Alabama Medicaid Agency

Pharmacy and Therapeutics Committee Meeting

Clinical Packet

February 11, 2009

Table of Contents

Pharmacotherapy Review of Centrally Acting Skeletal Muscle Relaxants 2
Pharmacotherapy Review of Direct-acting Skeletal Muscle Relaxants 23
Pharmacotherapy Review of GABA-derivative Skeletal Muscle Relaxants 34
Pharmacotherapy Review of Skeletal Muscle Relaxants, Miscellaneous 48
Pharmacotherapy Review of Opiate Agonists 57
Pharmacotherapy Review of Opiate Partial Agonists 99
Pharmacotherapy Review of Selective Serotonin Agonists 118
Pharmacotherapy Review of Antiemetics, Antihistamines 191
Pharmacotherapy Review of Antiemetics, 5-HT_3 Receptor Antagonists 212
Pharmacotherapy Review of Antiemetics, Miscellaneous 247
Pharmacotherapy Review of Proton-pump Inhibitors (Single Entity Agents) 272
Pharmacotherapy Review of Proton-pump Inhibitors (Combination Products) 310

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Centrally Acting Skeletal Muscle Relaxants
AHFS Class 122004
February 11, 2009

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.[21] Spasticity is associated with a number of central nervous system disorders including stroke, multiple sclerosis, as well as brain and spinal cord injuries.[21] 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.[24] Tizanidine is an agonist at α2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons.[25]

Back pain is a common problem and there are many different treatment options available for the management of this disorder. Back pain can be classified as acute, subacute and chronic. There are several centrally acting skeletal muscle relaxants that are FDA-approved for the treatment of acute pain/discomfort from musculoskeletal disorders. The use of these agents is generally limited to short-term therapy. The mechanism of action is unclear, but may be related to the sedative properties of the agents.[1,2,8,27-31] 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. It acts primarily at the brain stem and reduces 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. Metaxalone is the only centrally acting skeletal muscle relaxant that is not available in a generic formulation.

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

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Carisoprodol	tablet	Soma®*	none†
Carisoprodol, ASA	tablet	Soma Compound®*	none†
Carisoprodol, ASA, codeine	tablet	Soma Compound with Codeine®*	none†
Chlorzoxazone	tablet	Parafon Forte DSC®*	chlorzoxazone
Cyclobenzaprine	tablet, extended-release capsule	Flexeril®*, Fexmid®, Amrix®	cyclobenzaprine
Metaxalone	tablet	Skelaxin®	none
Methocarbamol	tablet, injection	Robaxin®*	methocarbamol
Tizanidine	tablet, capsule	Zanaflex®*	tizanidine

*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 DUR review
PDL=Preferred Drug List
ASA=aspirin

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)
American College of Physicians/ American Pain Society: **Diagnosis and Treatment of Low Back Pain**[37] **(2007)**	• 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**[38] **(2007)**	Recommendations for the treatment of acute low back pain include: • Nonsteroidal anti-inflammatory drugs (NSAIDs). • Cytoprotective medications for patients with contraindications for NSAIDs. • 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 LBP. • Skeletal muscle relaxants are not recommended for mild to moderate acute LBP or chronic use in subacute or chronic LBP (other than acute exacerbations).

National Collaborating Centre for Chronic Conditions: **Multiple Sclerosis. National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care**[20] **(2004)**	• Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin.
	• The following should be given only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable:
	  o Tizanidine
	  o Diazepam
	  o Clonazepam
	  o Dantrolene
	• Combinations of medicines and other medicines such as anticonvulsants should only be used after seeking further specialist advice.

VA/DoD Clinical Practice Guideline Working Group: **Management of Stroke Rehabilitation**[15] **(2003)**	• Consider use of tizanidine, dantrolene, and/or oral baclofen for spasticity resulting in pain, poor skin hygiene, or decreased function. • Tizanidine should be used specifically for chronic stroke patients.

LBP=low back pain

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[8,16-19,22-23,25]

Generic Name	Muscle Spasticity	Relief of Discomfort Associated with Acute, Painful Musculoskeletal Disorders	Other
Carisoprodol		✔	
Chlorzoxazone		✔	
Cyclobenzaprine		✔	
Metaxalone		✔	
Methocarbamol		✔	Spasm - Tetanus
Tizanidine	✔		

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Centrally Acting Skeletal Muscle Relaxants[8]

Generic Name	Cmax (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism	Renal Excretion (%)	Half-Life (hours)
Carisoprodol	4	No data	No data	Liver	No data	8
Chlorzoxazone	1-2	100	No data	Liver	75	1
Cyclobenzaprine	4	33-55	93	Liver	50	IR: 18 ER: 32
Metaxalone	2	No data	No data	Liver	No data	8 – 9
Methocarbamol	1-2	100	No data	Liver	50-65	1 – 2
Tizanidine	1-2	40	30	Liver	60	2

IR=immediate-release; ER=extended-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[2,8]

Generic Name	Significance Level	Interaction	Mechanism
Cyclobenzaprine	1	Monoamine oxidase (MAO) inhibitors	Cyclobenzaprine is closely related to the tricyclic antidepressants. Hypertensive crisis, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and MAO inhibitor drugs. Concomitant use of cyclobenzaprine and MAO inhibitors, or within 14 days after MAO inhibitor discontinuation is contraindicated.
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.

Generic Name	Significance Level	Interaction	Mechanism
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.
Cyclobenzaprine	1	Duloxetine	Increased risk of serotonin syndrome, therefore concomitant use is discouraged.
Cyclobenzaprine	1	Tramadol	Concomitant administration of tramadol and cyclobenzaprine increases the risk of seizures.
Carisoprodol	1	Benzodiazepines, barbiturates, opioid analgesics, and alcohol	Additive CNS and respiratory depression may occur when carisoprodol is administered concomitantly with other CNS depressants
Chlorzoxazone	1	Benzodiazepines, barbiturates, opioid analgesics, and alcohol	Additive CNS and respiratory depression may occur when carisoprodol is administered concomitantly with other CNS depressants
Metaxalone	1	Benzodiazepines, barbiturates, opioid analgesics, and alcohol	Additive CNS and respiratory depression may occur when carisoprodol is administered concomitantly with other CNS depressants
Methocarbamol	1	Benzodiazepines, barbiturates, opioid analgesics, and alcohol	Additive CNS and respiratory depression may occur when carisoprodol is administered concomitantly with other CNS depressants
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.
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.

Generic Name	Significance Level	Interaction	Mechanism
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	Oral contraceptives (ethinyl estradiol; mestranol)	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	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	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 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	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.

Generic Name	Significance Level	Interaction	Mechanism
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.
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.
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

There have been postmarketing reports of dependence, withdrawal, and abuse with prolonged use of carisoprodol.[16] 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. Withdrawal symptoms have been reported following abrupt cessation after prolonged use. The most common adverse drug events reported with the centrally acting skeletal muscle relaxants are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Centrally Acting Skeletal Muscle Relaxants[2,8,16-19,22-23,25]

Adverse Events	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine
Cardiovascular						
Arrhythmia	-	-	<1	-	-	-
Bradycardia	-	-	-	-	✔	✔

Adverse Events	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine
Hypotension	✔	-	<1	-	✔	0-20
Palpitations	-	-	6	-	-	✔
Tachy-arrhythmia	-	-	<1	-	-	-
Tachycardia	✔	-	-	-	-	-
Sinus tachycardia	✔	-	-	-	-	-
Syncope	-	-	<1	-	✔	-
Vasodilation	-	-	<1	-	-	-
Ventricular extrasystoles	-	-	-	-	-	✔
Central Nervous System						
Agitation	✔	✔	<1	-	-	-
Anxiety	-	-	<1	-	-	✔
Asthenia	-	-	1-3	-	-	-
Ataxia	✔	-	<1	-	✔	-
Confusion	✔	-	1-3	-	-	-
Delirium	-	-	✔	-	-	-
Depression	✔	-	<1	-	-	✔
Dis-orientation	✔	-	✔	-	-	-
Dizziness	2	✔	3-19	✔	✔	✔
Drowsiness	0-40	✔	✔	✔	✔	✔
Fatigue	✔	-	1-3	-	-	9-16
Hallu-cinations	-	-	<1	-	-	3
Headache	2	✔	1-17	✔	✔	✔
Impaired cognition	✔	-	-	-	-	-
Insomnia	✔	-	<1	-	-	6-16
Irritability	✔	-	-	✔	-	-
Lethargy	✔	-	-	-	-	-
Light-headedness	-	✔	-	-	✔	✔
Malaise	-	✔	-	-	-	-
Mania	-	-	✔	-	-	-
Nervousness	-	-	-	✔	-	✔
Over stimulation	-	✔	-	-	-	-
Paresthesia	-	-	<1	-	-	✔
Seizure	✔	-	<1	-	✔	-
Sedation	-	-	-	-	-	48
Somnolence	-	-	0-39	-	-	38
Syncope	✔	-	-	-	-	✔
Tremor	✔	-	0-6	-	-	✔
Vertigo	✔	-	-	-	✔	-
Weakness	✔	-	-	-	-	✔

Adverse Events	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine
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	-	-	-	-	-	✔
Hypo-glycemia	-	-	✔	-	-	-
Gastrointestinal						
Abdominal cramp/pain	-	-	-	-	-	✔
Anorexia	-	✔	<1	-	✔	-
Constipation	-	✔	1-3	-	-	<6
Diarrhea	-	✔	<1	-	-	<6
Dyspepsia	✔	✔	-	✔	-	✔
Epigastric pain or discomfort	✔	-	✔	-	-	-
Flatulence	-	-	<1	-	-	-
Gastritis	-	-	<1	-	-	-
Hiccups	✔	-	-	-	-	-
Indigestion	-	-	4	-	-	-
Ileus	-	-	-	-	✔	-
Increased bowel activity	✔	-	-	-	-	-
Nausea	✔	✔	3-8	✔	✔	✔
Pharyngeal dryness	-	-	8	-	-	-
Tongue edema	-	-	<1	-	-	-
Vomiting	✔	✔	<1	✔	-	✔
Xerostomia	-	-	6-58	-	-	39
Genitourinary						
Urine discoloration	-	✔	-	-	✔	-
Urinary frequency	-	-	<1	-	-	-
Urinary retention	-	-	<1	-	-	-

Adverse Events	Carisoprodol	Chlorzoxazone	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine
Hepatic						
Hepato-toxicity	-	✔	<1	-	-	5
Increased AST	-	-	-	-	-	5
Increased ALT	-	-	-	-	-	5
Jaundice	-	-	-	✔	-	-
Hematologic						
Hemolysis	-	-	-	-	✔	-
Hemolytic anemia	-	-	-	✔	-	-
Leukopenia	✔	-	-	✔	-	-
Pancytopenia	✔	-	-	-	-	-
Musculoskeletal						
Back ache	-	-	-	-	-	✔
Dysarthria	-	-	<1	-	-	-
Muscular incoordina-tion	-	-	-	-	✔	-
Muscular weakness	-	-	<1	-	-	-
Myasthenia	-	-	-	-	-	✔
Respiratory						
Broncho-spasm	-	-	-	-	✔	-
Nasal congestion	-	-	-	-	✔	-
Special Senses						
Ageusia	-	-	✔	-	-	-
Blurred vision	-	-	3	-	✔	-
Conjunct-ivitis	-	-	-	-	✔	-
Diplopia	-	-	<1	-	✔	-
Dysgeusia	-	-	1-6	-	-	-
Metallic taste	-	-	-	-	✔	-
Mydriasis	✔	-	-	-	-	-
Nystagmus	-	-	-	-	✔	-
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[2,8,16-19,22-23,25]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Carisoprodol	250 – 350 mg TID and QHS	Adolescents ≥16 years of age: 250 – 350 mg TID and QHS	Tablets: 250 mg, 350 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		Safety and efficacy in pediatric patients under 16 years of age have not been established.	
Carisoprodol, ASA	1 – 2 tablets QID	Safety and efficacy have not been established in pediatric patients.	Tablets: Carisoprodol 200 mg and aspirin 325 mg
Carisoprodol, ASA, codeine	1 – 2 tablets QID	Safety and efficacy have not been established in pediatric patients.	Tablets: Carisoprodol 200 mg, aspirin 325 mg, and codeine 16 mg
Chlorzoxazone	250 – 750 mg TID – QID	20 mg/kg/day or 600 mg/m^2/day in 3-4 divided doses	Tablets: 250 mg, 500 mg
Cyclobenzaprine	Immediate-Release Tablets: 5 – 10 mg TID Extended-Release Capsules: 15 – 30 mg QD	Immediate-Release Tablets Adolescents ≥15 years of age: 5 – 10 mg TID Extended-Release Capsules: Safety and efficacy in pediatric patients have not been established.	Tablets: 5 mg, 7.5 mg, 10mg Capsules, extended-release: 15 mg, 30 mg
Metaxalone	800 mg TID – QID	Children ≥12 years of age: 800 mg TID-QID Safety and efficacy have not been established in pediatric patients 12 years of age or younger.	Tablets: 800 mg
Methocarbamol	750 mg every 4 hours or 1500 mg TID	Children ≥16 years: 750 mg every 4 hours or 1500 mg TID Safety and efficacy in pediatric patients below the age of 16 have not been established.	Tablets: 500 mg, 750 mg Injection: 100mg/ml
Methocarbamol, ASA	2 tablets QID	Safety and efficacy have not been established in pediatric patients.	Tablets: Methocarbamol 400 mg and aspirin 325 mg
Tizanidine	4 – 8 mg every 6 – 8 hours, up to 3 doses in 24 hours	Safety and efficacy have not been established in pediatric patients.	Tablets: 2 mg, 4 mg Capsules: 2 mg, 4 mg, 6 mg

QD=once daily; TID=three times daily; QID=four times daily; QHS=at bedtime; ASA=aspirin

VIII. Effectiveness

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

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 conditions				
Rollings et al.[10] (1983) Carisoprodol 350 mg QID vs. cyclobenzaprine 10 mg QID	RCT, DB, PC Male/female patients between 19 – 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	Primary: Pain at baseline and day 8: Carisoprodol (70, 30); Cyclobenzaprine (74, 28) Muscle spasm at baseline and day 8: Carisoprodol (64,22); Cyclobenzaprine (67,25) Activity impairment at baseline and day 8: Carisoprodol (74,32); cyclobenzaprine (76,26) Overall improvement (very good to excellent) at end of treatment: Carisoprodol (70%) and cyclobenzaprine (70%). No differences between groups.
Boyles et al.[11] (1983) Carisoprodol 350 mg QID vs. diazepam 5 mg QID	RCT, DB Male/female patients between 19 – 65 years of age with acute LBP.	N=80 7 Days	Primary: Improvement of pain, muscle stiffness, activity, sleep impairment, tension, and overall improvement.	Primary: Pain day 7 – 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)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Results were statistically significant for muscle stiffness, activity, tension and relief. Overall improvement (very good + excellent): Carisoprodol (70%); Diazepam (45%)
Bragstad et al.[12] (1979) Chlorzoxazone 500 mg TID vs. tizanidine 2 mg TID	RCT, DB	N=27 7 Days	Primary: Pain, muscle tension, limitation of movement and overall effectiveness by patient	Primary: Levels at baseline and day 7 Pain 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) Chlorzoxazone (excellent= 9; moderate/poor = 3)
Hennies et al.[13] (1981) Diazepam 5 mg TID vs. tizanidine 4 mg TID	RCT, DB	N=30 7 Days	Primary: Pain improvement; daily activity improvement	Primary: Number of cases with pain improvement on day 3 and 7 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 3 and 7 Tizanidine (12,13); Diazepam (10, 14)
Hindle et al.[33] (1972) Carisoprodol 350 mg QID vs. butabarbital 15 mg QID	RCT, MC, DB Male/female patients aged 18 – 70 years with acute LBP and Mexican migrant farm laborers with acute lumbar strain and spasm.	N=48 4 days	Primary: Pain (100 mm VAS), muscle spasm, interference with daily activities at baseline, day 2 and day 4; number of patients with global improvement.	Primary: Pain (100 mm VAS) at baseline, day 2 and day 4: 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 2 and day 4: Carisoprodol (3.1, 2.4, 1.8); butabarbital (3.1, 2.8, 2.6); placebo (3.0, 2.9, 2.9). No significant difference between the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. placebo				Interference with daily activities (4-point scale) at baseline, day 2 and day 4: 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. Number of patients with global improvement Carisoprodol = 12; butabarbital = 2; placebo = 2. Carisoprodol was significantly better than butabarbital and placebo.
Borenstein et al.[36] (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	RCT, DB, PC, PG, MC 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 3 and 7 Secondary: physician's rating of muscle spasm.	Primary: Study 1 Patients receiving cyclobenzaprine 5 mg or 10 mg had significantly higher mean scores on all the primary efficacy measures compared with those receiving placebo ($p \leq 0.001$). 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 3 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 3 or day 7 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 mg and 10 mg compared with 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 with 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 mg or 5 mg or placebo, respectively in study 2.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Childers el al.[35] (2005) Cyclobenzaprine 5 mg TID (CYC5) vs. cyclobenzaprine 5 mg TID + ibuprofen 400 mg TID (CYC5/IBU400) vs. cyclobenzaprine 5 mg TID + ibuprofen 800 mg TID (CYC5/IBU800)	OL, PG, MC Adults aged 18 – 65 years old; with cervical or thoracolumbar pain and spasm for ≤14 days.	N = 867 7 days	Primary: Patient Global Impression of Change (PGIC) after 7 days of treatment. Secondary: PGIC after 3 days; patient-rated scales: (spasm intensity, functional disability, medication helpfulness for pain/spasm); responders after 3 and 7 days	Primary: No significant differences were found in patients with combined neck/back or neck pain only in the 7-day PGIC outcome. Secondary: No significant differences were found in patients with combined neck/back pain in the 3-day PGIC outcome Mean PGIC was significantly different from 'no change' after 3 and 7 days of therapy in all 3 treatment groups (p<0.001). All three treatment groups demonstrated significant improvements from baseline in spasm and pain from baseline after 3 and 7 days (p<0.001 for all comparisons). There was no difference among the 3 treatment groups. Mean % Oswestry Disability Index scores improved from baseline to after 3 days and after 7 days in all 3 treatment groups (p<0.001 for all comparisons). There was no difference among the 3 treatment groups. No significant differences were detected in medication helpfulness scores among the treatment groups after 3 and 7 days of therapy.
Ralph et al.[34] (2008) Carisoprodol 250 mg TID and QHS vs. placebo	RCT, MC, DB, PC, PG 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 3). Secondary: Roland-Morris Disability Questionnaire (RMDQ), time to symptom improvement,	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 3. Significant differences were also found on treatment day 7 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 3 and 7 (p<0.0001). A greater improvement in RMDQ score was observed in the carisoprodol group than in the placebo group at days 3 and 7 (p<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patient-rated medication helpfulness, physician assessment of range of motion.	The median time to symptom improvement was earlier with carisoprodol (day 3) compared to placebo (day 6) p<0.0001. There was no difference between the treatment groups with regards to range of motion at day 3 or 7.
Spasticity				
Lapierre et al.[3] (1987) Tizanidine (up to 36 mg) vs. placebo	RCT, DB, PC, PG Patients aged 18-60 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, electrophysiological studies	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.
Smith et al.[4] (1994) Tizanidine (2-36 mg) vs. placebo	RCT, MC, PC, DB Patients aged 18-70 years 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, ADL, 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[32] (1994) Tizanidine (up to 36 mg)	RCT, DB, PC, MC, PG Patients aged 18-75 years old with multiple sclerosis	N=187 9 weeks	Primary: Muscle tone (Ashworth Scale) Secondary: Muscle power;	Primary: Muscle tone (Ashworth Scale) was significantly reduced with tizanidine compared with placebo (p=0.004). Tizanidine achieved a 20% mean reduction in muscle tone. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. placebo			EDSS score; reflexes; clonus; spasm score; 8m walking time; motor skills and upper limb functions; ADL; overall effect on function; efficacy and tolerability	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.
Bass et al.[40] (1988) Baclofen (up to 80 mg) vs. tizanidine (up to 32 mg)	RCT, DB, 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	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.
Eysette et al.[41] (1988) Baclofen (up to 60 mg) vs. tizanidine (up to 24 mg)	RCT, DB, MC Patients aged 18-70 years 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.
Smolenski et al.[42] (1981) Baclofen (up to 80 mg)	RCT, DB, PG Hospitalized patients aged 42-73 years with multiple sclerosis	N=21 6 weeks	Primary: Muscle tone (Ashworth scale); EDSS score, spasm score, muscle power, global	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. tizanidine (up to 36 mg)			impression, side effects	Tiredness was the most frequent side effect on tizanidine and muscle weakness on baclofen.
Stien et al.[43] (1987) Baclofen (up to 90 mg) vs. tizanidine (up to 36 mg)	RCT, DB Seriously handicapped patients with multiple sclerosis	N=40 6 weeks	Primary: Muscle tone (Ashworth Scale); EDSS; Pedersen rating scales; overall impression	Primary: There was no significant difference in spastic state, spasms and clonus in baclofen-treated patients compared to tizanidine-treated patients.
Nance et al.[44] (1994) Tizanidine (up to 36 mg) vs. placebo	RCT, PC, MC Patients with spinal cord injury of >12 months	N=124 7 weeks	Primary: Muscle tone (Ashworth Scale); muscle strength; ADL	Primary: Patients receiving tizanidine had a significant reduction in muscle tone and frequency of spasms compared to placebo (p=0.0001). No significant changes in muscle strength or activities of daily living were demonstrated with tizanidine compared to placebo.
Gelber et al.[45] (2001) Tizanidine (up to 36 mg)	OL, MC 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	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).

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: CI=confidence interval, SB=single-blind, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=crossover, LBP=low back pain

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Carisoprodol	tablet	Soma®*	$$$$$	$
Carisoprodol, ASA	tablet	Soma Compound®*	$$$$$	$
Carisoprodol, ASA, codeine	tablet	Soma Compound with Codeine®*	$$$$$	$
Chlorzoxazone	tablet	Parafon Forte DSC®*	$ - $$$$	$
Cyclobenzaprine	tablet, extended-release capsule	Flexeril®*, Fexmid®, Amrix®	$$ - $$$$$	$
Metaxalone	tablet	Skelaxin®	$$$$	N/A
Methocarbamol	tablet, injection	Robaxin®*	$-$$$$	$
Tizanidine	tablet, capsule	Zanaflex®*	$$$$$	$$

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

X. Conclusions

The centrally acting skeletal muscle relaxants are indicated for the treatment of spasticity and pain/discomfort associated with musculoskeletal disorders. Tizanidine is the only centrally acting skeletal muscle relaxant approved for the treatment spasticity. Clinical trials have enrolled small numbers of patients and data to support the long-term use of tizanidine is limited.[3,4,32,40-45] However, tizanidine has consistently been found to be more effective than placebo in clinical trials.[3,4,32] There are limited head-to-head trials comparing tizanidine to other antispasticity agents.[40-43] Guidelines on the diagnosis and management of multiple sclerosis recommend tizanidine

only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable.[20] Guidelines for the management of stroke rehabilitation recommend considering the use of tizanidine for spasticity resulting in pain, poor skin hygiene, or decreased function.[15] To date, there is insufficient evidence to conclude that tizanidine exhibits clinical advantages over other antispasticity agents.[39,46]

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.[1] However, adverse events require that they be used with caution.[1] Guidelines on the treatment of low back pain (LBP) recommend acetaminophen or nonsteroidal anti-inflammatory drugs as the first-line medication.[37-38] Skeletal muscle relaxants are recommended as second-line treatment in select cases of moderate to severe acute LBP.[38] They are not recommended for mild to moderate acute LBP or chronic use in subacute or chronic LBP (other than acute exacerbations).[38] There is no compelling evidence to indicate that centrally acting skeletal muscle relaxants differ in efficacy or safety for the treatment of LBP.[37]

Adverse events are problematic with the centrally acting skeletal muscle relaxants, with drowsiness and dizziness being common with all of the agents. Using lower doses may alleviate some of the adverse events without compromising efficacy.[36] Carisoprodol has been associated with dependence, withdrawal, and abuse with prolonged use.[16] It should not be used for more than two to three weeks for the relief of acute musculoskeletal discomfort. Tizanidine occasionally causes liver injury, most often hepatocellular in type.[25] Monitoring of aminotransferase levels is recommended during the first 6 months of treatment and periodically thereafter.[25] There are many drug interactions to take into consideration with tizanidine. Medications that inhibit the CYP1A2 isozyme may increase serum levels of tizanidine and lead to excessive sedation and hypotension.

Therefore, all brand centrally acting skeletal muscle relaxants within the class reviewed are comparable to each other and to the generics and OTC 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 ore more preferred brands.

XII. References

1. van Tulder MW, Touray T, Furlan AD, et al. Muscle relaxants for nonspecific low back pain: a systematic review within the framework of the Cochrane Collaboration. Spine 2003;28(17):1978-92.
2. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November, 2008.
3. Lapierre Y, Bouchard S, Tansey C, et al. Treatment of spasticity with tizanidine in multiple sclerosis. Can J Neurol Sci 1987;14:513-7.
4. 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.
5. Toth PP, Urtis J. Commonly used muscle relaxant therapies for acute low back pain: a review of carisoprodol, cyclobenzaprine and metaxalone. Clinical Therapeutics 2004:26(9):1355-67.
6. Knight CL, Deyo RA, Staiger TO, et al. Treatment of acute low back pain. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
7. Koes BW, van Tulder MW, Ostelo R, et al. Clinical guidelines for the management of low back pain in primary care: an international comparison. Spine 2001;26(22):2505-14.
8. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November, 2008.
9. Johnson-Rochee M, ed. In the Spotlight: Carisoprodol. On-Line With Industry. Winter 2002/2003;02(1):3-6.
10. 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.
11. 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.
12. 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.
13. 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.
14. Beard S, Hunn A, Wight J. Treatments of spasticity and pain in multiple sclerosis: a systematic review. Health Technol Assess 2003;7(40).
15. Management of Stroke Rehabilitation. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, February 2003. Office of Quality and Performance publication 10Q CPG/STR-03. Available at: http://www.oqp.med.va.gov/cpg/STR/str_cpg/frameset.htm. Accessed December 2008.
16. Product Information: SOMA®, carisoprodol. MedPointe Pharmaceuticals, Somerset, NJ, 2007.
17. Product Information: Parafon Forte DSC®, chlorzoxazone. Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, 2000.
18. Product Information: Amrix®, cyclobenzaprine. Cephalon, Inc., Frazer, PA, 2007.
19. Product Information: Flexeril®, cyclobenzaprine. Merck & Co. Inc., West Point, PA, 2003.
20. National Collaborating Centre for Chronic Conditions. Multiple sclerosis. National clinical guideline for diagnosis and management in primary and secondary care. London (UK): National Institute for Clinical Excellence (NICE); 2004. Available at: http://www.nice.org.uk/nicemedia/pdf/cg008guidance.pdf. Accessed December, 2008.
21. Stein, Joel, Spasticity. In: Walter R. Frontera, Julie K. Silver, Thomas D. Rizzo Jr., eds. Essentials of Physical Medicine and Rehabilitation: Musculoskeletal Disorders, Pain, and Rehabilitation. 2nd ed. Philadelphia, PA: Saunders; 2008. Available at: http://www.mdconsult.com/das/book/body/114498507-3/785570078/1678/202.html#4-u1.0-B978-1-4160-4007-1..50146-2_2450. Accessed December, 2008.
22. Product Information: Skelaxin®, metaxalone. King Pharmaceuticals, Inc., Bristol, TN, 2008.
23. Product Information: Robaxin®, methocarbamol. Schwarz Pharma, Milwaukee, WI, 2003.
24. Montane, E. Vallana, A, Laporte, JR. Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. Neurology 2004; 63: 1357.
25. Product Information: Zanaflex®, tizanidine. Acorda Therapeutics, Inc., Hawthorne, NY, 2006.
26. Carisoprodol, aspirin, and codeine: Drug information. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
27. Carisoprodol: Drug information. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.

