert]. Parsippany, NJ: Novartis Consumer Health, Inc.; April 2013.
9. Akynzeo® [package insert]. Woodcliff Lake, NJ: Eisai Inc.; April 2015.
10. Longstreth GF, Hesketh PJ. Characteristics of antiemetic drugs. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2015 [cited 2015 Oct 21]. Available from: http://www.utdol.com/utd/index.do.
11. National Comprehensive Cancer Network (NCCN): Clinical Practice Guidelines in Oncology: Antiemesis [guideline on the Internet]. 2015 Feb [cited 2015 Sep 29]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
12. Roila F, Herrstedt J, Aapro M, et al.; ESMO/MASCC Guidelines Working Group. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010;21(Suppl 5):v232-43.
13. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014 Jan;118(1):85-113.
14. Basch E, Prestrund AA, Hesketh PJ, Kris MG, Feyr PC, Somerfield MR, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2011 Nov 1;29(31):4189-98.
15. Mahadevan U, Kane S. American gastroenterological association institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology. 2006;131:278-82.
16. Nausea and vomiting of pregnancy. Practice Bulletin No. 153. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015; 126:e12–24.
17. Arsenault M, Lane C, MacKinnon C, et al. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2002;24:817-31.
18. Quigley EMM, Hasler WL, Parkman HP. American Gastroenterological Association (AGA) technical review: nausea and vomiting. Gastroenterology. 2001;120:263-86.
19. American Gastroenterological Association Medical Position Statement: Nausea and Vomiting. Gastroenterology. 2001 Jan;120(1):261-2.
20. Beal J, Olson R, et al. Dronabinol as a treatment for anorexia associated with weight loss in AIDS. Journal of Pain & Symptom Management. 1995;10(2):89-97.
21. Struwe M, Kaempfer S, et al. Effect of dronabinol on nutritional status in HIV infection. Annals of Pharmacotherapy. 1993;27(7-8):827-31.
22. Jatoi A, Windschitl H, Loprinzi CL. Dronabinol vs megestrol acetate vs combination therapy for cancer-associated anorexia: A North Central Cancer Treatment Group study. J Clin Obcol. 2002;20:567-73.
23. Timpone J, Wright D, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. AIDS Research & Human Retroviruses. 1997;13(4):305-15.
24. Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer. 2010;18:423-31.
25. Yeo W, Mo FK, Suen JJ, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. Breast Cancer Res Treat. 2009;113:529-35.
26. Herrstedt J, Muss H, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. Cancer. 2005;104(7):1548-55.
27. Warr DG, Hesketh PJ, Gralla R. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol. 2005;23(12):2822-30.

28. Gralla R, de Wit R, Herrstedt J, et al. Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5HT3 antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of combined data from two Phase III randomized clinical trials. Cancer. 2005;104(4):864-8.
29. De Wit R, Herrstedt J, Rapoport B. The oral NK (1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomized, placebo-controlled phase III clinical trials. Eur J Cancer. 2004; 40(3):403-10.
30. Poli-Bigelli S, Rodrigues-Pereira J, et al. Addition of the neurokinin 1 receptor aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Cancer. 2003; 97(12):3090-8.
31. Hesketh PJ, Grunberg SM, Gralla RJ. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. J Clin Oncol. 2003; 21 (22):4112-9.
32. Martin A, Carides A. Functional relevance of antiemetic control. Experience using the FLIE questionnaire in a randomized study of the NK-1 antagonist aprepitant. Eur J Cancer. 2003;39(10):1395-401.
33. Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015 Apr;16(4):385-94.
34. Gore L, Chawla S, Petrilli A, et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. Pediatr Blood Cancer. 2009;52:242-7.
35. Schmitt T, Goldschmidt H, Neben K. Aprepitant, granisetron, and dexamethasone for prevention of chemotherapy-induced nausea and vomiting after high-dose melphalan in autologous transplantation for multiple myeloma: results of a randomized, placebo-controlled phase III trial. J Clin Oncol. 2014 Oct 20;32(30):3413-20.
36. Nishimura J, Satoh T, Fukunaga M, et al. Combination antiemetic therapy with aprepitant/fosaprepitant in patients with colorectal cancer receiving oxaliplatin-based chemotherapy (SENRI trial): a multicentre, randomised, controlled phase 3 trial. Eur J Cancer. 2015 Jul;51(10):1274-82.
37. Jordan K, Kinitz I, Voigt W, et al. Safety and efficacy of a triple antiemetic combination with the NK-1 antagonist aprepitant in highly and moderately emetogenic multiple-day chemotherapy. Eur J Cancer. 2009;45:1184-7.
38. Grunberg SM, Dugan M, Muss H, et al. Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. Support Care Cancer. 2009;17:589-94.
39. Gao HF, Liang Y, Zhou, Zhang DS, and Wu HY. Aprepitant plus palonosetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy. Internal medicine Journal. 2013;43(1):73-6.
40. Hesketh PJ and Sanz-Altamira P. Aprepitant, dexamethasone, and palonosetron in the prevention of doxorubicin/cyclophosphamide-induced nausea and vomiting. Support Care Cancer. 2012;20:653–6.
41. Longo F, Mansueto G, Lapadula V, De Sanctis R, Quadrini S, Grande R, et al. Palonosetron plus 3-day aprepitant and dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer. 2011;19:1159–64.
42. Herrington J, Jaskiewicz, Song J. Randomized, placebo-controlled, pilot study evaluating aprepitant single dose plus palonosetron and dexamethasone for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. Cancer. 2008;112:2080-7.
43. Grunberg S, Chua D, Maru A, Dinis J, DeVandry S, Boice J, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol—EASE. J Clin Oncol. 2011;29:1495-501.
44. Jin Y, Wu X, Guan Y, Gu D, Shen Y, and Xu Z. Efficacy and safety of aprepitant in the prevention of chemotherapy-induced nausea and vomiting: a pooled analysis. Support Care Cancer. 2012;20:1815–22.
45. Roila F, Ruggeri B, Ballatori E, Del Favero A, Tonato M. Aprepitant versus dexamethasone for preventing chemotherapy-induced delayed emesis in patients with breast cancer: a randomized double-blind study. J Clin Oncol. 2014 Jan 10;32(2):101-6.

46. Moon HY, Baek CW, Choi GJ, et al. Palonosetron and aprepitant for the prevention of postoperative nausea and vomiting in patients indicated for laparoscopic gynaecologic surgery: a double-blind randomised trial. BMC Anesthesiol. 2014 Aug 10;14:68.
47. Saito1 H, Yoshizawa H, Yoshimori K, Katakami N, Katsumata N, Kawahara M, and Eguchi K. Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose cisplatin: a multicentre, randomized, double-blind, placebo-controlled phase 3 trial. Annals of Oncology. 2013;24:1067–73.
48. Tsutsumi YM, Kakuta N, Soga T, et al. The effects of intravenous fosaprepitant and ondansetron for the prevention of postoperative nausea and vomiting in neurosurgery patients: a prospective, randomized, double-blinded study. Biomed Res Int. 2014;2014:307025.
49. Meiri E, Jhangiani H, Vredenburgh J, et al. Efficacy of dronabinol alone and in combination with ondansetron vs ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin. 2007; 23:533-43.
50. Lane M, Vogel CL, Ferguson J. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. J Pain Symptom Manage. 1991;6(6):352-9.
51. Machado Rocha FC, Stéfano SC, De Cássia Haiek R, et al. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer Care (Engl). 2008;17:431-43.
52. Niiranen A, Mattson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. Am J Clin Oncol. 1985;8:336-40.
53. Einhorn L, Nagy C, Furnas B, et al. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. J Clin Pharmacol. 1981;21:64S-69S.
54. Tramer MR, Carroll D, Campbell FA, et al. Cannabinoids for control of chemotherapy-induced nausea and vomiting: quantitative systematic review. BMJ. 2001 Jul 7;323(7303):16-21.
55. Aapro M, Rugo H, Rossi G, et al. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Ann Oncol. 2014 Jul;25(7):1328-33.
56. Hesketh PJ, Rossi G, Rizzi G, et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: A randomized dose-ranging pivotal study. Ann Oncol. 2014;25(7):1340–1346.
57. Gralla RJ, Bosnjak SM, Hontsa A, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol. 2014 Jul;25(7):1333-9.
58. Spinks AB, Wasiak J. Scopolamine (hyoscine) for preventing and treating motion sickness. Cochrane Database Syst Rev. 2011 Apr 13;(6): CD002851.
59. Dahl E, Offer-Ohlsen D, Lillevold PE, et al. Transdermal scopolamine, oral meclizine, and placebo in motion sickness. Clin Pharmacol Ther. 1984;36:116-20.
60. Sinha AC, Singh PM, Williams NW, Ochroch EA, Goudra BG. Aprepitant's prophylactic efficacy in decreasing postoperative nausea and vomiting in morbidly obese patients undergoing bariatric surgery. Obes Surg. 2014 Feb;24(2):225-31.
61. Green MS, Green P, Malayaman SN, Hepler M, Neubert LJ, Horrow JC. Randomized, double-blind comparison of oral aprepitant alone compared to aprepitant and transdermal scopolamine for prevention of postoperative nausea and vomiting. British Journal of Anaesthesia. 2012;109(5) 716–22.
62. Hartrick CT, Tang YS, Hunstad D, et al. Aprepitant vs multimodal prophylaxis in the prevention of nausea and vomiting following extended-release epidural morphine. Pain Pract. 2010;10:245-8.
63. Diemunsch P, Gan T, Philip B, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. Br J Anaesth. 2007;99:202-11.
64. Gan T, Apfel C, Kovac A, et al. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, vs ondansetron for the prevention of postoperative nausea and vomiting. Anesth Analg. 2007;104:1082-9.
65. Layeeque R, Siegel E, et al. Prevention of nausea and vomiting following breast surgery. The American Journal of Surgery. 2006;(191):767-72.
66. Jones S, Strobl R, Crosby D. The effect of transdermal scopolamine on the incidence and severity of postoperative nausea and vomiting in a group of high-risk patients given prophylactic intravenous ondansetron. AANA Journal. 2006;74(2):127-32.
67. White P, Tang J Song D, et al. Transdermal scopolamine: an alternative to ondansetron and droperidol for the prevention of postoperative and postdischarge emetic symptoms. Anesth Analg. 2007;104:92-6.

68. Gan TJ, Sinha AC, Kovac AL, et al. A randomized, double-blind, multicenter trial comparing transdermal scopolamine plus ondansetron to ondansetron alone for the prevention of postoperative nausea and vomiting in the outpatient setting. Anesth Analg. 2009;108:1498-504.
69. Sah N, Ramesh V, Kaul B, et al. Transdermal scopolamine patch in addition to ondansetron for postoperative nausea and vomiting prophylaxis in patients undergoing ambulatory cosmetic surgery. J Clin Anesth. 2009;21:249-52.
70. Tarkkila P, Torn K, Tuominen M, Lindgren L. Pre-medication with promethazine and transdermal scopolamine reduces the incidence of nausea and vomiting after intrathecal morphine. Acta Anaesthesiol Scand. 1995;39(7):983-6.
71. Schmitt LG, Shaw JE. Alleviation of induced vertigo. Therapy with transdermal scopolamine and oral meclizine. Arch Otolaryngol Head Neck Surg. 1986;112(1):88-91.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Proton-Pump Inhibitors
AHFS Class 562836
February 10, 2016

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.[1-13] They suppress gastric acid secretion and are generally recognized as the most potent acid suppressants available.[14] 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.[14-15] 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.[14-16]

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.[17] 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).[18] 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.

Esomeprazole strontium was FDA-approved in August 2013 without a proprietary name; it was approved based on bioequivalence of esomeprazole strontium 24.65 mg and 49.3 mg delayed-release capsules to esomeprazole magnesium 20 and 40 mg delayed-release capsules. Esomeprazole strontium will be included in Table 1, but no additional references to esomeprazole strontium will be made in this review as all data are similar between esomeprazole magnesium and esomeprazole strontium.[4-17]

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 dexlansoprazole are available in a generic formulation. This class was last reviewed in November 2013.

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®	none
Esomeprazole magnesium	delayed-release capsule, delayed-release powder for suspension	Nexium®*	esomeprazole
Esomeprazole sodium	Injection^	Nexium I.V.®*	esomeprazole
Esomeprazole strontium	delayed-release capsule	N/A	none
Lansoprazole	delayed-release capsule, delayed-release orally	Prevacid®*	lansoprazole

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	disintegrating tablet		
Omeprazole	delayed-release capsule, delayed-release powder for suspension	Prilosec®*	omeprazole
Pantoprazole	delayed-release tablet, delayed-release granules for suspension, injection	Protonix®*, Protonix IV®*	pantoprazole
Rabeprazole	delayed-release capsule, delayed-release tablet	Aciphex®*, Aciphex Sprinkle®,	rabeprazole
Combination Products			
Omeprazole and sodium bicarbonate	capsule§	N/A	none
Lansoprazole, amoxicillin, and clarithromycin	combination pack	Prevpac®*	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 (2013)**[19]	Gastroesophageal Reflux Disease (GERD) • Weight loss is recommended for GERD patients who are overweight or have had recent weight gain. • Head of bed elevation and avoidance of meals two to three hours before bedtime should be recommended for patients with nocturnal GERD. • Routine global elimination of food that can trigger reflux (including chocolate, caffeine, alcohol, acidic and/or spicy foods) is not recommended in the treatment of GERD. • An eight-week course of proton pump inhibitors (PPIs) is the therapy of choice for symptom relief and healing of erosive esophagitis. There are no major differences in efficacy between the different PPIs. Traditional delayed release PPIs should be administered 30 to 60 minutes before meal for maximal pH control. Newer PPIs may offer dosing flexibility relative to meal timing. • PPI therapy should be initiated at once a day dosing, before the first meal of the day. For patients with partial response to once daily therapy, tailored therapy with adjustment of dose timing and/or twice daily dosing should be considered in patients with night-time symptoms, variable schedules, and/or sleep disturbance. Non-responders to PPI should be referred for evaluation. In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief. • Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after PPI is discontinued and in patients with complications including erosive esophagitis and Barrett's esophagus. For patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on demand or intermittent therapy. • H 2-receptor antagonist (H_2RAs) therapy can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief. Bedtime H_2RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but may be associated with the

Clinical Guideline	Recommendation(s)
	development of tachyphylaxis after several weeks of use. • Therapy for GERD other than acid suppression, including prokinetic therapy and/or baclofen, should not be used in GERD patients without diagnostic evaluation. • There is no role for sucralfate in the non-pregnant GERD patient. • PPIs are safe in pregnant patients if clinically indicated.
North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition/ European Society for Pediatric Gastroenterology, Hepatology, and Nutrition: **Pediatric Gastroesophageal Reflux Clinical Practice Guidelines (2009)**[20]	General considerations • The major pharmacologic agents currently used for treating GERD in children are gastric acid–buffering agents, mucosal surface barriers, and gastric antisecretory agents. • Acid-suppressant agents are the mainstay of treatment for all but the patient with occasional symptoms. • In an older child or adolescent with typical symptoms suggesting GERD, an empiric trial of PPIs is justified for up to four weeks. There is no evidence to support an empiric trial of acid suppression as a diagnostic test in infants and young children where symptoms suggestive of GERD are less specific. • For the treatment of chronic heartburn in older children or adolescents, lifestyle changes with a four-week PPI trial are recommended. If symptoms resolve, continue PPIs for three months. • In pediatric patients with endoscopically diagnosed reflux esophagitis or established nonerosive reflux disease, PPIs for three months constitute initial therapy. Pharmacologic therapies • H_2RAs exhibit tachyphylaxis or tolerance, which is a drawback to chronic use. H_2RAs have a rapid onset of action and are useful for on-demand treatment. • PPIs are more efficacious to H_2RAs for healing of erosive esophagitis and relief of GERD symptoms. • When acid suppression is required, the smallest effective dose of a PPI should be used. • Most patients require only once-daily PPI; routine use of twice-daily doses is not indicated. • If symptoms resolve, PPIs may be continued for up to three months. • Because more effective alternatives (H_2RAs and PPIs) are available, chronic therapy with buffering agents, alginates, and sucralfate is not recommended for GERD. • Potential side effects of prokinetic agents outweigh the potential benefits. There is insufficient support to justify the routine use of metoclopramide, erythromycin, bethanechol, or domperidone for 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.
Canadian Association	• PPIs are more effective than H_2RAs for the reduction of heart burn and healing of

Clinical Guideline	Recommendation(s)
of Gastroenterology: **Canadian Consensus Conference on the Management of GERD in Adults–Update (2004)**[22]	esophagitis. • Initial therapy for GERD symptoms should be a once-daily PPI, unless symptoms are mild and infrequent (fewer than three times per week). • Twice-daily PPI therapy is not generally required as initial therapy for typical GERD symptoms. • Twice-daily, standard dose PPI therapy may be used for patients with severe symptoms despite standard once-daily PPI therapy. • An individual whose reflux symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy. • Long-term maintenance therapy should be given at the lowest dose and frequency that is sufficient to achieve optimal control of the patient's symptoms. • Long-term PPI therapy has not been associated with any clinically significant adverse events.
European *Helicobacter pylori* Study Group: **Management of *Helicobacter pylori* Infection–The Maastricht IV/Florence Consensus Report (2013)**[23]	Treatment • Recommended first-line treatment is a PPI, clarithromycin and amoxicillin or metronidazole in populations with less than 15 to 20% clarithromycin resistance. Bismuth-containing quadruple therapy is also an alternative. • In areas of high clarithromycin resistance (>20%), bismuth-containing quadruple treatments are recommended for first-line empirical treatment. If this regimen is not available sequential treatment or a non-bismuth quadruple treatment is recommended. • The use of high-dose (twice a day) PPI increases the efficacy of triple therapy. • Extending the duration of PPI-clarithromycin-containing triple treatment from seven to 10 to 14 days improves the eradication success by approximately 5% and may be considered. • PPI-clarithromycin-metronidazole and PPI-clarithromycin-amoxicillin regimens are equivalent. • PPI-clarithromycin-containing treatments do not need to be adapted to patient factors except for dosing. • After failure of a PPI-clarithromycin containing therapy, either a bismuth containing quadruple therapy or levofloxacin containing triple therapy are recommended. • After failure of second-line treatment, treatment should be guided by antimicrobial susceptibility testing whenever possible.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition/ European Society for Pediatric Gastroenterology, Hepatology, and Nutrition: **Evidence-based Guidelines From European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition for**	• 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.
	• Diagnostic testing for *H pylori* infection is not recommended in children with functional abdominal pain. However, testing may be considered in children with first-degree relatives with gastric cancer and those patients with refractory iron-deficiency anemia (in which other causes have been ruled out).
	• It is recommended that the initial diagnosis of *H pylori* infection be based on a positive histopathology plus a positive rapid urease test or a positive culture.
	• It is recommended that clinicians wait at least two weeks after stopping PPI therapy and four weeks after stopping antibiotics to perform biopsy-based and noninvasive tests (urea breath test, stool test) for *H pylori*.
	• Treatment may be considered:
	  o In the presence of *H pylori*–positive peptic ulcer disease (PUD).
	  o When *H pylori* infection is detected by biopsy-based methods in the absence of PUD.
	  o In children who are infected with *H pylori* and whose first-degree relative has gastric cancer.
	• Surveillance of antibiotic resistance rates of *H pylori* strains in children and adolescents is recommended in the different countries and geographic areas.
	• First-line eradication regimens are the following: triple therapy with a PPI,

Clinical Guideline	Recommendation(s)
Helicobacter pylori Infection in Children (2011)[24]	amoxicillin and clarithromycin or an imidazole or bismuth salts, amoxicillin and an imidazole or sequential therapy. • It is recommended that the duration of triple therapy be seven to 14 days. Compliance and adverse effects should be taken into account. • A reliable noninvasive test for eradication is recommended at least four to eight weeks following completion of therapy. • If treatment has failed, three options are recommended: esophagogastroduodenoscopy, with culture and susceptibility testing including alternative antibiotics, if not performed before guide therapy; fluorescence in situ hybridization on previous paraffin embedded biopsies if clarithromycin susceptibility testing has not been performed before guide therapy; modification of therapy by adding an antibiotic, using different antibiotics, adding bismuth, and/or increasing the dose and/or duration of therapy.
American College of Gastroenterology: **Guideline on the Management of *Helicobacter pylori* Infection (2007)[25]**	• The recommended primary therapies for *H pylori* infection include: a PPI, clarithromycin, and amoxicillin or metronidazole. (clarithromycin-based triple therapy) for 14 days or a PPI or H_2RA, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10 to 14 days. • The currently available PPIs perform comparably when used in the triple therapy regimens. A meta-analysis of 13 studies suggests that twice daily dosing of a PPI (lansoprazole, omeprazole, pantoprazole, and rabeprazole) in clarithromycin-based triple regimens is more effective than once- daily dosing. • Sequential therapy consisting of a PPI and amoxicillin for five days followed by a PPI, clarithromycin and tinidazole for an additional five days may provide an alternative to clarithromycin-based triple or bismuth-based quadruple therapy but requires validation within the United States before it can be recommended as a first-line therapy. • In patients with persistent *H pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient. Bismuth-based quadruple therapy for seven to 14 days is an accepted salvage therapy. Levofloxacin-based triple therapy for 10 days is another option for patients with persistent infection but this regimen requires validation in the United States.
Canadian Helicobacter Study Group: **Update on the Management of *Helicobacter pylori* (2004)[26]**	• A quadruple combination of a PPI, bismuth, tetracycline, and metronidazole for 10 to 14 days can be considered first-line therapy for the eradication of *H pylori.* • Eradication rates with the recommended quadruple therapy are comparable with those achieved with PPI-based triple therapy regimens in patients who adhere to the protocol. Given the lower number of tablets and twice daily dosing, in practice, PPI-based triple therapy may be the first choice.
American Gastroenterological Association: **Medical Position Statement on the Management of Barrett's Esophagus (2011)[27]**	• Patients with multiple risk factors associated with esophageal adenocarcinoma (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

Clinical Guideline	Recommendation(s)
	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 (2015)**[28]	• Patients with Barrett's esophagus should receive once-daily PPI therapy. Routine use of twice-daily dosing is not recommended, unless necessitated because of poor control of reflux symptoms or esophagitis. • Aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) should not be routinely prescribed as an antineoplastic strategy. Similarly, other putative chemopreventive agents currently lack sufficient evidence and should not be administered routinely. • Patients with nodularity in the Barrett's esophagus segment should undergo endoscopic mucosal resection of the nodular lesion(s) as the initial diagnostic and therapeutic maneuver. Histologic assessment of the endoscopic mucosal resection specimen should guide further therapy. In subjects with endoscopic mucosal resection specimens demonstrating high-grade dysplasia, or intramucosal carcinoma, endoscopic ablative therapy of the remaining Barrett's esophagus should be performed. • Following complete elimination of intestinal metaplasia, the goal of medical antireflux therapy should be control of reflux as determined by absence of frequent reflux symptoms (more than once a week) and/or esophagitis on endoscopic examination.
American College of Gastroenterology: **Management of Patients With Ulcer Bleeding (2012)**[29]	• Immediately assess hemodynamic status upon presentation and begin resuscitative measures as needed. • Blood transfusions should target hemoglobin ≥7 g/dL, with higher hemoglobin targeted in patients with intravascular volume depletion or comorbidities. • Discharge from the emergency department without endoscopy may be considered for patients with urea nitrogen <18.2 mg /dL, hemoglobin ≥13.0 g/dL for men (12.0 g/dL for women), systolic blood pressure ≥110 mm Hg; pulse <100 beats/min; and without evidence of melena, syncope, cardiac failure, and liver disease. • Consider administering intravenous erythromycin (250 mg ~30 minutes before endoscopy) to improve diagnostic yield and decrease the need for repeat endoscopy, although erythromycin has not consistently demonstrated improved clinical outcomes. • Pre-endoscopic intravenous PPI (e.g., 80 mg bolus followed by 8 mg/hour infusion) may be considered to decrease the proportion of patients who have higher risk stigmata of hemorrhage at endoscopy and who receive endoscopic therapy. The PPIs have not demonstrated improved clinical outcomes with regard to further bleeding, surgery or death. • If endoscopy is delayed or cannot be performed, administer intravenous PPI to reduce further bleeding. • Following endoscopic hemostasis, intravenous PPI therapy with 80 mg bolus followed by 8 mg/hour continuous infusion for 72 hours should be given to patients who have an ulcer with active bleeding, a non-bleeding visible vessel or an adherent clot. • Patients with flat-pigmented ulcer spots or clean bases can receive standard PPI

Clinical Guideline	Recommendation(s)
	therapy (e.g., oral PPI once daily). • Patients with clean-based ulcers may receive a regular diet and be discharged following endoscopy if they are hemodynamically stable, their hemoglobin is stable, no other medical problems, and they have a residence where they can be observed. • Patients with *H pylori*-associated bleeding ulcers should receive *H pylori* therapy. After eradication is documented, maintenance antisecretory therapy is not necessary unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) or antithrombotics. • Carefully assess and evaluate the need for continued NSAID therapy in patients with NSAID-induced ulcers. In patients who must resume NSAIDs, a cyclooxygenase (COX)-2 selective NSAID at the lowest effective dose plus daily PPI is recommended. • Assess the need for aspirin in patients with low-dose aspirin-induced bleeding ulcers. If given for secondary prevention (i.e., established cardiovascular disease), aspirin should be resumed as soon as possible after bleeding ceases in most patients. Long-term daily PPI therapy should also be provided. If given for primary prevention (i.e., no established cardiovascular disease), anti-platelet therapy likely should not be resumed in most patients. • In patients with idiopathic (non-*H pylori*, non-NSAID) ulcers, long-term antiulcer therapy (e.g., daily PPI) is recommended.

American College of Gastroenterology: **Guidelines for the Management of Dyspepsia (2005)**[30]	• In patients ≤55 years of age with no alarm features, the clinician may consider two approximately equivalent management options:
	  o Test and treat for *H pylori* using a validated noninvasive test and a trial of acid suppression if eradication is successful but symptoms do not resolve.
	  o An empiric trial of acid suppression with a PPI for four to eight weeks.
	• The test-and-treat option is preferable in populations with a moderate to high prevalence of *H pylori* infection (≥10%), whereas the empirical PPI strategy is preferable in low prevalence situations.

American College of Gastroenterology: **Guidelines for Prevention of Nonsteroidal Anti-inflammatory Drugs- Related Ulcer Complications (2009)**[31]	• Patients requiring NSAID therapy who are at high risk (e.g., prior ulcer bleeding) should receive alternative therapy, or if anti-inflammatory treatment is necessary, a COX-2 inhibitor, and co-therapy with misoprostol or high-dose PPI. • Patients at moderate risk can be treated with a COX-2 inhibitor alone or with a traditional nonselective NSAID plus misoprostol or a PPI. • Patients at low risk can be treated with a nonselective NSAID. • Patients for whom anti-inflammatory analgesics are recommended who also require low-dose aspirin therapy for cardiovascular disease can be treated with naproxen plus misoprostol or a PPI. • Patients at moderate gastrointestinal risk who are also at high cardiovascular risk should be treated with naproxen plus misoprostol or a PPI. Patients at high gastrointestinal and high cardiovascular risk should avoid using NSAIDS or COX-2 inhibitors. Alternative therapy should be prescribed. • High-dose H_2RAs are more effective than placebo in reducing the risk of NSAID-induced endoscopic peptic ulcers; however, the H_2RAs are significantly less effective than PPIs.

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[1-13]

Indication	Single Entity Agents						Combination Products	
	Dexlansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole and Sodium Bicarbonate	Lansoprazole 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* Eradication**								
In combination with amoxicillin and clarithromycin for the treatment of patients with *H pylori* infection and duodenal ulcer disease to eradicate *H pylori*		✔ §	✔	✔		✔		

Indication	Single Entity Agents						Combination Products	
	Dexlansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole and Sodium Bicarbonate	Lansoprazole and Amoxicillin and Clarithromycin
In combination with amoxicillin as dual therapy for the treatment of patients with *H pylori* infection and duodenal ulcer disease to eradicate *H 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*								✔
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 (Prevpac®). 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[1-13]

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 to 1.5
Lansoprazole	80	95	Liver	Renal (14 to 25)	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

Significant drug interactions with the proton-pump inhibitors are listed in Table 5.

Table 5. Significant Drug Interactions with the Proton-Pump Inhibitors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Proton-pump inhibitors (esomeprazole, omeprazole, pantoprazole, rabeprazole)	1	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)	1	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

Generic Name(s)	Significance Level	Interaction	Mechanism
			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 (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)	1	Erlotinib	Plasma concentration and pharmacologic effects of erlotinib may be decreased by proton-pump inhibitors. The solubility of erlotinib is pH dependent. The increase in gastric pH associated with proton-pump inhibitor therapy decreases the solubility and bioavailability of erlotinib.
Proton-pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)	2	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.
Proton-pump inhibitors (pantoprazole, rabeprazole)	2	Imidazoles	Bioavailability and antifungal effectiveness of imidazoles may be decreased by proton-pump inhibitors. Secondarily, imidazoles may increase plasma concentrations of proton-pump inhibitors.
Proton-pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)	2	Mycophenolate	Plasma concentrations and pharmacologic effects of mycophenolate may be decreased by proton-pump inhibitors. The mechanism of this interaction is unknown.
Proton-pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)	2	Nilotinib	Nilotinib pH-dependent solubility may be reduced, decreasing nilotinib GI absorption and decreasing the pharmacologic effects.
Proton-pump inhibitors (esomeprazole, lansoprazole)	2	Clarithromycin	Plasma concentrations of macrolide antibiotics may be increased by proton-pump inhibitors. The potential for toxicity due to macrolides may be increased.
Omeprazole	2	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 (dexlansoprazole, esomeprazole,	2	Tacrolimus	Concomitant administration of certain proton pump inhibitors and tacrolimus may increase tacrolimus

Generic Name(s)	Significance Level	Interaction	Mechanism
lansoprazole, and omeprazole)			levels in patients who are poor metabolizers of CYP 2C19.

Significance level 1=major severity, significance level 2=moderate severity.

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 (Prevpac®). 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 individuals components listed below. 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.

Table 6. Adverse Drug Events (%) Reported with the Proton-Pump Inhibitors[1-13]

Adverse Events	Single Entity Agents						Combination Products
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	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	-	-	-	-
Chills	-	-	<1	-	<1	-	-
Confusion	-	<1	<1	<1	<1	-	<1

Adverse Events	Single Entity Agents						Combination Products
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole/ Sodium Bicarbonate
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	-
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
Eczema	-	-	-	-	<1	-	-
Erythema	<2	-	-	-	-	-	-
Erythema multiforme	-	<1	<1	<1	<1	<1	<1
Hyperhidrosis	-	<1	-	<1	-	-	<1

Adverse Events	Single Entity Agents						Combination Products
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole/ Sodium Bicarbonate
Photosensitivity	-	<1	<1	<1	<1	<1	<1
Pruritus	<2	<1	<1	<1	<1	<1	<1
Rash	<2	<1	<1	1.5	<2	<1	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
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	-
Abnormal taste	<2	<1	<1	<1	<1	<1	<1
Anorexia	-	<1	<1	<1	<1	<1	<1

Adverse Events	Single Entity Agents						Combination Products
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole/ Sodium Bicarbonate
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	4
Duodenitis	<2	-	-	-	<1	<1	-
Dyspepsia	<2	<1	<1	-	≥1	<1	-
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	-	-	-	-	-
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	-	-

Adverse Events	Single Entity Agents						Combination Products
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole/ Sodium Bicarbonate
Impaired gastric emptying	<2	-	-	-	-	-	-
Irritable bowel syndrome	<2	-	-	-	-	-	-
Melena	-	-	<1	-	<1	<1	-
Nausea	3	6	1.3	4	2	2	✔
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	-
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	-
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
Vaginitis	-	<1	<1	-	<1	-	-
Hematologic							
Agranulocytosis	-	<1	<1	<1	-	<1	<1
Anemia	<2	>1	<1	<1	-	<1	8
Eosinophilia	-	-	<1	-	<1	-	-
Leukocytosis	-	<1	-	<1	<1	<1	<1

Adverse Events	Single Entity Agents						Combination Products
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole/ Sodium Bicarbonate
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 increased	<2	<1	<1	<1	<1	<1	<1
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	-	<1	-	-	-	-	-

Adverse Events	Single Entity Agents						Combination Products
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole/ Sodium Bicarbonate
increased							
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	-
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	-	-	-	-	-
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	-

Adverse Events	Single Entity Agents						Combination Products
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole/ Sodium Bicarbonate
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
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	✔	✔	✔	✔	✔	✔	✔

Adverse Events	Single Entity Agents						Combination Products
	Dex-lansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	Omeprazole/ Sodium Bicarbonate
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
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[1-13]

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 Gastroesophageal reflux disease: Capsule (DR): 30 mg once daily for four weeks	Safety and efficacy in children 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	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
	Pathological hypersecretory conditions: Capsule, powder for suspension: 40 mg twice daily (individual dose; doses up to 240 mg have been administered)		
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:	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 eight 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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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		
Omeprazole	Duodenal ulcer: Capsule, powder for suspension: treatment, 20 mg once daily for four to eight weeks Erosive esophagitis: 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	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 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	Capsule (DR): 10 mg 20 mg 40 mg Powder for suspension (DR): 2.5 mg 10 mg
Pantoprazole	Erosive esophagitis: Granules for suspension (DR),	Erosive esophagitis: Granules for suspension	Granules for suspension (DR):

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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	(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	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; 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	Gastroesophageal reflux disease: ≥12 years of age: Tablet (DR): 20 mg once daily for up to eight weeks 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	Capsule (DR; sprinkle): 5 mg 10 mg Tablet (DR): 20 mg
Combination Products			
Omeprazole and sodium bicarbonate	Duodenal ulcer: Capsule: treatment, 20 mg once daily for four to eight weeks Erosive esophagitis: Capsule: treatment, 20 mg once	Safety and efficacy in children have not been established.	Capsule: 20 mg-1.1 gram 40 mg-1.1 gram

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily for four to eight weeks; maintenance, 20 mg once daily Gastric ulcer: Capsule: treatment, 40 mg once daily for four to eight weeks Gastroesophageal reflux disease: Capsule: 20 mg once daily for four weeks Upper gastrointestinal bleeding: Capsule: 40 mg; followed by 40 mg six to eight hours later and 40 mg once daily thereafter for 14 days		
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.[32] (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.[33] (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.[34] (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.[35] (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.[36] (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.[37] (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.[38] (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.[39] (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.[40] (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.[41] (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.[42] (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.[43] (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.[44] (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.[45] (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.[46] (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.[47] (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.[48] (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.[49] (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.[50] (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.[51] (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.[52] (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.[53] (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.[54] (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 anytime 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.[55] (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.[56] (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.[57] (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.[58] (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.[59] (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.[60] (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.[61] (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.[62] (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.[63] (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.[64] (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.[65](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.[66] (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.[67] (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.[68] (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.[69] (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.[70] (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.[71] (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.[72] (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.[73] (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.[74] (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.[75] (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.[76] (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.[77] (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.[78] (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.[79] (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.[80] (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.[81] (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.[82] (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
Lamouliatte et al.[83] (1998)	PRO, RCT Adult patients	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
Triple therapy with 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	positive with *H pylori* and dyspepsia		Secondary: Not reported	Secondary: Not reported
Ulmer et al.[84] (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.[85] (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.[86] (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.[87] (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.[88]	OL	N=493	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) 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	Eradication rates 12 weeks following completion of therapy and adverse events Secondary: Not reported	In the ITT population, the eradication rate was 88.8% (95% CI, 86 to 92) 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.[89] (2012) Rabeprazole- or esomeprazole	MA RCTs investigating the use of rabeprazole- or	N=35 trials Treatment duration not reported	Primary: *H pylori* eradication rates based	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
based *H pylori* therapies vs lansoprazole-, omeprazole- or pantoprazole based *H pylori* therapies	esomeprazole-based *H pylori* therapies compared to first-generation PPIs (omeprazole-lansoprazole-pantoprazole) or with one another		Secondary: Not reported	Esomeprazole treatment was associated with a higher *H pylo*ri eradication 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.[90] (2002) Lansoprazole 30 to 120 mg/day or	OL, PRO Adult patients with Zollinger-Ellison syndrome	N=11 7 to 10 days	Primary: Median 24-hour intragastric pH and percentage of time at or below pH 3,	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
omeprazole 20 to 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.	maintained on omeprazole or lansoprazole		4, 5, and 6 Secondary: Basal acid output	There were no significant differences in percentage of time at or below pH 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.[91] (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.[92] (2005)	OL, RCT, XO	N=36	Primary: Control of	Primary: Median percentage of time with gastric pH>4 was significantly higher

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.	Adult patients 18 to 65 years of age with GERD with recurrent nighttime symptoms for the previous three months	16 days	nocturnal gastric acidity measured by the following: percentage of time with gastric pH>4, median gastric pH, and nocturnal acid breakthrough Secondary: Not reported	with immediate-release omeprazole (54.7%) compared to pantoprazole (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.[93] (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	N=595 6 months	Primary: Therapeutic failure (peptic ulcer, >10 erosions or petechiae in the stomach or duodenum, reflux esophagitis, or discontinuation due to	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pantoprazole 40 mg QD	gastrointestinal 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		gastrointestinal symptoms or an adverse event) and lack of endoscopic failure at six months and adverse events Secondary: Primary end points at three months	in each treatment group (29% of patients receiving pantoprazole 20 mg; 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).