28. Chlorzoxazone: Drug information. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
29. Cyclobenzaprine: Drug information. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
30. Metaxalone: Drug information. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
31. Methocarbamol: Drug information. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
32. 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):S70-79.
33. Hindle T. Comparison of carisoprodol, butabarbital, and placebo in treatment of the low back syndrome. California Medicine 1972;117:7-11.
34. 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.
35. Childers MK, Borenstein D, Brown RL Low-dose cyclobenzaprine versus combination therapy with ibuprofen for acute neck or back pain with muscle spasm: a randomized trial. Curr Med Res Opin 2005 9:1485-93.
36. 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.
37. 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.
38. 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/summary/summary.aspx?doc_id=12540&nbr=006456&string=skeletal+AND+muscle+AND+relaxants. Accessed November, 2008.
39. 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.
40. Bass B, Weinshenker B, Rice G, et al. Tizanidine versus baclofen in the treatment of spasticity in patients with multiple sclerosis. Can J Neurol Sci 1988;15:15-19.
41. 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.
42. 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.
43. 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 with baclofen. Acta Neurol Scand 1987;75:190-4.
44. 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.
45. 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.
46. Taricco M, Adone R, Pagliacci C. Pharmacological interventions for spasticity following spinal cord injury. Chocrane 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 11, 2009

I. Overview

Dantrolene is the only direct-acting skeletal muscle relaxant currently available. It is used to control the manifestations of clinical spasticity resulting from upper motor neuron syndromes (such as cerebral palsy or spinal cord injuries) and to treat or prevent malignant hyperthermia.[1-2]

While some treatments for spasticity (e.g., baclofen and tizanidine) 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.[4]

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.[12] 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.[12] 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.[13-14]

Malignant hyperthermia is a life-threatening, genetically-based disorder that occurs in susceptible individuals after exposure to certain drugs, usually anesthetic agents.[18] 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 in the myoplasm.[18] Dantrolene is indicated for both treatment and prophylaxis of this condition.[1]

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.

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

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dantrolene	capsule, injection	Dantrium®*	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)
American College of Physicians/ American Pain Society: **Diagnosis and Treatment of Low Back Pain[21] (2007)**	• 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[22]**	Recommendations for the treatment of acute low back pain include: • Nonsteroidal anti-inflammatory drugs (NSAIDs). • Cytoprotective medications for patients with contraindications for NSAIDs.

Clinical Guideline	Recommendation(s)
(2007)	• 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 LBP. • Skeletal muscle relaxants are not recommended for mild to moderate acute LBP or chronic use in subacute or chronic LBP (other than acute exacerbations).

National Collaborating Centre for Chronic Conditions. **Multiple Sclerosis. National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care[11] (2004)**	• Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin.
	• The following should be given only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable:
	  o Tizanidine
	  o Diazepam
	  o Clonazepam
	  o Dantrolene
	• Combinations of medicines and other medicines such as anticonvulsants should only be used after seeking further specialist advice.

VA/DoD Clinical Practice Guideline Working Group: **Management of Stroke Rehabilitation[10] (2003)**	• Consider use of tizanidine, dantrolene, and/or oral baclofen for spasticity resulting in pain, poor skin hygiene, or decreased function. Tizanidine should be used specifically for chronic stroke patients.

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[1,2]

Generic Name	Muscle Spasticity	Prevention of Malignant Hyperthermia	Prevention of Recurrence of Malignant Hyperthermia after IV therapy	Treatment of Malignant Hyperthermia
Dantrolene (oral)	✔	✔	✔	
Dantrolene (IV)		✔		✔

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[1,2,6]

Generic Name	Time to Cmax	Bioavailability (%)	Protein Binding	Metabolism	Renal Excretion (%)	Half-Life (hours)
Dantrolene	4-8 hours	70	No data	Liver	20	9

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Direct-acting Skeletal Muscle Relaxants[1-3]

Generic Name	Significance Level	Interaction	Mechanism
Dantrolene	1	Benzodiazepines, barbiturates, centrally acting muscle relaxants, chloral hydrate, opioid analgesics, and alcohol	Additive CNS and respiratory depression may occur when administered concomitantly with other CNS depressants
Dantrolene	1	Verapamil	Hyperkalemia and cardiac depression may occur.
Dantrolene	1	Methotrexate	Increased methotrexate concentration and toxicity

Significance Level 1 = major severity

VI. Adverse Drug Events

The most common adverse drug events reported with the direct-acting skeletal muscle relaxants are listed in Table 6. The boxed warnings for dantrolene are listed in Tables 7-8.

Table 6. Adverse Drug Events (%) Reported with the Direct-acting Skeletal Muscle Relaxants[1,2,6]

Adverse Events	Dantrolene
Cardiovascular	
Dyspnea	✔
Pericarditis	✔
Phlebitis	✔
Tachycardia	✔
Central Nervous System	
Confusion	✔
Delirium	✔
Depression	✔
Dizziness	✔
Drowsiness	✔
Fatigue	✔
Giddiness	✔
Incoordination	✔
Insomnia	✔
Lightheadedness	✔
Nervousness	✔
Somnolence	✔
Vertigo	✔
Dermatological	
Dermatosis	✔
Photosensitivity	✔
Rash	✔
Gastrointestinal	
Abdominal cramp/pain	✔
Anorexia	✔
Constipation	✔
Diarrhea	✔
Drooling	✔
Dysphagia	✔
Gastritis	✔
GI bleed	✔

Adverse Events	Dantrolene
Nausea	✔
Obstruction	✔
Vomiting	✔
Genitourinary	
Crystalluria	✔
Erectile dysfunction	✔
Hematuria	✔
Incontinence	✔
Nocturia	✔
Urinary frequency	✔
Urinary retention	✔
Hepatic	
Hepatotoxicity	1
Hematologic	
Aplastic anemia	✔
Leukopenia	✔
Lymphocytic lymphoma	✔
Thrombocytopenia	✔
Musculoskeletal	
Back ache	✔
Myalgia	✔
Respiratory	
Respiratory depression	✔
Special Senses	
Diplopia	✔
Dysgeusia	✔
Epiphora	✔
Visual impairment	✔

✔ Percent not specified

Table 7. Boxed Warning for Dantrolene Capsules[2]

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 AST or ALT. 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.

Table 8. Boxed Warning for Dantrolene Injection[1]

WARNING
Dantrolene has a potential for hepatotoxicity. Do not use in conditions other than those recommended. The incidence of symptomatic hepatitis (fatal and nonfatal) reported in patients taking up to 400 mg/day is much lower than in those taking ≥ 800 mg/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 liver enzyme elevations, has been observed in patients exposed to the drug for varying periods of time. Overt hepatitis has been most frequently observed between the third and twelfth months of therapy. Risk of hepatic

injury appears to be greater in females, in patients older than 35 years of age and in patients taking other medications in addition to dantrolene.

Monitor hepatic function, including frequent determinations of AST or ALT. If no observable benefit is derived from therapy after 45 days, discontinue use.

Use the lowest possible effective dose for each patient.

VII. Dosing and Administration

The usual dosing regimens for the direct-acting skeletal muscle relaxants are listed in Table 9.

Table 9. Usual Dosing Regimens for the Direct-acting Skeletal Muscle Relaxants[1,2,6]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Dantrolene	Spasticity: 25 – 100 mg orally TID Malignant hyperthermia: Post crisis: 4 – 8 mg/kg/day orally in 4 divided doses for 1-3 days Prophylaxis: 4 – 8 mg/kilogram/day orally in 3 or 4 divided doses for 1 or 2 days prior to surgery	Spasticity: 0.5 mg/kg – 2 mg/kg orally TID Malignant hyperthermia: Post crisis: 4 – 8 mg/kg/day orally in 4 divided doses for 1-3 days Prophylaxis: 4 – 8 mg/kilogram/day orally in 3 or 4 divided doses for 1 or 2 days prior to surgery	Capsules: 25 mg, 50 mg, 100 mg Powder for Injection: 20 mg/vial

TID=three times daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the direct-acting skeletal muscle relaxants for spasticity are summarized in Table 10. No controlled trials were found in the peer-reviewed literature regarding the use of dantrolene for malignant hyperthermia.

Table 10. 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.[14] (1974) Dantrolene (3-12 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; clinical evaluations	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.
Joynt et al.[15] (1980) Dantrolene (4-12 mg/kg/day) vs. placebo	RCT, DB, PC, PG Children aged 4-15 years 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, ADL, adverse events	Primary: There was no significant difference in muscle tone, muscle strength, range of motion, reflexes, clonus, spasms, or ADL 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 3.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ketel et al.[16] (1984) Dantrolene (25 mg every 8-12 hours) vs. placebo 1st phase: dantrolene 2nd phase: responders only 3rd phase: responders continued on dantrolene	Phase 1: OL Phase 2: RCT, DB, PC, PG Adults aged 48-78 years with stroke	Phase 1:N=18 Phase 2: N=14 Phase 3: N=13 Phase 1: 6 weeks Phase 2: 6 weeks Phase 3: 81-978 days	Primary: Spasticity grading scale; ADL	Primary: Phase 1: Spasticity was reduced in all 18 patients (no p values provided for measures) 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.
Katrak et al.[17] (1992) Dantrolene (50-200 mg/day) vs. placebo	DB, PC, XO Adults aged35-85 years with stroke	N=38 14 week	Primary: Muscle tone; motor function scale; isokinetic dynamometric measurements; ADL; adverse events	Primary: There was no significant difference in muscle tone, motor function scale, or ADL with dantrolene compared to placebo. Dantrolene improved of isokinetic measurements to a greater extent than placebo (no p values provided). Lethargy/drowsiness was reported in 45% of dantrolene-treated patients compared to 20% of placebo-treated patients (p=.03). Slurred speech occurred in 19% of dantrolene-treated patients compared to no patients in the placebo group (p=.01).

Study abbreviations: DB=double-blind, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover, ADL= activities of daily living

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Direct-acting Skeletal Muscle Relaxants

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

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

X. Conclusions

Dantrolene is the only direct-acting skeletal muscle relaxant approved for the treatment of spasticity and for the treatment and prevention of malignant hyperthermia. 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 in clinical trials.[14-17] There are no head-to-head trials comparing dantrolene to other antispasticity agents, and it is difficult to draw conclusions on the efficacy of dantrolene as no validated outcome measures were used in clinical trials.[8] Guidelines on the diagnosis and management of multiple sclerosis recommend dantrolene only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable.[11]

Adverse events are problematic with the skeletal muscle relaxants, with drowsiness and dizziness being common with all agents. Dantrolene has the potential to cause fatal or non-fatal hepatotoxicity, which has led to the placement of a boxed warning in the prescribing information.[1,2]

Dantrolene is the treatment of choice for malignant hyperthermia.[18, 20] When used, this treatment is emergent in nature and occurs in the inpatient or outpatient operative setting. Use of oral dantrolene for preoperative prophylaxis should be reserved for those patients with documented medical necessity.

Therefore, all brand direct-acting skeletal muscle relaxants within the class reviewed are comparable to each other and to the generics and OTC 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. Product Information: Dantrium® intravenous injection, dantrolene. Procter & Gamble Pharmaceuticals, Cincinnati, OH, 2007.
2. Product Information: Dantrium® oral capsules, dantrolene. Proctor & Gamble Pharmaceuticals, Cincinnati, OH, 2002.
3. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November, 2008.
4. McEvoy GK, Ed. American Hospital Formulary Service, AHFS Drug information. American Society of Health-System Pharmacists. Bethesda. 2005.
5. Electronic Orange Book. Available at: http://www.fda.gov.cder/ob/. Accessed November, 2008.
6. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November, 2008.
7. Beard S, Hunn A, Wight J. Treatments of spasticity and pain in multiple sclerosis: a systematic review. Health Technol Assess 2003;7(40).
8. 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.
9. Chou R, Peterson K. Oregon Health & Science University. Drug Class Review on Skeletal Muscle Relaxants. Final Report May 2005. Available at: http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/SMR_Final_Report_Update%2026.pdf. Accessed December 2008.
10. Management of Stroke Rehabilitation. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, February 2003. Office of Quality and Performance publication 10Q CPG/STR-03. Available at: http://www.oqp.med.va.gov/cpg/STR/str_cpg/frameset.htm. Accessed December, 2008.
11. National Collaborating Centre for Chronic Conditions. Multiple sclerosis. National clinical guideline for diagnosis and management in primary and secondary care. London (UK): National Institute for Clinical Excellence (NICE); 2004. Available at: http://www.nice.org.uk/nicemedia/pdf/cg008guidance.pdf. Accessed December, 2008.
12. Stein, Joel, Spasticity. In: Walter R. Frontera, Julie K. Silver, Thomas D. Rizzo Jr., eds. Essentials of Physical Medicine and Rehabilitation: Musculoskeletal Disorders, Pain, and Rehabilitation. 2nd ed. Philadelphia, PA: Saunders; 2008. Available at: http://www.mdconsult.com/das/book/body/114498507-3/785570078/1678/202.html#4-u1.0-B978-1-4160-4007-1..50146-2_2450. Accessed December, 2008.
13. Montane, E. Vallana, A, Laporte, JR. Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. Neurology 2004; 63: 1357.
14. Haslam, RHA, et al. Dantrolene sodium in children with spasticity. Arch Phys Med Rehabil 1974;55:384-388.
15. Joynt, RL, Leonard, JA. Dantrolene sodium suspension in treatment of spastic cerebral palsy. Dev Med Child Neurol 1980; 22: 755-767.
16. 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; 9:161-169.
17. Katrak, PH, et al. Objective assessment of spasticity, strength, and function with early exhibition of dantrolene sodium after cerebrovascular accident; a randomized, double-blind controlled study. Arch Phys Med Rehab 1992; 73:4-9.
18. 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/das/book/body/114566460-3/785759916/. Accessed December, 2008.
19. Kolb ME, Horne ML, Martz R. Dantrolene in human malignant hyperthermia. Anesthesiology 1982; 56: 254-62.
20. Gronert GA et al. Malignant hyperthermia. In: Miller, RD, ed. Miller's Anesthesia. 6th ed. Philadelphia, PA: Elsevier, Churchill Livingstone, 2005. Available at: http://www.mdconsult.com/das/book/body/114582244-3/0/1255/834.html?tocnode=53062459&fromURL=834.html#4-u1.0-B0-443-06618-3..50032-3--cesec34_1903. Accessed December, 2008.
21. 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.

22. 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/summary/summary.aspx?doc_id=12540&nbr=006456&string=skeletal+AND+muscle+AND+relaxants. Accessed November, 2008.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of GABA-derivative Skeletal Muscle Relaxants
AHFS Class 122012
February 11, 2009

I. Overview

Baclofen is the only GABA-derivative skeletal muscle relaxant currently available and it is FDA-approved for the treatment of spasticity.[5,12] Baclofen is an analog of gamma aminobutyric acid (GABA) and inhibits both monosynaptic and polysynaptic reflexes at the spinal level to cause muscle relaxation.[5,12]

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.[9] 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.[9] 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.[10]

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.

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

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Baclofen	tablet, intrathecal injection	Lioresal®*†, Lioresal Intrathecal®	baclofen

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
†Brand is no longer available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the 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)
American College of Physicians/ American Pain Society: **Diagnosis and Treatment of Low Back Pain[27] (2007)**	• 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[28] (2007)**	Recommendations for the treatment of acute low back pain include: • Nonsteroidal anti-inflammatory drugs (NSAIDs). • Cytoprotective medications for patients with contraindications for NSAIDs. • 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

Clinical Guideline	Recommendation(s)
	moderate to severe acute LBP. • Skeletal muscle relaxants are not recommended for mild to moderate acute LBP or chronic use in subacute or chronic LBP (other than acute exacerbations).
National Collaborating Centre for Chronic Conditions. **Multiple Sclerosis. National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care[11] (2004)**	• Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin. • The following should be given only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable: o Tizanidine o Diazepam o Clonazepam o Dantrolene • Combinations of medicines and other medicines such as anticonvulsants should only be used after seeking further specialist advice.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the 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[5,12]

Generic Name	Muscle Spasticity
Baclofen	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the GABA-derivative skeletal muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the GABA-derivative Skeletal Muscle Relaxants[3]

Generic Name	Onset	Bioavailability	Protein Binding	Metabolism	Renal Excretion (%)	Half-Life (hours)
Baclofen (oral)	3 – 4 days	100%	30%	Liver	69-85	3-7
Baclofen (injection)	30 – 60 minutes	No data	No data	Liver	69-85	3-7

V. Drug Interactions

Significant drug interactions with the GABA-derivative skeletal muscle relaxants are listed in Table 5.

Table 5. Significant Drug Interactions with the GABA-derivative Skeletal Muscle Relaxants[2-3]

Generic Name	Significance Level	Interaction	Mechanism
Baclofen	3	Amitriptyline, desipramine, doxepin, Protriptyline, trimipramine	Short-term memory loss and additive muscle relaxant effects

Significance Level 3 = minor severity

VI. Adverse Drug Events

The most common adverse drug events reported with the GABA-derivative skeletal muscle relaxants are listed in Table 6. The boxed warning for baclofen intrathecal injection is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the GABA-derivative Skeletal Muscle Relaxants[2-3,5,12]

Adverse Events	Baclofen
Cardiovascular	
Arrhythmia	✔
Chest pain	✔
Deep vein thrombosis	✔
Dyspnea	✔
Hypotension	0-9
Palpitations	✔
Peripheral edema	✔
Syncope	✔
Central Nervous System	
Agitation	✔
Amnesia	✔
Catatonia	✔
Confusion	1-11
Depression	✔
Disorientation	✔
Dizziness	5-15
Drowsiness	10-63
Dysarthria	✔
Euphoria	✔
Excitement	✔
Fatigue	2-4
Hallucinations	✔
Headache	4-8
Impaired cognition	✔
Insomnia	2-7
Lethargy	✔
Light-headedness	✔
Mania	✔
Paranoia	✔
Paresthesia	3-7
Psychosis	✔
Seizure	✔
Slurred speech	✔
Somnolence	✔
Suicidal ideation	✔
Weakness	5-15
Dermatological	
Diaphoresis	✔
Flushing	✔
Pruritus	✔
Rash	✔
Urticaria	✔
Endocrine and Metabolic	
Elevated glucose	✔
Weight gain	✔
Gastrointestinal	
Abdominal cramp/pain	✔

Adverse Events	Baclofen
Anorexia	✔
Bowel incontinence	✔
Constipation	2-6
Diarrhea	✔
Ileus	✔
Nausea	4-12
Vomiting	4-12
Xerostomia	✔
Genitourinary	
Ejaculation dysfunction	✔
Impotence	✔
Urinary frequency	2-6
Hepatic	
Increased AST	✔
Increased ALT	✔
Musculoskeletal	
Hypotonia	✔
Muscle rigidity	✔
Muscular weakness	✔
Myalgia	✔
Respiratory	
Bronchospasm	✔
Respiratory depression	✔
Nasal congestion	✔
Special Senses	
Blurred vision	✔
Diplopia	✔
Dysgeusia	✔
Miosis	✔
Mydriasis	✔
Tinnitus	✔
Other	
Septicemia	✔
Aspiration pneumonia	✔
Meningitis	✔
Intracranial bleeding	✔
Subdural hemorrhage	✔

✔ Percent not specified

Table 7. Boxed Warning for Baclofen Intrathecal Injection[12]

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 (see Warnings).

VII. Dosing and Administration

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

Table 8. Usual Dosing Regimens for the GABA-derivative Skeletal Muscle Relaxants[2-3,5,12]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Baclofen	Oral: 40 – 80 mg per day divided in 3 or 4 doses Intrathecal: Maintenance (spinal cord injury) dosages have ranged from 12 to 2003 mcg/day, (most patients:300 to 800 mcg/day) Maintenance (cerebral origin spasticity) dosages have ranged from 22 to 1400 mcg/day (most patients: 90 to 700 micrograms/day)	Oral: Safety and efficacy have not been established in pediatric patients under age 12. Intrathecal injection: Safety and effectiveness in pediatric patients below the age of 4 have not been established. Age >4 years: 25 – 50 mcg initial screening dose. After the first 24 hours, the daily dose should be increased slowly by 5-15% only once every 24 hours, until the desired clinical effect is achieved.	Tablets: 10 mg, 20 mg Intrathecal injection: 50 mcg/ml, 500 mcg/ml, 2000 mcg/ml

VIII. Effectiveness

Although skeletal muscle relaxants have been available for many years, there are limited head-to-head trials in the treatment of spasticity. Clinical studies evaluating the safety and efficacy of the GABA-derivative skeletal muscle relaxants are summarized in Table 9.

Table 9. 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
Brar et al.[18] (1991) Baclofen (20 mg) vs. placebo	B, XO, PC 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	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.
Sachais et al.[19] (1977) Baclofen (60-80 mg) vs. placebo	RCT, DB, MC 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	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.
Feldman et al.[20] (1978) Baclofen (up to 80 mg) vs. placebo	RCT, DB, XO Patients aged 38-53 with multiple sclerosis and any degree of spasticity	N=23 3 years	Primary: Daily spasm count; resistance to passive movement; clonus; Barthel score	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 compared to placebo.
Gerszten et al.[22] (1997)	RETRO	N=24	Primary: Ambulation graded	Primary: Level of ambulation improved by one functional level in 9 patients, did

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Intrathecal baclofen infusion	Patients with spastic cerebral palsy or traumatic brain injury who were ambulatory to some extent, either with or without assistive devices	52 months	on four functional levels (community, household, non-functional, and non-ambulatory)	not change for 12 patients, and was worse in 3 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 2 patients, and worse in 2 patients.
Gilmartin et al.[23] (2000) Intrathecal baclofen continuous infusion	MC, OL Patients aged 4-41 years with spastic cerebral palsy	N=51 39 months	Primary: Spasticity (Ashworth Scale score)	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 6 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 mcg at implantation to 402 mcg at 39 months. 42/51 patients experienced adverse events. Most commons adverse events were hypotonia (15%), seizures (no new onset, 9%), somnolence (9%), and nausea (4%) or vomiting (7%).
Van Schaeybroeck et al.[24] (2000) Intrathecal baclofen continuous infusion vs. placebo	PRO, PC, DB Patients aged 8-55 years with spasticity of cerebral origin (primarily cerebral palsy)	N=8 2 years	Primary: Spasticity (Ashworth Scale score and VAS); spasms; pain; functional abilities	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.
Ordia et al.[25] (1996)	OL	N=59	Primary: Rigidity (Ashworth	Primary: The mean Ashworth Scale score for rigidity decreased from 4.3

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Intrathecal baclofen continuous infusion	Patients with severe spasticity of spinal cord origin refractory to oral baclofen or who experienced intolerable side effects		Scale score)	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.
Meythaler et al.[26] (1997) Intrathecal baclofen continuous infusion	OL Patients aged 17-39 with acquired brain injury, severe, progressive spasticity, and dystonia refractory to maximal medical therapy, which interfered with activities of daily living	N=11 3 months	Primary: Muscle tone (Ashworth Scale score)	Primary: Lower-extremity Ashworth Scale scores decreased from 3.5 points before treatment to 2.2 points after 3 months of treatment (p<0.0001). The average lower-extremity spasm frequency scores decreased from 1.8 points before treatment to 0.2 points after 3 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 3 months of treatment (p=0.0033). The average upper extremity spasm score decreased from 1.8 points before treatment to 0.6 points after 3 months of treatment (p=0.0070). The biceps reflex score decreased from 2.7 points to 1.7 points after 3 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.
Loubser et al.[13] (1991) Stage 1: Intrathecal baclofen infusion Stage 2: Permanent programmable	PRO, PC Patients with spinal cord injuries whose spasticity had been refractory to oral medications	Stage 1: N=9 Stage 2: N=7 Stage 1: 5 days Stage 2:	Primary: Ashworth Scale score and reflex scores; functional abilities; somatosensory and brainstem auditory evoked potentials;	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 8 patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
baclofen infusion pump		3-22 months		Somatosensory and brainstem auditory evoked potentials were unchanged with both treatment groups. Urodynamic evaluation revealed increased bladder capacity in 3 patients, while in 4 no change was observed. <u>Stage 2</u> Mean Ashworth scale score decreased from 3.79 to 2 ($p< 0.001$) and mean reflex score decreased from 3.85 to 2.18 ($p<0.001$).
Bass et al.[14] (1988) Baclofen (up to 80 mg) vs. tizanidine (up to 32 mg)	RCT, DB, 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	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 baclofen-treated patients and tizanidine-treated patients.
Eysette et al.[15] (1988) Baclofen (up to 60 mg) vs. tizanidine (up to 24 mg)	RCT, DB, MC Patients aged 18-70 years 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.
Smolenski et al.[16] (1981) Baclofen (up to 80 mg) vs.	RCT, DB, PG Hospitalized patients aged 42-73 years with multiple sclerosis	N=21 6 weeks	Primary: Muscle tone (Ashworth scale); EDSS score, spasm score, muscle power, global impression, side	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tizanidine (up to 36 mg)			effects	Tiredness was the most frequent side effect on tizanidine and muscle weakness on baclofen.
Stien et al.[17] (1987) Baclofen (up to 90 mg) vs. tizanidine (up to 36 mg)	RCT, DB Seriously handicapped patients with multiple sclerosis	N=40 6 weeks	Primary: Muscle tone (Ashworth Scale); EDSS; Pedersen rating scales; overall impression	Primary: There was no significant difference in spastic state, spasms and clonus in baclofen-treated patients compared to tizanidine-treated patients.

Study abbreviations: DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 GABA-derivative Skeletal Muscle Relaxants

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Baclofen	tablet, intrathecal injection	Lioresal®*†, Lioresal Intrathecal®	$$ - $$$$	$ - $$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available

X. Conclusions

Baclofen is the only GABA-derivative skeletal muscle relaxant currently available and it is indicated for the treatment of spasticity. It has been shown to be an effective treatment option for muscular spasms due to conditions such as multiple sclerosis, cerebral palsy, and brain/spinal cord injuries.[5,12,13-20,22-26] Baclofen has consistently been found to be more effective than placebo in clinical trials.[18-20] However, there are limited head-to-head trials comparing baclofen to other antispasticity agents.[14-17] Guidelines on the diagnosis and management of multiple sclerosis recommend initial treatment with baclofen or gabapentin for bothersome regional or global spasticity or spasms.[11] Guidelines for the management of stroke rehabilitation consider the use of oral baclofen for spasticity resulting in pain, poor skin hygiene, or decreased function.[13] To date, there is insufficient evidence to conclude that baclofen exhibits clinical advantages over other antispasticity agents.[7,21]

Adverse events are problematic with skeletal muscle relaxants, with drowsiness and dizziness being common with all of the agents. Slow dose escalation is recommended to reduce the risk of adverse events. 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.