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®	$$$$$	N/A
Esomeprazole magnesium	delayed-release capsule, delayed-release powder for suspension, injection	Nexium®*	$$$$$	$$$$$
Esomeprazole	Injection^	Nexium I.V.®*	$$$$$	$$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
sodium				
Esomeprazole strontium	delayed-release capsule	N/A	N/A	$$$
Lansoprazole	delayed-release capsule, delayed-release orally disintegrating tablet	Prevacid®*	$$$$$	$$
Omeprazole	delayed-release capsule, delayed-release powder for suspension	Prilosec®*	$$$$$	$
Pantoprazole	delayed-release tablet, delayed-release granules for suspension, injection	Protonix®*, Protonix IV®*	$$$$$	$
Rabeprazole	delayed-release capsule, delayed-release tablet	Aciphex®*, Aciphex Sprinkle®,	$$$$$	$$$
Combination Products				
Omeprazole and sodium bicarbonate	capsule§	N/A	N/A	$$$$$
Lansoprazole, amoxicillin, and clarithromycin	combination pack	Prevpac®	$$$$$	$$$$$

*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 dexlansoprazole are available in a generic formulation.

PPI's 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.

The combination product, Prevpac®, contains lansoprazole in combination with amoxicillin and clarithromycin. The individual components are packaged separately on daily administration cards and are all marketed separately in a generic formulation.

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).[19-22, 27-28] Clinical trials have demonstrated similar efficacy among the PPIs for these indications.[32, 36-37, 42, 44-46, 50, 55-56, 60, 62-64, 66-69] While some studies have demonstrated greater efficacy with one PPI over another, the overall differences are small (often ranging from 3 to 9%).[35, 38,39-41, 43, 47, 51, 54,59, 64] 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.[19-22, 27-28]

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*.[23, 25-26] Clinical trials have generally demonstrated similar efficacy among the PPIs for this indication.[17-18, 71-73, 76-82, 84-86] 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.[87,89] Guidelines do not give preference to one PPI over another for the eradication of *H pylori*.[23-26]

In August 2010, the prescribing information was updated to include information on the risk of osteoporosis-related fractures of the hip, wrist, or spine.[3-6, 8, 10,11,13] 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).[18] 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. [3-6, 8, 10,11,13]

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.

XII. References

1. Drug Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited 2015 Nov]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2015 Nov]. Available from: http://www.thomsonhc.com/.
3. Aciphex® and Aciphex Sprinkle™ [package insert].Woodcliff Lake, NJ: Eisai inc.; December 2014.
4. Dexilant® [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; November 2014.
5. Esomeprazole strontium [package insert]. Glasgow (KY): Amneal Pharmaceuticals; December 2014.
6. Nexium® [package insert]. Wilmington, DE: AstraZeneca; December 2014.
7. Nexium IV® [package insert]. Wilmington, DE: AstraZeneca; December 2014.
8. Prevacid® [package insert]. Lake Forest, IL: Takeda Pharmaceuticals America, Inc.; December 2014.
9. Prevpac® [package insert]. Lake Forest, IL: Takeda Pharmaceuticals America, Inc.; November 2014.
10. Prilosec® [package insert]. Wilmington, DE: AstraZeneca; December 2014.
11. Protonix® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc; December 2014.
12. Protonix IV® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc; December 2014.
13. Zegerid® [package insert]. San Diego, CA: Santarus Inc.; December 2014.
14. Wolfe, MM, Sachs, G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 2000;118 (2 Suppl 1):S9-S31.
15. Welage LS. Pharmacologic features of proton-pump inhibitors and their potential relevance to clinical practice. Gastroenterol Clin North Am. 2003;32 (3 Suppl):S25-35.
16. Wolfe, MM**.** Overview and comparison of the proton-pump inhibitors for the treatment of acid-related disorders. In: UpToDate, Feldman, M (Ed), UpToDate, Waltham, MA, 2015.
17. FDA Drug Safety Communication: FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm. Accessed August 2013.
18. FDA Drug Safety Communication: Proton Pump Inhibitor drugs (PPIs): Drug Safety Communication - Low Magnesium Levels Can Be Associated With Long-Term Use. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm245275.htm. Accessed August 2013.
19. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013 Mar;108(3):308-28.
20. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009;49:498-547.
21. Kahrilas P, Shaheen N, Vaezi M, et al. AGAI medical position statement: management of gastroesophageal reflux disease. Gastroenterology. 2008;135:1383-91.
22. Armstrong D, Marshall JK, Chiba N, Enns RCT, et al. Canadian Association of Gastroenterology GERD Consensus Group. Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults - update 2004. Can J Gastroenterol. 2005; 19(1):15-35.
23. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F,et al.; European Helicobacter Study Group. Management of Helicobacter pylori infection—the Maastricht IV/ Florence Consensus Report. Gut. 2012 May;61(5):646-64.
24. Koletzko S, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr. 2011 Aug;53(2):230-43. doi: 10.1097/MPG.0b013e3182227e90.\
25. Chey W, Wong B. American College of Gastroenterology Guideline on the Management of Helicobacter pylori Infection. Am J Gastroenterol. 2007; 102:1808-25.
26. Hunt RCT, Fallone C, Veldhuyzan van Zanten S, Sherman P, et al., CHSG 2004 participants. Canadian Helicobacter Study Group Consensus Conference: Update on the management of Helicobacter pylori--an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for H pylori infection. Can J Gastroenterol. 2004; 18(9):547-54.
27. American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011 Mar;140(3):1084-91.

28. Shaheen NJ, Falk GW, Iyer PG, Gerson L. Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol advance online publication, 3 November 2015; doi: 10.1038/ajg.2015.322.
29. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012 Mar;107(3):345-60.
30. Talley NJ, Vakil N; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005;100(10):2324-37.
31. Lanza FL, Chan FKL, Quigley EMM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728-38.
32. Sharma P, Shaheen NJ, Perez MC, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation--results from two randomized controlled studies. Aliment Pharmacol Ther. 2009;29:731-41.
33. Peura DA, Metz DC, Dabholkar AH, et al. Safety profile of dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed release formulation: global clinical trial experience. Aliment Pharmacol Ther. 2009;30:1010-21.
34. Tsai, HH, Chapman, RCT, Shepherd, A, et al. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastro-oesophageal reflux patients: the COMMAND Study. Aliment Pharmacol Ther. 2004;20:657-65.
35. Castell, DO, Kahrilas, PJ, Richter, JE, et al. Esomeprazole (40 mg) compared to lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002;97:575-83.
36. Howden CW, Ballard EDI, Robieson W. Evidence for Therapeutic Equivalence of Lansoprazole 30 mg and Esomeprazole 40 mg in the Treatment of Erosive Oesophagitis. Clin Drug Invest.2002;22(2):99-109.
37. Chey W, Huang B. Jackson RL. Lansoprazole and Esomeprazole in Symptomatic GERD: A Double-Blind, Randomized, Multicentre Trial in 3000 Patients Confirms Comparable Symptom Relief. Oesophagitis. Clin Drug Invest. 2003;23(2):69-84.
38. Devault KR, Johanson JF, Johnson DA, et al. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. Clin Gastroenterol Hepatol. 2006;4:852-9.
39. Fennerty MB, Johanson JF, Hwang C, Sostek M. Efficacy of esomeprazole 40 mg vs lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. Aliment Pharmacol Ther.2005;21(4):455-63.
40. Lauritsen K, Deviere J, Bigard MA, Bayerdorffer E. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther. 2003;17(3):333-41.
41. Richter, JE, Kahrilas, PJ, Johanson, J, et al. Efficacy and safety of esomeprazole compared to omeprazole in GERD patients with erosive esophagitis: A randomized controlled trial. Am J Gastroenterol. 2001;96:656-65.
42. Armstrong D, Talley NJ, Lauritsen K, Moum B, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. Aliment Pharmacol Ther. 2004;20(4):413-421.
43. Kahrilas, PJ, Falk, GW, Johnson, DA, et al. Esomeprazole improves healing and symptom resolution as compared to omeprazole in reflux oesophagitis patients: A randomized controlled trial. Aliment Pharmacol Ther. 2000;14:1249-58.
44. Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci. 2006 May;51(5):844-50.
45. Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci. 2006 May;51(5):852-7.
46. Glatzel D, Abdel-Qader M, Gatz G, et al. Pantoprazole 40 mg is as effective as esomeprazole 40 mg to relieve symptoms of gastroesophageal reflux disease after 4 weeks of treatment and more efficacious regarding the prevention of symptomatic relapse. Digestion. 2006;74:145-54.
47. Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schutze K, Wallner G, Juergens H, Preiksaitis H, Keeling N, Naucler E, Eklund S; Expo Study Investigators. A randomized comparative study of esomeprazole 40 mg vs pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther. 2005;21(6):739-46.
48. Labenz J, Armstrong D, Zetterstrand S, et al. Clinical trial: factors associated with freedom from relapse of heartburn in patients with healed reflux oesophagitis--results from the maintenance phase of the EXPO study. Aliment Pharmacol Ther. 2009;29:1165-71.

49. Labenz J, Armstrong D, Zetterstrand S, et al. Clinical trial: factors associated with resolution of heartburn in patients with reflux oesophagitis--results from the EXPO study. Aliment Pharmacol Ther. 2009;29:959-66.
50. Scholten T, Gatz G, Hole U. Once-daily pantoprazole 40 mg and esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. Aliment Pharmacol Ther. 2003;18(6):587-94.
51. Klok RM, Postma MJ, van Hout BA, Brouwers JR. Meta-analysis: comparing the efficacy of proton-pump inhibitors in short-term use. Aliment Pharmacol Ther. 2003;17(10):1237-45.
52. Gralnek I, Dulai G, Fennerty M, et al. Esomeprazole vs other proton pump inhibitors in erosive esophagitis: a meta-analysis or randomized clinical trials. Clin Gastroenterol Hepatol. 2006;4:1452-58.
53. Hoogendoorn RJ, Groeneveld L, Kwee JA, et al. Patient satisfaction with switching to esomeprazole from existing proton pump inhibitor therapy for gastro-oesophageal reflux disease: an observational, multicentre study. Clin Drug Investig. 2009;29:803-10.
54. Richter JE, Kahrilas PJ, Sontag SJ, Kovacs TO, Huang B, Pencyla JL. Comparing lansoprazole and omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients. Am J Gastroenterol. 2001;96:3089-98.
55. Sharma VK, Leontiadis GI, Howden CW. Meta-analysis of randomized controlled trials comparing standard clinical doses of omeprazole and lansoprazole in erosive oesophagitis. Aliment Pharmacol Ther. 2001; 15(2):227-31.
56. Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared to omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. Clin Ther. 2001;23(7):998-1017.
57. Miner PB Jr, McKean LA, Gibb RD, et al. Omeprazole-Mg 20.6 mg is more efficacious to lansoprazole 15 mg for control of gastric acid: a comparison of over-the-counter doses of proton pump inhibitors. Aliment Pharmacol Ther. 2010;31:846-51.
58. Pilotto A, Franceschi M, Leandro G, et al. Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients. World J Gastroenterol. 2007;13:4467-72.
59. Katz PO, Koch FK, Ballard ED, Bagin RG, Gautille TC, Checani GC, et al. Comparison of the effects of immediate-release omeprazole oral suspension, delayed-release lansoprazole capsules and delayed-release esomeprazole capsules on nocturnal gastric acidity after bedtime dosing in patients with nighttime GERD symptoms. Aliment Pharmacol Ther. 2007 Jan 15;25(2):197-205.
60. Bardhan KD, Van Rensburg C. Comparable clinical efficacy and tolerability of 20 mg pantoprazole and 20 mg omeprazole in patients with grade I reflux oesophagitis. Aliment Pharmacol Ther. 2001;15:1585-91.
61. Zheng RN. Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for symptom relief in patients with reflux esophagitis. World J Gastroenterol. 2009;15:990-5.
62. Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to omeprazole, 20 mg once daily, in the healing of erosive gastroesophageal reflux disease. Scand J Gastroenterol. 2000;35:1245-50.
63. Pace F, Annese V, Prada A, Zambelli A, et al., Italian Rabeprazole Study Group. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomized, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Dig Liver Dis. 2005;37:741-50.
64. Edwards SJ, Lind T, Lundell L. Systematic review of proton-pump inhibitors for the acute treatment of reflux oesophagitis. Aliment Pharmacol Ther. 2001;15(11):1729-36.
65. Edwards SJ, Lind T, Lundell L, et al. Systematic review: standard- and double-dose proton pump inhibitors for the healing of severe erosive oesophagitis -- a mixed treatment comparison of randomized controlled trials. Aliment Pharmacol Ther. 2009;30:547-56.
66. Goh K, Benamouzig RCT, Sander P, et al. Efficacy of pantoprazole 20 mg daily compared to esomeprazole 20 mg daily in the maintenance of healed gastroesophageal reflux disease: a randomized, double-blind comparative trial – the EMANCIPATE study. Eur J Gastroenterol Hepatol. 2007;19:205-11.
67. Bardhan K, Achim A, Riddermann T, et al. A clinical trial comparing pantoprazole and esomeprazole to explore the concept of achieving 'complete remission' in gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2007;25:1451-9.
68. Eggleston A, Katelaris PH, Nandurkar S, et al. Clinical trial: the treatment of gastro-oesophageal reflux disease in primary care--prospective randomized comparison of rabeprazole 20 mg with esomeprazole 20 and 40 mg. Aliment Pharmacol Ther. 2009;29:967-78.
69. Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C, et al. Randomized clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe

erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther. 2011 Jan;33(2):203-12.
70. Haddad I, Kierkus J, Tron E, Ulmer A, Hu P, Sloan S, et al. Efficacy and Safety of Rabeprazole in Children (1-11 Years) with Gastroesophageal Reflux Disease: A Multicenter, Double-Blind, Parallel-Group Study. J Pediatr Gastroenterol Nutr. 2013 Dec;57(6):798-807.
71. Subei I, Cardona H, Bachelet E, et al. One week of esomeprazole triple therapy vs 1 week of omeprazole triple therapy plus 3 weeks of omeprazole for duodenal ulcer healing in Helicobacter pylori-positive patients. Dig Dis Sci. 2007;52:1505-12.
72. Gisbert JP, Pajares JM. Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis. Dig Liver Dis. 2004;36(4):253-9.
73. Wu I, Wu D, Hsu P, et al. Rabeprazole- vs esomeprazole-based eradication regimens for *H pylori* infection. Helicobacter. 2007;12:633-7.
74. Veldhuyzen van Zanten S, Fedorak RN, Lambert J, Cohen L, Vanjaka A. Absence of symptomatic benefit of lansoprazole, clarithromycin, and amoxicillin triple therapy in eradication of Helicobacter pylori positive, functional (nonulcer) dyspepsia. Am J Gastroenterol. 2003;98(9):1963-9.
75. Schwartz H, Krause RCT, Sahba B, Haber M, et al. Triple vs dual therapy for eradicating Helicobacter pylori and preventing ulcer recurrence: a randomized, double-blind, multicenter study of lansoprazole, clarithromycin, and/or amoxicillin in different dosing regimens. Am J Gastroenterol. 1998;93(4):584-90.
76. Bazzoli F, Pozzato P, Zagari M, Fossi S, et al. Efficacy of lansoprazole in eradicating Helicobacter pylori: a meta-analysis. Helicobacter. 1998;3(3):195-201.
77. Choi H, Park D, Hwang S, et al. Double-dose, new-generation proton pump inhibitors do not improve Helicobacter pylori eradication rate. Helicobacter 2007;12:638-42.
78. Gisbert JP, Khorrami S, Calvet X, Pajares JM. Pantoprazole based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2004;16(1):89-99.
79. Gisbert JP, Khorrami S, Calvet X, Pajares JM. Systematic review: Rabeprazole-based therapies in Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003;17(6):751-64.
80. Ji S, Kim J, Jee M, et al. Comparison of the efficacy of rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of peptic ulcer diseases. J Gastroenterol Hepatol. 2006;21:1381-7.
81. Liu MK, Wu IC, Lu CY, Kuo CH, et al. Randomized trial comparing rabeprazole- versus lansoprazole-based Helicobacter pylori eradication regimens. Kaohsiung J Med Sci. 2013 Jul;29(7)379-84. doi 10.1016j.kjms.2012.11.006. Epub 2013 Jan 12.
82. Murakami K, Okimoto T, Kodama M, et al. Evaluation of three different proton pump inhibitors with amoxicillin and metronidazole in retreatment for helicobacter pylori infection. J Clin Gastoenterol. 2008;42:139-42.
83. Lamouliatte H, Cayla RCT, Zerbib F, Forestier S, de Mascarel A, Joubert-Collin M, Megraud F. Dual therapy using a double dose of lansoprazole with amoxicillin vs triple therapy using a double dose of lansoprazole, amoxicillin, and clarithromycin to eradicate Helicobacter pylori infection: results of a prospective randomized open study. Am J Gastroenterol. 1998;93(9):1531-4.
84. Ulmer HJ, Beckerling A, Gatz G. Recent use of proton-pump inhibitor-based triple therapies for the eradication of H pylori: a broad data review. Helicobacter. 2003;8(2):95-104.
85. Vergara M, Vallve M, Gisbert JP, Calvet X. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003;18:647-54.
86. Wang X, Fang JY, Lu R, Sun DF. A meta-analysis: comparison of esomeprazole and other proton-pump inhibitors in eradicating Helicobacter pylori. Digestion. 2006;73(2-3):178-86.
87. Hsu PI, Lai KH, Lin CK, Chen WC, Yu HC, Cheng JS, et al. A prospective randomized trial of esomeprazole-vs pantoprazole-based triple therapy for Helicobacter pylori eradication. Am J Gastroenterol. 2005;100(11):2387-92.
88. Felga G, Silva FM, Barbuti RC, Navarro-Rodriguez T, Zaterka S, Eisig JN. Clarithromycin-based triple therapy for Helicobacter pylori treatment in peptic ulcer patients. J Infect Dev Ctries. 2010 Nov 24;4(11):712-6.
89. McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs first-generation pump inhibitors in the treatment of Helicobacter pylori infection. Aliment Pharmacol Ther. 2012 Sep;36(5):414-25.
90. Ramdani A, Mignon M, Samoyeau R. Effect of pantoprazole vs other proton-pump inhibitors on 24-hour intragastric pH and basal acid output in Zollinger-Ellison syndrome. Gastroenterol Clin Biol. 2002;26(4):5-359.

91. Conrad S, Gabrielli A, Margolis B, Quartin A, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension vs intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. Crit Care Med. 2005;33(4):760-5.
92. Castell D, Bagin RCT, Goldlust B, Major J, Hepburn B. Comparison of the effects of immediate-release omeprazole powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in patients with symptomatic gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2005;21(12):1467-74.
93. Regula J, Butruk E, Dekkers CP, de Boer SY, Raps D, Simon L, et al. Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole vs omeprazole. Am J Gastroenterol. 2006 Aug;101(8):1747-55.
94. Nelson W, Vermeulen L, Geurkink E, Ehlert D, Reichelderfer M. Clinical and Humanistic Outcomes in Patients with Gastroesophageal Reflux Disease Converted from Omeprazole to Lansoprazole. Arch Intern Med. 2000;160:2491-6.
95. Meineche-Schmidt V. Empiric treatment with high and standard dose of omeprazole in general practice: two-week randomized placebo-controlled trial and 12-month follow-up of health-care consumption. Am J Gastroenterol. 2004;99(6):1050-8.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review of Savaysa®
Anticoagulants, Oral: AHFS Class 201204
February 10, 2016

I. Overview

Edoxaban (Savaysa®) is a factor Xa inhibitor approved by the Food and Drug Administration (FDA) for the reduction in the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (NVAF) as well as for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant.[1] This agent is the fourth new oral anticoagulant (NOAC) to reach the market joining dabigatran (Pradaxa®), rivaroxaban (Xarelto®), and apixaban (Eliquis®). The other three NOACs received the same FDA approval as edoxaban; however, in addition they are indicated for the reduction in the risk of recurrence of a DVT or PE, and rivaroxaban and apixaban are also approved for prophylaxis of DVT following hip or knee replacement.[2,3]

The major advancement with all of the NOAC agents, including edoxaban, is that they do not have the same extensive food and drug interactions as warfarin nor do they require the same monitoring as warfarin therapy. The lack of therapeutic monitoring, however, may make it difficult for physicians to objectively assess adherence to therapy. Another important consideration is the lack of available reversal agents for many of the NOACs like there is with the use of vitamin K for warfarin. A specific reversal agent for dabigatran was recently FDA-approved, and an agent for the reversal of factor Xa inhibitors is underway.[1-6]

The edoxaban products included in this review are listed in Table 1. Edoxaban is not available in a generic formulation.

Table 1. Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Edoxaban	tablet	Savaysa®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Oral Anticoagulants

Clinical Guideline	Recommendation(s)
American College of Chest Physicians: **Antithrombotic Therapy and Prevention of Thrombosis, 9th edition (2012)**[5]	Management of anticoagulant therapy • For outpatients, vitamin K antagonist (VKA) therapy with warfarin 10 mg/day for the first two days, followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose is suggested. • Routine use of pharmacogenetic testing for guiding doses of VKA therapy is not recommended. • For acute venous thromboembolism (VTE), it is suggested that VKA therapy be started on day one or two of low molecular weight heparin (LMWH) or low dose unfractionated heparin (UFH) therapy rather than waiting for several days to start. • For VKA therapy with stable INRs, INR testing frequency of up to 12 weeks is suggested rather than every four weeks. • For patients receiving previously stable VKA therapy who present with a single out-of-range INR ≤0.5 below or above therapeutic, it is suggested to continue the current dose and test the INR within one to two weeks.

Clinical Guideline	Recommendation(s)
	• For patients receiving stable VKA therapy presenting with a single subtherapeutic INR value, routine administering of bridging heparin is not recommended. • Routine use of vitamin K supplementation is suggested against with VKA therapy. • For patients receiving VKA therapy who are motivated and can demonstrate competency in self-management strategies, it is suggested that patient self-management be utilized rather than usual outpatient INR monitoring. • For maintenance VKA dosing, it is suggested that validated decision support tools be utilized rather than no decision support. • Concomitant use of nonsteroidal anti-inflammatory drugs and certain antibiotics should be avoided in patients receiving VKA therapy. • Concomitant use of platelet inhibitors should be avoided in patients receiving VKA therapy, except in situations where benefit is known or is highly likely to be greater than harm from bleeding. • With VKA therapy, a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended rather than a lower (<2.0) or higher (range, 3.0 to 5.0) range. • In patients with antiphospholipid syndrome with previous arterial or VTE, VKA therapy should be titrated to a moderate intensity INR (range, 2.0 to 3.0) rather than higher intensity (range, 3.0 to 4.5). • For discontinuations of VKA therapy, it is suggested that discontinuation be done abruptly rather than gradual tapering of the dose. • For initiation of intravenous (IV) UFH, the initial bolus and rate of continuous infusion should be weight adjusted or fixed-dose rather than alternative regimens. • In outpatients with VTE receiving subcutaneous (SC) UFH, dosing should be weight-based without monitoring rather than fixed or weight-adjusted dosing with monitoring. • A reduction in therapeutic LMWH dose is suggested in patients with severe renal insufficiency rather than using standard doses. • In patients with VTE and body weight >100 kg, the treatment dose of fondaparinux should be increased from 7.5 to 10 mg/day SC. • For INRs between 4.5 and 10.0 with VKA therapy and no evidence of bleeding, routine use of vitamin K is not recommended. • For INRs >10.0 with VKA therapy and no evidence of bleeding, it is suggested that oral vitamin K be administered. • In patients initiating VKA therapy, routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy is not recommended. • For VKA-associated major bleeding, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate is suggested over plasma. Additional use of vitamin K 5 to 10 mg administered by slow IV injection is recommended rather than reversal with coagulation factors alone. <u>Prevention of VTE in nonsurgical patients</u> • Acutely ill hospitalized medical patients at increased risk of thrombosis: anticoagulant thromboprophylaxis with LMWH, low dose UFH (two or three times daily), or fondaparinux is recommended. Choice should be based on patient preference, compliance, and ease of administration, as well as on local factors affecting acquisition costs. • Acutely ill hospitalized patients at low risk of thrombosis: pharmacologic or mechanical prophylaxis is not recommended. • Acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding: anticoagulant thromboprophylaxis is not recommended. • Acutely ill hospitalized medical patients at increased risk for thrombosis who are bleeding or at high risk of major bleeding: optimal use of mechanical

Clinical Guideline	Recommendation(s)
	thromboprophylaxis is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, it is suggested that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis. • Acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis: extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay is suggested against. • Critically ill patients: routine ultrasound screening for deep vein thrombosis (DVT) is suggested against. • Critically ill patients: use of LMWH or low dose UFH thromboprophylaxis is suggested over no prophylaxis. • Critically ill patients who are bleeding or are at high risk for major bleeding: use of mechanical thromboprophylaxis until the bleeding risk decreases is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, pharmacologic thromboprophylaxis is suggested to be substituted for mechanical thromboprophylaxis. • Outpatients with cancer who have no additional risk factors for VTE: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is not recommended. • Outpatients with solid tumors who have additional risk factors for VTE with low risk of bleeding: prophylaxis with LMWH or low dose UFH is suggested over no prophylaxis. • Outpatients with cancer and indwelling central venous catheters: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is suggested against. • Chronically immobilized patients residing at home or at a nursing home: routine thromboprophylaxis is suggested against. • Long distance travelers at increased risk of VTE: frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible is suggested. • Long distance travelers at increased risk of VTE: use of properly fitted, below-knee graduated compression stockings during travel is suggested. For all other long distance travelers, use of graduated compression stockings is suggested against. • Long distance travelers: use of aspirin or anticoagulants to prevent VTE is suggested against. • Patients with asymptomatic thrombophilia: long term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE is not recommended. <u>Prevention of VTE in nonorthopedic surgical patients</u> • General and abdominal-pelvic surgery patients at very low risk for VTE: no specific pharmacologic or mechanical prophylaxis is recommended for use other than early ambulation. • General and abdominal-pelvic surgery patients at low risk for VTE: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are not at high risk major bleeding complications: LMWH, low dose UFH, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are at high risk for major bleeding complication or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at high risk for VTE who are not at high risk for major bleeding complications: LMWH or low dose UFH is recommended over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis.

Clinical Guideline	Recommendation(s)
	• High-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications: extended duration (four weeks) of LMWH prophylaxis is recommended over limited duration prophylaxis. • High-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • General and abdominal-pelvic surgery patients at high risk for VTE in whom both LMWH and UFH are contraindicated or unavailable and who are not at high risk for major bleeding complications: low dose aspirin, fondaparinux, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients: it is suggested that an inferior vena cava filter not be used for primary VTE prevention. • General and abdominal-pelvic surgery patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. • Cardiac surgery patients with an uncomplicated postoperative course: mechanical prophylaxis is suggested over either no prophylaxis or pharmacologic prophylaxis. • Cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications: adding pharmacologic prophylaxis with low dose UFH or LMWH to mechanical prophylaxis is suggested. • Thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding: low dose UFH or LWMH is suggested over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • Thoracic surgery patients who are at high risk for major bleeding: mechanical prophylaxis over no prophylaxis is suggested until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • Craniotomy patients: mechanical prophylaxis is suggested over no prophylaxis or pharmacologic prophylaxis. • Craniotomy patients at very high risk for VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Patients undergoing spinal surgery: mechanical prophylaxis is suggested over no prophylaxis, UFH, or LMWH. • Patients undergoing spinal surgery at high risk of VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Major trauma patients: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Major trauma patients at high risk for VTE: it is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis when not contraindicated by lower extremity injury. • Major trauma patients in whom LMWH and low dose UFH are contraindicated: mechanical prophylaxis is suggested over no prophylaxis when not contraindicated by lower extremity injury. It is suggested that either LMWH or low dose UFH be added when the risk of bleeding diminishes or the contraindication to heparin resolves. • Major trauma patients: it is suggested that an interior vena cava filter not be used for primary VTE prevention.

Clinical Guideline	Recommendation(s)
	• Major trauma patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. <u>Prevention of VTE in orthopedic surgery patients</u> • Total hip arthroplasty or total knee arthroplasty: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, aspirin, or an intermittent pneumatic compression device. • Hip fracture surgery: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, low dose UFH, adjusted-dose VKA, aspirin, or intermittent pneumatic compression device. • Patients undergoing major orthopedic surgery (total hip arthroplasty, total knee arthroplasty, hip fracture surgery) and receiving LMWH as thromboprophylaxis: it is recommended to start either 12 hours or more preoperatively or postoperatively rather than within four hours or less preoperatively or postoperatively. • Total hip or knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, or aspirin. • Hip replacement surgery, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, low dose UFH, adjusted-dose VKA, or aspirin. • Major orthopedic surgery: it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days. • Major orthopedic surgery: it is suggested to use dual prophylaxis with an antithrombotic agent and an intermittent pneumatic compression device during the hospital stay. • Major orthopedic surgery in patients at an increased risk of bleeding: intermittent pneumatic compression device or no prophylaxis is suggested over pharmacologic prophylaxis. • Major orthopedic surgery in patients who decline or are uncooperative with injections or intermittent pneumatic compression device: apixaban or dabigatran etexilate mesylate (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran etexilate mesylate are unavailable) is recommended over alternative forms of prophylaxis. • Major orthopedic surgery in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical prophylaxis: inferior vena cava filter placement for primary prevention of VTE is suggested against over no thromboprophylaxis. • Asymptomatic patients following major orthopedic surgery: Doppler ultrasound screening before hospital discharge is not recommended. • Patients with lower leg injuries requiring leg immobilization: no prophylaxis is suggested rather than pharmacologic thromboprophylaxis. • Knee arthroscopy in patients without a history of prior VTE: no thromboprophylaxis is suggested rather than prophylaxis. <u>Antithrombotic therapy for VTE disease</u> • Acute DVT of the leg or pulmonary embolism (PE) treated with VKA therapy: initial treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV

Clinical Guideline	Recommendation(s)
	or SC UFH) is recommended over no such initial treatment. • High clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment while awaiting the results of diagnostic tests. • Intermediate clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment if the results of diagnostic tests are expected to be delayed for more than four hours. • Low clinical suspicion of acute VTE or PE: it is suggested to not treat with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 hours. • Acute isolated distal DVT of the leg without severe symptoms or risk factors for extension: serial imaging of the deep veins for two weeks is suggested over initial anticoagulation. • Acute isolated distal DVT of the leg and severe symptoms or risk factors for extension: initial anticoagulation is suggested over serial imaging of the deep veins. • Acute isolated distal DVT of the leg in patients managed with initial anticoagulation: using the same approach as for patients with acute proximal DVT is recommended. • Acute isolated distal DVT of the leg who are managed with serial imaging: no anticoagulation if the thrombus does not extend is recommended; anticoagulation is suggested if the thrombus extends but remains confined to the distal veins; and anticoagulation is recommended if the thrombus extends into the proximal veins. • Acute DVT of the leg or PE: early initiation of VKA therapy is recommended over delayed initiation, and continuation of parenteral anticoagulation for a minimum on five days and until the INR is 2.0 or above for at least 24 hours. • Acute DVT of the leg or PE: LMWH or fondaparinux is suggested over IV or SC UFH. • Patients with acute DVT of the leg or PE receiving LMWH: once daily LMWH administration is suggested over twice daily administration. • Acute DVT of the leg and home circumstances are adequate: initial treatment at home is recommended over treatment in hospital. • Low risk PE and home circumstances are adequate: early discharge is suggested over standard discharge. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over catheter-directed thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over systemic thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over venous thrombectomy. • Acute DVT of the leg in patients who undergo thrombosis removal: the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal is recommended. • Acute DVT of the leg: use of an inferior vena cava filter in addition to anticoagulants is not recommended. • Acute proximal DVT of the leg in patients with contraindication to anticoagulation: use of an inferior vena cava filter is recommended. • Acute proximal DVT of the leg in patients with an inferior vena cava filter inserted as an alternative to anticoagulation: a conventional course of anticoagulant therapy is suggested if the risk of bleeding resolves. • Acute DVT of the leg: early ambulation is suggested over initial bed rest. • Acute VTE in patients receiving anticoagulant therapy: long term therapy is recommended over stopping anticoagulant therapy after about one week of initial therapy.

Clinical Guideline	Recommendation(s)
	• Acute symptomatic DVT of the leg: compression stockings are suggested. • Acute PE associated with hypotension in patients who do not have a high bleeding risk: systemically administered thrombolytic therapy is suggested over no such therapy. • In most patients with acute PE not associated with hypotension: systemically administered thrombolytic therapy is not recommended. • In selected patients with acute PE not associated with hypotension and with a low bleeding risk who initial clinical presentation or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension: administration of thrombolytic therapy is suggested. • Proximal DVT of the leg or PE provoked by surgery: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment of a longer time limited period, or extended therapy. • Proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment for a longer time limited period, extended therapy if there is high bleeding risk. Anticoagulation treatment for three months is suggested over extended therapy if there is a low or moderate bleeding risk. • Isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor: treatment with anticoagulation for three months is suggested over treatment for a shorter period, and anticoagulation treatment for three months is recommended over treatment of longer time limited period or extended therapy. • Unprovoked DVT of the leg or PE: treatment with anticoagulation for three months is recommended over treatment of a shorter duration. After three months, patients should be evaluated for the risk-benefit ratio of extended therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a low or moderate bleeding risk: extended anticoagulant therapy is suggested over three months of therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a high bleeding risk: three months of anticoagulant therapy is recommended over extended therapy. • First VTE that is an unprovoked isolated distal DVT of the leg: three months of anticoagulation therapy is suggested over extended therapy in those with a low or moderate bleeding risk, and three months of anticoagulant treatment is recommended in those with a high bleeding risk. • Second unprovoked VTE or PE: extended anticoagulant therapy is recommended over three months of therapy in those who have a low bleeding risk, and extended anticoagulant therapy is suggested in patients with a moderate bleeding risk. • Second unprovoked VTE or PE in patients with a high bleeding risk: three months of anticoagulant therapy is suggested over extended therapy. • DVT of the leg or PE and active cancer: if the risk of bleeding is not high, extended anticoagulation therapy is recommended over three months of therapy, and if there is a high bleeding risk, extended anticoagulant therapy is suggested. • DVT of the leg or PE in patients treated with VKA: a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended over a lower (<2.0) or higher (range, 3.0 to 5.0) range for all treatment durations. • DVT of the leg or PE in patients with no cancer: VKA therapy is suggested over LMWH for long-term therapy. For patients with DVT or PE and no cancer who are not treated with VKA therapy, LMWH is suggested over dabigatran etexilate mesylate or rivaroxaban for long term therapy. • DVT of the leg or PE and cancer: LMWH is suggested over VKA therapy. In patients with DVT of the leg or PE and cancer who are not treated with LMWH, VKA is suggested over dabigatran etexilate mesylate or rivaroxaban for long-