This has led to the placement of a boxed warning in the prescribing information.[12] Thus, the dose of baclofen (both oral and intrathecal) should be reduced slowly when the drug is discontinued.[5,12]

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

XI. Recommendations

No brand 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. Baclofen: Drug Information. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
2. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November, 2008.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November, 2008.
4. Beard S, Hunn A, Wight J. Treatments of spasticity and pain in multiple sclerosis: a systematic review. Health Technol Assess 2003;7(40).
5. Product Information: Baclofen. Watson, Corona, CA, 2004.
6. 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.
7. 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.
8. Chou R, Peterson K. Oregon Health & Science University. Drug Class Review on Skeletal Muscle Relaxants. Final Report May 2005.
9. Stein, Joel, Spasticity. In: Walter R. Frontera, Julie K. Silver, Thomas D. Rizzo Jr., eds. Essentials of Physical Medicine and Rehabilitation: Musculoskeletal Disorders, Pain, and Rehabilitation. 2nd ed. Philadelphia, PA: Saunders; 2008. Available at: http://www.mdconsult.com/das/book/body/114498507-3/785570078/1678/202.html#4-u1.0-B978-1-4160-4007-1..50146-2_2450. Accessed December, 2008.
10. Montane, E. Vallana, A, Laporte, JR. Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. Neurology 2004; 63: 1357.
11. National Collaborating Centre for Chronic Conditions. Multiple sclerosis. National clinical guideline for diagnosis and management in primary and secondary care. London (UK): National Institute for Clinical Excellence (NICE); 2004. Available at: http://www.nice.org.uk/nicemedia/pdf/cg008guidance.pdf. Accessed December, 2008.
12. Product Information: Lioresal Intrathecal. Medtronic, Inc., Minneapolis, MN, December 2008.
13. 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.
14. Bass B, Weinshenker B, Rice G, et al. Tizanidine versus baclofen in the treatment of spasticity in patients with multiple sclerosis. Can J Neurol Sci 1988;15:15-19.
15. 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.
16. 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.
17. 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 with baclofen. Acta Neurol Scand 1987;75:190-4.
18. Brar S, Smith M, Nelson L, et al. Evaluation of treatment protocols on minimal to moderate spasticity in multiple sclerosis. Arch Phys Med Rehabil 1001;72:186-9.
19. 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.
20. 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.
21. Taricco M, Adone R, Pagliacci C. Pharmacological interventions for spasticity following spinal cord injury. Chocrane Database of Systematic Review 2000, Issue 2. Art. No.: CD001131. DOI: 10.1002/14651858.CD001131.
22. Gerszten P, Albright A, Barry M. Effect on ambulation of continuous intrathecal baclofen infusion. Pediatr Neurosurg 1997;27:40-44.
23. 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.
24. 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.
25. 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.
26. 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.

27. 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.
28. 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/summary/summary.aspx?doc_id=12540&nbr=006456&string=skeletal+AND+muscle+AND+relaxants. Accessed November, 2008.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skeletal Muscle Relaxants, Miscellaneous
AHFS Class 122092
February 11, 2009

I. Overview

Back pain is a common problem and there are many treatments available for the management of this disorder.[3] Back pain can be classified as acute, subacute and chronic. Orphenadrine is the only miscellaneous skeletal muscle relaxant that is currently available. It is FDA-approved for the relief of discomfort associated with acute, painful musculoskeletal disorders.[5,10] Orphenadrine is an indirect skeletal muscle relaxant with central atropine-like effects. Although the exact mechanism of action has not been established, orphenadrine may exert a beneficial effect due to its analgesic properties.[5-6,10] Use of this agent is generally limited to short-term therapy.[3,6]

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.

Table 1. Miscellaneous Skeletal Muscle Relaxants Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Orphenadrine	extended-release tablet, injection	Norflex®*	orphenadrine
Orphenadrine, ASA, caffeine	tablet	N/A	orphenadine, ASA, caffeine

*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 skeletal muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Miscellaneous Skeletal Muscle Relaxants

Clinical Guideline	Recommendation(s)
American College of Physicians/ American Pain Society: **Diagnosis and Treatment of Low Back Pain[7] (2007)**	• 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[8] (2007)**	Recommendations for the treatment of acute low back pain include: • Nonsteroidal anti-inflammatory drugs (NSAIDs). • Cytoprotective medications for patients with contraindications for NSAIDs. • 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 LBP. • Skeletal muscle relaxants are not recommended for mild to moderate acute LBP or chronic use in subacute or chronic LBP (other than acute exacerbations).

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 Miscellaneous Skeletal Muscle Relaxants[5,10]

Generic Name	Relief of Discomfort Associated with Acute, Painful Musculoskeletal Disorders
Orphenadrine	✔

IV. Pharmacokinetics

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

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

Generic Name	Cmax	Bioavailability	Protein Binding	Metabolism	Renal Excretion	Half-Life
Orphenadrine	2-4 hours	95%	No data	No data	60%	13 – 20 hours

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Miscellaneous Skeletal Muscle Relaxants[2,4]

Generic Name	Significance Level	Interaction	Mechanism
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 behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects.
Orphenadrine	2	Bupropion	Concomitant use of orphenadrine and bupropion may increase bupropion plasma concentrations.
Orphenadrine	2	Potassium chlroide	Orphenadrine may slow GI motility, delaying potassium chloride tablet passage through the GI tract. Solid dosage forms of potassium chloride are contraindicated with anticholinergics Potassium chloride liquid may be a suitable alternative.
Orphenadrine	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.

Significance Level 2 = moderate severity

VI. Adverse Drug Events

Orphenadrine has been chronically abused for its euphoric effects.[5,10] The mood elevating effects may occur at therapeutic doses.[5,10] The most common adverse drug events reported with the miscellaneous skeletal muscle relaxants are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Miscellaneous Skeletal Muscle Relaxants[4,5,10]

Adverse Events	Orphenadrine
Cardiovascular	
Palpitations	✔
Shock	✔
Tachycardia	✔
Central Nervous System	
Agitation	✔
Confusion	✔
Dizziness	✔
Drowsiness	✔
Dyskinesia	✔
Euphoria	✔
Excitement	✔
Hallucinations	✔
Light-headedness	✔
Syncope	✔
Tremor	✔
Dermatological	
Flushing	✔
Pruritus	✔
Urticaria	✔
Endocrine and Metabolic	
Hypoglycemia	✔
Gastrointestinal	
Abdominal distension	✔
Constipation	✔
Fecal impaction	✔
Nausea	✔
Obstruction	✔
Vomiting	✔
Xerostomia	✔
Genitourinary	
Urinary hesitancy	✔
Urinary retention	✔
Special Senses	
Blurred vision	✔
Mydriasis	✔
Increased ocular tension	✔

✔ Percent not specified

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 Miscellaneous Skeletal Muscle Relaxants[5,10]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Orphenadrine	Oral: 100 mg PO BID	Safety and efficacy have not been established in pediatric	Tablets, extended-release: 100 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	IV or IM: 60 mg which may be repeated every 12 hours	patients.	Injection: 30 mg/ml
Orphenadrine, ASA, caffeine	1 – 2 tablets TID – QID	Safety and efficacy have not been established in pediatric patients.	Tablets: Orphenadrine 25 mg, aspirin 385 mg, and caffeine 30 mg Orphenadrine 50 mg, aspirin 770 mg, and caffeine 60 mg

BID=twice daily; TID=three times daily; QID=four times daily; IV=intravenous; IM=intramuscular

VIII. Effectiveness

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

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gold et al.[9] (1978) Orphenadrine 100 mg BID vs. phenobarbital 32 mg BID vs. placebo	RCT, PC, DB Patients with acute LBP and muscle spasms and limited work/daily activities	N=60 7 days	Primary: Reduced pain at 2 days; overall improvement at 2 days	Primary: <u>Reduced pain at 2 days:</u> Orphenadrine (9/20); Phenobarbital (3/20); placebo (4/20). Orphenadrine was significantly better than phenobarbital and placebo (p value not given). <u>Overall improvement at 2 days:</u> Orphenadrine (7/20); Phenobarbital (3/20); placebo (0/20). Orphenadrine was significantly better than placebo (p value not given).
Klinger et al.[11] (1988) Orphenadrine 60 mg IV vs. placebo	RCT, PC, DB Patients aged 14-62 years 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	Primary: <u>Self-assessment of pain (none, slight, moderate or severe):</u> Orphenadrine was significantly 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; p value not give). 92% of orphenadrine-treated patients experienced global improvement compared to 12% of placebo-treated patients (orphenadrine significantly better than placebo; p value not give).
Tervo et al.[12] (1976)	RCT, PC, DB Patients with acute	N=25 7 days	Primary: Mean duration of disability;	Primary: Treatment with orphenadrine significantly reduced the mean duration of disability by 8.6 days compared to 12.9 days with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Orphenadrine 60 mg IM followed by orphenadrine 35 mg + acetaminophen (450 mg) 2 tablets TID vs. saline IM followed by paracetamol (450 mg) 2 tablets TID	LBP		subjective impressions of the treatments Secondary: Objective clinical examinations (gait, sitting posture, scoliosis, spinal flexion, muscle spasm, Lasegue)	There was no significant differences between orphenadrine/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.[13] (1983) Orphenadrine (35 mg) + acetaminophen (450 mg) 1 tablet TID vs. placebo	RCT, PC, DB, PG Patients suffering from pain due to tension of the cervical and upper thoracic musculature	N=44 7 days	Primary: Pain using VAS	Primary: Orphenadrine/acetaminophen significantly relieved pain compared to placebo. The combination of orphenadrine/acetaminophen produced significant pain relief by the second day of treatment compared to placebo.

Drug regimen abbreviations: BID=twice daily, TID=three times daily, QID=four times daily, IV=intravenous, IM=intramuscular
Study abbreviations: DB=double-blind, LBP=low back pain, MC=multicenter, 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Miscellaneous Skeletal Muscle Relaxants

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Orphenadrine	extended-release tablet, injection	Norflex®*	$	$
Orphenadrine, ASA, caffeine*	tablet	N/A	N/A	$$ - $$$

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

X. Conclusions

Orphenadrine is an effective treatment for musculoskeletal disorders, including the short-term symptomatic relief of non-specific low back pain.[1,9,11-13] However, adverse events require that it be used with caution.[1] Guidelines on the treatment of low back pain (LBP) recommend acetaminophen or nonsteroidal anti-inflammatory drugs as the first-line medication.[7-8] Skeletal muscle relaxants are recommended as second-line treatment in select cases of moderate to severe acute LBP.[8] They are not recommended for mild to moderate acute LBP or chronic use in subacute or chronic LBP (other than acute exacerbations).[8] There are no published head-to-head trials comparing orphenadrine to other skeletal muscle relaxants.

Adverse events with orphenadrine are mainly due to the mild anticholinergic action of this agent, and are usually associated with higher doses. Dryness of the mouth is usually the first adverse event to appear.[5-6,10] Orphenadrine has been chronically abused for its euphoric effects.[5,10] The mood elevating effects may occur at therapeutic doses.[5,10]

Therefore, all brand miscellaneous skeletal muscle relaxants within the class reviewed are comparable to each other and to the generics and OTC 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. van Tulder MW, Touray T, Furlan AD, et al. Muscle relaxants for nonspecific low back pain: a systematic review within the framework of the Cochrane Collaboration. Spine 2003;28(17):1978-92.
2. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November, 2008.
3. Knight CL, Deyo RA, Staiger TO, et al. Treatment of acute low back pain. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
4. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November, 2008.
5. Product Information: Norflex® injection, orphenadrine. Graceway Pharmaceuticals, LLC, Bristol, TN, 2008.
6. Orphenadrine: Drug information. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
7. 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.
8. 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/summary/summary.aspx?doc_id=12540&nbr=006456&string=skeletal+AND+muscle+AND+relaxants. Accessed November, 2008.
9. Gold R. Orphenadrine citrate: sedative or muscle relaxant? Clin Ther 1978;1:451-453.
10. Product Information: Norflex®, orphenadrine. 3M Pharmaceuticals, Northridge, CA, 2006.
11. Klinger N, Wilson R, Kanniainen C, et al. Intravenous orphenadrine for the treatment of lumbar paravertebral muscle strain. Curr Ther Res 1988;43:247-254.
12. 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;30:62-64.
13. 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 11, 2009

I. Overview

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of damage.[1] It is a subjective experience that is unique to the individual. There are numerous etiologies of pain and successful pain management can be a difficult goal to attain. An individual's reaction to pain and response to pain management can be highly variable.

Pain management is multifaceted and may incorporate both pharmacologic and nonpharmacologic treatments. Successful pain management may require frequent reassessment of pain level and response to therapy. There are numerous pharmacologic agents available to help manage pain, including the opiate agonists.

Opioids have been used for thousands of years to treat pain. There are several opioid receptors within the central nervous system and peripheral tissues, including mu, delta, kappa, and sigma. Opiate agonists are selective for the mu receptor and are the most potent analgesics. Binding and activation of the mu receptor causes analgesia, euphoria, respiratory depression, sedation, decreased gastrointestinal motility, and dependence. Opiate agonists have no ceiling to their analgesic effect; the degree of analgesia is only limited by dose-related adverse events.[2-5]

The opiate agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The sustained-release opiate agonists are not included in this review as they are already included in the Alabama Medicaid Prior Authorization Program, which is outside of the Preferred Drug List. Any information on oral extended-release formulations included in this review is for informational purposes only and is not part of the evaluation for preferred drug list status.

Table 1. Opiate Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Alfentanil	injection	Alfenta®*	alfentanil
Codeine	tablet, injection	N/A	codeine
Codeine/APAP	elixir, suspension, tablet	Capital w/Codeine®, Tylenol w/Codeine #3®*, Tylenol w/Codeine #4®*, Vopac®	codeine/APAP
Codeine/ASA	tablet	N/A	codeine/ASA
Codeine/APAP/butalbital/ caffeine	capsule	Fioricet w/codeine®*, Phrenilin-Caffeine-Codeine®*	codeine/APAP/butalbital/ caffeine
Codeine/ASA/butalbital/ caffeine	capsule	Fiorinal w/codeine #3®*	codeine/ASA/butalbital/ caffeine
Dihydrocodeine/APAP/ caffeine	capsule, tablet	Panlor DC®, Panlor SS®*	dihydrocodeine/APAP/ caffeine
Fentanyl	buccal tablet, extended-release transdermal patch, transmucosal lozenge, injection	Duragesic®*, Actiq®*, Fentora®, Sublimaze®*	fentanyl
Hydrocodone/APAP	capsule, tablet, solution	Liquicet®, Lortab®*, Hycet®, Maxidone®*, Norco®*, Vicodin®*, Xodol 10-300®*, Zamicet®*, Zydone®	hydrocodone/APAP

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Hydrocodone/ibuprofen	tablet	Ibudone®, Reprexain®*, Vicoprofen®*	hydrocodone/ibuprofen
Hydromorphone	liquid, tablet, rectal suppository, injection	Dilaudid®*	hydromorphone
Levorphanol	tablet, injection	Levo-Dromoran®*	levorphanol
Meperidine	solution, tablet, injection	Demerol®*	meperidine
Methadone	oral concentrate, solution, tablet	Dolophine®*, Methadose®*,	methadone
Morphine sulfate	injection, intravenous, epidural, tablet, solution, rectal suppository	Roxanol®*, Depodur®*, Duramorph®*, Astramorph®*, Infumorph®*	morphine sulfate
Opium/belladonna	rectal suppository	N/A	opium/belladonna
Oxycodone	capsule, oral concentrate, solution, tablet	OxyIR®*, Dazidox®*, Roxicodone®*	oxycodone
Oxycodone/APAP	capsule, solution, tablet	Percocet®*, Perloxx®, Lynox®, Narvox®, Magnacet®, Alcet®, Primalev®, Tylox®*	oxycodone/APAP
Oxycodone/ASA	tablet	Percodan®*	oxycodone/ASA
Oxycodone/ibuprofen	tablet	Combunox®*	oxycodone/ibuprofen
Oxymorphone	tablet, injection	Opana®, Numorphan®	none
Propoxyphene HCL	capsule	Darvon®*	propoxyphene HCL
Propoxyphene HCL/APAP	tablet	N/A	propoxyphene HCL/ APAP
Propoxyphene napsylate	tablet	Darvon-N®	none
Propoxyphene napsylate/ APAP	tablet	Darvocet-N 50®*, Darvocet-N 100®*, Darvocet A500®*	propoxyphene napsylate/ APAP
Remifentanil	intravenous	Ultiva®	none
Sufentanil	intravenous	Sufenta®*	sufentanil
Tramadol	tablet, sustained-release tablet	Ultram®*, Ultram ER®	tramadol
Tramadol/APAP	tablet	Ultracet®*	tramadol/APAP

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
APAP=acetaminophen; ASA=aspirin; ER=extended-release

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)
Annals of Oncology: **Management of Cancer Pain: ESMO Clinical Recommendations[25] (2008)**	• Step-wise escalation of analgesic therapy should usually follow the 'pain ladder' as described by the WHO: ○ Step I, Mild Pain: non-opiate analgesics (e.g., APAP, NSAIDs) +/- adjuvant pain meds ○ Step II, Mild-Moderate Pain: mild opiate (e.g. codeine) +/- non-opiate analgesics +/- adjuvant meds ○ Step III, Moderate-Severe Pain: strong opiate (e.g. morphine) +/- non-opiate analgesics +/- adjuvant pain meds • Patients presenting with severe pain that needs urgent relief should be treated with parenteral opioids, usually administered by IV or SC

Clinical Guideline	Recommendation(s)
	route. • 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 4 '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.
American Society of the Interventional Pain Physicians: **Opioids in the Management of Chronic Non-Cancer Pain: An Update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines[26] (2008)**	• Opioids are extensively used in managing chronic pain. • The clinical effectiveness of opioid medications for non-cancer pain in humans is difficult to measure. • Based on the review of multiple systematic reviews and the available literature, the evidence for the effectiveness of long-term opioids in reducing pain and improving the functional status for 6 months or longer is variable. • Opioid pharmacology is variable and essential to understand for proper management of patients. Periodic review of the patient on opioids is essential, using appropriate adjustments, with routine assessment of analgesia, activity, aberrant behavior, and adverse effects. The rationalization and importance of these guidelines lies in the fact that most available evidence documents a wide degree of variance in the prescribing patterns of opioids for chronic pain. The strength of available evidence in the use opioids for chronic non-cancer pain is weak. <u>Initial dose adjustment phase (up to 8 to 12 weeks)</u> • Start low dose. • Utilize opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and adjuvants • Discontinue due to lack of analgesia, side effects or lack of functional improvement. <u>Stable phase (stable - moderate doses)</u> • Monthly refills. • Assess for four A's: analgesia, activity, aberrant behavior, adverse effects. • Manage side effects.
Center for Substance Abuse Treatment. **Medication-Assisted Treatment For Opioid Addiction in Opioid Treatment Programs. A Treatment Improvement Protocol (TIP 43)[37] (2005)**	• Observed dosing with methadone should be part of the medical safety procedure and diversion control plan in an opioid treatment program (OTP). • Because methadone overdose deaths have occurred in the first few days of treatment, it is important to adjust methadone dosage carefully until stabilization and tolerance are established. Federal regulations require that methadone initially be given daily under observation for either 6 or 7 days per week. (A take-home dose is allowed for all patients when the opioid treatment program is closed on Sunday).

Clinical Guideline	Recommendation(s)
	• The maintenance stage of opioid pharmacotherapy begins when a patient is responding optimally to medication treatment and routine dosage adjustments are no longer needed. Patients at this stage have stopped abusing opioids and other substances and have resumed productive lifestyles away from the people, places, and things associated with their addictions. These patients typically receive scheduled take-home medication privileges. • For patients who neither qualify for nor desire opioid maintenance treatment, methadone may be used to control withdrawal from illicit opioids or from abuse of prescription opioids (detoxification) and then can be tapered gradually (medically supervised withdrawal). • Regulations specify two kinds of detoxification with methadone: short-term treatment of less than 30 days and long-term treatment of 30 to 180 days. These regulations specify that patients who fail two detoxification attempts in 12 months must be evaluated for a different treatment.

Veterans Health Administration, Department of Defense: **VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain[7] (2003)**	• The use of opioid therapy is indicated for moderate to severe pain that has failed to adequately respond to other non-opioid therapeutic interventions.
	• Opioid therapy can be initiated in the form of a therapeutic trial.
	• Initiate Trial of Opioid Therapy
	  ○ Initiation phase: Find the medication(s) that provides the best pain relief with the fewest adverse effects at the lowest effective dose. Effective therapy is achieved when the patient reports improvement in pain relief and/or function along with minimal or acceptable adverse effects.
	  ○ Titration phase: Adjust the dose of opioid to achieve satisfactory pain relief and tolerable adverse effect profile.
	• Maintenance phase: Maintain reliable pain control and improvement in function by repeating the effective dose in a routine schedule, varying the timing or dose only to accommodate changes in activity level or exacerbations of pain.

APAP=acetaminophen; NSAIDs=nonsteroidal anti-inflammatory drugs; IV=intravenous; SC=subcutaneous

III. Indications

The Food and Drug Administration (FDA)-approved indications for the opiate 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 Agonists[4,5]

Generic Name	Analgesia	Anesthesia	Cough	Detoxification	Headache
Alfentanil	✔	✔			
Codeine	✔		✔ [a]		
Codeine/APAP	✔				
Codeine/ASA	✔				
Codeine/APAP/ butalbital/caffeine					✔
Codeine/ASA/ butalbital/caffeine					✔
Dihydrocodeine/ APAP/caffeine	✔				
Fentanyl injection	✔	✔			

Generic Name	Analgesia	Anesthesia	Cough	Detoxification	Headache
Fentanyl transdermal/ transmucosal	✔				
Hydrocodone/APAP	✔				
Hydrocodone/ ibuprofen	✔				
Hydromorphone	✔				
Levorphanol	✔				
Meperidine	✔	✔			
Methadone	✔			✔	
Morphine sulfate	✔	✔			
Opium/belladonna	✔				
Oxycodone	✔				
Oxycodone/APAP	✔				
Oxycodone/ASA	✔				
Oxycodone/ibuprofen	✔				
Oxymorphone*	✔	✔			
Propoxyphene HCL	✔				
Propoxyphene HCL/ APAP	✔				
Propoxyphene napsylate	✔				
Propoxyphene napsylate/APAP	✔				
Remifentanil	✔	✔			
Sufentanil	✔	✔			
Tramadol	✔				
Tramadol ER	✔				
Tramadol/APAP	✔				

*Also indicated for relief of anxiety in patients with dyspnea associated with pulmonary edema

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Opiate Agonists[4,5]

Generic Name	Onset	Peak	Half-life	Metabolism	Renal Excretion (%)
Alfentanil	Immediate	1.5-2 min	90-111 min	Hepatic	1
Codeine	All routes: 30-60 min (analgesic) 1-2 hours (antitussive)	Oral: 1-2 hours IM: 30 min	2.5-3.5	Hepatic CYP2D6, CYP3A4 (24-89%)	11
Dihydrocodeine/ APAP/caffeine	No data	1.6-1.8 hours	3.3-4.5 hours	No data	No data
Fentanyl	Parenteral: 7-8 min Transdermal: 12-24 hours Buccal: 5-15min	Transdermal: 24-72 hours Buccal: 20-40 min	Parenteral: 219 min Transdermal: 17 hours Buccal: 7 hours	Hepatic CYP3A4	10
Hydrocodone	1 hour	1.3 hour	3.8-4.5 hours	Hepatic CYP2D6	6-20
Hydromorphone	Oral:30 min	48-60 min	2.5 hours	Hepatic	1-13

Generic Name	Onset	Peak	Half-life	Metabolism	Renal Excretion (%)
	Parenteral: 15 min			Glucuronidation (95%)	
Levorphanol	Parenteral: 15-30 min Oral:10-60 min	Parenteral–20-90 min Oral–60 min	11 hours	Hepatic	No data
Meperidine	Parenteral: 5-30 min Oral: no data	IM: 25 min	3.2-3.7 hours	Hepatic	0.5-2
Methadone	30-60 min	2-4 hours	23 hours	Hepatic CYP3A4, CYP2D6	21
Morphine sulfate	Oral: No data Parenteral: 15-60 min Rectal: 20-60 min	Oral–60 min Parenteral: No data	1.5-2 hours	Hepatic Glucuronidation	9
Opium/belladonna	No data	No data	No data	No data	No data
Oxycodone	Oral:1 hour	1.6 hours	3.2 hours	Hepatic CYP2D6	19
Oxymorphone	Oral:1 hour Parenteral: 5-10 min	Oral:1-2 hours Parenteral: No data	Oral: 7-9 hours Parenteral: 1.3 hours	Hepatic glucuronic acid conjugation	1-2
Propoxyphene	0.25 – 1 hour	2 - 2.5 hours	6 -12 hours	Hepatic, 25% conversion to norpropoxy-phene	100
Remifentanil	Rapid	3 -10 min	10-20 min	Hydrolysis by esterases	<5
Sufentanil	IV–1-3 min	20 min	2.6 hours	Hepatic + small intestines	No data
Tramadol	IR: 30-60 min ER: no data	IR: 30-60 min ER: 12 hours	IR: 6.3 hours ER:7.9 hours	Hepatic CYP2D6	30

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Opiate Agonists[4,5]

Generic Name	Significance Level	Interaction	Mechanism
Alfentanil	1	Cimetidine	Increased potential for CNS toxicity due to decreased alfentanil clearance
Opiate agonists	1	Neuromuscular blocking agents	Increased risk for respiratory depression
Opiate agonists	1	Skeletal muscle relaxants	Increased risk for respiratory depression
Fentanyl	1	MAO inhibitors	Increased potential for CNS toxicity and hypotension

Generic Name	Significance Level	Interaction	Mechanism
Fentanyl	1	Droperidol	Decreased pulmonary arterial pressure and increased risk of hypotension
Hydrocodone	1	MAO inhibitors	Increased potential for CNS toxicity and hypotension
Meperidine	1	MAO inhibitors	Increased potential for CNS toxicity and hypotension
Methadone	1	MAO inhibitors	Increased potential for CNS toxicity and hypotension
Morphine	1	Cimetidine	Increased potential for CNS toxicity
Morphine	1	MAO inhibitors	Increased potential for CNS toxicity and hypotension
Oxycodone	1	MAO inhibitors	Increased potential for CNS toxicity and hypotension
Oxymorphone	1	MAO inhibitors	Increased potential for CNS toxicity and hypotension
Tramadol	1	MAO inhibitors	Increased potential for CNS toxicity, hypotension and seizure
Tramadol	1	SSRIs	Increased risk of seizures and serotonin syndrome
Alfentanil	2	Diazepam	Synergism, causing need to reduction in dose of both drugs
Alfentanil	2	CYP3A4 inhibitors	Increased potential for CNS/respiratory depression due to significant ↓alfentanil clearance
Opiate agonists	2	Anticholinergics	Increased anticholinergic effects; ↑risk of urinary retention and/or severe constipation, possible paralytic ileus
Opiate agonists	2	Partial opiate agonists	Concomitant administration may precipitate withdrawal
Opiate agonists	2	CNS depressants	Increased CNS /or respiratory depression
Hydrocodone	2	Tricyclic antidepressants	Increased sedation; Decreased psychomotor function
Methadone	2	Rifampin	Methadone withdrawal may be precipitated due to increased enzymatic metabolism by rifampin.
Sufentanil	2	Beta-blockers; calcium channel blockers	Increased incidence of bradycardia or hypotension
Sufentanil	2	Benzodiazepines	Synergism, causing need to reduction in dose of both drugs; Decrease in pulmonary arterial pressure and increased risk of hypotension
Tramadol	2	Carbamazepine	Increased metabolic elimination of tramadol due to hepatic microsomal enzyme induction; Increased seizure risk related to concomitant tramadol use
Tramadol	2	Warfarin	Possible increased hypoprothrombinemic effects of warfarin; patient monitoring required

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 Table 6. The boxed warning for propoxyphene is listed in Table 7. The boxed warning for morphine sulfate injection is listed in Table 8. The boxed warning for fentanyl transmucosal is listed in Table 9. The boxed warning for fentanyl transdermal is listed in Table 10. The boxed warning for methadone is listed in Table 11. The boxed warning for hydromorphone HP injection is listed in Table 12.