Clinical Guideline	Recommendation(s)
	term therapy. • DVT of the leg or PE in patients who receive extended therapy: treatment with the same anticoagulant chosen for the first three months is suggested. • Patients incidentally found to have asymptomatic DVT of the leg or PE: treatment with the same anticoagulant is suggested as for comparable patients with symptomatic DVT or PE. • In patients with chronic thromboembolic pulmonary hypertension, extended anticoagulation is recommended over stopping therapy. • Superficial vein thrombosis of the lower limb of at least 5 cm in length: use of a prophylactic dose of fondaparinux or LMWH for 45 days is suggested over no anticoagulation. • Superficial vein thrombosis in patients treated with anticoagulation: fondaparinux 2.5 mg/day is suggested over a prophylactic dose of LMWH. • Upper-extremity DVT that involves the axillary or more proximal veins: acute treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) over no such acute treatment. • Acute upper-extremity DVT that involves the axillary or more proximal veins: LMWH or fondaparinux is suggested over IV or SC UFH, and anticoagulation therapy alone is suggested over thrombolysis. • Upper-extremity DVT in patients undergoing thrombolysis: the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis is recommended. • In most patients with upper-extremity DVT that is associated with a central venous catheter: it is suggested that the catheter not be removed if it is functional and there is an ongoing need for the catheter. • Upper-extremity DVT that involves the axillary or more proximal veins: a minimum duration of anticoagulation of three months is suggested over a shorter duration. • Upper-extremity DVT that is associated with a central venous catheter that is removed: three months of anticoagulation is recommended over a longer duration of therapy in patients with no cancer, and this is suggested in patients with cancer. • Upper-extremity DVT that is associated with a central venous catheter that is not removed: it is recommended that anticoagulation is continued as long as the central venous catheter remains over stopping after three months of treatment in patients with cancer, and this is suggested in patients with no cancer. • Upper-extremity DVT that is not associated with a central venous catheter or with cancer: three months of anticoagulation is recommended over a longer duration of therapy. • Acute symptomatic upper-extremity DVT: use of compression sleeves or venoactive medications is suggested against. • Symptomatic splanchnic vein thrombosis: anticoagulation is recommended over no anticoagulation. • Symptomatic hepatic vein thrombosis: anticoagulation is suggested over no anticoagulation. • In patients with incidentally detected splanchnic vein thrombosis or hepatic vein thrombosis: no anticoagulation is suggested over anticoagulation. <u>Antithrombotic therapy for atrial fibrillation (AF)</u> • Patients with AF, including those with paroxysmal AF, who are at low risk of stroke: no therapy is suggested over antithrombotic therapy. For patients who choose antithrombotic therapy, aspirin is suggested over oral anticoagulation or combination therapy with aspirin and clopidogrel. • Patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke: oral anticoagulation is recommended over no therapy. Oral

Clinical Guideline	Recommendation(s)
	anticoagulation is suggested over aspirin or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel are suggested over aspirin. • Patients with AF, including those with paroxysmal AF, who are at high risk of stroke: oral anticoagulation is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel is recommended over aspirin. • Patients with AF, including those with paroxysmal AF: for recommendations in favor of oral anticoagulation, dabigatran etexilate mesylate 150 mg twice daily is suggested over adjusted-dose VKA therapy (target INR range, 2.0 to 3.0). • Patients with AF and mitral stenosis: adjusted-dose VKA therapy is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take adjusted-dose VKA therapy, combination therapy with aspirin and clopidogrel is recommended over aspirin alone. • Patients with AF and stable coronary artery disease and who choose oral anticoagulation: adjusted-dose VKA therapy alone is suggested over the combination of adjusted-dose VKA therapy and aspirin. • Patients with AF at high risk of stroke during the first month after placement of a bare-metal stent or the first three to six months after placement of a drug-eluting stent: triple therapy (e.g., VKA therapy, aspirin, and clopidogrel) is suggested over dual antiplatelet therapy (e.g., aspirin and clopidogrel). After this initial period, a VKA plus a single antiplatelet agent is suggested over a VKA alone. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate risk of stroke during the first 12 months after placement of a stent: dual antiplatelet therapy is suggested over triple therapy. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate to high risk of stroke who experience an acute coronary syndrome (ACS) and do not undergo stent placement, for the first 12 months: adjusted-dose VKA therapy plus single antiplatelet therapy is suggested over dual antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at low risk of stroke: dual antiplatelet therapy is suggested over adjusted-dose VKA therapy plus single antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF being managed with a rhythm control strategy: it is suggested that antithrombotic therapy decisions follow the general risk-based recommendations for patients with nonrheumatic AF, regardless of the apparent persistence of normal sinus rhythm. • Patients with atrial flutter: it is suggested that antithrombotic therapy decisions follow the same risk-based recommendations as for AF. <u>Antithrombotic therapy for ischemic stroke</u> • In patients with acute ischemic stroke or transient ischemic attack (TIA), early (within 48 hours) aspirin 160 to 325 mg is recommended over therapeutic parenteral anticoagulation. • In patients with a history of noncardioembolic ischemic stroke or TIA, aspirin (75 to 100 mg daily), clopidogrel (75 mg daily), aspirin-dipyridamole extended-release (ER) (25 mg-200 mg twice daily) or cilostazol (100 mg twice daily) is

Clinical Guideline	Recommendation(s)
	recommended over oral anticoagulants, the combination of clopidogrel plus aspirin or triflusal. o Clopidogrel or aspirin-dipyridamole ER is recommended over aspirin or cilostazol. • In patients with a history of ischemic stroke or TIA and AF, oral anticoagulation with dabigatran 150 mg twice daily is recommended over VKA therapy. o In patients who are unable to or choose not to take an oral anticoagulant, the combination of aspirin plus clopidogrel is recommended over aspirin alone. <u>Primary and secondary prevention of cardiovascular disease</u> • Patients ≥50 years of age without symptomatic cardiovascular disease: low dose aspirin (75 to 100 mg/day) is suggested over no aspirin therapy. • Patients with established coronary artery disease: long term single antiplatelet therapy with aspirin (75 to 100 mg/day) or clopidogrel (75 mg/day) is recommended over no antiplatelet therapy, and single antiplatelet therapy is suggested over dual antiplatelet therapy. • Patients in the first year after ACS who have not undergone percutaneous coronary intervention (PCI): dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day or clopidogrel 75 mg/day plus low dose aspirin 75 to 100 mg/day) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients in the first year after an ACS who have undergone PCI with stent placement: dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day, clopidogrel 75 mg/day plus low dose aspirin, or prasugrel 10 mg/day plus low dose aspirin) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients with anterior myocardial infarction (MI) and left ventricular thrombus, or at high risk for left ventricular thrombus, who do not undergo stenting: warfarin plus low dose aspirin (75 to 100 mg/day) is recommended over single antiplatelet therapy or dual antiplatelet therapy for the first three months. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, single antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who undergo bare-metal stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for one month is suggested over dual antiplatelet therapy. Warfarin and single antiplatelet therapy for the second and third month post-bare-metal stent is suggested over alternative regimens and alternative time frames for warfarin use. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus who undergo drug-eluting stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for up to three to six months is suggested over alternative regimens and alternative durations of warfarin therapy. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective PCI with placement of bare-metal stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75

Clinical Guideline	Recommendation(s)
	mg/day for one month is recommended over single antiplatelet therapy. For the subsequent 11 months, dual antiplatelet therapy with combination low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. • Patients who have undergone elective PCI with placement of drug-eluting stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for three to six months is recommended over single antiplatelet therapy. After three to six months, continuation of dual antiplatelet therapy with low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested to be continued until 12 months over antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective bare-metal stent or drug-eluting stent placement: low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is recommended over cilostazol in addition to these drugs. Aspirin 75 to 100 mg/day or clopidogrel 75 mg/day as part of dual antiplatelet therapy is suggested over the use of either drug with cilostazol. Cilostazol 100 mg twice daily as a substitute for either low dose aspirin or clopidogrel as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class is suggested. • Patients with coronary artery disease undergoing elective PCI but no stent placement: for the first month dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients with systolic left ventricular dysfunction without established coronary artery disease and no left ventricular thrombus: it is suggested that antiplatelet therapy and warfarin not be used. • Patients with systolic left ventricular dysfunction without established coronary artery disease with identified acute left thrombus: moderate intensity warfarin for at least three months is suggested. • Patients with systolic left ventricular dysfunction and established coronary artery disease: recommendations are as per the established coronary artery disease recommendations. <u>Antithrombotic therapy in peripheral artery disease (PAD)</u> • In patients with asymptomatic PAD, aspirin 75 to 100 mg daily is recommended. • In patients with symptomatic PAD, long-term therapy with aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) is recommended for secondary prevention of cardiovascular events. Dual antiplatelet therapy or the combination of an antiplatelet agent with moderate-intensity warfarin is not recommended. • Use of cilostazol in addition to aspirin or clopidogrel is recommended in patients with intermittent claudication refractory to exercise therapy and smoking cessation. • Use of prostanoids in addition to aspirin or clopidogrel is recommended in patients with symptomatic PAD and critical leg ischemia who are not candidates for vascular intervention. • In patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting, long-term therapy with aspirin or clopidogrel is recommended over dual antiplatelet therapy. • Following peripheral artery bypass graft surgery, long-term therapy with aspirin

Clinical Guideline	Recommendation(s)

	or clopidogrel is recommended over the combination of antiplatelet agent plus warfarin. Clopidogrel plus aspirin for one year is recommended in patients undergoing below-knee bypass graft surgery with prosthetic grafts.
	• In patients with asymptomatic carotid stenosis, aspirin 75 to 100 mg daily is recommended.
	• In patients with symptomatic carotid stenosis, long-term therapy with clopidogrel (75 mg daily) or aspirin/dipyridamole ER (25 mg/200 mg twice daily) is recommended over aspirin (75 to 100 mg daily).
	
	<u>Antithrombotic and thrombolytic therapy for valvular disease</u>
	• Antithrombotic therapy in the first three months after surgery:
	  o In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, aspirin (50 to 100 mg/day) over VKA therapy is suggested in the first three months.
	  o In patients with transcatheter aortic bioprosthetic valves, aspirin (50 to 100 mg/day) plus clopidogrel (75 mg/day) is suggested over VKA therapy and over no antiplatelet therapy in the first three months.
	  o In patients with a bioprosthetic valve in the mitral position, VKA therapy over no VKA therapy for the first three months after valve insertion is suggested.
	• Long-term antithrombotic therapy for patients with bioprosthetic valves:
	  o In patients with bioprosthetic valves in normal sinus rhythm, aspirin therapy over no aspirin therapy after three months postoperative is suggested.
	• Early postoperative bridging to intermediate/long-term therapy (postoperative day 0 to 5):
	  o In patients with mechanical heart valves, bridging with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) over intravenous (IV) therapeutic UFH until stable on VKA therapy.
	• Long-term antithrombotic therapy for patients with mechanical valves:
	  o VKA therapy is recommended over no VKA therapy for long-term management.
	• Intensity of VKA therapy for patients with mechanical aortic valve prostheses:
	  o VKA therapy at a target of 2.5 over lower targets is suggested. A target of 2.5 is recommended over higher targets.
	• Intensity of VKA therapy for patients with mechanical mitral valve prostheses:
	  o VKA therapy with a target of 3.0 over lower INR targets is suggested.
	• Intensity of VKA therapy in patients with double mechanical valve or with additional risk factors:
	  o VKA therapy with a target of 3.0 is suggested over target INR 2.5.
	• Antiplatelet agent in addition to VKA therapy for patients with mechanical aortic or mitral valve prostheses:
	  o Patients who are at low risk of bleeding, adding over not adding an antiplatelet agent such as low-dose (50 to 100 mg/day) to VKA therapy is suggested.
	• For patients with mechanical aortic or mitral valves VKA therapy over antiplatelet agents is recommended.
	• In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, the use of antiplatelet therapy for the first three months is suggested over VKA therapy.
	• In patients undergoing aortic valve repair, aspirin (50 to 100 mg/day) is suggested over VKA therapy.

American Heart Association/American Stroke Association:	<u>Prevention of stroke in nonvalvular AF</u> • Apixaban, dabigatran etexilate mesylate, rivaroxaban and warfarin are all indicated for the prevention of first and recurrent stroke in patients with

Clinical Guideline	Recommendation(s)
Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation: A Science Advisory for Healthcare Professionals (2012)[6]	nonvalvular AF. • The choice of antithrombotic treatment should be individualized based on risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range if the patient has been taking warfarin. • Dabigatran etexilate mesylate 150 mg twice daily is an efficacious alternative to warfarin for the prevention of first and recurrent stroke in patients with nonvalvular AF who have at least one additional risk factor and a creatinine clearance (CrCl) >30 mL/min. • The use of dabigatran etexilate mesylate 75 mg twice daily in patients with AF and at least one additional risk factor who have a low CrCl (15 to 30 mL/min) may be considered, but its safety and efficacy have not been established. The use of dabigatran etexilate mesylate in patients with more severe renal failure is not recommended in patients with a CrCl <15 mL/min. • Apixaban 5 mg twice daily is an effective alternative to aspirin in patients with nonvalvular AF deemed unsuitable for VKA therapy with one or more additional risk factor and no more than one of the following characteristics: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL. • Although safety and efficacy have not been established, apixaban 2.5 mg twice daily may be considered as an alternative to aspirin in patients with nonvalvular AF deemed unsuitable for VKA therapy who have one or more additional risk factor and two or more of the following criteria: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL. • Apixaban 5 mg twice daily is a relatively safe and efficacious alternative to warfarin in patients with nonvalvular AF deemed appropriate for VKA therapy that have one or more risk factors and no more than one of the following: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. • Apixaban should not be used if the CrCl is <25 mL/min. • In patients with nonvalvular AF who are at moderate to high risk of stroke (prior history of transient ischemic attack [TIA], stroke, or systemic embolization or have two additional risk factors), rivaroxaban 20 mg daily is a reasonable alternative to warfarin. • In patients with renal impairment and nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or two or more additional risk factors), with a CrCl 15 to 50 mL/min, rivaroxaban 15 mg daily may be considered; however, its safety and efficacy have not been established. • Rivaroxaban should not be used if the CrCl is <15 mL/min. • The safety and efficacy of combining dabigatran, rivaroxaban, or apixaban with an antiplatelet agent have not been established.
American Heart Association/American College of Cardiology/ Heart Rhythm Society: **Guideline for the Management of Patients with Atrial Fibrillation (2014)[7]**	Recommendations for risk-based antithrombotic therapy: Class I • In patients with atrial fibrillation (AF), antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding and the patient's values and preferences (Level of Evidence: C). • Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF patter is paroxysmal, persistent, or permanent (Level of Evidence: B). • In patients with nonvalvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (Level of Evidence: B). • For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) should be based on type and location of the prosthesis (Level of Evidence: B). • For patients with nonvalvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc

Clinical Guideline	Recommendation(s)
	score ≥2, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran, rivaroxaban, or apixaban (Level of Evidence: B). • For patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable (Level of Evidence: A) • For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor is recommended (Level of Evidence: C). • Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks (Level of Evidence: C). • Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding (Level of Evidence: C). • For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated (Level of Evidence: C). • Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (Level of Evidence: B). • For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF (Level of Evidence: C). Class IIa • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Level of Evidence: B). • For patients with nonvalvular AF with a CHA_2DS_2-VASc score of ≥2 and who have end-stage chronic kidney disease (creatine clearance <15 mL/min) or who are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (Level of Evidence: B). Class IIb • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (Level of Evidence: C). • For patients with nonvalvular AF and moderate-to-severe chronic kidney disease with a CHA_2DS_2-VASc score of ≥2, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established (Level of Evidence: C). • In patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding ant the site of peripheral arterial puncture (Level of Evidence: C). • Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (Level of Evidence: B). Class III: No Benefit • The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (Level of Evidence: C). Class III: Harm

Clinical Guideline	Recommendation(s)
	• The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (Level of Evidence: B). <u>Recommendations for rate control:</u> Class I • Control of the ventricular rate using a beta blocker or nondihydropyridine (non-DHP) calcium channel blocker (CCB) is recommended for patients with paroxysmal, persistent, or permanent AF (Level of Evidence: B). • Intravenous administration of a beta blocker or non-DHP CCB is recommended to slow the ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (Level of Evidence: B). • In patients who experience AF-related symptoms during activity, the adequacy of heart rate control should be assessed during exertion, adjusting pharmacological treatment as necessary to keep the ventricular rate within the physiological range (Level of Evidence: C). Class IIa • A heart rate control (resting heart rate <80 beats per minute [bpm]) strategy is reasonable for symptomatic management of AF (Level of Evidence: B). • Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (Level of Evidence: B). • Atrioventricular (AV) nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate and rhythm control is not achievable (Level of Evidence: B). Class IIb • A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as long as patients remain asymptomatic and left ventricular systolic function is preserved (Level of Evidence: B). • Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated (Level of Evidence: C). Class III: Harm • AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications (Level of Evidence: C). • Non-DHP CCBs should not be used in patients with decompensated HF as these may lead to further hemodynamic compromise (Level of Evidence: C). • In patients with pre-excitation and AF, digoxin, non-DHP CCBs, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation. (Level of Evidence: B). • Dronedarone should not be used to control the ventricular rate in patients with permanent AF as it increases the risk of the combined endpoint of stroke, myocardial infarction, systemic embolism, or cardiovascular death (Level of Evidence: B). <u>Recommendations for Thromboembolism Prevention</u>: Class I • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method used to restore sinus rhythm (Level of Evidence: B). • For patients with AF or atrial flutter of more than 48 hours duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated (Level of Evidence: C).

Clinical Guideline	Recommendation(s)

	• For patients with AF or atrial flutter of less than 48-hour duration and with high risk stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy (Level of Evidence: C).
	• Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile (Level of Evidence: C).
	Class IIa
	• For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least four weeks (Level of Evidence: B).
	• For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least three weeks prior to and four weeks after cardioversion (Level of Evidence: C).
	Class IIb
	• For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for post cardioversion oral anticoagulation (Level of Evidence: C).
	
	<u>Recommendations for pharmacological cardioversion</u>
	Class I
	• Flecainide, dofetilide, propafenone, and intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (Level of Evidence: A).
	Class IIa
	• Administration of oral amiodarone is a reasonable option for pharmacological cardioversion of AF (Level of Evidence: A).
	• Propafenone or flecainide ("pill-in-the-pocket") in addition to a beta blocker or non-DHP CCB is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (Level of Evidence: B).
	Class III: Harm
	• Dofetilide therapy should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause torsades de pointes (Level of Evidence: B).
	
	<u>Recommendations for antiarrhythmic drugs to maintain sinus rhythm</u>
	Class I
	• Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended (Level of Evidence: C).
	• The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities (Level of Evidence: A):
	  o Amiodarone
	  o Dofetilide
	  o Dronedarone
	  o Flecainide
	  o Propafenone
	  o Sotalol

Clinical Guideline	Recommendation(s)
	• The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug (Level of Evidence: C). • Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated (Level of Evidence: C). Class IIa • A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy (Level of Evidence: C). Class IIb • It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF when the drug has reduced the frequency or symptoms of AF (Level of Evidence: C). Class III: Harm • Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent (Level of Evidence: C), including dronedarone (Level of Evidence: B). • Dronedarone should not be used for treatment of AF in patients with New York Heart Association class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks. (Level of Evidence: B). <u>Upstream therapy</u> Class IIa • An angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF with reduced left ventricular ejection fraction (Level of Evidence: B). Class IIb • Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (Level of Evidence: B). • Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (Level of Evidence: A). Class III: No Benefit • Therapy with an ACE inhibitor, ARB, or statin is not beneficial for primary prevention of AF in patients without cardiovascular disease (Level of Evidence: B).

American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2014)[8]**	<u>Recommendations for Nonvalvular Atrial Fibrillation:</u>
	• For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (~30 days) for AF is reasonable within six months of the index event (Level of Evidence: C).
	• VKA therapy (Level of Evidence: A), apixaban, dabigatran and rivaroxaban (Level of Evidence: B) are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent.
	  o Selection of agent should be individualized based on risk factors, cost, tolerability, patient preference, drug interactions and other characteristics including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.
	• Target INR for patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent or permanent AF on VKA therapy is 2.5 (range 2.0 to 3.0) (Level of Evidence: A).
	• Combination oral anticoagulation (warfarin or a newer agent) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA.
	  o Combination therapy is reasonable in patients with clinically apparent coronary artery disease particularly an acute coronary syndrome or stent placement (Level of Evidence: C).

Clinical Guideline	Recommendation(s)

	• For patients with ischemic stroke or TIA and AF who unable to take oral anticoagulants, aspirin alone is recommended (Level of Evidence: A).
	  o Adding clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable (Level of Evidence: B).
	• For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms (Level of Evidence: B).
	• In the presence of high risk for hemorrhagic conversion, it is reasonable to delay initiation of oral anticoagulation beyond 14 days (Level of Evidence: B).
	• For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH (or equivalent) is reasonable, depending on perceived risk for thromboembolism and bleeding (Level of Evidence: C).
	• The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain (Level of Evidence: B).
	
	<u>Recommendations for Acute MI and LV Thrombus:</u>
	• Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months is recommended in most patients with ischemic stroke or TIA in this setting (Level of Evidence: C).
	  o Additional antiplatelet therapy for cardiac protection may be guided by recommendations such as those from the American College of Chest Physicians.
	• Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable LV mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging (Level of Evidence: C).
	• In patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation or anterior or apical wall-motion abnormalities with an LV ejection fraction <40% who are intolerant to VKA therapy because of nonhemorrhagic adverse events, treatment with an LMWH, dabigatran, rivaroxaban, or apixaban for three months may be considered as an alternative to VKA therapy for prevention of recurrent stroke or TIA (Level of Evidence: C).
	
	<u>Recommendations for Cardiomyopathy:</u>
	• In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or LV thrombus, anticoagulant therapy with a VKA is recommended for ≥3 months (Level of Evidence: C).
	• In patients with ischemic stroke or TIA in the setting of a mechanical LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) is reasonable in the absence of major contraindications (Level of Evidence: C).
	• In patients with ischemic stroke or TIA in sinus rhythm with either dilated cardiomyopathy (LV ejection fraction ≤35%) or restrictive cardiomyopathy without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized (Level of Evidence: B).
	• In patients with ischemic stroke or TIA in sinus rhythm with dilated cardiomyopathy (LV ejection fraction ≤35%), restrictive cardiomyopathy, or a mechanical LVAD who are intolerant to VKA therapy because of nonhemorrhagic adverse events, the effectiveness of treatment with dabigatran, rivaroxaban, or apixaban is uncertain compared with VKA therapy for prevention of recurrent stroke (Level of Evidence: C).

Clinical Guideline	Recommendation(s)
	Recommendations for Mitral Stenosis, Mitral Regurgitation, Mitral Prolapse, Mitral Annular Calcification, and Aortic Valve Disease: • For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with INR target of 2.5 (range, 2.0 to 3.0) is recommended (Level of Evidence: A). • For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (e.g., carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered instead of antiplatelet therapy (Level of Evidence: C). • For patients with rheumatic mitral valve disease who are prescribed VKA therapy after an ischemic stroke or TIA, antiplatelet therapy should not be routinely added (Level of Evidence: C). • For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered (Level of Evidence: C). • For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended (Level of Evidence: C). • For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification (Level of Evidence: C). • For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse (Level of Evidence: C). Recommendations for Prosthetic Heart Valves: • For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0 to 3.0) (Level of Evidence: B). • For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5 to 3.5) (Level of Evidence: B). • For patients with a mechanical aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/day to VKA therapy is recommended (Level of Evidence: B). • For patients with a mechanical heart valve who have an ischemic stroke or systemic embolism despite adequate antithrombotic therapy, it is reasonable to intensify therapy by increasing the dose of aspirin to 325 mg/day or increasing the target INR, depending on bleeding risk (Level of Evidence: C). • For patients with a bioprosthetic aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and no other indication for anticoagulation therapy beyond three to six months form the valve placement, long-term therapy with aspirin 75 to 100 mg/day is recommended in preference to long-term anticoagulation (Level of Evidence: C). • For patients with a bioprosthetic aortic or mitral valve who have a TIA, ischemic stroke, or systemic embolism despite antiplatelet therapy, the addition of VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered (Level of Evidence: C). Recommendations for Noncardioembolic Stroke or TIA: • For patients with noncardioembolic ischemic stroke or TIA, the use of

Clinical Guideline	Recommendation(s)
	antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Level of Evidence: A). • Aspirin (50 to 325 mg/day) monotherapy (Level of Evidence: A) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Level of Evidence: B) is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. • Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole (Level of Evidence: B). This recommendation also applies to patients who are allergic to aspirin. • The selection of an antiplatelet agent should be individualized on the basis of patient risk facto profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics (Level of Evidence: C). • The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stork or TIA and for continuation for 90 days (Level of Evidence: B). • The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for two to three years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA (Level of Evidence: A). • For patients who have an ischemic stroke or TIA while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have had an event while receiving aspirin (Level of Evidence: C). • For patients with a history of ischemic stroke or TIA, AF and coronary artery disease, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events (Level of Evidence: C). Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet or VKA therapy. • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Level of Evidence: A).

III. Indications

The Food and Drug Administration (FDA)-approved indications for edoxaban 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 Edoxaban[1]

Indication	Edoxaban
Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation[†]	✔
Treatment of deep vein thrombosis and pulmonary embolism following 5 to 10 days of initial therapy with a parenteral anticoagulant	✔

[†]Edoxaban should not be used in patients with CrCl >95 mL/min because of an increased risk of ischemic stroke compared to warfarin.

IV. Pharmacokinetics

The pharmacokinetic parameters of edoxaban are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Edoxaban[3]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
Edoxaban	62	50	M-4 (<10% exposure of edoxaban)	10 to 14

V. Drug Interactions

Co-administration of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding. Use of edoxaban with rifampin should be avoided due to P-glycoprotein induction.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with edoxaban are listed in Table 5. The boxed warning is included in Table 6.

Table 5. Adverse Drug Events (%) Reported with Edoxaban[2]

Adverse Event	Edoxaban
Abnormal hepatic function tests	5 to 8
Anemia	2
Decreased hemoglobin	1
Dermal hemorrhage	6
Epistaxis	5
Gastrointestinal bleeding	3
Gastrointestinal hemorrhage	2 to 4
Hematuria	≤2
Hemorrhage	22
Oral hemorrhage	≤3
Pharyngeal bleeding	≤3
Rash	4
Urethral bleeding	≤2
Vaginal hemorrhage	9

✓ Percent not specified.
- Event not reported.

Table 6. Boxed Warning for Edoxaban[1]

WARNING
WARNING: REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) >95 ML/MIN; PREMATURE DISCONTINUATION OF EDOXABAN INCREASES THE RISK OF ISCHEMIC EVENTS; SPINAL/EPIDURAL HEMATOMA Reduced efficacy in nonvalvular atrial fibrillation patients with CrCl >95 ml/min • Edoxaban should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used. Premature discontinuation of edoxaban increases the risk of ischemic events

- Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If edoxaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance.

Spinal/epidural hematoma

- Epidural or spinal hematomas may occur in patients treated with edoxaban who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
  - use of indwelling epidural catheters
  - concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
  - a history of traumatic or repeated epidural or spinal punctures
  - a history of spinal deformity or spinal surgery
  - optimal timing between the administration of edoxaban and neuraxial procedures is not known
- Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
- Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

VII. Dosing and Administration

The usual dosing regimens for edoxaban are listed in Table 7.

Table 7. Usual Dosing Regimens for Edoxaban[1]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Edoxaban	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: Tablet: 60 mg once daily Treatment of deep vein thrombosis and pulmonary embolism†: Tablet: 60 mg once daily	Safety and efficacy have not been established in pediatric patients.	Tablet: 15 mg 30 mg 60 mg

†Indicated for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for five to 10 days.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of edoxaban are summarized in Table 8.

Table 8. Comparative Clinical Trials with Edoxaban

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Giugliano et al.[9] (2013) ENGAGE AF-TIMI 48 Study Edoxaban 60 mg QD† vs edoxaban 30 mg QD† vs warfarin (adjusted dose to maintain an INR between 2.0 and 3.0) †Individuals had their dose halved (60 mg halved to 30 mg or 30 mg halved to 15 mg) if CrCl ≤ 50 mL/min, body weight ≤ 60 kg, or concomitant use of a P-glycoprotein inhibitor such as verapamil or	DB, DD, NI, RCT Patients ≥ 21 years of age with non-valvular atrial fibrillation documented by means of electrical tracing within the 12 months preceding randomization, a score of 2 or higher on the $CHADS_2$ risk assessment and anticoagulation therapy planned for the duration of the trial	N=21,105 (median follow-up 2.8 years)	Primary efficacy: Occurrence of the first stroke (ischemic or hemorrhagic) or of a systemic embolic event that occurred during treatment or within three days from the last dose taken Primary safety: Major bleeding during treatment Secondary: Composite of stroke, systemic embolism or death from cardiovascular causes	Primary efficacy: The annualized rate of stroke or systemic embolism during treatment was 1.50% (232 of 2,641 patients) with warfarin as compared with 1.18% (182 of 2,669 patients) with high-dose edoxaban (HR, 0.79; 97.5% CI, 0.63 to 0.99; P<0.001) and 1.61% (253 of 2,730 patients) with low-dose edoxaban (HR, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005). Primary safety: The annualized rate of major bleeding was 3.43% with warfarin compared with 2.75% with high-dose edoxaban (HR, 0.80; 95% CI, 0.71 to 0.91; P<0.001) and 1.61% with low-dose edoxaban (HR, 0.47; 95% CI, 0.41 to 0.55; P<0.001). The annualized rate of major gastrointestinal bleeding was higher with high-dose edoxaban, 1.51% compared with warfarin, 1.23% (HR, 1.23; 95% CI, 1.02 to 1.50; P=0.03). The rate was lowest with low-dose edoxaban at 0.82% (HR, 0.67; 95% CI, 0.53 to 0.83; P<0.001). Secondary: The key secondary end point of composite of stroke, systemic embolism or death from cardiovascular causes were 4.43% with warfarin compared with 3.85% for high-dose edoxaban tosylate (HR, 0.87; 95% CI, 0.78 to 0.96; P=0.005) and 4.23% for low-dose edoxaban tosylate (HR, 0.95; 95% CI, 0.86 to 1.05; P=0.32)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
quinidine				
Buller et al.[10] (2013) HOKUSAI-VTE Study Edoxaban 60 mg QD vs edoxaban 30 mg QD (patients with CrCl 30 to 50 mL/min, a body weight < 60 kg, or receiving a concomitant P-glycoprotein inhibitor such as verapamil or quinidine) vs warfarin (adjusted dose to maintain an INR between 2.0 and 3.0)	DB, NI, RCT Patients ≥ 18 years of age with objectively diagnosed, acute, symptomatic DVT or PE initially started on heparin therapy with either LMWH or unfractionated heparin	N=8,292 12 months	Primary Efficacy: Incidence of adjudicated symptomatic recurrent venous thromboembolism, defined as a composite of DVT or nonfatal or fatal PE Primary Safety: Incidence of adjudicated clinically relevant bleeding, defined as a composite of major or clinically relevant non major bleeding Secondary: Not reported	Primary Efficacy: A recurrence of venous thromboembolism during the overall study period occurred in 130 of 4118 patients (3.2%) in the edoxaban group and in 146 of 4122 patients (3.5%) in the warfarin group (HR, 0.89; 95% CI, 0.70 to 1.13; P<0.001). Primary Safety: Clinically relevant bleeding (major or non-major) occurred in 349 of 4118 patients (8.5%) in the edoxaban group as compared with 423 of 4122 patients (10.3%) in the warfarin group (HR, 0.81; 95% CI, 0.71 to 0.94; P=0.004). Secondary: Not reported
Fuji et al.[11] (2014) STARS E-3 Edoxaban 30 mg QD vs	DB, DD, RCT Men and women aged 20 to 84 years who were scheduled to undergo unilateral TKA, excluding revision	N=716 11 to 14 days	Primary: Composite of symptomatic PE and symptomatic and asymptomatic DVT, bleeding, adverse events	Primary: The composite primary efficacy occurred in 22 of 299 (7.4%) patients receiving edoxaban and 41 of 295 (13.9%) patients receiving enoxaparin (relative risk reduction, 46.8%), indicating non-inferiority (P<0.001) and superiority (P=0.010) of edoxaban relative to enoxaparin. The incidence of major bleeding events was 1.1% (4/354) compared with 0.3% (1/349) in the edoxaban and enoxaparin treatment groups,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enoxaparin 2000 IU SC BID	arthroplasty		Secondary: Proportion of patients with one or more thromboembolic events	respectively (P=0.373). The incidence of all bleeding events (major bleeding, clinically relevant non-major bleeding, and minor bleeding) was 22.3% (79/354) in the edoxaban group and 18.9% (66/349) in the enoxaparin group (P=0.265). The incidence of adverse events was slightly lower in the edoxaban group (66.9% [237/354]) compared with the enoxaparin group (73.4% [256/349]), and no difference was observed in the incidence of serious adverse events between the treatment groups. Secondary: The incidence of symptomatic DVT, proximal DVT, symptomatic PE, or VTE-related mortality, were 1.3% (4/299) in the edoxaban group and 0.7% (2/295) in the enoxaparin group (P=NS).

Drug regimen abbreviations: BID=twice daily, SC=subcutaneous, QD=once daily
Study abbreviations: AC=active control, ARR=absolute risk reduction, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, NI=non inferiority, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PP=per-protocol, PRO=prospective, RCT=randomized controlled trial, RR=relative risk
Miscellaneous abbreviations: ACS=acute coronary syndrome, AF=atrial fibrillation, CrCl= creatinine clearance, DVT=deep vein thrombosis, FDA=Food and Drug Administration, INR=International Normalized Ratio, LMWH=low molecular weight heparin, LVEF=left ventricular ejection fraction, MI=myocardial infarction, NSAID=nonsteroidal anti-inflammatory drug, PE=pulmonary embolism, TIA=transient ischemic attack, TKA=total knee arthroplasty, TTR=time in therapeutic range, UFH=unfractionated heparin, VKA=vitamin k antagonist, VTE=venous thromboembolism

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 Edoxaban

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Edoxaban	tablet	Savaysa®	$$$$$	N/A

N/A=Not available

X. Conclusions

Edoxaban is the newest factor Xa inhibitor recently approved for the reduction in the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (AF) patients as well as for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] There are currently no generic products available.

As with the other NOACs, edoxaban is predominately cleared by the kidneys. Recommendations per the package insert are to decrease the dose if CrCl is < 50 mL/min and to avoid use altogether in AF patients with normal renal function (CrCl is > 95 mL/min).[1] For the treatment of nonvalvular AF, the ENGAGE AF-TIMI 48 study demonstrated that high dose edoxaban (60 mg or 30 mg dose adjusted) was noninferior to adjusted dose warfarin for the reduction of the primary composite endpoint of stroke (ischemic or hemorrhagic) or systemic embolic event (P<0.001 for noninferiority). The rate of ischemic stroke was similar with high-dose edoxaban and warfarin but was higher with the low-dose edoxaban regimen.[9] Results from the HOKUSAI-VTE study demonstrated noninferiority of edoxaban to adjusted dose warfarin for the reduction of recurrent, symptomatic DVT and PE in

patients treated up to 12 months.[10] Edoxaban has demonstrated a favorable bleeding profile compared to warfarin except for more reports of gastrointestinal hemorrhages with the 60 mg dose.[9-11]

Although the use of this new anticoagulant has not been addressed in the most recent consensus guidelines, the guidelines do mention that all the other NOAC agents are appropriate alternatives to warfarin for the management of individuals with AF.[5-8] The 2014 American Heart Association/American College of Cardiology guidelines state that antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute relative risks of stroke and bleeding and the patient's values and preferences.[6]

Due to the lack of unanimous recommendations from guidelines preferring one of the newer agents over another, the reports of significant adverse drug reactions reported to the FDA, and the lack of long-term safety data, it is recommended that edoxaban be managed via the prior authorization process.

XI. Recommendations

No brand edoxaban product 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

1. Savaysa® [package insert]. Parsippany (NJ): Daiichi Sankyo Co.; 2015 September.
2. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited Dec 2015]. Available from: http://online.factsandcomparisons.com.
3. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2015 [cited 2015 Dec]. Available from: http://www.thomsonhc.com/.
4. Unger, EF. Atrial fibrillation, oral anticoagulant drugs, and their reversal agents. Rockville (MD): Food and Drug Administration (US); 2015 Oct 16 [cited 2015 Dec 14]. Available from: http://www.fda.gov/Drugs/NewsEvents/ucm467203.htm.
5. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(Suppl 2):7-47.
6. Furie KL, Goldstein LB, Albers GW, Khatri P, Neyens R, Turakhia MP, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012 Dec;43(12):3442-53.
7. January CT, Wann L, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1-e76. doi:10.1016/j.jacc.2014.03.022.
8. Kernan WN, Ovbiagele B, Black HR, Bravata DW, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45:2160-2236.
9. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013 Nov;369(22): 2093-104.
10. Buller HR, Decousus H, Grosso MA, Mercuri M, Middleldorp S, Prins MH, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013 Oct;369(15): 1406-1415.
11. Fuji T, Wang CJ, Fujita S, et al. Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxaparin for thromboprophylaxis after total knee arthroplasty: the STARS E-3 trial. Thromb Res. 2014 Dec;134(6):1198-204.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review of Toujeo®
Insulins: AHFS Class 682008
February 10, 2016

I. Overview

Insulins stimulate peripheral glucose uptake by skeletal muscle and fat, decrease hepatic glucose production, inhibit lipolysis and proteolysis, and enhance protein synthesis.[1-3] There are two types of insulin preparations currently available: human insulin and insulin analogs. Human insulin is derived from a biosynthetic process and is structurally identical to endogenous insulin. Insulin analogs are structurally different than human insulin. Each insulin analog differs in the addition, deletion, or substitution of amino acids on the B chain. These modifications lead to a faster onset and shorter duration of action (for rapid-acting insulin analogs) or slower absorption and a longer duration of action (for long-acting insulin analogs) than human insulins.[1,2]

The insulin preparations are further categorized based on their duration of action. Rapid- and short-acting insulins are administered as a bolus prior to meals to control postprandial glucose excursions. They may also be administered continuously via an infusion pump. Intermediate- and long-acting insulins are administered once or twice daily. They act as basal insulin to decrease hepatic glucose production and lower fasting plasma glucose concentrations.[1,2]

Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection.[1-4] All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Two agents are also formulated with a higher concentration, regular insulin as 500 units/mL (U-500; Humulin® R U-500) and insulin glargine as 300 units/mL (U-300; Toujeo®).[1-3] Toujeo® shows a more flat-line pharmacokinetic profile and prolonged duration of activity versus insulin glargine U-100 (Lantus®).[5]

The insulins that are included in this review are listed in Table 1. There are no generic formulations of insulin; however, there are several products available over-the-counter.