Table 6. Adverse Drug Events (%) Reported with the Opiate Agonists and Opiate Partial Agonists[4,5]

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
Cardiovascular																	
Abnormal ECG	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-	✔
Angina	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-	-
Arrythmia	14	-	-	-	-	-	-	✔	-	✔	-	-	-	-	-	<1	-
Atrial fibrillation	-	-	-	-	-	-	-		-	-	✔	-	-	-	<1	-	-
Bradycardia	14	-	✔	-	✔	-	✔	✔	✔	✔	✔		✔	-	1-7	3-9	✔
Cardiac arrest	-	-	✔	-	✔	-	✔	✔	✔	✔	✔	✔	-	-	-	-	-
Chest pain	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	<1	-	-
Circulatory depression/ collapse	-	-	✔	-	✔	-	✔	-	✔	✔	✔	✔	-	-	-	-	-
CHF	-	-	-	-	-	-	✔	-	-	-	-	<3	-	-	-	-	-
Deep thrombophlebitis	-	-	-	-	✔	-	✔	-	-	-	-	<3	-	-	-	-	-
Extrasystoles	-	-	-	-	-	-	-	✔	-	-	✔	-	-	-	-	-	-
Faintness		-	✔	-	-	-	✔			✔	✔	-	-	-	-	-	-
Flushing	-	-	✔	-	✔	-	✔	✔	✔	✔	-	-	✔	-	1	-	-
Hemorrhage	-	-	-	-	-	-	-	-	-	-	-	<3	-	-	-	-	-
Hypertension	18	-	-	-	✔	-	✔	-	-	✔	-	-	-	-	1-2	3-9	✔
Hypotension	10	-	✔	-	✔	-	✔	✔	✔	✔	✔	1-5	✔	-	4-19	3-9	<1
Migraine	-	-	-	-	✔	-	-	-	-	-	-	<3	-	-	-	-	✔
Myocardial ischemia	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-	✔
Palpitation	-	-	-	-	✔	-	✔	✔	✔	-	✔	<3	-	-	-	-	✔
Pallor	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Peripheral vascular disorder	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Phlebitis	-	-	-	-	-	-	-	-	✔	✔	✔	-	-	-	-	-	-
Prolonged QT	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-	-

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
interval																	
ST suppression	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-	-	-
Syncope	-	-	✔	-	✔	-	✔	✔	✔	✔	✔	-	-	-	<1	-	<1
Tachycardia	12	-	✔	-	✔	-	✔	✔	✔	✔	✔	<3	✔	-	<1	<1	<1
Vascular disorder	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Vasodilation	-	-	-	-	≤4	-	-	-	-	-	✔	<3	-	-	-	-	1-5
Central Nervous System																	
Abnormal coordination	-	-	-	-	- / ≥1 / -	-	-	-	-	-	-	-	-	-	-	-	-
Abnormal dreams	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Abnormal gait	-	-	-	-	1-5	-	-	-	-	-	✔	-	-	-	-	-	<1
Abnormal thinking	-	-	-	-	1-2	-	-	-	-	-	✔	-	-	-	-	-	<1
Acute brain syndrome	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Addiction	-	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	-
Agitation	-	-	✔	-	✔	-	-	-	✔	✔	✔	<1	-	-	<1	-	-
Amnesia	-	-		-	✔	-	-	-		-	✔	-	-	-	<1	-	<1
Anxiety	-	-	✔	-	3-15	-	✔	-	-	-	✔	-	-	-	<1	-	1-5
Aphasia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Asthenia	-	-	-	-	0-38	-	-	-	-	-	✔	6	-	-	-	-	6-12
Ataxia	-	-	-	-		-	-	-	-	-	✔	-	-	-	-	-	-
Cerebral ischemia	-	-	-	-	✔	-	-	-	-	-		-	-	-	-	-	-
CNS stimulation	-	-	-	-	-	-	-	✔	-	-	-	-	✔	-	-	-	7-14
Coma	-	-	-	-	-	-	-	✔	-	-	✔	-	-	-	<1	-	-
Confusion	-	-	-	-	10-13	-	-	✔	-	✔	✔	1-5	✔	-	<1	-	1-5
Convulsion	-	-	✔	-	0-2	-	-	✔	✔	✔	✔	<1	-	-	-	-	<1
Delirium	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Depersonalization		-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Depression	-	-	-	-	2-10	-	-	✔	-	-	✔	<1	✔	-	-	-	<1
Disorientation	-	-	✔	-	-	-	✔	✔	✔	✔	✔	<1	-	-	<1	-	-
Dizziness	3-9	-	✔	-	3-17	-	✔	-	-	✔	✔	13	-	<1	<5	-	26-33
Drowsiness	-	-	-	-	-	-	✔	✔	-	-	✔	-	✔	-	-	-	-
Dysphoria	-	-	✔	-	-	-	✔	-	✔	✔	-	✔	-	<1	<1	-	-
Emotional lability	-	-	-	-	✔	-	-	-	-	-	-	<1	-	-	-	-	-

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
Euphoria	<1	-	✔	-	3-10	-	✔	-	✔	✔	✔	1-5	✔	<1	-	-	1-5
Fear	-	-	✔	-	-	-	✔	-	-	-	-	-	-	-	-	-	-
Hallucinations	-	-	-	-	3-10	-	✔	-	✔	-	-	<1	✔	<1	<1	-	<1
Headache	<1	-	✔	-	3-20	-	✔	-	✔	✔	✔	7	✔	<1	≤ 18	-	18-32
Hemiplegia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hostility	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	-	-	✔	-	-	-	<1	-	-	-	-	-
Hypertonia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	1-5
Hypesthesia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hypokinesia	-	-	-	-	✔	-	-	✔	-	-	-	-	-	-	-	-	-
Hypotonia	-	-	-	-	✔	-	-	-	-	-	-	<1	-	-	-	-	-
Impairment of physical/mental performance	-	-	✔	-	-	-	✔	-	-	-	-	-	-	-	-	-	-
Incoordination	-	-	-	-	✔	-	✔	-	✔	-	-	-	-	-	-	-	-
Increased intracranial pressure	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-
Insomnia	-	-	✔	-	1-10	-	✔	✔	-	✔	✔	1-5	-	-	-	-	-
Lethargy	-	-	✔	-	-	-	✔	✔	✔	-	-	-	-	<1	-	-	-
Lightheadedness	-	-	✔	-	-	-	✔	-	-	✔	✔	-	-	-	-	-	-
Mental clouding	-	-	✔	-	-	-	✔	-	-	-	-	-	-	-	-	-	-
Mood changes	-	-	✔	-	-	-	✔	-	-	-	-	-	-	-	-	-	-
Myoclonic movements	✔	-	-	-	1-4	-	-	-	✔	-	-	-	-	-	-	-	-
Nervousness	-	-	-	-	1-10	-	-	✔	-	-	-	1-5	-	-	-	-	1-5
Paranoid reaction	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	✔	-	✔	-	-	-	✔	-	-	-	<1	-	<1
Personality disorder	-	-	-	-	-	-	-	✔	-	-	-	<3	-	-	-	-	-
Post-op confusion	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Restlessness	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-
Serotonin syndrome	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1
Shivering	1-3	-	-	-	✔	-	-	-	-	-	-	-	-	-	1-5	-	-
Sedation	-	-	✔	-	3-20	-	✔	-	✔	✔	✔	23	✔	<1	-	3-9	16-

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
																	25
Speech disorder	-	-	-	-	✔	-	-	-	-	-	-	<1	-	-	<1	-	✔
Stupor	-	-	-	-	1-4	-	-	-	-	-	-	<1	-	-	-	-	-
Subdural hematoma	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Suicide attempt/ tendency	-	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	<1
Tremor	-	-	-	-	1-2	-	✔	-	✔	-	✔	<3	-	-	<1	-	<1
Twitching	-	-	-	-	-	-	-	-	✔	-	-	1-5	-	-	<1	-	26-33
Vertigo	-	-	-	-	✔	-	-	-		-	✔	<1	-	-	-	-	-
Weakness	-	-	✔	-		-	✔	-	✔	✔	✔	-	✔	<1	-	-	-
Withdrawal syndrome	-	-	-	-	-	-	-	✔	-	-	✔	<1	-	-	-	-	-
Dermatological																	
Alopecia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Application-site reactions	-	-	-	-	1-10	-	-	-	-	-	-	-	-	-	-	-	-
Dry skin	-	-	-	-	-	-	-	-	-	-	✔	-	<1	-	-	-	-
Erythema	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Exfoliative dermatitis	-	-	-	-	✔	-	-	-	-	-	-	-	<1	-	-	-	-
Herpes simplex	-	-	-	-	-	-	-	-	-	-	-	-	<3	-	-	-	-
Herpes zoster	-	-	-	-	✔	-	-	-	-	-	-	-		-	-	-	-
Itching/pruritus	<1	-	✔	-	1-10	-	✔	✔	-	✔	✔	✔	13	-	≤18	25	8-11
Localized skin reaction	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	<1	-	-
Pustules	-	-	-	-	✔	-	-	-	-	✔	-	-	-	-	<1	-	-
Rash	-	-	-	-	1-8	-	✔	✔	-	-	✔	-	1-5	<1	-	-	1-5
Skin discoloration	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Skin ulcer	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Stevens-Johnson Syndrome	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1
Sweating	-	-	✔	-	-	-	✔	✔	✔	✔	✔	✔	5	-	6	-	6-9
Urticaria	<1	-	-	-	✔	-	✔	✔	-	✔	✔	-	<3	-	<1	-	<1
Vesicles	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1
Vesiculobullous	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
rash																	
Endocrine and Metabolic																	
Acidosis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Cyanosis	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-
Gout	-	-	-	-	-	-	-	-	-	-	-	-	<3	-	-	-	-
Hypercalcemia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hyperglycemia	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	<1	-	-
Hypocalcemia	-	-	-	-	✔	-	-	<1	-	-	-	-	-	-	-	-	-
Hypoglycemia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hypokalemia	-	-	-	-	✔	-	-	-	✔	✔	-	-	-	-	-	-	-
Hypomagnesemia	-	-	-	-	✔	-	-	-	✔	✔	-	-	-	-	-	-	-
Hyponatremia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hypoproteinemia	-	-	-	-	✔	-	-	-		-	-	-	-	-	-	-	-
Gastrointestinal																	
Abdominal distention	-	-	-	-	✔	-	-	-	-	-	-	-	1-5	-	-	-	-
Abdominal pain	-	-	-	-	1-10	-	-	✔	-	✔	-	✔	-	<1	-	-	1-5
Abnormal LFTs	-	-	-	-	-	-	-	-	-	-	✔	-	-	<1	-	-	✔
Anorexia	-	-	✔	-	-	-	-	-	-	✔	✔	✔	1-5	-	-	-	1-5
Appetite increased	-	-	-	-	-	-	-	-	-	-		-	<1	-	-	-	-
Biliary spasm	-	-	✔	-	-	-	-	✔	✔	✔	✔	✔	✔	-	-	-	-
Cheilitis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Colon hemorrhage	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Colonic motility increased	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Constipation	-	-	✔	-	3-20	-	✔	-	✔	✔	✔	✔	23	<1	<1	-	24-46
Cramps	-	-		-	-	-	✔		-	✔	✔	-	✔	-	-	-	-
Dry mouth	-	-	✔	-	1-10	-	✔	✔	✔	✔	✔	✔	6	-	-	-	5-10
Diarrhea	-	-	-	-	3-10	-	✔	-	-	-	✔	-	1-5	<1	<1	-	5-10
Dyspepsia	-	-	-	-	3-10	-	-	✔	-	-	✔	-	1-5	-	-	-	5-13
Dysphagia	-	-	-	-	✔	-	-	-	-	-	✔	-	<1	<1	<1	-	-
Eructation	-	-	-	-	✔	-	-	-	-	-	-	-	<1	-	-	-	-
Esophageal stenosis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Esophagitis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
Fecal impaction	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Fecal incontinence	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Flatulence	-	-	-	-	✔	-	-	-	-	-	-	-	<1	-	-	-	1-5
Gastritis	-	-	-	-	✔	-	-	-	-	-	-	-	1-5	-	-	-	-
Gastroenteritis	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
GI disorder	-	-	-	-	✔	-	-	-	-	-	-	-	<1	-	-	-	-
GI hemorrhage	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	✔
Gingivitis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Glossitis	-	-	-	-	✔	-	-	-	-	✔	-	-	-	-	-	-	-
Gum hemorrhage	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hepatic failure	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Hepatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Hepatorenal syndrome	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Ileus	-	-		-	-	-	✔	-	-	-	✔	✔	<1	-	<1	-	-
Increased biliary tract pressure	-	-	✔	-	1-4	-	-	-	-	-	-	-	-	-	-	-	-
Intestinal obstruction	-	-	-	-	-	-	-	-	-	-	✔	-	-	<1	-	-	-
Jaundice	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Liver tenderness	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Mouth ulceration	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Nausea	28	-	✔	-	10-45	-	✔	✔	✔	✔	✔	✔	23	<1	1-4	3-9	24-40
Oral moniliasis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Periodontal abscess	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Rectal disorder	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Rectal hemorrhage	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Stomatitis	-	-	-	-	✔	-	-	-	-	-	-	-	<1	-	-	-	✔
Tooth caries	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Tooth disorder	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Toxic megacolon	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-
Vomiting	18	-	✔	-	6-31	-	-	✔	✔	✔	✔	✔	12	<1	≤ 22	3-9	9-17
Weight loss	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	<1
Genitourinary																	

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
Abnormal ejaculation	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Amenorrhea	-	-	-	-	-	-	-	-	-	✔	✔	-	<1	<1	-	-	-
Antidiuretic effect	-	-	✔	-	-	-	✔	-	✔	✔	-	✔	<1	<1	-	-	-
Bladder pain	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Breast neoplasm	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Breast pain	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Creatinine increased	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Decreased libido/potency	-	-	✔	-	✔	-	-	-	-	✔	-	-	<1	<1	-	-	-
Dysmenorrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1
Dysuria	-	-	-	-	✔	-	-	-	-	-	✔	-	<1	<1	<1	-	-
Hematuria	-	-	-	-	✔	-	-	-	-	-	-	-	<1	<1	-	-	-
Hydronephrosis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Impotence	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Kidney failure	-	-	-	-	✔	-	-	✔	-	-	-	-	-	-	-	-	-
Kidney pain	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Menopausal symptoms	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-5
Menstrual disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1
Nocturia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Oliguria	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	<1	-	-
Polyuria	-	-	-	-	✔	-	-	-	-	-	-	-	<1	<1	-	-	-
Proteinuria	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Pyelonephritis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Scrotal edema	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Spasm of vesical sphincters	-	-	✔	-	-	-	✔	-	-	-	✔	-	-	-	-	-	-
Ureteral spasm	-	-	✔	-	-	-	-	-	-	-	✔	✔	-	-	-	-	-
Urinary frequency	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	1-5
Urinary hesitancy	-	-	✔	-	-	-	✔	-	-	✔	✔	✔	-	-	-	-	-
Urinary incontinence	-	-	-	-	✔	-	✔	-	-	-	-	-	-	-	<1	✔	-
Urinary retention	-	-	✔	-	1-10	-	✔	-	✔	✔	✔	✔	-	<1	<1	-	1-5
Urinary urgency	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
UTI	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Urination impaired	-	-	-	-	✔	-	-	-	-	-	-	-	-	<1	-	-	-
Vaginal hemorrhage	-		-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Vaginitis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hematologic																	
Anemia	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Bleeding time increased	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Ecchymosis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hemoglobin disease	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	✔
Leukopenia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Leukocytosis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Lymph-adenopathy	-	-	-	-	✔	-	-	-	-	-	-	-	<1	<1	-	-	-
Lymphedema	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Lymphoma-like reaction	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Pancytopenia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Petechia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Thrombo-cytopenia	-	-	-	-	✔	-	-	-	-	✔	✔	-	-	-	-	-	-
Musculoskeletal																	
Arthralgia	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Arthritis	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Bone disorder	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Chest wall rigidity	17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3-9	-
Joint disorder	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Leg cramps	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Muscle tremor	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Myasthenia	-		-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Myopathy	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Neck/extreme rigidity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
Pathological fracture	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Skeletal muscle movement	3-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Synovitis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Tendon disorder	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory																	
Apnea	1-3	-	-	-	-	-	-	-	-	-	-	-	-	-	≤30	<1	-
Asthma	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Bronchitis	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	<1	-	-
Bronchospasm	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	<1	-
Cough	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	<1	-	-
Dyspnea	-	-	-	-	2-22	-	-	-	-	-	-	-	1-5	-	<1	-	<1
Epistaxis	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Hemoptysis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hiccoughs	-	-	-	-	✔	-	-	-	-	-	-	-	1-5	-	<1	-	-
Hypercarbia	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperventilation	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hypoxia	-	-	-	-	-	-	-	-	-	-	-	-	<3	-	<1	-	-
Laryngospasm	<1	-	-	-	✔	-	✔	-	-	-	✔	-	<3	-	<1	-	-
Lung disorder	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Pharyngitis	-	-	-	-	3-10	-	-	-	-	-	-	-	-	-	<1	-	-
Pleural effusion	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	<1	-	-
Pneumonia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Pneumothorax	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Pulmonary edema	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	<1	-	✔
Pulmonary embolus	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	✔
Respiratory arrest	-	-	✔	-	✔	-	✔	-	✔	✔	✔	-	-	-	-	-	-
Respiratory depression	3-9	-	✔	-	✔	-	✔	-	✔	✔	✔	✔	-	-	<1	<1	-
Respiratory disorder	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory insufficiency	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Sinusitis	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
Sputum increased	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Stertorous breathing	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Suppressed cough reflex	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other																	
Abnormal vision	-	-	-	-	0-3	-	-	✔	-	-	-	-	<1	-	-	-	-
Abscess	-	-	-	-	✔	-	-	-	-	-	✔	-		-	-	-	<1
Accidental injury	-	-	-	-	0-9	-	-	-	-	-	-	-	<3	-	-	-	<1
Allergic laryngeal edema	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-
Allergic laryngospasm	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-
Allergic reaction	-	-	✔	-	✔	-	✔	-	-	-	-	✔	<3	-	-	-	<1
Amblyopia	-	-	-	-	✔	-	-	-	-	-	-	<3	-	-	-	-	-
Anaphylaxis	✔	-	-	-	✔	-	-	-	-	✔	✔	-	<1	<1	<1	-	<1
Ascites	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Back pain	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Blurred vision	1-3	-	-	-	✔	-	-	-	-	-	-	✔	-	-	-	-	-
Bone pain	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Cataracts	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	✔
Cellulitis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	1	-	-
Chills	-	-	-	-	✔	-	✔	-	-	-	✔	-	<3	-	-	-	-
Conjunctivitis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Dehydration	-	-	-	-	✔	-	-	-	-	-	✔	-	<3	-	-	-	-
Diplopia	-	-	-	-	✔	-	-	✔	-	-	✔	✔	-	-	-	-	-
Dry eyes	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	<1
Dysgeusia	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Ear disorder	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Ear pain	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Edema	-	-	-	-	✔	-	-	-	-	✔	✔	-	-	-	-	-	-
Eye hemorrhage	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Fever	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Flank pain	-	-	-	-	-	-	-	-	-	-	-	-	<3	-	<10	-	-
Flu syndrome	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Fungal infection	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Hyperacusis	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alf	B/O	Cod	Dihydro-cod	Fen	Hydro-cod	Hydro-mor	Lev	Mep	Meth	Mor	Oxycod	Oxymor	Prop	Rem	Suf	Tram
Infection	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Injection site pain/reaction	<1	-	-	-	-	-	✔	✔	-	-	-	-	-	-	1	-	-
Intraoperative muscle movement	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Lacrimation disorder	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Malaise	-	-	-	-	✔	-	-	-	-	-	✔	-	-	-	-	-	1-5
Miosis	-	-	✔	-	✔	-	✔	-	-	-	✔	✔	-	-	-	-	-
Neck pain	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Nystagmus	-	-	-	-	✔	-	✔	-	-	-	✔	-	-	-	-	-	-
Pain	-	-	-	-	✔	-	-	-	-	-	-	-	<3	-	-	-	-
Partial permanent/ transitory deafness	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	✔
Pelvic pain	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Sepsis	-	-	-	-	✔	-	-	-	-	-	✔	-	<3	-	-	-	-
Shock	<1	-	✔	-		-	✔	✔	✔	✔	✔	-	✔	-	-	-	-
Taste perversion	-	-	-	-	✔	-	✔	-	-	-	✔	-	<1	-	-	-	-
Tinnitus	-	-	-	-	✔	-	-	-	✔	-	-	-	<1	-	-	-	✔
Viral infection	-	-	-	-	✔	-	-	-	-		-	-	-				
Visual disturbances	-	-	✔	-	✔	-	✔	✔	✔	-	✔	-	-	-	-	-	-
Wheal/flare	-	-	-	-	-	-	✔	-	-	✔	✔	-	-	-	-	-	1-5

Alf=alfentanil; B/O=belladonna/opium; Cod=codeine; Dihydrocod=dihydrocodeine; Fen=fentanyl; Hydrocod=hydrocodone; Hydromor=hydromorphone; Lev=levorphanol; Mep=meperidine; Meth=methadone; Mor=morphine; Oxycod=oxycodone; Oxymor=oxymorphine; Propox=propoxyphene; Rem=remifentanil; Suf=sufentanil; Tram=tramadol.

✔ Percent not specified

- Event not reported

Table 7. Boxed Warning for Propoxyphene[5]

WARNING
Do not prescribe propoxyphene for patients who are suicidal or addiction-prone. Prescribe with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.

Table 8. Boxed Warning for Morphine Sulfate Injection[5]

WARNING
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. Morphine injection (Infumorph®) is not recommended for single-dose intravenous (IV), intramuscular (IM), or subcutaneous (SC) administration because of the very large amount of morphine in the ampul and the associated risk of overdosage.

Table 9. Boxed Warning for Fentanyl Transmucosal[5]

WARNING
Fentanyl is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. Fentanyl can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing fentanyl in situations in which the health care provider or pharmacist is concerned about in increased risk of misuse, abuse, or diversion. Schedule II opioid substances, which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. The fentanyl lozenge and buccal tablet are indicated only for the management of breakthrough cancer pain in patients with cancer already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid-tolerant are those who are taking oral morphine 60 mg/day or more, transdermal fentanyl 25 mcg/h, oxycodone 30 mg/day, oral hydromorphone 8 mg/day, or an equianalgesic dose of another opioid for a week or longer. Because life-threatening respiratory depression could occur at any dose in patients not taking chronic opiates, it is contraindicated in the management of acute or postoperative pain. This product is not indicated for use in opioid-non tolerant patients. Instruct patients and their caregivers that this drug contains a medicine in an amount that can be fatal to a child. Keep all units out of the reach of children, and discard opened units properly. This medicine should be used only in the care of cancer patients and only by health care providers who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.[1 2] **Tablet:** Because of the higher bioavailability of fentanyl in the buccal tablet, when converting patients from other oral fentanyl products (including the fentanyl lozenge) to the buccal tablet, do not substitute the buccal tablet on a mcg per mcg basis. Adjust dosage as appropriate .

Table 10. Boxed Warning for Fentanyl Transdermal[5]

WARNING
Fentanyl transdermal systems contain a high concentration of the potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances, which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and associated risk of fatal overdose caused by respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches may be a particular target for abuse and diversion. Fentanyl transdermal system is indicated for management of persistent, moderate to severe chronic pain (such as

that of malignancy) that:

- requires continuous, around-the-clock opioid administration for an extended period of time, and
- cannot be managed by other means such as acetaminophen-opioid combinations, nonsteroidal analgesics, opioid combination products, or immediate-release opioids, or as-needed dosing with short-acting opioids.

Only use the 50, 75, and 100 mcg/h dosages in patients who are already on and are tolerant of opioid therapy.

Only use fentanyl transdermal system in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to fentanyl 25 mcg/h transdermal system. Patients who are considered opioid tolerant are those who have been taking, for a week or longer, morphine 60 mg/day or more, or oral oxycodone 30 mg/day or more, or oral hydromorphone 8 mg/day or more, or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal is contraindicated:

- in patients who are not opioid tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of acute or postoperative pain, including use after outpatient or day surgeries (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain responsive to as-needed therapy or nonopioid therapy
- in doses exceeding 25 mcg/h at the initiation of opioid therapy.

Because the peak fentanyl levels occur between 24 and 72 hours of treatment, be aware that serious or life-threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period.

The concomitant use of fentanyl transdermal system with potent CYP-450 3A4 inhibitors (i.e., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug reactions and may cause potentially fatal respiratory depression. Carefully monitor patients receiving fentanyl transdermal system and potent CYP3A4 inhibitors for an extended period of time and make dosage adjustments if warranted.

The safety of fentanyl has not been established in children younger than 2 years of age. Only administer fentanyl to children if they are opioid tolerant and 2 years of age and older.

Fentanyl transdermal system is only for use in patients who are already tolerant to opioid therapy of comparable potency. Use in nonopioid-tolerant patients may lead to fatal respiratory depression. Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Because of the 17-hour mean elimination half-life of fentanyl transdermal system, patients who are thought to have had a serious adverse reaction, including overdose, will require monitoring and treatment for at least 24 hours.

Fentanyl transdermal system can be abused in a manner similar to other opioid agonists, legal or illicit. Consider this risk when administering, prescribing, or dispensing in situations in which there is concern about increased risk of misuse, abuse, or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Assess patients for their clinical risks for opioid abuse or addiction prior to prescribing opioids. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Fentanyl transdermal patches are intended for transdermal use (on intact skin) only. Using damaged or cut fentanyl transdermal patches can lead to the rapid release of the contents of the fentanyl transdermal patch and absorption of a potentially fatal dose of fentanyl.

Table 11. Boxed Warning for Methadone[5]

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 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. Methadone dispersible tablets are for oral administration only. This preparation contains insoluble excipients and therefore must not be injected. It is recommended that methadone dispersible tablets, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion. **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 12. Boxed Warning for Hydromorphone HP (high-potency) Injection[5]

WARNING
HP injection is a highly concentrated solution of hydromorphone intended for use in opioid-tolerant patients. Do not confuse HP injection with standard parenteral formulations of injection or other opioids. Overdose and death could result

VII. Dosing and Administration

The usual dosing regimens for the opiate agonists are listed in Table 13.

Table 13. Usual Dosing Regimens for the Opiate Agonists[4,5]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Alfentanil	Dose and titration is based upon weight, physical status, underlying condition, and use of other drugs. Given as incremental injection with expected duration of less than 1 hr or by continuous infusion	≥12 yrs: Dose and titration is based upon weight and other conditions including physical status, underlying condition, and use of other drugs. Given as incremental injection with expected duration of less than 1 hr or by continuous infusion	Injection: 500mcg/ml
Codeine	Tablet: 15 to 60mg every 4 to 6 hrs Injection: 30mg SC or IM every 4 hrs as needed	Injection: ≥ 3 yrs- 500mcg/kg or 15mg/m^2 SC or IM every 4 hrs as necessary	Tablet: 15mg, 30mg, 60mg (sulfate) Injection: 15mg/ml, 30mg/ml, 60mg/ml (phosphate)
Codeine/APAP	Tablet: 0.5-2 tablets every 4 hrs	Tablet: 0.5-1mg codeine/kg/dose every 4-6 hrs (10-15mg APAP/kg/dose every 4 hrs)	Tablet: 15/300mg,

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		liquid: ≥12 yrs: 15ml every 4 hrs as needed 7-12 yrs: 10ml 3 to 4 times daily as needed 3-6 yrs: 5ml 3 to 4 times daily as needed	30/300mg, 30/650mg, 60/300mg Elixir and Suspension: 12/120mg per 5ml
Codeine/ASA	30mg tablets: 1-2 tablets every 4 hours as needed 60mg tablets: 1 tablet every 4 hours as needed	Safety and efficacy in children have not been established	Tablet: 30/325mg, 60/325mg
Codeine/ butalbital/ APAP/caffeine	1 or 2 capsules every 4 hours	≥12 yrs: 1 or 2 tablets or capsules every 4 hours <12 yrs: Safety and efficacy in children have not been established.	Capsules: 30/50/325/ 40mg
Codeine/ASA/ butalbital/caffeine	1 or 2 capsules every 4 hours	≥12 yrs: 1 or 2 tablets or capsules every 4 hours <12 yrs: Safety and efficacy in children have not been established.	Capsules: 30/50/325/ 40mg
Dihydrocodeine/ APAP/caffeine	2 capsules every 4 hours	Safety and efficacy in children have not been established	Capsule: 16/356/30mg Tablet: 32/713/60mg
Fentanyl	Lozenge: Initial dose is 200mcg. Titrate as necessary for breakthrough pain, allowing up to 4 units/day Buccal tablet: Initial dose of 200mcg. May repeat dosing after 30 minutes for single episode of breakthrough pain. Titrate as necessary. If more than 4 breakthrough pain episodes per day occur, re-evaluate dose. Injection: 50-100mcg IM or slow IV Transdermal: 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.	Lozenge: Safety and efficacy in children have not been established Buccal tablet: ≥16 yrs: Same as adult dose <16 yrs: Safety and efficacy in children have not been established Injection: ≥12 yrs: same as adult dose. 2 to 12 yrs: 2 to 3 mcg/kg Transdermal: ≥2 yrs: Same as adult dosing. Children starting therapy on 25mcg/hr should be receiving at least morphine 60mg equivalents per day and opioid tolerant <2 yrs: Safety and efficacy in children have not been established.	Buccal tablets: 100mcg, 200mcg, 300mcg, 400mcg, 600mcg, 800mcg Lozenge: 200mcg, 400mcg, 600mcg, 800mcg, 1,200mcg, 1,600mcg Injection (Ampule, syringe, vial): 50mcg/ml Transdermal: 12.5mcg/h, 25mcg/hr, 50mcg/hr, 75mcg/hr, 100mcg/hr
Hydrocodone/ APAP	1 to 2 tablets/capsules or 15ml every 4 to 6 hours as needed	≥15 yrs: 1 to 2 tablets/capsules or 15ml every 4 to 6 hours as needed 2-14 yrs: 0.27ml/kg every 4 to 6 hours as needed	Tablet: 2.5/500mg, 5/300mg, 5/325mg,

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
			5/400mg, 5/500mg, 7.5/300mg, 7.5/325mg, 7.5/400mg, 7.5/500mg, 7.5/650mg, 7.5/750mg, 10/300mg, 10/325mg, 10/400mg, 10/500mg, 10/650mg, 10/660mg Solution: 2.5/167mg per 5ml, 3.33/167mg per 5ml, 5/333mg per 10ml, 7.5/325mg per 15ml, 7.5/500mg per 15ml, 10/325mg per 15ml
Hydrocodone/ ibuprofen	1 tablet every 4 to 6 hours	≥ 16 yrs: 1 tablet every 4 to 6 hours <16 yrs: Safety and efficacy in children have not been established.	Tablet: 10/200mg, 5/200mg, 7.5/200mg
Hydromorphone	Tablets: 2-4mg every 4 to 6 hours as necessary Oral solution: 2.5-10mg (2.5-10ml) every 3 to 6 hours as directed. Injection: 1-2mg SC or IM every 4 to 6 hours as needed. If given IV, inject slowly over at least 2 to 3 minutes. Rectal: 1 suppository inserted rectally every 6 to 8 hours or as directed by health care provider.	Safety and efficacy in children have not been established	Tablets: 2mg, 4mg, 8mg Injection: 1mg/ml, 2mg/ml, 4mg/ml, Injection, concentrate: 10mg/ml, 250mg (10mg/ml after reconstitution) Oral Solution: 1mg/ml Rectal Suppository: 3mg
Levorphanol	1 tablet every 6 to 8 hours (Levo-Dromoran®) or 3 to	Safety and efficacy in children have not been established	Tablets: 2mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	6 hours (levorphanol) as needed. May increase Levo-Dromoran to 3mg every 6 to 8 hours		Injection: 2mg/ml
Meperidine	Oral: 50-150mg every 3 to 4 hours as necessary Injection: 50-150mg IM or SC every 3 to 4 hours as necessary Preoperative: 50-100mg IM or SC 30 to 90 minutes before beginning anesthesia	Oral: 1.1 to1.75mg/kg (0.5 to 0.8mg/lb) up to the adult dose, every 3 to 4 hours as necessary Injection: 1.1 to 1.75mg/kg (0.5 to 0.8mg/lb) IM or SC up to the adult dose every 3 to 4 hours as necessary Preoperative: 1.1 to 2.2mg/kg (0.5 to 1mg/lb) IM or SC up to the adult dose 30 to 90 minutes before beginning anesthesia.	Tablet: 50mg, 100mg Oral liquid: 50mg/5ml Injection (vial, cartridge, ampule, syringe): 10mg/ml, 25mg/ml, 50mg/ml, 75mg/ml, 100mg/ml
Methadone	Pain: 2.5 to 10mg every 3 to 4 hours as necessary. Detoxification treatment: Initial dose of 15 to 20mg to suppress withdrawal symptoms. Individualize and adjust dose as tolerated and required up to 120mg/day.	Safety and efficacy in children have not been established	Tablets: 5mg, 10mg Tablets, dispersible: 40mg Solution: 5mg/5ml, 10mg/5ml Concentrate, oral: 10mg/ml
Morphine	Oral: 5 to 30mg every 4 hours or as directed Injection: 5-20mg SC or IM every 4 hours as needed IV injection: 2-10mg per 70kg of body weight given over 4 to 5 minutes. Can be given every 4 hours Rectal suppository: 10-20mg every 4 hours	Oral: Safety and efficacy in children have not been established IM or SC Injection ; 0.1 to 0.2mg/kg every 4 hours as needed IV injection: 50-100mcg IV per kg of body weight, not to exceed 10mg/dose. Rectal suppository: Safety and efficacy in children have not been established	Tablet: 15mg, 30mg Injection: 0.5mg/ml, 1mg/ml, 2mg/ml, 4mg/ml, 5mg/ml, 8mg/ml, 10mg/ml, 15mg/ml Injection, solution: 25mg/ml, 50mg/ml Injection in 5% dextrose: 100mg/0.1L, 250mg/250ml

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
			Injection, extended-release liposomal: 10mg/ml, 15mg/1.5ml Intravenous: 30mg/30mg, 100mg/4ml, 150mg/30ml, 250mg/10ml Solution, oral: 5mg/0.25ml, 10mg/0.5ml, 10mg/5ml, 20mg/5ml, Solution, oral concentrate: 20mg/ml, 100mg/5ml Rectal Suppository: 5mg, 10mg, 20mg, 30mg
Opium/belladonna	1 or 2 suppositories/day	Safety and efficacy in children have not been established.	Rectal Suppository: 30/16.2mg, 60/16.2mg
Oxycodone	Tablets: 10-30mg every 4 hours (for OxyIR caps: 5mg every 6 hours) as needed Solution, oral: 10-30mg every 4 hours as needed for pain Solution, oral concentrate: 5mg every 6 hours as needed for pain. (Fill dropper to required dose and add to 30ml of juice, applesauce, or pudding)	Safety and efficacy in children have not been established	Tablets: 5mg, 10mg, 15mg, 20mg, 30mg Capsules: 5mg Solution, Oral: 5mg/5ml Solution, Oral Concentrate: 20mg/ml
Oxycodone/APAP	5mg/7.5mg/10mg oxycodone strength: 1 tablet, caplet, or teaspoonful every 6 hours as needed. 2.mg oxycodone strength: 1-2 tablets every 6 hours as needed	Safety and efficacy in children have not been established	Tablet: 2.5/300mg, 2.5/325mg, 2.5/400mg, 5/300mg, 5/325mg, 5/400mg, 7.5/300mg, 7.5/325mg, 7.5/400mg,

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
			7.5/500mg, 10/300mg, 10/325mg, 10/400mg, 10/500mg, 10/650mg Capsule: 5/500mg Solution, oral: 5/325 per 5ml
Oxycodone/ASA	1 tablet every 6 hrs as needed for pain (max 12 tablets per 24 hrs)	Safety and efficacy in children have not been established	Tablet: 4.8355/325mg, 4.88/325mg
Oxycodone/ ibuprofen	1 tablet every 6 hours	≥14 yrs: 1 tablet every 6 hours <14 yrs: Safety and efficacy in children have not been established	Tablet: 5/400mg
Oxymorphone	10-20mg every 4 to 6 hours	Safety and efficacy in children have not been established	Tablets: 5mg, 10mg Injection: 1mg/ml
Propoxyphene HCL	65mg every 4 hours as needed	Safety and efficacy in children have not been established	Capsule: 65mg
Propoxyphene HCL/APAP	65mg (with 650mg acetaminophen) every 4 hours as needed	Safety and efficacy in children have not been established	Tablet: 65/650mg
Propoxyphene napsylate	100mg every 4 hours as needed	Safety and efficacy in children have not been established	Tablet: 100mg
Propoxyphene napsylate/APAP	100mg (with 325, 500, or 625mg acetaminophen) every 4 hrs as needed	Safety and efficacy in children have not been established	Tablet: 50/325mg, 100/325mg, 100/500mg, 100/650mg
Remifentanil	Individualize dose given as IV use only	≥1 yrs. Individualize dose, given as IV use only <1 yr: Safety and efficacy in children have not been established	Intravenous: 1mg, 2mg, 5mg
Sufentanil	Individualize dose given as slow IV or IV infusion.	2-12 yrs: 10 to 25mcg/kg given with 100% oxygen <2 yrs: limited experience	Intravenous: 50mcg/ml
Tramadol	Initial as 25mg in the morning, titrating in 25mg increments every 3 day to 100mg/day, given as 25mg times daily. Increase by 50mg every 3 days thereafter up to 50-100mg every 4 to 6 hours as needed to a maximum of 400mg/day.	≥16 yrs: Same as adult dose. Initial as 25mg in the morning, titrating in 25mg increments every 3 day to 100mg/day, given as 25mg times daily. Increase by 50mg every 3 days thereafter up to 50-100mg every 4 to 6 hours as needed to a maximum of 400mg/day. ≤16 yrs: Safety and efficacy in children have not been established	Tablet: 50mg
Tramadol ER	100-300mg daily	Safety and efficacy in children have not been established	Tablet: 100mg, 200mg, 300mg
Tramadol/APAP	2 tablets every 4 to 6 hours as needed	Safety and efficacy in children have not been established	Tablet: 37.5mg/325mg

SC=Subcutaneous; IM=Intramuscular

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the opiate agonists are summarized in Table 14.

Table 14. 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				
Plummer et al.[14] (1997) Morphine patient-controlled analgesia (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	Primary: Pain at rest and on sitting Secondary: Incidence of nausea; unusual dreams; performance on standardized tests measuring mood and ability to concentrate.	Primary: No difference in pain while at rest (*P*=0.8). Significantly higher pain relief in morphine group (*P*=0.037) vs. meperidine group in sitting position Secondary: No difference in incidence of nausea or unusual dreams, or mood measurements between groups. Lower concentration ability in meperidine group
van Seventer et al.[15] (2003) Fentanyl 25 µg/hour TD q 3 days vs. Morphine ER 30 mg q 12 hours	CS, MC, RCT Patients with moderate-to-severe cancer-related pain	N=131 4 weeks	Primary: Analgesia Secondary: Constipation; tolerability; safety	Primary: 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 1 week of treatment (27% vs 57%; *P* = 0.003). Transdermal fentanyl better tolerated than oral morphine. Higher number of patients taking morphine dropped out due to incidence 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				interruption of daily activities (absence of any interruption of daily activities in 88% vs 63% of patients; *P* = 0.012).
Sudheer et al.[19] (2007) Morphine PCA (max. 50 mg/4 hours) vs. Tramadol PCA (max. 200 mg/4 hours) vs. Codeine phosphate 60 mg IM, then 60mg after 1 hour if needed, then 60mg every 4 hours as needed.	RCT Post-op pain control following elective craniotomy	N=60	Primary: P_aCO_2 4 hours after eye opening; a 20% increase in P_aCO_2 is considered significant and is a characteristic of respiratory acidosis; analgesia Secondary: Patient satisfaction; adverse effects	Primary: 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 8–28 breaths.min) nor sedation showed differences between groups. Baseline values of pain score (0–10), sedation and arterial carbon dioxide tension were recorded at the time of first analgesic administration and at 30 minutes, 1, 4, 8, 12, 18 and 24 hours. Patient satisfaction was assessed at 24 hours. Morphine produced significantly better analgesia than tramadol at all time points ($P < 0.005$) and better analgesia than codeine at 4, 12 and 18 hours. Secondary: Patients were more satisfied with morphine than with codeine or tramadol ($P < 0.001$). Vomiting and retching occurred in 50% of patients with tramadol, compared with 20% with morphine and 29% with codeine.
Hewitt et al.[21] (2007) Tramadol/APAP 75 mg/650 mg vs. hydrocodone/APAP 7.5 mg/650 mg vs.	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 2 standardized pain relief/pain intensity scales. Reports recorded hourly for 4 hours after the first dose of study med and daily for 5 days, with as-needed	Primary: Tramadol/APAP and hydrocodone/APAP provided greater total pain relief than placebo ($P<0.001$) during the first 4 hours, decreased pain intensity during the first 4 hours and increased average pain relief on days 1 to 5. No efficacy measure was significantly different between the tramadol/APAP and hydrocodone/APAP groups. Secondary: Common adverse events included somnolence, nausea, dizziness, and vomiting.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			dosing Secondary: Adverse events	
Chang et al.[22] (2006) Hydromorphone 0.015 mg/kg IV single dose vs. morphine 0.1 mg/kg IV single dose	Double-blind, RCT Adults between 21 and 65 years of age, presenting to an emergency department with acute pain (< 7 days in duration) of severity, warranting use of intravenous opioids.	N=191 Single dose	Primary: Difference between the 2 groups in pain reduction at 30 minutes as measured on a standard numeric rating scale Secondary: Adverse effects	Primary: Mean change of pain from baseline to 30 minutes post-baseline in IV hydromorphone group was not significantly different from IV morphine group: -5.5 numeric rating scale units' vs. -4.1 (difference -1.3; 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 IV hydromorphone group (0% vs. 6% [difference -6%; 95% CI -11% to -1%]).
Karaman et al.[23] (2006) Morphine 0.2mg vs. sufentanil 5 µg	DB, RCT Female patients undergoing cesarean section, receiving bupivacaine in spinal anesthesia	N=54 Single dose	Primary: Quality of anesthesia and post-op analgesia Secondary: Adverse effects on mother and neonate	Primary: There were no differences between 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 +/- 4.7 hours vs. 6.3 +/- 5.2 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.
Lazaraki et al.[24] (2007) Midazolam 2-5 mg IV	RCT Adult patients scheduled for	N=126 Single dose	Primary: Patient discomfort as measured on a 0-4 scale, and pain	Primary: Mean discomfort scores were 0.4 in the fentanyl group and 1.0 in the midazolam group (P= 0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(titration - mean dose 4.6 mg) vs. fentanyl 25-50 µg IV (titration - mean dose 36 µg)	ambulatory colonoscopy		on a 0-10 scale Secondary: Adverse effects and recovery time	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 min (*P*=0.012), respectively]. Secondary: No adverse events were reported in the fentanyl group, while in the midazolam group a decrease in oxygen saturation was noted in 23/60 (35%) patients. Mean recovery time was 5.6 min in the fentanyl group and 16 min in the midazolam group (*P* =0.014).
Rahman Al-Refai et al.[28] (2007) Group I: remifentanil 0.25 µg/kg Group II: remifentanil 0.µg/kg Group III: alfentanil 15 µg/ kg Group IV: alfentanil 20 µg /kg (Groups I-IV administered 60 seconds prior to propofol and mixed with 1 ml of 0.9% normal saline.) Group V: 1 ml of 1% lidocaine (10 mg) added to 100 mg of	DB, PC, RCT Patients 5-12 years of age undergoing adenotonsillectomy	N=335 in 6 treatment groups Single pre-op dose administered concomitantly with 3 mg/kg IV propofol	Primary: Decreased propofol-induced pain ; pain perception assessed with a four-point behavioral scale	Primary: Pain results (% experiencing pain) by group: Group I – 63.46% Group II - 39.21% Group III - 38.77% Group IV – 36.53% Group V – 38.46% Group VI – 84.61% Groups II, III, IV and V were significantly better than placebo in the reduction of propofol pain (*P*<0.0001). Groups II, III and IV significantly reduced the pain in comparison with Group I (*P*<0.001). Pretreatment with remifentanil 0.5 µg/ kg), alfentanil 15 µg/ kg and alfentanil 20 µg/ kg were equally effective in reducing pain associated with propofol injection.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propofol Group VI: normal saline placebo				
Motamed et al.[29] (2006) Fentanyl IV bolus 2-3 µg/kg vs. Sufentanil IV bolus 0.2-0.3 µg/kg vs. Remifentanil IV bolus 0.4-5 µg/kg All trial meds administered intraoperatively.	RCT Adults scheduled for elective total thyroidectomy.	N=75 24 hours post-op	Primary: Maximum post- op pain scores, Secondary: Necessity of morphine injection in both surgical ward and postoperative care unit (PACU); incidence of opioid related side effects (nausea/vomiting, sedation)	Primary: Post-op pain scores in PACU were significantly lower in the sufentanil and fentanyl group compared to remifentanil group, (P<0.05). Secondary: Necessity and total amount of morphine titration in the PACU 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.
Silberstein et al.[31] (2005) Tramadol-APAP 75mg/650mg PO (2 tablets) vs. placebo	DB, PC, PG, RCT Patients with history of migraine of moderate or severe intensity for ≥ 12 months, with a frequency of 1- 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, 1, 2, 3, 4, 6, and 24 hours post-dose	Primary: Treatment response was higher for tramadol/APAP vs. placebo at 2 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 6 hours (64.9% vs. 37.7%; all $P \leq 0.022$). Subjects in tramadol/APAP group vs. placebo group were more likely to be pain-free at 2 hours (22.1% vs. 9.3%), 6 hours (42.9% vs. 25.2%), and 24 hours (52.7% vs. 37.9%; all $P \leq 0.007$). Two hours post-dose, moderate-to-severe symptoms that were less

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Incidence of adverse events	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, no treatment-related adverse event was reported by more than 2% of subjects.
Özalevli et al.[32] (2005) Tramadol PCA 0.2mg/kg bolus vs. morphine PCA 0.02mg/kg bolus.	DB, RCT Children 6 to 12 years of age scheduled for tonsillectomy with general anesthesia	N=60 24 hours post-op	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	Scores on all three scales were recorded at 5, 15 and 30 minutes, and 1, 2, 4, 6 and 24 hours during PCA administration. Pain scores decreased significantly with time in both groups (P <0.05), but were lower in morphine group vs. tramadol group at 1, 2 and 4 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 4, 6 and 24 hours (P<0.05).
Smith et al.[34] (2004) Tramadol-APAP 75mg/650mg PO (2 tablets) vs. APAP-codeine 300mg/30mg PO vs. placebo	DB, MC, PC, RCT Patients with moderate to severe abdominal or orthopedic postsurgical pain.	N=305 6 days	Primary: Total pain relief, sum of pain intensity differences, and sum of pain relief and pain intensity differences during the first 4 hours after the first dose of study medication on day 1. Secondary:	Primary: Tramadol-APAP was more effective than placebo for total pain relief, sum of pain intensity differences and sum of pain relief and pain intensity differences ($P \leq 0.015$); tramadol-APAP and codeine-APAP did not separate ($P \geq 0.281$). Secondary: For average daily pain relief, average daily pain intensity, and overall medication assessment, tramadol-APAP was more effective than placebo ($P \leq 0.038$); codeine-APAP did not separate from placebo ($P \geq 0.125$). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All study meds were administered as 2 tablets PO stat, then 1-2 tablets PO q 4-6 hours PRN			Average daily pain intensity scores and average daily pain relief scores reported on days 1 to 6; overall rating of study medication by both patients and investigators using a five-point scale; incidence of adverse events.	active treatments.
Joshi et al.[35] (2007) Fentanyl 2 µg/kg IV vs. sufentanil 0.2 µg/Kg IV vs. 2 ml isotonic normal saline IV (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 100mm visual analog scale pain score 10 minutes before removing chest tubes and 5 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+/-5.2, 25.10+/-5.39 and 23.64+/-6.10 respectively. The pain scores 5 minutes after chest tube removal were reduced to 20.11+/-6.9 ($P<0.05$) in the fentanyl group vs.13.60+/-6.60 ($P<0.05$) in the sufentanil group; an increase to 27.97+/-8.39 ($P<0.05$) was noted in placebo group. The pain scores in sufentanil group were significantly lower compared with fentanyl or control group. Secondary: - Sedation scores remained low in all groups and 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.
Chronic pain				
Bruera et al.[16] (2004) Methadone 7.5 mg PO	RCT Patients with pain requiring initiation	N=103 4 weeks	Primary: ≥ 20% reduction in pain intensity by end of trial	Primary: Proportion of patients with a ≥ 20% or more improvement in pain at 4 weeks in the methadone group was 0.49 (95% CI, 0.34 to 0.64) and was similar in the morphine group (0.56; 95% CI, 0.41 to 0.70)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
q 12 hours PLUS 5 mg q 4 hours as needed vs. morphine ER 15mg Q12 hours +5 mg Q4 hours as needed	of strong opioids		Secondary: Adverse effects	Secondary: Methadone group had higher rate of dropout due to opioid related events (22%) vs. morphine (6%)
Rodriguez et al.[20] (2007) Codeine/APAP vs. hydrocodone/APAP vs. tramadol	DB, RCT Patients with persistent moderate or severe cancer-associated pain	N=177 3 weeks	Primary: Analgesic efficacy Secondary: Adverse effects	Primary: No significant statistical difference in the analgesic efficacy of the three opioids (P= 0.69; X^2=0.73). Secondary: Tramadol produced higher rates of adverse events than codeine and hydrocodone: vomiting, dizziness, loss of appetite, and weakness (P < 0.05).
DeConno et al.[30] (2008) Morphine 5 mg IR Q4 hours, if taking Step 1 analgesics or Morphine 10mg IR Q4 hours, if taking Step 2 analgesics	OL Cancer patients ≥ 18 years of age, never treated with strong opioids, and with pain score of >5 points on a 0 – 11 point standard scale for ≥ 24 hours. Patients currently receiving treatment with WHO Step I or Step II analgesics.	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: Incidence of adverse events	Primary: Pain control was observed for 75% (95% CI 70-80) of the follow-up period in the intent-to-treat population. Overall, 50% and 75% of patients achieved pain control 8-24 hours after starting 5mg and 10mg 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 3 and 5 respectively. Secondary: The most commonly reported adverse events were somnolence (24% of patients), constipation (22%), vomiting (13%), nausea (10%) and confusion (7%).
Le Loët et al.[33] (2005)	OL, MC	N=159	Primary: Pain control,	Primary: At baseline, 25% of patients reported very poor pain control, 48% poor

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fentanyl 25µg/hour TD q 72 hours (TDF)	Patients ≥ 50 years of age with osteoarthritis (OA) of knee or hip established via radiography, and waiting for 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.	28 days	evaluated weekly on a five-point assessment scale ranging from very poor to excellent. Secondary: Pain assessment; pain intensity; treatment assessment; quality of life; functionality using the Western Ontario and McMaster Universities Osteoarthritis Index LK 3.1 (WOMAC); adverse events	and 25% moderate pain control. After first week of treatment, 74% of patients reported adequate pain control, 37% reported moderate, 29% good and 8% 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, 38% good, and 8% 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% mild pain and only two patients were without pain, by endpoint 41% reported moderate pain, 30% mild pain and 7% no pain. In their assessment of treatment, 63% of patients rated TDF positively with respect to pain control and 84% would recommend TDF for their type of pain. 93% thought it easy/extremely easy to use; 85% were very/somewhat pleased by the way it's used), and 53% considered side effects were not an issue. In assessing how they had felt over the past week, the percentage of all patients who answered good or very good increased during the study from 7% to 32% in 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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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. There were no clinically significant changes in vital signs during the study.
Reid et al.[36] (2006) Oxycodone IM/PO, various doses morphine IM/PO, various doses hydromorphone IM/PO, various doses	MA Patients with moderate to severe cancer pain	N=1013	Primary: Pain relief, as assessed on 2 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 (pooled standardized mean difference, 0.04; 95% confidence interval [CI], -0.29 to 0.36; P =0.8). In meta-regression analyses, pain scores were higher for oxycodone compared with morphine (0.20; 95% CI, -0.04 to 0.44) and lower compared with hydromorphone (-0.36; 95% CI, -0.71 to 0.00), although these effect sizes were small. The investigators estimated that for oxycodone compared with morphine or hydromorphone, the pooled standardized differences represented only 2 to 3 mm on a 100-mm visual analog scale, and suggested such standardized differences are unlikely to be clinically important or meaningful to patients. Secondary: No differences in patient preference or quality of life were demonstrated, although one study suggested that nighttime acceptability of morphine was better than that of oxycodone. The point estimates for the pooled data comparing oxycodone with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				control groups were 0.75 (95% CI, 0.51-1.10) for nausea and 0.2 (95% CI, 0.49-1.06) for vomiting. Estimates of the association of oxycodone with dry mouth and drowsiness varied widely across trials. When the meta-analysis 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.
Furlan et al.[37] (2006) Weak opioids: Tramadol PO, various doses propoxyphene PO, various doses codeine PO, various doses Strong opioids: morphine PO, various doses oxycodone, various doses	MA Patients with nociceptive pain (osteoarthritis, rheumatoid arthritis or back pain) 80%; neuropathic pain (postherpetic neuralgia, diabetic neuropathy or phantom limb pain) 12%; fibromyalgia 7%; and mixed pain 1%	N=6019 1-16 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 or neuropathic pain or fibromyalgia. Strong opioids were significantly more effective than naproxen and nortriptyline, and only for pain relief. 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.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, SB=single-blind, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 15. Relative Cost of the Opiate Agonists