Table 1. Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Insulin glargine	Injection	Toujeo®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines for Diabetes Mellitus

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Medical Care in Diabetes (2015)**[6]	<u>Current criteria for the diagnosis of diabetes</u> • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <u>Prevention/delay of type 2 diabetes</u> • An ongoing support program for weight loss of 7% of body weight and an

Clinical Guideline	Recommendation(s)

	increase in physical activity to ≥150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%.
	• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.7%, especially for those with a body mass index >35 kg/m^2, age <60 years, and women with prior gestational diabetes mellitus.
	
	<u>Glycemic goals in adults</u>
	• Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%.
	• It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.
	• Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.
	
	<u>Pharmacologic and overall approaches to treatment-type 1 diabetes</u>
	• Recommended therapy consists of the following components:
	  o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy.
	  o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity.
	  o Most patients should use of insulin analogs to reduce hypoglycemia risk.
	
	<u>Pharmacologic and overall approaches to treatment-type 2 diabetes</u>
	• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.
	• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset.
	• A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences.
	• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin.
	• Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.

American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in**	<u>Key points</u> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line

Clinical Guideline	Recommendation(s)
Type 2 Diabetes: A Patient-Centered Approach (2012)[4]	drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <u>Initial drug therapy</u> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <u>Advancing to dual combination therapy</u> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability.

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td>
<u>Advancing to triple combination therapy</u>

Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations
<table>
<tr><td>Initial Drug Monotherapy</td><td colspan="5">Metformin</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td colspan="5">High</td></tr>
<tr><td>Hypoglycemia</td><td colspan="5">Low risk</td></tr>
<tr><td>Weight</td><td colspan="5">Neutral/loss</td></tr>
<tr><td>Side Effects</td><td colspan="5">Gastrointestinal/lactic acidosis</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Two Drug Combin-ations</td><td>Metformin + sulfonyl-urea</td><td>Metformin + thia-zolidinedione (TZD)</td><td>Metformin + DPP-4 inhibitor</td><td>Metformin + GLP-1 receptor agonist</td><td>Metformin + insulin (usually basal)</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td>High</td><td>High</td><td>Inter-mediate</td><td>High</td><td>Highest</td></tr>
<tr><td>Hypo-glycemia</td><td>Moderate risk</td><td>Low risk</td><td>Low risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>Weight</td><td>Gain</td><td>Gain</td><td>Neutral</td><td>Loss</td><td>Gain</td></tr>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Edema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td rowspan="2">Three Drug Combin-ations</td><td>Metformin + sulfonyl-urea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td>TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
</table>
</td></tr>
<tr><td>American Diabetes Association/ European Association for the Study of Diabetes: Management of Hyperglycemia in</td><td>
This article should be read as an addendum to the previous full account, summarized above.

<u>Sodium–Glucose Cotransporter 2 Inhibitors</u>

These agents reduce HbA_{1c} by 0.5 to 1.0% (5.5 to 11 mmol/mol) versus placebo
Advantages include: action independent of insulin allowing use even after

</td></tr>
</table>

Clinical Guideline	Recommendation(s)
Type 2 Diabetes: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes (2015)[7]	insulin secretion has waned, modest weight loss (about 2 kg, stabilizing over 6 to 12 months), lowering of blood pressure by about 2 to 4/ 1 to 2 mmHg. • Side effects include genital mycotic infections, at rates of about 11% higher in women and about 4% higher in men compared with placebo, diuretic effect, increased urine calcium excretion, increase in LDL cholesterol (about 5%), and renal function restrictions. <u>Thiazolidinediones</u> • Earlier concerns with risk of bladder cancer have been allayed by subsequent evidence. Dipeptidyl Peptidase 4 Inhibitors • There is mixed evidence for DPP-4 inhibitors and cardiovascular risk or benefit. Until further trials are completed these agents should be used cautiously, if at all, in patients with preexisting heart failure. <u>Initial drug therapy</u> • Metformin remains the optimal drug for monotherapy. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015)[8]**	<u>Management of prediabetes</u> • Lifestyle modifications, including initial attempts to lose 5 to 10% of body weight if overweight or obese and participate in moderate physical activity (e.g., walking) at least 150 minutes per week should be initiated. • Medications including metformin, acarbose, or thiazolidinediones (TZDs) should be considered for patients who are at moderate-to-high risk for developing diabetes mellitus, such as those with a first-degree relative with diabetes. <u>Antihyperglycemic pharmacotherapy for type 2 diabetes</u> • Pharmacotherapy should be prescribed based on sustainability for the individual patient. • Initiate with metformin, a glucagon-like peptide 1 (GLP-1) receptor agonist, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium glucose cotransporter 2 (SGLT2) inhibitor, or an α-glucosidase inhibitor for patients with an entry A1C <7.5%. • A TZD, sulfonylurea, or glinide may be considered as alternative therapies but should be used with caution due to side-effect profiles. • For patients with entry A1C levels >7.5%, initiate treatment with metformin (unless contraindicated) plus a second agent, with preference given to agents with a low potential for hypoglycemia that are weight neutral or associated with weight loss. This includes GLP-1 receptor agonists, SGLT2 inhibitors, or DPP-4 inhibitors as the preferred second agents. • Colesevelam, bromocriptine, or an α-glucosidase inhibitor have limited glucose-lowering potential but also carry a low risk of adverse effects and may be useful for glycemic control in some situations. • Sulfonylureas and glinides are considered the least desirable alternatives due to the risk of hypoglycemia. • For patients with an entry A1C >9.0% who have symptoms of hyperglycemia, insulin therapy alone or in combination with metformin or other oral agents is

Clinical Guideline	Recommendation(s)

	recommended.
	• Insulin should be considered for T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.
	• Therapy with long-acting basal insulin should be the initial choice in most cases. The insulin analogs glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because analog insulins are associated with less hypoglycemia.
	• When control of postprandial hyperglycemia is needed, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or inhaled insulin) over regular human insulin because the former have a more rapid onset and offset of action and are associated with less hypoglycemia.
	
	<u>Management of type 1 diabetes</u>
	• Insulin must be used to treat type 1 diabetes. Physiologic insulin regimens, which provide both basal and prandial insulin, should be used. Approaches include:
	  • Multiple daily injections (MDI), which usually involve 1 to 2 subcutaneous injections daily of basal insulin to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or inhaled insulin before each meal to control meal-related glycemia.
	  • Continuous subcutaneous insulin infusion (CSII) to provide a more physiologic way to deliver insulin, which may improve glucose control while reducing risks of hypoglycemia.

American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[9]	<u>Principles underlying the algorithm</u> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. • Long-acting insulin analogs are superior to neutral protamine Hagedorn insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. <u>Monotherapy</u> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a

Clinical Guideline	Recommendation(s)

	majority of patients.
	• In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include:
	  o GLP-1 receptor agonists.
	  o DPP-4 inhibitors.
	  o Alpha-glucosidase inhibitors.
	  o Sodium glucose cotransporter 2 (SGLT-2) inhibitors.
	• TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia.
	
	<u>Combination therapy</u>
	• Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin.
	• Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy.
	• In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used.
	• Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus:
	  o GLP-1 receptor agonists.
	  o DPP-4 inhibitors.
	  o TZD.
	  o SGLT-2 inhibitors.
	  o Basal insulin.
	  o Colesevelam.
	  o Bromocriptine quick release.
	  o Alpha-glucosidase inhibitors.
	  o Sulfonylureas and glinides.
	
	<u>Three-drug combination therapy</u>
	• Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent.
	• Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy.
	• Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent.
	• Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered.
	• Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin.
	• Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus:
	  o GLP-1 receptor agonists.
	  o TZD.
	  o SGLT-2 inhibitors.
	  o Basal insulin.
	  o DPP-4 inhibitors.
	  o Colesevelam.

Clinical Guideline	Recommendation(s)
	o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfonylureas and glinides <u>Insulin therapy algorithm</u> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <u>Basal insulin</u> • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <u>Basal-bolus insulin regimens</u> • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. <u>Basal insulin and incretin therapy regimens</u> • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
National Institute for Health and Care Excellence: **The Management of Type 2 Diabetes (Issued 2009, last**	<u>Metformin</u> • Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone. • Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight. • Continue metformin if blood glucose control remains or becomes inadequate

Clinical Guideline	Recommendation(s)

modified July 2014)[10]	and another oral glucose-lowering medication (usually a sulfonylurea) is added.
	• Step up metformin therapy gradually over weeks to minimize risk of gastrointestinal (GI) side effects. Consider a trial of extended release metformin if GI tolerability prevents continuation of therapy.
	
	<u>Insulin secretagogues</u>
	• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or it is contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms.
	• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.
	• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.
	• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.
	
	<u>Rapid-acting insulin secretagogues</u>
	• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.
	
	<u>Acarbose</u>
	• Consider acarbose for a patient unable to use other oral glucose-lowering medications.
	
	<u>DPP-4 inhibitors</u>
	• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate (HbA_{1c} ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.
	• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate (HbA_{1c} ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.
	• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥7.5%) and insulin is unacceptable or inappropriate.
	• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (≥0.5% reduction in HbA_{1c} in 6 months).
	• A DPP-4 inhibitor may be preferable to a thiazolidinedione (TZD) if:
	  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.
	  o A thiazolidinedione is contraindicated.
	  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.
	There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.
	
	<u>TZDs</u>
	• Consider adding a TZD to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate (HbA_{1c} ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.
	• Consider adding a TZD to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate (HbA_{1c} ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.

Clinical Guideline	Recommendation(s)

	• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥7.5%) and insulin is unacceptable or inappropriate.
	• Do not use a TZD is people who have heart failure, or who are at higher risk of fracture.
	• Only continue TZD therapy if the person has had a beneficial metabolic response (≥0.5% reduction in HbA_{1c} in 6 months).
	• Consider combining TZD with insulin therapy for a person who previously had a marked glucose-lowering response to TZD therapy or who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.
	• A TZD may be preferable to a DPP-4 inhibitor if:
	  o The person has marked insulin insensitivity.
	  o A DPP-4 inhibitor is contraindicated.
	  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.
	There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.
	
	<u>Gliptins: GLP-1 enhancers</u>
	• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.
	
	<u>GLP-1 mimetics</u>
	• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate (HbA_{1c} ≥7.5%) and the person has:
	  o A body mass index ≥35 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups).
	  o A BMI <35 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.
	• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (≥1% reduction in HbA_{1c} and weight loss ≥3% of initial body weight at six months).
	
	<u>Insulin therapy</u>
	• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.
	• When starting basal insulin therapy:
	  o Continue with metformin and the sulfonylurea (and acarbose, if used).
	  o Review the use of the sulfonylurea if hypoglycemia occurs.
	• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):
	  o Continue with metformin.
	  o Continue the sulfonylurea initially and discontinue if hypoglycemia occurs.
	• Begin with human NPH insulin injected at bedtime or twice daily according to need.
	• Consider using a long-acting insulin analogue if:
	  o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.
	  o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.
	  o The person would otherwise need twice-daily NPH insulin injections

Clinical Guideline	Recommendation(s)
	in combination with oral glucose-lowering drugs. o The person cannot use the device to inject NPH insulin. • Consider twice-daily pre-mixed (biphasic) human insulin (particularly if HbA_{1c} ≥9.0%). A once-daily regimen may be an option. • Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if: o A person prefers injecting insulin immediately before a meal. o Hypoglycemia is a problem. o Blood glucose levels rise markedly after meals. • Consider switching to a long-acting insulin analogue from NPH insulin in people: o Who do not reach their target HbA_{1c} because of significant hypoglycemia. o Who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached. o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made. o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections. • Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation).
Institute for Clinical Systems Improvement: **Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)**[11]	• Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: o Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). o Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. o Inability to comply with standard goals, such as polypharmacy issues. o Limited life expectancy or estimated survival of less than 10 years. o Cognitive impairment. o Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. o Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. o Metformin can also be used in combination with all other glucose-lowering agents. • Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
International Diabetes Federation Clinical	<u>Lifestyle management</u> • Changing patterns of eating and physical activity can be effective in controlling

Clinical Guideline	Recommendation(s)

Guidelines Task Force: **Global Guideline for Type 2 Diabetes (2012)**[12]	many of the adverse risk factors found in type 2 diabetes.
	• Match the timing of medication (including insulin) and meals.
	• Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol.
	• Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals.
	• Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week.
	• Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity.
	
	<u>Glucose control levels</u>
	• Maintaining HbA_{1c} below 7% minimizes the risk of developing complications.
	• A lower HbA_{1c} target may be considered if it is easily and safely achieved.
	• A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia.
	
	<u>Oral therapy</u>
	• Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications.
	• Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months.
	• First-line therapy
	  o Begin with metformin unless there is evidence of renal impairment or other contraindication.
	  o Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m^2.
	  o Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot.
	  o In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets.
	• Second-line therapy
	  o When glucose control targets are not achieved, add a sulfonylurea.
	  o Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas.
	• Third-line therapy
	  o When glucose control targets are no longer being achieved, start insulin or add a third oral agent.
	  o If starting insulin, add basal insulin or use premix insulin.
	  o If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD.
	  o Another option is to add a glucagon-like peptide-1 (GLP-1) agonist.
	• Fourth-line therapy

Clinical Guideline	Recommendation(s)
	o Begin insulin therapy when optimized oral blood glucose lowering mediations (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. <u>Insulin therapy</u> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
American Diabetes Association: **Care of Children and Adolescents with Type 1 Diabetes (2005)[13]**	• Insulin type, mixture of insulins, site of injection, and individual patient response differences can all affect the onset, peak, and duration of insulin activity. • Children with diabetes often require multiple daily injections of insulin, using combinations of rapid-, short-, intermediate-, or long-acting insulin before meals and at bedtime to maintain optimal blood glucose control. • The basal/bolus insulin regimen uses a long-acting insulin analog combined with a rapid-acting insulin analog given before meals and snacks. This regimen has been shown to result in stable glycemic control and less hypoglycemia compared with regimens using intermediate and short insulin regimens. • Many young children and teenagers consume multiple snacks throughout the day. An ideal basal/bolus regimen may consist of as many as six to seven insulin injections per day. A combination of rapid-acting insulin with small amounts of intermediate-acting insulin to allow coverage for snacks may be an appropriate alternative to the basal/bolus plan. However, two or three doses of mixed rapid-acting or short-acting insulin with intermediate-acting insulin generally cannot maintain HbA_{1c} levels within the target range. Recommendations now support moving toward a basal/bolus insulin regimen for most patients. • The combination of rapid-acting insulin analogs and a long-acting insulin offers an excellent option for basal and bolus insulin administration. • Basal/bolus regimens have been shown to result in lower fasting blood glucose levels with less nocturnal hypoglycemia than regimens that use NPH insulin in children/adolescents, as well as in adults.
American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)[14]**	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients o Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL. o Whose HbA_{1c} is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.

Clinical Guideline	Recommendation(s)

	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  o Are taking insulin or other medications with a risk of hypoglycemia; or
	  o Are initiating or changing their diabetes treatment regimen; or
	  o Have not met treatment goals; or
	  o Have intercurrent illnesses.
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.
	• Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.

National Institute for Health and Care Excellence:
Type 1 diabetes in adults: diagnosis and management (2015)[15]
	<u>Blood glucose management</u>
	• Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes.
	• Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target.
	• Use methods to measure HbA1c that have been calibrated according to International Federation of Clinical Chemistry (IFCC) standardization.
	• Support adults with type 1 diabetes to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimize the risk of long-term vascular complications.
	• Agree an individualized HbA1c target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia.
	• Ensure that aiming for an HbA1c target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes.
	• Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least 4 times a day, including before each meal and before bed.
	
	<u>Insulin therapy</u>
	• Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens.
	• Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only).
	• Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes.
	• Consider, as an alternative basal insulin therapy for adults with type 1 diabetes:
	  o An existing insulin regimen being used by the person that is achieving their agreed targets.
	  o Once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated.
	• Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes.

Clinical Guideline	Recommendation(s)
	• Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. • If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. • Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. • Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. • Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m^2 (23 kg/m^2 for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <u>Insulin delivery</u> • Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. • Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. • Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. • Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. • Check injection site condition at least annually and if new problems with blood glucose control occur.

National Institute for Health and Care Excellence: **Diabetes (type 1 and type 2) in children and young people: diagnosis and management (2015)**[16]	<u>Insulin therapy for children and young people with type 1 diabetes</u>
	• While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen:
	  o Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with 1 or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue.
	  o Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula.
	  o One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin.
	• Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen.
	• Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy.
	
	<u>Oral medicines for children and young people with type 1 diabetes</u>
	• Metformin in combination with insulin is suitable for use only within research

Clinical Guideline	Recommendation(s)
	studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. <u>Management for children and young people with type 2 diabetes</u> • At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. • Offer standard‑release metformin from diagnosis to children and young people with type 2 diabetes.
American Diabetes Association: **Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)**[17]	<u>Nutritional therapy</u> • Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. • If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. <u>Physical activity and exercise</u> • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <u>Glycemic control goals</u> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant

Clinical Guideline	Recommendation(s)
	hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <u>Insulin therapy</u> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <u>Adjunctive therapies</u> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for insulin glargine U-300 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 Insulin Glargine U-300[3]

Indication	Insulin Glargine U-300
Improve glycemic control in adult patients with diabetes mellitus	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of insulin glargine U-300 are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Insulin Glargine U-300[1]

Generic Name(s)	Onset (hours)	Peak (hours)	Duration (hours)	Half-Life (hours)	Mixing of Insulins
Insulin glargine U-300	Not reported	12	Not reported	Not reported	None

V. Drug Interactions

Significant drug interactions with the insulins are listed in Table 5.