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Alfentanil	injection	Alfenta®*	$	$
Codeine	tablet, injection	N/A	N/A	$-$$
Codeine/APAP	elixir, suspension, tablet	Capital w/Codeine®, Tylenol w/Codeine #3®*, Tylenol w/Codeine #4®*, Vopac®	$-$$$	$
Codeine/ASA	tablet	N/A	N/A	$
Codeine/APAP/butalbital/ caffeine	capsule	Fioricet w/codeine®*, Phrenilin-Caffeine-Codeine®*	$$$-$$$$	$$
Codeine/ASA/butalbital/ caffeine	capsule	Fiorinal w/codeine #3®*	$$$-$$$$	$$
Dihydrocodeine/APAP/ caffeine	capsule, tablet	Panlor DC®, Panlor SS®*	$$-$$$	$$
Fentanyl	buccal tablet, extended-release transdermal patch, transmucosal lozenge,	Duragesic®*, Actiq®*, Fentora®, Sublimaze®*	$$$$-$$$$$	$$$$-$$$$$

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
	injection			
Hydrocodone/APAP	capsule, tablet, solution	Liquicet®, Lortab®*, Hycet®, Maxidone®*, Norco®*, Vicodin®*, Xodol 10-300®*, Zamicet®*, Zydone®	$$-$$$$$	$-$$$
Hydrocodone/ibuprofen	tablet	Ibudone®, Reprexain®*, Vicoprofen®*	$-$$$$$	$
Hydromorphone	liquid, tablet, rectal suppository, injection	Dilaudid®*	$-$$$$	$-$$$$
Levorphanol	tablet, injection	Levo-Dromoran®*	$$$$	$$$
Meperidine	solution, tablet, injection	Demerol®*	$-$$$$	$-$$
Methadone	oral concentrate, solution, tablet	Dolophine®*, Methadose®*	$$	$-$$$
Morphine sulfate	injection, intravenous, epidural, tablet, solution, rectal suppository	Roxanol®*, Depodur®*, Duramorph®*, Astramorph®*, Infumorph®*	$$-$$$$$	$-$$$$$
Opium/belladonna	rectal suppository	N/A	N/A	$-$$$
Oxycodone	capsule, oral concentrate, solution, tablet	OxyIR®*, Dazidox®*, Roxicodone®*	$$$-$$$$$	$-$$$
Oxycodone/APAP	capsule, solution, tablet	Percocet®*, Perloxx®, Lynox®, Narvox®, Magnacet®, Alcet®, Primalev®, Tylox®*	$$-$$$$$	$-$$$
Oxycodone/ASA	tablet	Percodan®*	$$$	$$
Oxycodone/ibuprofen	tablet	Combunox®*	$$	$
Oxymorphone	tablet, injection	Opana®, Numorphan®	$$$$-$$$$$	N/A
Propoxyphene HCL	capsule	Darvon®*	$$-$$$	$
Propoxyphene HCL/APAP	tablet	N/A	N/A	$
Propoxyphene napsylate	tablet	Darvon-N®	$$$$$	N/A
Propoxyphene napsylate/ APAP	tablet	Darvocet-N 50®*, Darvocet-N 100®*, Darvocet A500®*	$$$$	$-$$$
Remifentanil	intravenous	Ultiva®	$$-$$$$	N/A
Sufentanil	intravenous	Sufenta®*	$	$
Tramadol	tablet, sustained-release tablet	Ultram®*, Ultram ER®	$$$$-$$$$$	$
Tramadol/APAP	tablet	Ultracet®*	$$-$$$$	$$

*Generic is available in at least one dosage form or strength.
N/A=not available
APAP=acetaminophen; ASA=aspirin; ER=extended-release

X. Conclusions

Currently, there is no standard opiate regimen that will satisfy the pain needs of all patients. The role of the 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.[6-9]

The efficacy of opiates for non-cancer pain has been demonstrated in short-term trials. However, the available evidence is highly variable for the long-term (>6 months) treatment of non-cancer pain.[26] Guidelines for the management of non-cancer pain recommend opiates for moderate to severe pain.[7] Opiate therapy is generally initiated in the form of a therapeutic trial utilizing low doses.[7,26] Medications should be titrated to provide reliable pain control with minimal adverse events. Assessments of pain relief, activity level, and adverse events should be conducted on an ongoing basis.[7,26]

Patients with cancer often suffer from pain due to tumor infiltration, which significantly affects quality of life. Pain is classified as either acute or chronic, and should be addressed at every visit. Guidelines for the management of cancer pain recommend mild opiates for mild to moderate pain, and strong opiates for moderate to severe pain.[25] Doses should be titrated to effect as rapidly as possible with around-the-clock dosing and as-needed breakthrough doses to manage transient pain exacerbations.[25]

The opiate agonists are used for a variety of indications, including treatment of pain, supplement to anesthesia, cough, headache, and opioid dependence. They can be administered via several different routes, including oral, rectal, intravenous, intramuscular, subcutaneous, and transdermal routes. Opiate agonists have no ceiling to their analgesic effect; the degree of analgesia is only limited by dose-related adverse events.[2-5] Numerous clinical trials have demonstrated similar efficacy among the opioid agonists for the treatment of acute pain.[14-15,19,21-23,28,34] Current guidelines for cancer and non-cancer pain do not give preference to one opiate over another.[7,25-26]

Therefore, all brand opiate agonists within the class reviewed are comparable to each other and to the generics and OTC 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. IASP Pain Terminology. http://www.iasp-pain.org/terms-p.html#Pain. Accessed December, 2008.
2. Ballantyne J (ed). Opioids. Massachusetts General Hospital Handbook of Pain Management. 2nd ed Philadelphia: Lippincott Williams & Wilkins. 2002 p. 104-124.
3. Micromedex® Healthcare Series [Internet database]. Drug Consults: Narcotic Analgesic Comparative Review. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 2008.
4. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 2008.
5. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Wickerhsam R. (ed) Narcotic Agonists Analgesics. Available from Wolters Kluwer Health, Inc. Accessed November 2008.
6. Mercadante S. World Health Organization Guidelines: Problem Areas in Cancer Pain Management. Cancer Control 1999 Mar ; 6(2):191-197.
7. 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; 2003 Mar. http://www.guideline.gov/summary/summary.aspx?doc_id=4812&nbr=3474. Accessed November 14, 2008.
8. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain 1997 Mar; 13(1):6-8.
9. Practice guidelines for chronic pain management. A report by the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. Anesthesiology 1997 Apr; 86(4):995-1004.
10. United States Food and Drug Administration. FDA Public Health Advisory. Safety Warnings Regarding Use of Fentanyl Transdermal (Skin) Patches. Accessed 08/15/05 at: http://www.fda.gov/cder/drug/advisory/fentanyl.htm
11. DEA US Drug Enforcement Administration. Butorphanol.: http://www.usdoj.gov/dea/concern/butorphanolp.html. Accessed August 19, 2005.
12. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November 2008.
13. McEvoy GK, Ed. American Hospital Formulary Service, AHFS Drug Information. American Society of Health-System Pharmacists. Bethesda. 2005.
14. Plummer JL, Owen H, Ilsley AH, Inglis S. Morphine patient-controlled analgesia is superior to meperidine patient-controlled analgesia for postoperative pain. Anesth Analg 1997 Apr; 84(4):794-9.
15. 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(6)457-69.
16. Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. Clin Oncol 2004 Jan 1; 22(1):185-92.
17. White A, Birnbaum H, Mareva M, Daher M, Vallow S, Schein J, et al. Direct costs of opioid abuse in an insured population in the United States. J Manag Care Pharm 2005 Jul-Aug; 11(6):469-79.
18. Kornick CA, Santiago-Palma J, Moryl N, Payne R, Obbens EA. Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. Drug Saf 2003; 26(13):951-73.
19. 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 Jun; 62 (6): 555-60
20. 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 Feb; 10 (1):56-60
21. 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 Apr 01; 49(4): 468-80
22. 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 Aug 01; 48(2):164-72
23. 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 Apr; 23 (4):285-91 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 Sep; 21 (9):1631-36

24. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November 2008.
25. Jost L, Roila F on behalf of the ESMO Guidelines Working Group. Management of cancer pain: ESMO Clinical Recommendations. Ann Oncol 2008; 19 (Supplement 2): ii119–ii121
26. Trescot AM, Helm S, Hansen H et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) guidelines. Pain Physician 2008;11:S5-62
27. Rahman Al-Refai A, Al-Mujadi H, Petrova Ivanova M et al. Prevention of pain on injection of propofol: a comparison of remifentanil with alfentanil in children. Minerva Anestesiol. 2007 Apr; 73(4):219-23.
28. 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(1):11-13. Epub 2006 Jan 1.
29. 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 Apr; 22 (3):214-21
30. 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 Nov-Dec; 45(10):1317-27
31. 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 Nov; 15 (11): 979-84
32. 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 Jun 15; 6:31.
33. Smith AB, Ravikumar TS, Kamin M et al. Combination tramadol plus acetaminophen for postsurgical pain. Am J Surg 2004 Apr 01; 187(4):521-27.
34. 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 Jan; 10 (1):42-45
35. Reid CM, Martin RM, Sterne JA et al. Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. Arch Intern Med 2006 Apr 24; 166(8):837-43
36. Furlan AD, Sandoval JA, Mailis-Gagnon A et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ 2006 May 23; 174 (11):1589-94.
37. 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 January, 2009.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Opiate Partial Agonists
AHFS Class 280812
February 11, 2009

I. Overview

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of damage.[1] It is a subjective experience that is unique to the individual. There are numerous etiologies of pain and successful pain management can be a difficult goal to attain. An individual's reaction to pain and response to pain management can be highly variable.

Pain management is multifaceted and generally incorporates both pharmacologic and nonpharmacologic treatments. Successful pain management requires frequent reassessment of pain level and response to therapy. There are numerous pharmacologic agents available to help manage pain, including the opiate partial agonists.

Opioids have been used for thousands of years to treat pain. There are several opioid receptors within the central nervous system and peripheral tissues, including mu, delta, kappa, and sigma. Several opiate partial agonists (butorphanol, nalbuphine, and pentazocine) act as mu receptor antagonists and kappa receptor agonists. Activation of kappa receptors cause analgesia, sedation, dyspnea, dysphoria, respiratory depression, and dependence. Buprenorphine is a kappa receptor antagonist and partial mu receptor agonist. It is able to block the effects of morphine and other opioids, while offering mild opioid-like effects. In addition to analgesia, buprenorphine is used in detoxification and maintenance therapy programs. Naloxone is a competitive antagonist at the mu receptor and lacks any mu receptor efficacy. It has been combined with opiate partial agonists to reduce the risk of abuse. Opiate partial agonists generally have a ceiling to their analgesic effect.[2-5] Therefore, increasing the dose will only result in additional adverse events, which may decrease the abuse potential.

The opiate partial agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Opiate Partial Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Buprenorphine	sublingual tablet, injection	Buprenex®*, Subutex®	buprenorphine
Buprenorphine/naloxone	sublingual tablet	Suboxone®	none
Butorphanol	nasal, injection	N/A	butorphanol
Nalbuphine	injection	N/A	nalbuphine
Pentazocine	injection	Talwin®	none
Pentazocine/APAP	tablet	Talacen®*	pentazocine/APAP
Pentazocine/naloxone	tablet	Talwin NX®*	pentazocine/naloxone

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

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)
Annals of Oncology: **Management of Cancer Pain: ESMO Clinical Recommendations[14] (2008)**	• Step-wise escalation of analgesic therapy should usually follow the 'pain ladder' as described by the WHO: ○ Step I, Mild Pain: non-opiate analgesics (e.g., APAP, NSAIDs) +/- adjuvant pain meds ○ Step II, Mild-Moderate Pain: mild opiate (e.g. codeine) +/- non-opiate analgesics +/- adjuvant meds

Clinical Guideline	Recommendation(s)
	○ Step III, Moderate-Severe Pain: strong opiate (e.g. morphine) +/- non-opiate analgesics +/- adjuvant pain meds • Patients presenting with severe pain that needs urgent relief should be treated with parenteral opioids, usually administered by IV or SC route. • 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 4 '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.
American Society of the Interventional Pain Physicians: **Opioids in the Management of Chronic Non-Cancer Pain: An Update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines[15] (2008)**	• Opioids are extensively used in managing chronic pain. • The clinical effectiveness of opioid medications for non-cancer pain in humans is difficult to measure. • Based on the review of multiple systematic reviews and the available literature, the evidence for the effectiveness of long-term opioids in reducing pain and improving the functional status for 6 months or longer is variable. • Opioid pharmacology is variable and essential to understand for proper management of patients. Periodic review of the patient on opioids is essential, using appropriate adjustments, with routine assessment of analgesia, activity, aberrant behavior, and adverse effects. The rationalization and importance of these guidelines lies in the fact that most available evidence documents a wide degree of variance in the prescribing patterns of opioids for chronic pain. The strength of available evidence in the use opioids for chronic non-cancer pain is weak. Initial dose adjustment phase (up to 8 to 12 weeks) • Start low dose. • Utilize opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and adjuvants • Discontinue due to lack of analgesia, side effects or lack of functional improvement. Stable phase (stable - moderate doses) • Monthly refills. • Assess for four A's: analgesia, activity, aberrant behavior, adverse effects. • Manage side effects.
Center for Substance Abuse Treatment. **Clinical Guidelines For the Use of Buprenorphine in the Treatment of Opioid Addiction[34]**	• As a general rule, to be considered for buprenorphine maintenance, patients should have a diagnosis of opioid dependence, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). • The consensus panel recommends that the buprenorphine/naloxone

Clinical Guideline	Recommendation(s)
(2004)	combination be used for induction treatment (and for stabilization and maintenance) for most patients. The consensus panel further recommends that initial induction doses 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 (e.g., methadone, sustained release morphine, sustained release oxycodone) to buprenorphine should be inducted using buprenorphine monotherapy, but switched to buprenorphine/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 (LAAM). 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 (and avoiding side effects of buprenorphine). • The consensus panel recommends that patients dependent on short-acting opioids (e.g., hydromorphone, oxycodone, heroin) who will be receiving medically supervised withdrawal be inducted directly onto buprenorphine/naloxone tablets. The use of buprenorphine (either as buprenorphine monotherapy or buprenorphine/naloxone combination treatment) 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 (OTPs).

Veterans Health Administration, Department of Defense:
VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain[7]
(2003)
	• The use of opioid therapy is indicated for moderate to severe pain that has failed to adequately respond to other non-opioid therapeutic interventions.
	• Opioid therapy can be initiated in the form of a therapeutic trial.
	• Initiate Trial of Opioid Therapy
	  ○ Initiation phase: Find the medication(s) that provides the best pain relief with the fewest adverse effects at the lowest effective dose. Effective therapy is achieved when the patient reports improvement in pain relief and/or function along with minimal or acceptable adverse effects.
	  ○ Titration phase: Adjust the dose of opioid to achieve satisfactory pain relief and tolerable adverse effect profile.
	  ○ Maintenance phase: Maintain reliable pain control and improvement in function by repeating the effective dose in a routine schedule, varying the timing or dose only to accommodate changes in activity level or exacerbations of pain.

APAP=acetaminophen; NSAIDs=nonsteroidal anti-inflammatory drugs; IV=intravenous; SC=subcutaneous

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[4-5,10-13,16-17]

Generic Name	Analgesia	Opioid Dependence
Buprenorphine	✔ [a]	✔ [b]
Buprenorphine/ naloxone		✔
Butorphanol	✔	
Nalbuphine	✔	
Pentazocine	✔	
Pentazocine/APAP	✔	
Pentazocine/naloxone	✔	

[a] Injection only
[b] Oral formulation only

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Opiate Partial Agonists[4-5,10-13,16-17]

Generic Name	Onset	Peak	Half-life (hours)	Metabolism	Renal Excretion (%)
Buprenorphine	IM: 15-30 min Sublingual: No data	IM:60 min Sublingual: No data	IM/IV: 2 Sublingual: 37	Liver	1
Buprenorphine w/naloxone	No data	No data	37/1	Liver	1
Butorphanol	IV: 1-10 min Intranasal: 15 min	IV:4-5 min IM: 30-60 min	4-7	Liver	5
Nalbuphine	2-15 min	30 min	5	Liver	7
Pentazocine	2-20 min	15-60 min	2-3	Liver	5

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[5]

Generic Name	Significance Level	Interaction	Mechanism
Nalbuphine	1	Cimetidine	Increased potential for CNS toxicity
Buprenorphine	2	CYP3A4 inhibitors	Increased potential for CNS/respiratory depression due to hepatic microsomal enzyme induction
Buprenorphine	2	MAO inhibitors	Increased potential for CNS toxicity and hypotension
Opiate partial agonists	2	CNS depressants (other opioids, general anesthetics, barbiturates, phenothiazines, tranquilizers, sedatives, hypnotics, alcohol)	Increased CNS or respiratory depression

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 pentazocine/naloxone is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Opiate Partial Agonists[4-5,10-13,16-17]

Adverse Events	Buprenorphine	Buprenorphine/ naloxone	Butorphanol	Nalbuphine	Pentazocine
Cardiovascular					
Atrial fibrillation	-	✔	-	-	-
Bradycardia	<1	<1	-	≤ 1	-
Circulatory depression/ collapse	-	-	-	-	✔
Hypertension	<1	✔	-	≤ 1	✔
Hypotension	1-5	✔	<1	≤ 1	-
Palpitation	-	-	>1	-	-
Syncope	-	-	<1	-	✔
Tachycardia	<1	✔	-	≤ 1	✔
Vasodilation	4-10	✔	>1	-	-
Central Nervous System					
Abnormal dreams	-	-	<1	≤ 1	✔
Agitation	-	-	<1	-	-
Anxiety	12	✔	>1	-	-
Asthenia	5-7	✔	>1	-	-
Confusion	<1	<1	>1	≤ 1	✔
Depression	11	✔	-	≤ 1	✔
Disorientation	-	-	-	-	✔
Dizziness	4	✔	19	5	✔
Drowsiness	-	✔	-	-	-
Dysphoria	-	-	<1	≤ 1	-
Euphoria	-	-	>1	≤ 1	✔
Foot drop	-	-	<1	-	-
Hallucinations	-	-	-	≤ 1	✔
Headache	30-36	✔	>1	-	✔
Hostility	-	-	<1	≤ 1	-
Impairment of physical/mental performance	-	-	-	-	✔
Insomnia	15-22	✔	-	-	✔
Nervousness	6	✔	>1	≤ 1	-
Paresthesia	<1	<1	>1	-	✔
Restlessness	-	✔	-	≤ 1	-
Sedation	-	-	43	-	✔
Tremor	-	-	>1	-	-
Weakness	<1	<1	-	-	✔
Withdrawal syndrome	19-27	✔	<1	-	-
Dermatological					
Itching/pruritus	<1	<1	>1	≤ 1	-
Skin discoloration	-	-	>1	-	-
Sweating	13-15	✔	-	9	-
Urticaria	-	-	<1	≤ 1	-
Gastrointestinal					
Abdominal pain	-	✔	-	-	-

Adverse Events	Buprenorphine	Buprenorphine/ naloxone	Butorphanol	Nalbuphine	Pentazocine
Abnormal LFTs	12	✔	>1	-	-
Appetite increased	-	-	>1	-	-
Constipation	✔	✔	-	-	-
Cramps	8-13	✔	>1	-	✔
Dry mouth	-	-	-	≤ 1	-
Diarrhea	<1	✔	-	4	✔
Dyspepsia	4-5	✔	-	-	-
Dysphagia	-	-	-	≤ 1	-
Hepatitis	-	✔	-	-	-
Nausea	✔	✔	-	-	-
Oral moniliasis	14-16	-	13	6	✔
Vomiting	✔	✔	-	-	-
Weight loss	8	-	13	6	✔
Genitourinary					
Urinary urgency	-	-	<1	-	✔
UTI	-	-	-	≤ 1	-
Bronchitis	-	-	-	≤ 1	-
Bronchospasm	-	✔	-	-	-
Cough	-	-	>1	-	-
Dyspnea	-	✔	-	-	-
Epistaxis	-	-	>1	-	-
Hemoptysis	<1	<1	>1	≤ 1	✔
Hiccoughs	-	-	>1	-	-
Pharyngitis	-	✔	-	-	-
Pulmonary edema	-	✔	-	-	-
Respiratory insufficiency	-	-	-	≤ 1	✔
Rhinitis	-	✔	-	-	-
Sputum increased	5-10	-	>1	-	-
Stertorous breathing	-	-	>1	-	-
Other					
Allergic laryngeal edema	1-2	-	-	-	-
Allergic laryngospasm	3	-	-	-	-
Allergic reaction	-	✔	-	-	-
Anaphylaxis	-	✔	-	✔	-
Back pain	-	✔	-	✔	✔
Bone pain	4-8	-	-	-	-
Carcinoma	>1	-	>1	≤ 1	✔
Chills	-	✔	-	-	-
Dehydration	8	-	-	-	-
Dysgeusia	<1	<1	-	-	-
Ear pain	-	-	>1	-	-
Edema	-	-	>1	-	-
Fever	-	✔	-	-	-
Flu syndrome	-	✔	-	-	-
Hyperacusis	6	-	-	-	-
Infection	-	✔	-	-	-
Intraoperative muscle movement	6-12	-	-	-	-
Lacrimation	<1	✔	-	-	✔

Adverse Events	Buprenorphine	Buprenorphine/ naloxone	Butorphanol	Nalbuphine	Pentazocine
disorder					
Malaise	-	✔	-	-	-
Miosis	5	-	-	-	-
Neck pain	1-5	-	-	-	-
Pelvic pain	19-24	-	-	-	-
Tinnitus	-	-	-	-	✔
Visual disturbances	-	-	>1	-	✔
Wheal/flare over vein with IV injection	-	-	-	-	✔

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Pentazocine/Naloxone[16]

WARNING
Pentazocine/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 8.

Table 8. Usual Dosing Regimens for the Opiate Partial Agonists[4-5,10-13,16-17]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Buprenorphine	12 to 16mg daily placed under the tongue until dissolved	≥16 yrs: 12 to 16mg daily placed under the tongue until dissolved	Tablet: 2mg, 8mg Injection: 0.3mg/ml
Buprenorphine/ naloxone	12 to 16mg daily placed under the tongue until dissolved	≥16 yrs: 12 to 16mg daily placed under the tongue until dissolved	Tablet: 2/0.5mg, 8/2mg
Butorphanol	Injection: IV: 1mg IV every 3 to 4 hours as needed. IM: 2mg IM every 3 to 4 hours as needed Pre-op: 2mg IM given 60 to 90 minutes before surgery Nasal spray: 1 spray (1mg) in 1 nostril. An additional dose within 60 to 90 minutes may be given if adequate pain relief is not achieved. This 2 dose sequence can be given every 3 to 4 hours as needed.	Safety and efficacy in children have not been established	Injection: 1mg/ml, 2mg/ml Nasal spray: 10mg/ml
Nalbuphine	10mg (for a 70mg individual) given SC, IM, or IV every 3 to 6 hours as needed. Anesthesia supplement: 0.3mg/kg IV given over a 10 to 15 minute period initially and then 0.25mg to 0.5mg/kg	Safety and efficacy in children have not been established	Injection: 10mg/ml, 20mg/ml

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	as a single IV admin for maintenance.		
Pentazocine	30mg IM, SC, or IV every 3 to 4 hours	≥12 yrs: 30mg IM, SC, or IV every 3 to 4 hours <12 yrs: Safety and efficacy in children have not been established	Injection: 30mg/ml
Pentazocine/ APAP	1 tablet every 4 hours	≥12 yrs: Clinical experience is limited. <12 yrs: Safety and efficacy in children have not been established	Tablet: 25/650mg
Pentazocine/ naloxone	50mg every 3 to 4 hours. may increase to 100mg if necessary.	≥12 yrs: Clinical experience is limited. <12 yrs: Safety and efficacy in children have not been established	Tablet: 50/0.5mg

SC-Subcutaneous; IM- Intramuscular

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the opiate partial agonists are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Opiate Partial Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Woody et al.[18] (2008) Buprenorphine/ naloxone 24 mg per day for 9 weeks and then tapered to week 12 (extended) vs. buprenorphine/ naloxone up to 14 mg per day and then tapered to day 14 (detox)	RCT Opioid-addicted youth aged 15 to 21 years	N=152 12 weeks (extended) 14 day (detox)	Primary: Opioid-positive urine test result at weeks 4, 8, and 12. Secondary: Proportion of patients remaining in treatment; reported opioid use, injection use, non-study addiction treatments	Primary: Patients in the detox group (61%) had higher proportions of opioid-positive urine test results at week 4 compared to the extended treatment group (26%) (P=0.09). Patients in the detox group (54%) had higher proportions of opioid-positive urine test results at week 8 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 8 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 1 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.
Strain et al.[20] (2000) Buprenorphine 4mg, 8mg, and 16 mg (sublingual) vs. buprenorphine/ naloxone 1/0.25 mg, 2/0.5 mg, 4/1 mg, 8/2	DB, DD, PC Adults with active opioid abuse, but not physically dependent	N=7	Primary: Peak drug effect; physiologic and psychomotor measures	Primary: Dose-related increases in ratings of Drug Effects, High, Good Effects, and Liking were seen for hydromorphone, for buprenorphine, and for the combination of buprenorphine/naloxone. The predominant effects were seen with the highest doses tested (hydromorphone 4 mg, buprenorphine/naloxone 8/2 and 16/4 mg, and buprenorphine 8 and 16 mg). None of the treatments produced significant changes in ratings of Bad Effects or Sick. For ratings of Drug Effects, only the two higher doses of buprenorphine alone (8 and 16 mg) produced significantly increased ratings compared to placebo (*P*<0.05 and *P*<0.01, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg, 16/4 mg (sublingual) vs. hydromorphone 2mg and 4 mg as control (intramuscular) vs. placebo				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.
Soyka et al.[21] (2008) Buprenorphine (mean daily dose 9-12 mg) vs. methadone (mean daily dose 44-50 mg) (flexible-dose study)	RCT Opioid-dependent patients who had been without opioid substitution therapy	N=140 6 months	Primary: Retention rate; substance use; predictors of outcome	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.
Gibson et al.[22] (2008) Buprenorphine vs. methadone	RCT Heroin-dependent patients aged 18 years and above	N=405 10 years of follow-up	Primary: Mortality	Primary: There was an overall mortality rate of 8.84 deaths per 1000 person-years of follow-up. Increased exposure to episodes of opioid treatment longer than 7 days reduced the risk of mortality. There was no difference in mortality among methadone versus 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 participants randomized to buprenorphine treatment had significantly improved survival.
Bell et al.[23] (2007) Buprenorphine/ naloxone (observed vs. unobserved treatment) and weekly clinical reviews	RCT Heroin users seeking maintenance treatment	N=119 3 months	Primary: Retention in treatment and heroin use at 3 months	Primary: At 3 months, 33/58 (57%) randomized to unobserved treatment, and 37/61 (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 3 months, did not differ significantly; 18.5 days (95% CI: 21.8-15.3) and 22 days (95% CI: 24.3-19.7), respectively (P=0.13).
Maremmani et al.[24] (2007) Buprenorphine vs. methadone	OL Patients involved in a long-term treatment program with buprenorphine or methadone	N=213 12 months	Primary: Opioid use, psychiatric status, quality of life	Primary: There were significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for buprenorphine-treated and methadone-treated patients.
Kakko et al.[25] (2007) Buprenorphine/ naloxone (stepped treatment) vs. methadone (maintenance treatment)	RCT, DB induction phase, SB flexible dosing phase Heroin dependence >1 year, age >20 years, and acceptance of the stated treatment principles	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 odds ratio=1.02, 95% CI=0.65–1.60). 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). 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).
Fiellin et al.[26] (2008) Buprenorphine/	OS Patients meeting criteria for opioid	N=166 2-5 years	Primary: Retention in treatment; percentage of	Primary: During the follow-up period, 40 patients left treatment. One thousand and five of the 1106 specimens (91%) had no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
naloxone (dose titration)	dependence		opioid-negative urine specimens Secondary: Percentage of cocaine-negative urine specimens; buprenorphine dose; patient satisfaction; serum transaminases; adverse events	evidence of illicit opioids. Secondary: 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 AST or ALT values that required changes in buprenorphine/naloxone dose or discontinuation. No serious adverse events directly related to buprenorphine/naloxone treatment occurred over the 2–5-year follow-up period.
Petti[27] (1985) Pentazocine 25 mg and acetaminophen 650 mg vs. codeine 30 mg and acetaminophen 300 mg vs. propoxyphene napsylate 100 mg and acetaminophen 650 mg vs.	SB, PG, PC Patients with moderate postoperative pain	N=129 6 hours	Primary: Intensity of pain and degree of pain relief	Primary: Pentazocine/acetaminophen was significantly better than placebo and equivalent to codeine/acetaminophen and propoxyphene/acetaminophen in patients with moderate postoperative pain. No adverse events were reported with acetaminophen/pentazocine, acetaminophen/propoxyphene napsylate, or placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Levine et al.[28] (1988) Naloxone 0.4 mg IV vs. morphine 8 mg or 15 mg IV vs. pentazocine 60 mg IV vs. naloxone 0.4 mg with morphine 8 mg IV vs. naloxone 0.4 mg with pentazocine 60 mg IV vs. placebo	RCT, DB Patients undergoing standardized surgery for the removal of impacted third molars	N=105 Single dose	Primary: Pain intensity using a visual-analogue scale;	Primary: The mean pain intensity, measured 50 min after injections, was increased in the group receiving placebo. Compared with this control group, mean pain intensity was decreased in 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, however, produced less analgesia when compared with the same dose of morphine alone ($p<0.05$) or with high-dose morphine ($p<0.01$) but not when compared with low-dose naloxone administered alone. Compared with the control group, the mean pain intensity measured at 3 hours and 10 min after injection of single analgesic agents was not significantly decreased. 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 with either agent alone (both $p<0.01$). By 3 hours and 10 min after injection only the group of patients receiving low-dose naloxone plus pentazocine still reported significant analgesia.
Zenz et al.[29] (1992) Buprenorphine, dihydrocodeine (SR), and morphine (SR)	OL Patients receiving chronic opioids for treatment of nonmalignant pain	N=100	Primary: Pain reduction with visual analogue scales (VAS); patient function using the Karnofsky Performance Status	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 VAS values ($r = 0.983$; $p<0.0001$)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Scale	Pain reduction was associated with an increase in performance (p<0.0001).
Desjardins et al.[30] (2000) Butorphanol 0.25 mg vs. butorphanol 0.5 mg vs. butorphanol 1 mg vs. butorphanol 2 mg vs. placebo	RCT, DB, PG, MC Patients with pain after the removal of impacted third molars	N=151 Single dose intranasal formulation	Primary: Patient-rated pain intensity (PI), pain relief (PAR), pain half gone (PHG), adverse events at 0.25, 0.5, 1, 2, 3, 4, 5, and 6 hours after treatment; global evaluation	Primary: A linear dose-response regression (p<0.05) was observed for the means of PI difference, PAR, and PHG at 0.25, 0.5, and 1 hour, and for sum of PI differences, sum of pain relief, peak PID and PAR, and global evaluation. The 1.0- and 2.0-mg groups experienced greater pain relief compared with 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.
Scott et al.[31] (1994) Butorphanol 1 mg	PRO, OL Patients with strains, fractures, contusions, and stab wounds	N=28 Single dose intranasal formulation	Primary: Pain relief	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 5 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, but drowsiness occurred in 82% and dizziness in 54% of the patients.
Wermeling et al.[32] (2005)	RCT, DB, PC, PG	N=30	Primary: Summed pain	Primary: A dose response was observed in SPID scores, with the 2-mg dose of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Butorphanol 1 mg vs. butorphanol 2 mg vs. placebo	Patients receiving standard anesthesia with moderate to severe pain after dental impaction surgery	Single dose intranasal formulation	intensity difference (SPID) at 2, 4, and 6 hours after administration of study medication and total pain relief at 6 hours (TOTPAR-6)	butorphanol providing the greatest response compared with placebo ($p<0.05$). Overall, 86.7% patients requested rescue medication: 91.7% in the 1mg group, 79.2% in the 2mg group, and 91.7% in the placebo group. The time to use of rescue medication occurred 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 TOTPAR-6 showed no significant differences overall or in pairwise comparisons. On the global assessment, 58.3% of patients in each of the active-treatment groups and 83.3% of patients in the placebo group evaluated the study drug as "poor." Patients receiving butorphanol nasal spray reported central nervous system adverse effects compared with 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.
Olsen et al.[33] (2008) Butorphanol 1 mg IV vs. ketorolac 30 mg IV	RCT, DB 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	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.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: CI=confidence interval, SB=single-blind, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, 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
Data from a 4-month retrospective study examined the effects of switching 26 patients from buprenorphine to buprenorphine plus naloxone.[19] During the first 4 weeks, 50% of the patients reported adverse events compared to 26.6% of patients at the 4-month time point. During the follow-up period, buprenorphine plus naloxone was misused intravenously by 5 patients. The patients reported that injecting buprenorphine plus naloxone was like injecting "nothing" with regards to euphoria, or that it was a bad experience. The authors concluded that buprenorphine plus naloxone seems to have less potential for abuse compared to buprenorphine alone. Dose adjustments may be necessary when patients are transferred from high doses (> 22 mg) of buprenorphine to the buprenorphine plus naloxone, especially in the later phase of the treatment. The authors recommend that the transition from buprenorphine to buprenorphine plus naloxone be planned in advance and that adverse events should be regularly monitored. The combination seems to have less abuse potential than 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Opiate Partial Agonists

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Buprenorphine	sublingual tablet, injection	Buprenex®*, Subutex®	$$$$-$$$$$	$
Buprenorphine/naloxone	sublingual tablet	Suboxone®	$$$$$	N/A
Butorphanol	nasal, injection	N/A	N/A	$-$$$
Nalbuphine	injection	N/A	N/A	$-$$
Pentazocine	injection	Talwin®	$-$$$$	N/A
Pentazocine/APAP	tablet	Talacen®*	$$$	$
Pentazocine/naloxone	tablet	Talwin NX®*	$$$	$$

*Generic is available in at least one dosage form or strength.
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 opiate partial 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. [6-9]

The efficacy of opiates for non-cancer pain has been demonstrated in short-term trials. However, the available evidence is highly variable for the long-term (>6 months) treatment of non-cancer pain.[15] Guidelines for the management of non-cancer pain recommend opiates for moderate to severe pain.[7] Opiate therapy is generally initiated in the form of a therapeutic trial utilizing low doses.[7,15] Medications should be titrated to provide reliable pain control with minimal adverse events. Assessments of pain relief, activity level, and adverse events should be conducted on an ongoing basis.[7,15]

Patients with cancer often suffer from pain due to tumor infiltration, which significantly affects quality of life. Pain is classified as either acute or chronic, and should be addressed at every visit. Guidelines for the management of cancer pain recommend mild opiates for mild to moderate pain, and strong opiates for moderate to severe pain.[14] Doses should be titrated to effect as rapidly as possible with around-the-clock dosing and as-needed breakthrough doses to manage transient pain exacerbations.[14]

The opiate partial agonists are indicated for the treatment of pain, as well as opioid dependence (buprenorphine), and are available in a variety of formulations. Opiate partial agonists generally have a ceiling to their analgesic effect.[2-5] Therefore, increasing the dose will only result in additional adverse events, which may decrease the abuse potential. There are limited head-to-head trials with the opiate partial agonists, and guidelines do not give preference to one opiate over another.[7,14-15]

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

XI. Recommendations

No brand partial 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. IASP Pain Terminology. http://www.iasp-pain.org/terms-p.html#Pain. Accessed December, 2008.
2. Ballantyne J (ed). Opioids. Massachusetts General Hospital Handbook of Pain Management. 2nd ed Philadelphia: Lippincott Williams & Wilkins. 2002 p. 104-124.
3. Micromedex® Healthcare Series [Internet database]. Drug Consults: Narcotic Analgesic Comparative Review. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 2008.
4. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 2008.
5. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November 2008.
6. Mercadante S. World Health Organization Guidelines: Problem Areas in Cancer Pain Management. Cancer Control 1999 Mar ; 6(2):191-197.
7. 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; 2003 Mar. http://www.guideline.gov/summary/summary.aspx?doc_id=4812&nbr=3474. Accessed November 14, 2008.
8. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain 1997 Mar; 13(1):6-8.
9. Practice guidelines for chronic pain management. A report by the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. Anesthesiology 1997 Apr; 86(4):995-1004.
10. Product Information: Buprenex®, buprenorphine. Reckitt Benckiser Pharmaceuticals, Richmond, VA, 2001.
11. DEA US Drug Enforcement Administration. Butorphanol. Available at: http://www.usdoj.gov/dea/concern/butorphanolp.html. Accessed December, 2008.
12. Product Information: Suboxone®, buprenorphine and naloxone. Reckitt Benckiser Pharmaceuticals, Richmond, VA, 2006.
13. Product Information: Subutex®, buprenorphine. Reckitt Benckiser Pharmaceuticals, Richmond, VA, 2006.
14. Jost L, Roila F on behalf of the ESMO Guidelines Working Group. Management of cancer pain: ESMO Clinical Recommendations. Ann Oncol 2008; 19 (Supplement 2): ii119–ii121
15. Trescot AM, Helm S, Hansen H et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) guidelines. Pain Physician 2008 Mar-Apr; 11(2S):S5-62.
16. Product Information: Talwin NX®, pentazocine and naloxone. Sanofi-Aventis, Bridgewater, NJ, 2007.
17. Product Information: Talacen®, pentazocine and acetaminophen. Sanofi-Aventis, Bridgewater, NJ, 2008.
18. 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.
19. 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.
20. Strain E, Stoller K, Walsh S, et al. Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers. Psychopharmacology 2000;148:374-83.
21. 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.
22. Gibson A, Degenhardt L, Mattick R, et al. Exposure to opioid maintenance treatment reduces long-term mortality. Addiction 2008;103:462-8.
23. Bell J, Shanahan M, Mutch C, et al. A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine-naloxone for heroin dependence. Addiction 2007;102:1899-907.
24. 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.
25. Kakko J, Grönbladh L, Svanborg K, et al. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial. Am J Psychiatry 2007;164:797-803.

26. 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.
27. Petti A. Postoperative pain relief with pentazocine and acetaminophen: comparison with other analgesic combinations and placebo. Clin Ther 1985;8:126-33.
28. Levine J, Gordon N, Taiwo Y, et al. Potentiation of pentazocine analgesia by low-dose naloxone. J Clin Invest 1988;82:1574-7.
29. 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.
30. 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.
31. 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.
32. 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.
33. Olsen J, McGrath N Schwarz D, et al. A double-blind randomized clinical trial evaluating the analgesic efficacy of ketorolac versus butorphanol for patients with suspected biliary colic in the emergency department. Acad Emerg Med 2008;15:718-22.
34. 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://www.buprenorphine.samhsa.gov/Bup_Guidelines.pdf. Accessed January, 2009.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Selective Serotonin Agonists
AHFS Class 283228
February 11, 2009

I. Overview

Migraine is an idiopathic headache disorder, which is characterized by a moderate to severe pulsating headache that can last up to 72 hours.[1-3] It is often accompanied by nausea, photophobia, lightheadedness, and vomiting. There are many effective treatments for acute migraines. The successful treatment of a migraine attack in clinical trials is generally defined as one or more of the following: 1) pain free after 2 hours, 2) improvement of headache from moderate or severe to mild or none after 2 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).[9]

The selective serotonin agonists (triptans) are FDA-approved for the treatment of acute migraines, with or without aura. They are chemically and structurally related to the neurotransmitter 5-hydroxytryptamine (5-HT), which is present in the blood and in the peripheral and central nervous systems.[2] They are potent, highly selective 5-HT_1 receptor agonists, with no significant affinity for other 5-HT subgroups. The selective serotonin agonists stimulate receptors located on cerebral vessels to redistribute blood flow and relieve pain.[3]

The selective serotonin agonists are a very homogenous group of agents with respect to efficacy, pharmacology, and safety. There are currently 7 triptans approved for use in the U.S. In April, 2008, a fixed-dose combination tablet containing sumatriptan and naproxen sodium was approved by the FDA for the treatment of migraines (Treximet®), which will also be included in this review.

The selective serotonin agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All sumatriptan formulations are available generically.

Table 1. Selective Serotonin Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Almotriptan	tablet	Axert®	none
Eletriptan	tablet	Relpax®	Relpax®
Frovatriptan	tablet	Frova®	none
Naratriptan	tablet	Amerge®	Amerge®
Rizatriptan	tablet, orally disintegrating tablet	Maxalt®, Maxalt MLT®	Maxalt®, Maxalt MLT®
Sumatriptan	tablet, nasal spray, subcutaneous injection	Imitrex®*	Imitrex®, sumatriptan
Sumatriptan/ naproxen	tablet	Treximet®	none
Zolmitriptan	tablet, orally disintegrating tablet, nasal spray	Zomig®, Zomig ZMT®	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 selective serotonin agonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Selective Serotonin Agonists

Clinical Guideline	Recommendation(s)
European Federation of Neurological Societies (EFNS) **Guideline on the Drug Treatment of Migraine—Report of an EFNS Task Force**[9]	• For the acute treatment of migraine attacks, oral non-steroidal anti-inflammatory drugs and triptans are recommended. • It is important to notice that a triptan can be efficacious even if another (or more) triptan was not.

Clinical Guideline	Recommendation(s)
(2006)	• The 5-HT_1 receptor agonists are specific migraine medications and should not be administered in other headache disorders except cluster headache.
American Academy of Neurology/Child Neurology Society: **Practice Parameter: Pharmacological Treatment of Migraine Headache in Children and Adolescents**[5] **(2004)**	• Ibuprofen is effective and should be considered for the acute treatment of migraine in children. • Acetaminophen is probably effective and should be considered for the acute treatment of migraine in children. • Sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine in adolescents. • There are no data to support or refute use of any oral triptan preparations in children or adolescents. • There are inadequate data to make a judgment 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 Headache**[6] **(2002)**	• Use NSAIDs as first-line therapy. • In patients whose migraines fail to respond to NSAIDs, use migraine-specific agents. Recommended agents include intranasal DHE, oral naratriptan, oral rizatriptan, SC or oral sumatriptan, and oral 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.
American Academy of Neurology: **Practice Parameter: Evidence-Based Guidelines for Migraine Headache**[4] **(2000)**	• Triptans are effective and relatively safe for the acute treatment of migraine headaches and are an appropriate initial treatment choice in patients with moderate to severe migraine who have no contraindications for its use. • Initial treatment with any triptan is a reasonable choice when the headache is moderate to severe or in migraine of any severity when nonspecific medication has failed to provide adequate relief in the past. • Patients with nausea and vomiting may be given intranasal or subcutaneous sumatriptan.
US Headache Consortium: **Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management of Acute Attacks**[7] **(2000)**	• Use migraine-specific agents (triptans, DHE, ergotamine) in patients with more severe migraine and in those whose headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen plus caffeine. • 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. • Triptans are effective and relatively safe for the acute treatment of migraine headaches. To date, no evidence supports their use during the aura phase of a migraine attack. • The triptans are an appropriate treatment choice and may be considered for use in patients with moderate-to-severe migraine who have no contraindications for its use. • Because of their inability to take oral medications, patients with nausea and vomiting may be given intranasal or subcutaneous sumatriptan. Use migraine-specific agents (triptans, DHE, ergotamine) in patients with more severe migraine and in those whose headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen plus caffeine.

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[10-17, 91]

Generic Name(s)	Migraine, Acute, with or without Aura	Cluster Headache
Almotriptan	✔	
Eletriptan	✔	
Frovatriptan	✔	
Naratriptan	✔	
Rizatriptan	✔	
Sumatriptan	✔	✔ [a]
Sumatriptan/naproxen	✔	
Zolmitriptan	✔	

[a] Subcutaneous formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters for the selective serotonin agonists are summarized in Table 4.

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

Generic Name(s)	Route of Administration	Onset (hours)	T_{max} (hours)	Bioavailability (%)	Half-Life (hours)	Protein Binding (%)
Almotriptan	Oral	1-2	2.5	70-80	3.5	35
Eletriptan	Oral	1	2	50	4-5	85
Frovatriptan	Oral	2	2-4	24-30	25	15
Naratriptan	Oral	1	2-3	70	5-6	28-31
Rizatriptan	Oral	0.5-2	0.5-2.5	40-50	2-3	14
Sumatriptan	Subcutaneous	0.2-1	0.25	97	2	10-21
	Oral	1-2	2-2.5	15	2	
	Intranasal	1	1-1.75	10	2	
Sumatriptan/ naproxen	Oral	0.5-2	1 / 5	15 / 95	2 / 19	14-21 / 99
Zolmitriptan	Oral	1	2-4	39-48	2.5-3	25
	Intranasal	0.25	3-4	102[†]		

[†]Compared with oral tablet

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[19]

Generic Name	Significance Level	Interaction	Mechanism
Naproxen	1	Warfarin	Risk of hemorrhagic adverse reactions may be increased and gastric erosion. Monitor warfarin levels.

Generic Name	Significance Level	Interaction	Mechanism
Eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	1	Ergot alkaloids (dihydroergotamine, ergotamine)	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.
Naproxen	1	Methotrexate	Naproxen may contribute to reduced renal clearance and increased methotrexate toxicity. Co administration of some NSAIDs with high-dose methotrexate therapy has resulted in death from severe hematologic and GI toxicity. Use combination with caution.
Naproxen	1	Salicylates	Pharmacologic effects of naproxen may be reduced. Risk of GI irritation may be increased. Concomitant administration is not recommended.
Naratriptan, rizatriptan, sumatriptan, zolmitriptan	1	Sibutramine	A "serotonin syndrome," including CNS irritability, motor weakness, shivering, myoclonus, and altered consciousness may occur. The serotonergic effects of these agents may be additive. Monitor the patient for adverse effects if concurrent use cannot be avoided.
Rizatriptan, sumatriptan, zolmitriptan	1	Monoamine oxidase inhibitors (MAOIs) (isocarboxazid, phenelzine, tranylcypromine)	Inhibition of metabolism via MAO, subtype-A. Use of certain 5-HT_1 agonists concomitantly with or within 2 weeks following the discontinuation of an MAOI is contraindicated. If it is necessary to use such agents together, naratriptan appears to be less likely to interact with MAOIs.
All selective serotonin agonists	2	Citalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine	A "serotonin syndrome," including central nervous system (CNS) irritability, motor weakness, shivering, myoclonus, and altered consciousness may occur in some patients. Rapid accumulation of serotonin in the CNS may occur. If co administration of these agents is indicated, start with low dosages and closely monitor the patient.
Almotriptan, eletriptan	2	Azole antifungals/ CYP3A4 inhibitors (e.g., ketoconazole, itraconazole)	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 7 days of itraconazole or ketoconazole.
Naproxen	2	Ace Inhibitors	Naproxen may reduce the antihypertensive effect of ACE inhibitors and may potentiate renal disease states.

Generic Name	Significance Level	Interaction	Mechanism
Naproxen	2	Aminoglycosides	Plasma aminoglycoside levels may be elevated by administration of naproxen. Monitor clinical status.
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.
Rizatriptan	2	Propranolol	Rizatriptan plasma concentrations may be elevated, increasing the pharmacologic and adverse effects. Inhibition of rizatriptan metabolism (MAO, subtype-A) by propranolol is suspected.

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 noted in Table 6. The boxed warning for sumatriptan/naproxen is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Selective Serotonin Agonists[10-17,20-21,91]

Adverse Event(s)	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Sumatriptan/ naproxen	Zolmitriptan
Cardiovascular								
Angina	-	<1	-	-	<1	-	-	<1
Arrhythmia	-	<1	-	-	<1	<1	-	<1
Atrial fibrillation	-	-	-	<1	-	<1	-	<1
Atrial flutter	-	-	-	<1	-	-	<1	-
Bradycardia	-	-	<1	-	<1	-	-	<1
Chest tightness / pain	-	1-4	2	-	5	1-3	3	1-4
Coronary artery vasospasm	<1	-	-	<1	-	-	-	<1
Cyanosis	-	-	-	-	-	-	-	<1
ECG changes	-	-	<1	-	-	<1	-	-
Flushing	-	-	4	-	-	-	<1	-
Heart block	-	-	-	-	-	<1	-	-
Hypertension	<1	<1	-	-	1-10	1	<1	<1
Hypertensive crisis	-	-	-	-	-	-	-	<1
Hypotension	-	-	-	-	-	1	-	-
Myocardial ischemia	<1	-	-	-	<1	<1	-	<1
Myocardial infarction	<1	-	-	<1	<1	-	-	<1
Palpitation	-	>1	1	-	1-10	1	-	1-2
Peripheral vascular disease	-	<1	-	-	-	-	-	-
PR prolongation	-	-	-	<1	-	-	-	-
Premature ventricle contractions	-	-	-	<1	-	-	-	-
Prinzmetal' s angina	-	-	-	-	-	<1	-	-
Pulmonary embolism	-	-	-	-	-	<1	-	-

Adverse Event(s)	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Sumatriptan/ naproxen	Zolmitriptan
QTc prolongation	-	-	-	<1	-	-	-	<1
Syncope	-	-	-	-	-	-	-	<1
Tachycardia	<1	<1	<1	-	<1	-	<1	-
Thrombophlebitis	-	-	-	-	-	<1	-	<1
Thrombosis	-	-	-	-	-	<1	-	-
Vascular disorder	-	-	-	-	-	-	-	<1
Vasodilation	-	-	-	-	-	-	-	<1
Vasospasm	-	<1	-	-	-	-	-	-
Ventricular fibrillation	<1	-	-	<1	-	-	-	-
Ventricular tachycardia	<1	-	-	<1	-	-	-	-
Central Nervous System								
Abnormal coordination	-	-	-	-	-	-	-	<1
Abnormal dreams	-	<1	-	-	-	-	-	<1
Agitation	-	<1	<1	-	-	<1	-	<1
Amnesia	-	-	<1	-	-	1	-	<1
Anxiety	-	-	1	-	-	1	<1	-
Ataxia	-	-	-	-	-	-	-	<1
Back pain	-	>1	<1	-	-	-	-	-
Burning	-	-	-	-	-	1-7	<1	<1
Chills	-	>1	-	-	-	-	-	-
Cerebral ischemia	-	-	-	-	-	<1	-	<1
Cerebrovascular accident	-	-	-	-	-	<1	-	-
Circumoral paresthesia	-	-	-	-	-	-	-	<1
Cold sensation	-	-	-	-	-	1	-	-
Confusion	-	<1	<1	-	-	-	-	<1
Convulsions	-	-	-	-	-	<1	-	<1
Depersonalization	-	<1	<1	-	-	-	-	<1
Depression	-	<1	<1	-	-	-	<1	<1
Disturbance of attention	-	-	-	-	-	-	<1	-
Dizziness	>1	3-7	8	1-10	1-10	1-12	4	3-10
Drowsiness	-	-	-	1-10	1-10	1-3	-	-

Adverse Event(s)	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Sumatriptan/ naproxen	Zolmitriptan
Dysesthesia	-	-	1	-	-	-	-	-
Emotional lability	-	<1	<1	-	-	-	-	-
Euphoria	-	<1	<1	-	-	-	-	<1
Fatigue	-	-	5	1-10	13-30	1	<1	-
Feeling jittery	-	-	-	-	-	-	<1	-
Feeling strange	-	-	-	-	-	2	-	-
Hallucination	-	-	-	<1	-	<1	-	<1
Headache	>1	3-4	4	-	-	1-2	-	1-2
Hearing loss	-	-	-	-	-	1	-	-
Heaviness	-	-	-	-	-	7	-	-
Hot/cold sensation	-	-	3	-	-	-	-	-
Hyperacusis	-	-	<1	-	-	1	-	5
Hyperesthesia	-	<1	<1	-	-	-	-	-
Hyperkinesia	-	<1	-	-	-	-	-	-
Hypertonia	-	>1	<1	-	-	-	-	<1
Hypoesthesia	-	>1	1	-	-	-	-	1-2
Hypotonia	-	-	<1	-	-	-	-	-
Impaired concentration	-	-	<1	-	-	-	-	-
Incoordination	-	<1	-	-	-	-	-	-
Insomnia	-	<1	1	-	-	-	<1	1-2
Irritability							<1	<1
Intracranial pressure increased	-	-	-	-	-	<1	-	-
Lethargy	-	-	-	-	-	-	<1	-
Malaise	-	-	-	2	-	2-3	<1	-
Mental impairment	-	-	-	-	-	-	<1	<1
Nervousness	-	<1	<1	-	-	-	<1	-
Neuropathy	<1	-	-	-	-	-	-	<1
Optic neuropathy	-	-	-	-	-	<1	-	-
Paresthesia	1	3-4	4	1-10		3-14	2	5-10
Pain	-	>1	1	-	-	1-2	-	2-4
Personality disorder	-	-	<1	-	-	-	-	<1
Psychomotor disorders	-	-	-	-	-	<1	-	-
Somnolence	>1	3-7	-	-	-	-	3	4-8

Adverse Event(s)	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Sumatriptan/ naproxen	Zolmitriptan
Stupor	-	<1	-	-	-	-	-	-
Subarachnoid hemorrhage	-	-	-	-	-	<1	-	-
Vertigo	<1	>1	<1	-	-	<2	-	1-2
Warm/cold sensation	-	-	-	-	-	-	-	5-7
Warm/hot sensation	-	-	-	-	-	11	-	-
Weakness	-	4-10	-	-	-	5	-	3-9
Dermatological								
Angioedema	-	-	-	-	<1	-	-	-
Bullous eruption	-	-	<1	-	-	-	-	-
Cheilitis	-	-	<1	-	-	-	-	-
Facial swelling	-	-	-	-	-	-	<1	<1
Flushing	-	-	-	-	1-10	1-7	-	-
Hyperhidrosis	-	-	-	-	-	2	<1	<1
Itching	-	<1	<1	-	<1	<1	<1	<1
Photosensitivity	-	-	-	-	-	<1	-	<1
Rash	<1	<1	-	-	-	<1	<1	<1
Sweating	-	>1	1	-	-	2	-	1-3
Toxic epidermal necrolysis	-	-	-	-	<1	-	-	-
Urticaria	-	-	-	-	-	-	<1	<1
Vasculitis	-	-	-	-	-	<1	-	-
Endocrine and Metabolic								
Edema	-	<1	-	-	-	<1	-	<1
Growth hormone increase (mild)	-	-	-	-	1-10	-	-	-
Hot flashes	-	-	<1	-	1-10	-	-	-
Hypocalcemia	-	-	<1	-	-	-	-	-
Hypoglycemia	-	-	<1	-	-	-	<1	-
Liver function tests abnormal or elevated	-	<1	-	-	-	<1	-	-
Menstrual irregularity	-	-	-	-	-	<1	-	-
TSH levels	-	-	-	-	-	<1	-	-