Table 5. Significant Drug Interactions with the Insulins[2]

Generic Name(s)	Significance Level	Interaction	Mechanism
Insulin	2	β-Adrenergic blocking agents (β-blockers), nonselective	β-blockers may blunt the sympathetic mediated response to hypoglycemia and may mask hypoglycemic symptoms. Discontinue nonselective β-blocker therapy or switch to a β-blocker with selective activity if possible.
Insulin	2	Monoamine oxidase inhibitors (MAOIs)	MAOIs may potentiate the hypoglycemic effects of insulin by stimulating insulin secretion and inhibiting gluconeogenesis. Monitor blood glucose concentrations and adjust the dose of insulin as needed.
Insulin	2	Salicylates	Salicylates increase basal insulin secretion and acute insulin response to a glucose load. The hypoglycemic effects of insulin may be potentiated. Monitor blood glucose concentrations and adjust the dose of insulin as needed.

Significance level 1 = major severity, significance level 2 = moderate severity

VI. Adverse Drug Events

Adverse events with the insulin products are rare and are similar among the various products.[1-3]

Hypoglycemia is the most common adverse event reported with insulin therapy. Because of the differences in onset and duration of action, the timing of hypoglycemia can vary between insulin formulations. Hypoglycemia risk may be increased when patients receive excessive doses of insulin, reduce their caloric intake, increase physical activity, during illnesses, or when receiving medications that increase the hypoglycemic effects of insulin.[1-3]

Redness, swelling, and itching at the injection site may result if administration is not done properly, if the skin is sensitive to cleansing solution, or if the patient is allergic to insulin or components of the insulin formulation.[1-3]

Generalized insulin allergies are rare but may present as a skin rash over the body, shortness of breath, fast pulse, sweating, a drop in blood pressure, bronchospasm, shock, anaphylaxis, or angioedema.[1-3]

VII. Dosing and Administration

The usual dosing regimens for insulin glargine U-300 are listed in Table 6.

Table 6. Usual Dosing Regimens for Insulin Glargine U-300 [3]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Insulin glargine U-300	<u>To improve glycemic control in diabetes mellitus</u>: Dosage must be individualized. For patients controlled on Lantus®, expect a higher daily dose of Toujeo®. SC injection: administer QD at the same time every day; maintenance, 1 to 80 units/day	Safety and efficacy have not been established in pediatric patients.	Pen: 300 units/mL

QD=once daily, SC=subcutaneous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of insulin glargine U-300 are summarized in Table 7.

Table 7. Comparative Clinical Trials with Insulin Glargine U-300 (Toujeo®)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Riddle et al.[18] EDITION 1 (2014) Insulin glargine U-300 via modified SoloSTAR® pen QPM vs insulin glargine U-100 via SoloSTAR® pen QPM Dose adjustment weekly, but no more often than every three days. Metformin was continued at prior dosage throughout the study.	MC, OL, PG Patients ≥18 years of age with a diagnosis of T2DM, HbA_{1c} 7.0 to 10.0%, and use of basal insulin therapy (≥42 units/day) with or without metformin for at least one year	N=804 6 months	Primary: HbA_{1c} change from baseline at month six Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events	Primary: Mean HbA_{1c} decreased similarly in the two treatment groups with a final HbA_{1c} of 7.25% (SD 0.85) in the U-300 group compared to 7.28% (0.92) in the U-100 group. The LS mean change was 0.83% for both groups; difference 0.00% (95% CI, 0.11 to 0.11). Because the upper CI limit was below the 0.4% threshold, U-300 met the non-inferiority criterion. Secondary: Similar reductions to HbA_{1c} were observed for FPG in both treatment groups (from 8.72 mmol/L [SD 2.83] to 7.24 mmol/L [2.57] with U-300 and 8.90 mmol/L [2.94] to 7.21 mmol/L [2.40] with U-100). The percentages of participants attaining target HbA_{1c} levels were similar with U-300 and U-100 (39.6 and 40.9% for HbA_{1c} <7.0%, 21.0 and 21.6% for HbA_{1c} ≤6.5%, 46.3 and 44.9% for FPG ≤6.7, and 26.5 and 23.2% for FPG <5.6 mmol/L, respectively). Daily basal insulin dosage increased for both U-300 and U-100 at the end of the six month study. The dose increase was higher with U-300 than with U-100; LS mean difference was 0.09 units/kg/day (95% CI, 0.062 to 0.124). Mealtime insulin doses increased slightly in the first two weeks but were unchanged from baseline and alike in the two groups thereafter. Body weight increased by 0.9 kg in both treatment groups. The SMPG profiles declined in both treatment groups. No significant differences between changes in means at individual time points were demonstrated. The reduction of preinjection SMPG (combination of pre- and post-dinner measurements) from baseline to month six was similar between treatments. There was also no between-treatment difference in the change of day-to-day variability of preinjection SMPG during treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The proportion of participants with one or more confirmed or severe nocturnal hypoglycemic events between the start of week nine and month six was 36% (146/404) on U-300, compared with 46% (184/400) on U-100. Analysis of this prespecified main measure of hypoglycemia demonstrated superiority of U-300 over U-100 with a significantly lower relative risk (RR 0.79; 95% CI, 0.67 to 0.93; P=0.0045). The percentage of participants reporting severe hypoglycemia at any time was similar for the two groups with 5.0% for U-300 compared with 5.7% for U-100 (RR 0.87; 95% CI, 0.48 to 1.55). The most common adverse events were infections, gastrointestinal events, or musculoskeletal complaints; these were equally distributed between the groups.
Yki-Järvinen et al.[19] EDITION 2 (2014) Insulin glargine U-300 via modified SoloSTAR® pen QPM vs insulin glargine U-100 via SoloSTAR® pen QPM Insulin dose adjustment weekly. Other oral antidiabetic agents were continued.	MC, OL, PG, RCT Patients ≥18 years of age with a diagnosis of T2DM, HbA_{1c} 7.0 to 10.0%, use of basal insulin therapy (≥42 units/day)	N=808 6 months	Primary: HbA_{1c} change from baseline at month six or last visit on treatment without rescue therapy Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including	Primary: Mean HbA_{1c} decreased similarly in the two treatment groups with a final HbA_{1c} at six months of 7.57% for U-300 and 7.56% for U-100, representing a mean treatment difference of -0.01% (95% CI, -0.14 to 0.12). Because the upper CI limit was below the 0.4% threshold, U-300 met the non-inferiority criterion. Secondary: Similar reductions in FPG from baseline (-1.14 and -1.06), percentage of participants attaining HbA_{1c} <7.0% (30.6% and 30.4%) and ≤6.5% (14.5% and 14.8%), were observed in the U-300 and U-100 groups respectively. Numerically, percentage of participants attaining a FPG ≤6.7 mmol/L (48.7% and 54.1%) and <5.6 mmol/L (29.4% and 33.6%) were higher for the U-300 group than U-100 group, the difference was not statistically significant. Overall, glucose measurements of the 8-point profile showed a comparable decrease in SMPG for both the U-300 and U-100 groups. However, the mean prebreakfast SMPG was lower with U-100 than with U-300 during the first eight weeks, and a more gradual decrease in prebreakfast SMPG was observed with U-300 than with U-100. At month six, a similar average prebreakfast SMPG was reached in both groups (119 mg/dL for U-300 and 113 mg/dL for U-100). Comparable results were observed between U-300 and U-100 for change in preinjection SMPG and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events	variability in preinjection SMPG. The daily basal insulin dose increased from baseline to month six in both groups, mainly during the first 12 weeks. There was a significant difference in insulin dose between treatment groups at month six, with a LS mean difference of 11 units/day (95% CI, 8 to 14), with those in the U-300 group requiring 10% more basal insulin (units/kg/day) than those receiving U-100. Overall, 123 participants (30.5%) in the U-300 group experienced 379 nocturnal hypoglycemic events, and 169 participants (41.6%) in the U-100 group experienced 766 nocturnal hypoglycemic events. A significantly lower percentage of participants reported at least one nocturnal or severe hypoglycemic event from week nine to month six with U-300 (21.6%) compared with U-100 (27.9%). Analysis of this prespecified main secondary end point demonstrated superiority of U-300 over U-100 (RR 0.77; 95% CI, 0.61 to 0.99, P=0.038). . The risk of nocturnal confirmed or severe hypoglycemia was also reduced with U-300 compared with U-100 during the six-month study period (RR 0.71, 95% CI, 0.58 to 0.86). During the six-month treatment period, 288 participants (71.5%) treated with U-300 and 322 participants (79.3%) treated with U-100 reported one or more hypoglycemic events. In total, 2,750 hypoglycemic events were reported in the U-300 group and 3,675 in the U-100 group. The most common adverse events in the U-300 and U-100 groups were infections, nervous system disorders, gastrointestinal events and musculoskeletal complaints. These were equally distributed between the treatment groups.
Bolli et al.[20] EDITION 3 (2015) Insulin glargine U-300 via TactiPen® injector QPM	MC, OL, PG, RCT Patients ≥18 years of age with a diagnosis of T2DM for at least one year, use of oral glucose-lowering drugs in	N=873 6 months	Primary: HbA_{1c} change from baseline at month six Secondary: FPG change from baseline,	Primary: The mean decrease in HbA_{1c} was equivalent in the two treatment groups. At month six, the LS mean difference in change of HbA_{1c} was 0.04% (95% CI, −0.09 to 0.17) meeting the non-inferiority criterion. Secondary: The proportion of participants reaching target HbA_{1c} or laboratory-measured FPG at month six was much the same in the two treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin glargine U-100 via SoloSTAR® pen QPM Insulin dose adjustment weekly.	the last six months, and insulin naïve		percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events	groups. Similar results in both the U-300 and U-100 groups were observed for change in pre-injection SMPG and variability in pre-injection SMPG. FPG from baseline to month six was somewhat greater in the U-100 group than in the U-300 group (LS mean difference, 0.39; 95% CI, 0.10 to 0.68). Over the 24-hour period, the eight-point SMPG profiles showed a similar decrease from baseline to month six with both U-300 and U-100 (LS mean difference 0.18; 95% CI, −0.07 to 0.42). The pre-breakfast SMPG decreased more gradually with U-300 than with U-100. The basal insulin dose increased throughout the six-month treatment period in both treatment groups, but more so with U-300; mean increase was 0.62 (0.29) U/kg/day U-300, and to 0.53 (0.24) U/kg/day with U-100 (no P value reported). Between the start of week nine and month six, the percentage of participants experiencing at least one nocturnal confirmed or severe hypoglycemic event was 16% with U-300 and 17% with U-100 (RR 0.89; 95% CI, 0.66 to 1.20). The percentage of participants who experienced ≥1 confirmed or severe hypoglycemic event was lower with U-300 (201/435, 46%) than with U-100 (230/438, 53%) over the six-month study period (RR 0.88; 95% CI, 0.77 to 1.01). Weight gain during the treatment period was lower with U-300 (LS mean increase 0.49 [95% CI, 0.14 to 0.83] kg) than with U-100 (LS mean increase 0.71; 95% CI, 0.36 to 1.06 kg; P value was non-significant).
Ritzel et al.[21] (2015) Insulin glargine U-300 via pen injector QPM vs insulin glargine U-	MA of EDITION 1, 2, and 3 Patients ≥18 years of age with a diagnosis of T2DM	N=2496 6 months	Primary: Change in HbA_{1c} from baseline, proportion of participants with HbA_{1c} <7.0, change in average pre-injection SMPG from baseline, and	Primary: The mean decrease in HbA_{1c} was similar in the two treatment groups. The proportion of participants who reached target HbA_{1c} after 6 months of treatment was similar in both treatment groups: 449 participants (36.2%) on U-300 and 438 participants (35.5%) on U-100. Laboratory-measured FPG decreased similarly in both groups. There was also no between-treatment difference in the variability of pre-injection SMPG at month six. Secondary: The annualized rate (events per participant-year) of confirmed (≤70 mg/dl)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 via SoloSTAR® pen QPM Insulin dose adjustment weekly.			change in laboratory-measured FPG from baseline Secondary: Safety and tolerability	or severe hypoglycemia at any time of day over the six-month study period was 15.22 with U-300 and 17.73 with U-100 (rate ratio 0.86, 95% CI 0.77 to 0.97; P=0.0116), corresponding to a relative difference of 14% in favor of U-300. No between-treatment differences in safety profile were identified, with similar rates of adverse events reported across all three studies.

Drug regimen abbreviations: QD=once-daily, QPM=once every evening
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, LS=least squares, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial, RR=relative risk
Miscellaneous: BMI=body mass index, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, PPG=postprandial glucose, SMPG=self-monitored plasma glucose, T2DM=type 2 diabetes mellitus

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 8. Relative Cost of Insulin Glargine U-300

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Insulin glargine	Injection	Toujeo®	$$$$$	N/A

N/A=Not available

X. Conclusions

Insulin glargine U-300 (Toujeo®) is approved to improve glycemic control in adult patients with diabetes mellitus.[3] There are currently no generic products available.

According to current clinical guidelines regarding the management of type 1 diabetes, initiation of individualized, intensive insulin therapy at the time of diagnosis is recommended. Furthermore, overall approaches for management include the use of multiple dose injections or a subcutaneous insulin infusion, and matching of pre-prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. According to the American Diabetes Association, insulin analogs should be utilized in most patients. In addition, use of a continuous subcutaneous insulin infusion is indicated in certain clinical settings, particularly when glycemic control is difficult to achieve, during pregnancy, or when the patient does not demonstrate a willingness to comply with a multiple injection regimen. As mentioned previously, insulin regimens should be tailored to the specific clinical circumstances in individual patients, and patients should have access to the types (preparation and species) of insulin therapy they find allow them optimal well-being. In general, pre-prandial rapid-acting insulin analogs

should be administered 20 to 30 minutes prior to a meal. Some patients treated with basal, or long-acting, insulin may require twice-daily dosing to achieve greater control. In general, no one specific insulin product among the various classifications is recommended or preferred over another. Again, insulin therapy must be individualized as the products within the different classifications play specific roles in achieving adequate glycemic control in patients with type 1 diabetes. Insulin therapy may also be appropriate in the management of type 2 diabetes; however, traditionally oral antidiabetic agents are utilized. Of note, many patients with type 2 diabetes will ultimately require insulin therapy, alone or in combination with other agents, to maintain glucose control. Insulin is recognized as a potential option to be added to current oral antidiabetic agent regimens in patients not achieving glycemic goals. It may also be appropriate to initiate insulin therapy at the time of diagnosis in certain clinical settings, particularly in patients with a high baseline glycosylated hemoglobin (HbA_{1c}) (≥9.0%), or in patients presenting with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c}. Furthermore, such therapy is mandatory when catabolic features are exhibited or if ketonuria is demonstrated. There is insufficient evidence to conclude that one long-acting insulin analog is safer or more efficacious than another.[4,6-17]

The safety and efficacy of insulin glargine U-300 (Toujeo®) was evaluated in the EDITION trials. Each study compared insulin glargine U-300 to insulin glargine U-100. The EDITION studies evaluated the safety and effectiveness of insulin glargine U-300 in patients with type 2 diabetes. EDITION 1 evaluated insulin glargine U-300 in combination with mealtime insulin, while EDITION 2 and 3 evaluated combination therapy with non-insulin oral antidiabetic agents; in EDITION 3, patients were also insulin-naïve.71-73 In all three studies, insulin glargine U-300 was shown to be non-inferior to insulin glargine U-100. Additionally, the dose of basal glargine insulin required was higher in all three studies for U-300, requiring 11, 12, and 15% more units. Generally, both U-100 and U-300 had similar rates of adverse events, including hypoglycemia and all three studies showed similar changes in weight.[18-21]

At this time, there is insufficient data to conclude that insulin glargine U-300 is safer or more efficacious than other brand or generic products within its class and that it offers a significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand insulin glargine U-300 product 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

1. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2015 [cited 2015 Dec]. Available from: http://www.thomsonhc.com/.
2. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2015 [cited Dec 2015]. Available from: http://online.factsandcomparisons.com.
3. Toujeo® [package insert]. Bridgewater (NJ): sanofi-aventis U.S. LLC; 2015 February.
4. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.
5. Goldman J, White JR Jr. New Insulin Glargine 300 U/mL for the Treatment of Type 1 and Type 2 Diabetes Mellitus. Ann Pharmacother. 2015 Oct;49(10):1153-61.
6. The American Diabetes Association. Standards of medical care in diabetes-2015. Diabetes Care. 2015 Jan;38(Suppl 1):S1-93. doi: 10.2337/dc15-S001.
7. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2015 Jan;38(1):140-149.
8. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology – Clinical Practice Guidelines for developing a diabetes mellitus comprehensive care plan. Endocrine Practice. 2015;21(suppl 1):1-87.
9. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA et al. American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013. Endocr Pract. 2013;19(2):327-36.
10. National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes. [guideline on the Internet]. London: NICE; 2009 May [cited 2014 Oct]. Available from: http://www.nice.org.uk/guidance/cg87.
11. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
12. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
13. Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care 2005;28:186-212.
14. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131(2):364-382.
15. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 Aug [cited 2015 Sep]. Available from: http://www.nice.org.uk/guidance/ng17.
16. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 Aug [cited 2015 Sep]. Available from: http://www.nice.org.uk/guidance/ng18.
17. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care 2014;37(7):2034-2054.
18. Riddle MC, Bolli GB, Ziemen M, Muehlen-Bartmer I, Bizet F, Home PD, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). Diabetes Care. 2014 Oct;37(10):2755-62. doi: 10.2337/dc14-0991. Epub 2014 Jul 30.
19. Yki-Järvinen H, Bergenstal R, Ziemen M, Wardecki M, Muehlen-Bartmer I, Boelle E, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and

basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care. 2014 Dec;37(12):3235-43. doi: 10.2337/dc14-0990. Epub 2014 Sep 5.
20. Bolli GB, Riddle MC, Bergenstal RM, Ziemen M, Sestakauskas K, Goyeau H, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab. 2015 Apr;17(4):386-94. doi: 10.1111/dom.12438. Epub 2015 Feb 12.
21. Ritzel R, Roussel R, Bolli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. Diabetes Obes Metab. 2015 Sep;17(9):859-67.