Adverse Event(s)	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Sumatriptan/ naproxen	Zolmitriptan
increased								
Gastrointestinal								
Abdominal aortic aneurysm	-	-	-	-	-	<1	-	-
Abdominal pain	-	1-2	1	-	1-10	1	≥1	1-2
Bad taste	-	-	-	-	-	13-24	-	-
Colitis	<1	-	-	-	-	<1	-	<1
Constipation	-	<1	<1	-	-	-	<1	<1
Diarrhea	-	<1	1	-	-	<1	<1	<1
Dysgeusia	-	-	-	-	-	-	<1	-
Dehydration	-	-	<1	-	-	-	-	<1
Dysphagia	-	1-2	<1	-	-	1	<1	<2
Dyspepsia	-	1-2	2	-	-	<1	2	1-3
Esophagospasm	-	-	<1	-	-	-	-	-
Eructation	-	-	<1	-	-	-	<1	<1
Gastroesophageal reflex	-	-	<1	-	-	-	<1	<1
Gastrointestinal pain	-	-	-	-	-	<1	<1	<1
Hematemesis	-	-	-	-	-	-	-	<1
Hiccup	-	-	<1	-	-	-	-	-
Hypersalivation	-	-	<1	-	-	-	-	-
Hyposalivation	-	-	3	-	-	-	-	-
Intestinal obstruction	-	-	-	-	-	<1	-	-
Melena	-	-	-	-	-	-	-	<1
Nausea	1-2	4-8	-	1-10	1-10	11-13	3	4-9
Pancreatitis	-	-	-	-	-	-	-	<1
Peptic ulcer disease	-	-	<1	-	-	-	-	<1
Splenic infarction	-	-	-	-	-	-	-	<1
Stomatitis	-	-	-	-	-	-	-	<1
Swallowing disorders	-	-	-	-	-	<1	-	-
Taste alteration	-	<1	<1	-	-	-	-	21
Thirst	-	-	-	-	-	-	-	<1
Tongue edema	-	-	-	-	-	-	-	<1
Vomiting	1-2	-	1	1-10	-	-	<1	1-2

Adverse Event(s)	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Sumatriptan/ naproxen	Zolmitriptan
Xerostomia	1	2-4	-	-	-	<1	2	2-5
Genitourinary								
Acute renal failure	-	-	-	-	-	<1	-	-
Dysuria	-	-	<1	-	-	-	-	-
Gastrointestinal infarction/necrosis	-	-	-	-	-	-	-	<1
Hematuria	-	-	-	-	-	<1	-	-
Impotence	-	<1	-	-	-	-	-	-
Menorrhagia	-	-	-	-	-	-	-	<1
Micturition	-	-	<1	-	-	-	-	-
Nocturia	-	-	<1	-	-	-	-	-
Polyuria	-	<1	<1	-	-	-	-	<1
Hematologic								
Cyanosis	-	-	-	-	-	-	-	<1
Eosinophilia	-	-	-	-	-	-	-	<1
Hemolytic anemia	-	-	-	-	-	<1	-	-
Lymphadenopathy	-	-	-	-	-	-	<1	-
Pancytopenia	-	-	-	-	-	<1	-	-
Purpura	-	-	<1	-	-	-	-	-
Thrombocytopenia	-	-	-	-	-	<1	-	<1
Musculoskeletal								
Abnormal gait	-	-	<1	-	-	-	-	-
Abnormal reflexes	-	-	<1	-	-	-	-	-
Arthralgia	-	-	<1	-	-	-	<1	<1
Arthrosis	-	-	<1	-	-	-	-	-
Akinesia	-	-	-	-	<1	-	-	-
Asthenia	-	-	<1	-	-	-	-	3
Ataxia	-	-	<1	-	-	-	-	-
Bradykinesia	-	-	-	-	<1	-	-	-
CPK increase	-	<1	<1	-	-	-	-	-
Dystonias	-	-	-	-	-	<1	-	-
Involuntary muscle contractions	-	-	<1	-	-	-	-	-
Joint ache	-	-	-	-	-	<1	-	<1
Muscle cramps	-	-	<1	-	-	1	-	-
Muscle stiffness	-	-	-	-	-	<1	-	-
Muscle weakness	-	-	<1	-	-	1	<1	<1

Adverse Event(s)	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Sumatriptan/ naproxen	Zolmitriptan
Myalgia	-	<1	<1	-	<1	1-2	<1	1-2
Myasthenia	-	<1	-	-	-	-	-	<2
Numbness	-	-	-	-	-	1-5	-	-
Rigors	-	-	<1	-	-	-	-	-
Skeletal pain	-	-	3	-	-	-	-	-
Tardive dyskinesia	-	-	-	-	-	-	-	<1
Tremor	-	<1	<1	-	-	-	<1	<1
Tetany	-	-	-	-	-	-	-	<1
Respiratory								
Asthma	-	-	-	-	-	-	<1	-
Bronchitis	-	-	-	-	-	-	-	<1
Bronchospasm	-	-	-	-	-	<1	-	<1
Cough	-	-	-	-	-	-	<1	<1
Dyspnea	-	<1	<1	-	1-10	1	<1	<1
Esophagitis	-	<1	-	-	-	-	-	<1
Hyperventilation	-	-	<1	-	-	-	-	-
Laryngitis	-	-	<1	-	-	-	-	<1
Nasal disorder/ discomfort	-	-	-	-	-	2-4	-	3
Nasal inflammation	-	-	-	-	-	1	-	-
Nose/throat hemorrhage	-	-	-	-	-	1	-	-
Oropharyngeal swelling	-	-	-	-	-	-	<1	-
Pharyngitis	-	>1	<1	-	-	-	-	<1
Pneumonia	-	-	-	-	-	-	-	<1
Rhinitis	-	-	1	-	-	-	-	<1
Sinusitis	-	-	1	-	-	-	-	<1
Throat discomfort	-	-	-	-	-	1-3	-	2
Throat or neck pain/pressure	-	-	-	1-10	<1	-	-	4
Voice alteration	-	-	-	-	-	-	-	<1
Wheezing	-	-	-	-	<1	-	-	-
Other								
Accommodation disorders	-	-	-	-	-	<1	-	-
Allergic reaction	-	<1	-	<1	-	<1	-	1

Adverse Event(s)	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Sumatriptan/ naproxen	Zolmitriptan
Amblyopia	-	-	-	-	-	-	-	<1
Angioneurotic edema	-	-	-	-	-	<1	-	-
Anaphylactoid reaction	-	-	-	-	-	<1	-	<1
Anaphylaxis	-	-	-	-	-	<1	-	<1
Conjunctivitis	-	-	<1	-	-	-	<1	-
Deafness	-	-	-	-	-	<1	-	-
Death	-	-	-	-	-	<1	-	-
Decreased appetite	-	-	-	-	-	<1	-	-
Decreased mental activity	-	-	-	-	<1	-	-	-
Dental pain	-	-	-	-	-	<1	-	-
Dry mouth	-	-	-	-	<5	-	-	-
Earache	-	-	<1	-	-	-	<1	<1
Ear hemorrhage	-	-	-	-	-	1	-	-
Epistaxis	-	-	<1	-	-	-	-	<1
Eye pain	-	-	<1	-	-	-	-	<1
Fever	-	-	<1	-	-	-	<1	<1
Hiccups	-	-	-	-	-	<1	-	-
Lacrimation disorder	-	<1	<1	-	-	-	-	<1
Miscarriage	-	-	-	-	-	-	-	<1
Mouth/tongue discomfort	-	-	-	-	-	5	-	-
Neck/throat/jaw pain/tightness/ pressure	-	-	-	-	-	2-5	3	1-10
Nephrolithiasis	-	-	-	-	-	-	<1	-
Neurological/ psychiatric abnormalities	-	-	-	-	<1	-	-	-
Numbness of tongue	-	-	-	-	-	<1	-	-
Optic neuropathy (ischemic)	-	-	-	-	-	<1	-	-
Peripheral edema	-	-	-	-	-	-	<1	-

Adverse Event(s)	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Sumatriptan/ naproxen	Zolmitriptan
Photophobia	-	<1	-	-	-	-	-	-
Pressure sensation	-	-	-	-	-	1-7	-	-
Raynaud's syndrome	-	-	-	-	-	<1	-	-
Seizure	-	-	-	<1	-	-	-	-
Sensation changes	-	-	-	-	-	<1	-	-
Shock	-	<1	-	-	-	<1	-	-
Speech disorder	-	<1	<1	-	-	-	-	-
Stomatitis	-	-	<1	-	-	-	-	-
Stroke	-	-	-	-	<1	-	-	-
Syncope	<1	-	<1	-	<1	<1	-	<1
Temperature intolerance	-	-	3	-	-	2-11	<1	5-7
Thirst	-	-	<1	-	-	-	<1	-
Thrombophlebitis	-	<1	-	-	-	-	-	-
Tightness feeling	-	-	-	-	-	5	-	-
Tinnitus	-	<1	1	-	<1	-	<1	<1
Tongue edema	-	<1	-	-	-	-	-	-
Vision abnormalities	-	<1	1	-	-	1	<1	-
Vision loss	-	-	-	-	-	<1	-	-

CPK=creatinine phosphokinase, ECG=electrocardiogram, TSH=thyrotropin stimulating hormone

✓ Percent not specified

- Event not reported

Table 7. Boxed Warning for Sumatriptan/Naproxen[91]

Warning
Cardiovascular Risk: Treximet may cause an increased risk of serious cardiovascular thrombotic events, 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 (see WARNINGS: Cardiovascular Effects). Gastrointestinal Risk: Treximet contains a nonsteroidal anti-inflammatory drug (NSAID). NSAID-containing products cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS: Risk of Gastrointestinal Ulceration, Bleeding, and Perforation With Nonsteroidal Anti-inflammatory Drug Therapy).

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[10-17, 91]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Almotriptan	Migraine, with or without aura: Oral: initial, 6.25-12.5 mg, may repeat after 2 hours; maximum 2 doses per 24 hours	Safety and efficacy in children have not been established.	Tablet: 6.25 mg, 12.5 mg
Eletriptan	Migraine, acute treatment: Oral: initial, 20-40 mg, may repeat after 2 hours if headache returns; maximum single dose, 40 mg; maximum daily dose, 80 mg	Safety and efficacy in children have not been established.	Tablet: 20 mg, 40 mg
Frovatriptan	Migraine: Oral: initial, 2.5 mg, may repeat after 2 hours; maximum, 7.5 mg per 24 hours	Safety and efficacy in children have not been established.	Tablet: 2.5 mg
Naratriptan	Migraine, with or without aura, acute treatment: Oral: initial, 1-2.5 mg, may repeat once after 4 hours; maximum, 5 mg per 24 hours	Safety and efficacy in children have not been established.	Tablet: 1 mg, 2.5 mg
Rizatriptan	Migraine, with or without aura, acute treatment: Oral: 5 to 10 mg, may repeat after 2 hours; maximum, 30 mg per 24 hours	Safety and efficacy in children have not been established.	Tablet: 5 mg, 10 mg Oral disintegrating tablet: 5 mg, 10 mg
Sumatriptan	Migraine, with or without aura, acute treatment: Oral: initial, 25-100 mg, repeat after 2 hours if needed; maximum 200 mg per 24 hours Subcutaneous: initial, 6 mg, repeat in 1 hour if needed; maximum 6 mg per dose and 12 mg per 24 hours; lower doses may be used if side effects are dose limiting	Safety and efficacy in children have not been established.	Nasal spray: 5 mg, 20 mg Tablet: 25 mg, 50 mg, 100 mg Subcutaneous injection: 4 mg/0.5 mL, 6 mg/0.5 mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Nasal spray: initial, 5-20 mg, if headache returns may repeat dose once after 2 hours; maximum, 40 mg per 24 hours Cluster headache: Subcutaneous: initial, 6 mg, repeat in 1 hour if needed; maximum 6 mg per dose and 12 mg per 24 hours; lower doses may be used if side effects are dose limiting		
Sumatriptan/ naproxen	Migraine, with or without aura, acute treatment: Oral: one tablet, repeat after 2 hours if needed; maximum 2 tablets per 24 hours	Safety and efficacy in children have not been established	Tablet: 85 mg/500 mg
Zolmitriptan	Migraine, with or without aura, acute treatment: Oral: initial, 2.5 mg (or lower), may repeat after 2 hours; maximum 10 mg per 24 hours Intranasal: initial, 5 mg into one nostril, may repeat after 2 hours; maximum 10 mg per 24 hours	Safety and efficacy in children have not been established.	Nasal spray: 5 mg Tablet: 2.5 mg, 5 mg Oral disintegrating tablet: 2.5 mg, 5 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	Sample Size and Study Duration	End Points	Results
Migraine With or Without Aura				
Cabarrocas et al.[22] (2001) Almotriptan 12.5 mg	OL	N=747 1 year	Primary: Headache response rates at 1 and 2 hours Secondary: Safety and efficacy	Primary: Headache response rates at 1 and 2 hours were 43% and 73%, respectively (*P* value not reported). Secondary: The most common adverse effects were back pain, bronchitis, and flu-like symptoms (*P* value not reported).
Diener et al.[23] (2005) Almotriptan 12.5 mg vs. placebo All patients were poor responders to sumatriptan 50 mg.	RCT, PC, DB, MC Eligible patients were adults aged 18 to 65 years who had suffered from migraine with or without aura for at least 1 year, and had experienced unsatisfactory responses to sumatriptan on at least two occasions	N=328 1 attack	Primary: Relief from headache at 2 hours after dosing Secondary: Pain-free efficacy at 2 hours, and use of rescue medication within 24 hours	Primary: In the almotriptan group, 47.5% of patients achieved pain relief at 2 hours after dosing which was significantly higher percentage than in the placebo group, 23.2% ($P<0.01$). Secondary: A significantly higher number of patients treated with almotriptan 12.5 mg achieved pain-free status at 2 hours than with placebo (33.3% vs. 14.1% $P<0.005$). Rescue medications were required by significantly fewer patients in the almotriptan group than with placebo (26.6% vs. 46.9%; $P<0.005$).
Pascual et al.[24] (2001) Almotriptan 6.25 mg vs. almotriptan 12.5 mg	OL, DB Patients 18-65 years old with at least 1 year history of migraine, with or without aura, all patients experienced 1-6 migraine attacks per month with at least 24 hours of freedom between attacks	N=762 1 year	Primary: The primary measure of tolerability was the incidence of treatment-emergent adverse events (including abnormalities in clinical laboratory tests, electrocardiogram	Primary: During the study, 391 patients receiving active drug (51.3%) experienced at least 1 adverse event (AE). Patients reported at least 1 AE in 11% of attacks treated. The incidence of AEs decreased during the study; 30.7% of patients had at least 1 AE during the first 3 months in the study compared with only 21.5% during the last 3 months. The majority (88.6%) of AEs were of mild-to-moderate intensity. Only 28.8% of AEs were considered to be possibly, probably or definitely related to the study drug. Of these drug-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			[ECG], vital signs or physical examination) Secondary: Percent of attacks resolved (to mild or no pain) by 2 hours after dose (attacks of moderate/severe baseline intensity only)	related events, those which occurred in at least 1% 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 2 hours after the initial dose was achieved in 84.2% of moderate/severe attacks. Patients were pain free at 2 hours after dose in 58.2% of all attacks (*P* values not reported).
Dowson et al.[25] (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 2-24 hours after first dose. Escape medication	RCT, DB, PC, PG, MC, SD Patients 18-65 years old with migraine with or without aura for >1 year	N=668 Single dose	Primary: Relief from migraine pain at 2 hours after dosing Secondary: Relief from migraine pain at 1 hour, pain-free status at 1 and 2 hours, migraine recurrence within 24 hours postdose, need for escape medication	Primary: Pain relief was higher in the treatment groups vs. placebo as follows: almotriptan 12.5 mg=56.8% (achieved pain relief), almotriptan 25 mg=56.5%, sumatriptan 100 mg=63.7%, and placebo=42.2% (*P* values not reported). Both doses of almotriptan were equivalent to sumatriptan 100 mg with the 90% CI interval inside the range of the equivalence region. Secondary: Relief from migraine pain at 1 hour was not statistically different for all three treatment arms. Migraine recurrence within 24 hours postdose 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%, placebo=16.7% (*P* values not reported). Migraine recurrence within 24 hours postdose for patients with severe pain at baseline was reported as follows: almotriptan 12.5 mg=8.8%, almotriptan 25 mg=16.2%, sumatriptan 100 mg=28.9%, placebo=27.3% (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
was allowed if pain persisted beyond 2 hours.				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%, placebo=55.5% (*P* values not reported).
Dahlof et al.[26] (2001) Almotriptan 2 mg vs. almotriptan 6.25 mg vs. almotriptan 12.5 mg vs. almotriptan 25 mg vs. placebo Another dose of study drug was allowed if pain severity increased within 2-24 hours. Escape medication was allowed if pain did not decrease after 2 hours.	RCT, PC, DB, MC, PG Patients 18-65 years old with migraine with or without aura for >1 year, migraines occurring one-six times per month	N=742 Single dose	Primary: Change in headache pain intensity at 2 hours without rescue medication Secondary: Freedom from pain, relief from migraine-associated symptoms	Primary: Almotriptan demonstrated a dose-dependent increase in the number 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. Secondary: With regards to freedom from pain, almotriptan produced a significant dose-dependent increase over placebo at 1, 1.5, and 2 hours (*P*<0.0001). Almotriptan 12.5 mg produced significant improvement compared to placebo at 0.5 hours (*P*<0.0485). Almotriptan demonstrated a significant dose-dependent improvement in pain-free state at 2 hours both with almotriptan 12.5 mg and almotriptan 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. A dose-dependent decrease in the incidence of migraine-associated symptoms was noted for almotriptan. The incidence of migraine recurrence was not significantly different among the treatment groups, ranging from 25.2% to 28.7%.
Dahlof et al.[27] (2006)	Meta-analysis of 4 R, PC, DB, dose comparison studies	N=2294 First attack	Primary: Efficacy, speed of onset and tolerability	Primary: As early as 30 minutes after dosing, almotriptan 12.5 mg was significantly more effective than placebo for pain relief

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Almotriptan 2 mg vs. almotriptan 5 mg vs. almotriptan 6.25 mg vs. almotriptan 12.5 mg vs. almotriptan 25 mg vs. almotriptan 100 mg vs. almotriptan 150 mg vs. placebo	Male and female patients between 18 and 65 years of age who had at least a 6-month history of migraine, and experienced 1 to 6 migraine attacks per month		of almotriptan in the acute treatment of migraine Percentage (proportion) of patients achieving sustained pain free (SPF) with no adverse events (SNAE): the percentage of patients who achieved SPF and did not report any adverse events (AEs) Drug vs. placebo comparisons were made. No drug vs. drug comparisons were made.	(14.9% vs. 8.2%; *P*<0.05) and pain free (2.5% vs. 0.7%; *P* <0.05). At 2 hours, pain-relief rates were 56.0%, 63.7% and 66.0% for almotriptan 6.25, 12.5 and 25 mg, respectively, compared with 35% for placebo; 2-hour pain-free rates were 26.7%, 36.4% and 43.4% compared with 13.9% for placebo. All almotriptan dosages were significantly more effective than placebo in eliminating migraine-associated symptoms (*P*<0.05) and in achieving sustained pain relief up to 24 hours (*P*<0.05). The incidence of adverse events for almotriptan 6.25 mg and 12.5 mg was not significantly different from that of placebo.
Colman et al.[28] (2001) Almotriptan 12.5 mg vs. sumatriptan 50 mg	RCT, DB Patients aged 18-71 years who had not been treated previously with a triptan, suffering with migraine with or without aura for ≥6 months	N= 1,173 48 hours	Primary: Change in treatment satisfaction measure, functional status measure, and Migraine Quality of Life Questionnaire (MqoLQ) values	Primary: There were no significant differences between the 2 treatment groups in terms of satisfaction with pain relief (mean score 50.85 for almotriptan and 52.10 for sumatriptan; *P*=0.67). Functional status was not significantly different. Both groups improved by ~44 points on the 100-point functional status scale after 24 hours. Patients from both groups reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			from baseline to 48 hours	improvement in functional status after treatment, from marginally functional at onset of migraine (mean scores for almotriptan and sumatriptan, 42.54 and 42.50 respectively) to ~90% of normal (mean scores 86.49 and 86.99, respectively) at 24 hours. Similarly, no difference was found between the 2 treatment groups in a comparison of MqoLQ at 24 hours after treatment. Patients in the almotriptan group were significantly more satisfied and experienced fewer side effects than patients receiving sumatriptan (*P*=0.016).
Spierings et al.[29] (2001) Almotriptan 12.5 mg vs. sumatriptan 50 mg	R, DB, PG, MC Men and women between 18 and 65 years who suffered from migraine with or without aura	N=1,255 24 hours	Primary: Headache relief from moderate or severe to mild or no headache and pain-free status at 2 hours Secondary: Migraine relief and freedom from headache pain at 0.5 and 1 hours after intake of study medication, improvement of migraine associated symptoms, incidence of migraine recurrence at 24 hours after dosing, and the use of rescue medication	Primary: Headache relief at 2 hours was observed in 58% of patients in the almotriptan group and 57.3% of patients in the sumatriptan group with no significant difference between the groups. Pain-free response rate at 2 hours was observed in 17.9% of patients in the almotriptan group and 24.6% of patients in the sumatriptan group (*P*=0.005) in favor of sumatriptan. Secondary: There was no significant difference between the groups with regards to relief from migraine-associated symptoms of nausea, vomiting, photophobia, and phonophobia. Rescue medications were taken by 36.7% of almotriptan patients and 33.2% of sumatriptan patients (*P* value not reported). Of the 343 responders in the almotriptan group, 27.4% experienced a migraine recurrence within 24 hours, compared to 24.0% of the 333 responders in the sumatriptan group. The differences were not statistically significant (*P* value not reported).
Olesen et al.[30] (2004)	R, DB, PC	N=123	Primary: Proportion of	Primary: Treatment with eletriptan during the aura phase was not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Eletriptan 80 mg vs. placebo	Male and female patients aged 18 years and older with migraine with aura every 4 weeks	24 hours	subjects not developing a migraine headache of moderate or severe intensity within 6 hours of dosing with a double-blind study drug Secondary: Time to headache development, duration of aura symptoms, use of second dose, response to the second dose, use of rescue medication, treatment acceptability, and time to rescue medication	effective in preventing the onset of moderate-to-severe headache post-aura. There was no significant difference in the proportions of patients developing a headache on eletriptan (61%) compared with placebo (46%) (*P* value not reported). Secondary: Eletriptan did not increase the duration of the aura phase compared with placebo (0.7 hour vs. 0.8 hour), nor was it associated with a significant delay in the median time to headache onset (1.3 hour vs. 1.0 hour) (*P* value not reported). A second dose of eletriptan 40 mg was permitted for patients in both the eletriptan and placebo treatment groups who developed a moderate-to-severe headache. Response rates to the 40-mg dose of eletriptan were similar in both (initial) treatment groups (*P* value not reported). Additional rescue medication was taken by 28% of patients initially randomized to eletriptan 80 mg, and by 17% of patients initially randomized to placebo (*P* value not reported). The percentage of patients rating study medication as acceptable was comparable for both eletriptan and placebo (76% vs. 72%; *P* value not reported). There was no significant difference between groups on any efficacy measure.
Farkkila et al.[31] (2003) Eletriptan 40 mg vs. eletriptan 80 mg	R, DB, OG, PC, MC Male and female subjects age ≥18 years with International Headache Society (NAÏVE) diagnostic criteria for migraine, with or without aura	N=446 3 migraine attacks	Primary: 2-hour headache response rates Secondary: Onset of action, 2-hour pain-free response rates, incidence of nausea,	Primary: 2-hour headache response, based on first-dose, first-attack data, was 59% for eletriptan 40 mg, 70% for eletriptan 80 mg, and 30% for placebo ($P<0.0001$ for both doses of eletriptan vs. placebo; $P<0.05$ for eletriptan 80 mg vs. eletriptan 40 mg). Secondary: Onset of action was rapid, with 1-hour headache response rates significantly higher for eletriptan 40 mg and eletriptan

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. placebo			vomiting and headache recurrence, consistency of response	80 mg vs. placebo (40%, 48%, 15%; *P*<0.0005). Both eletriptan 40 mg and eletriptan 80 mg were significantly better than placebo, based on first-dose, first-attack data, for 2-hour pain-free response (35%, 42%, and 7%; *P*<0.0001). Both eletriptan 40 mg and eletriptan 80 mg demonstrated significant consistency of response, with headache relief rates at 2 hours on at least two of three attacks of 66% and 72%, respectively, vs. 15% on placebo (*P*<0.001).
Garcia-Ramos et al.[32] (2003) Eletriptan 40 mg vs. naratriptan 2.5 mg vs. placebo	R, DB, PG Male or female adults, aged 18–80 years with migraine with or without aura and who reported a minimum of 1 acute migraine attack every 6 weeks	N=548 Single attack	Primary: Headache response at 2 hours after the first dose of study medication Secondary: Headache response at 0.5, 1, 4, and 24 hours; pain-free response at 0.5, 1, 2, 4, and 24 hours; presence or absence of associated symptoms at the same time-points; functional status; headache recurrence and time-to-headache-recurrence; use of rescue medication and time-to-use; sustained headache; sustained pain-free response; global evaluation of medication;	Primary: Headache response rates at 2 hours and 4 hours, respectively, were 56% and 80% for eletriptan, 42% and 67% for naratriptan (*P*<0.01 for both time-points vs. eletriptan), and 31% and 44% for placebo (*P*<0.0001 vs. both active drugs). Secondary: Headache response was also significantly higher for eletriptan at 1 hour and 4 hours, respectively, compared with both naratriptan (34% vs. 25%, *P*<0.05; 80% vs. 67%, *P*<0.01) and placebo (21%, *P*<0.01; 44%, *P*<0.0001). Headache response rates were not significantly different from placebo at 30 minutes for either eletriptan (12% vs. 5%; *P*=0.063) or for naratriptan (9%; *P*=0.391 vs. placebo). Eletriptan showed higher pain-free rates at both 2 and 4 hours (35% and 56%, respectively) compared with both naratriptan (18%; *P*<0.001 and 41%, *P*<0.01) and placebo (19%, *P*<0.001; 24%, *P*<0.0001). By 1 hour, pain-free rates were significantly higher for eletriptan (12%) compared with naratriptan (6%; *P*<0.05). Pain-free response for naratriptan was significantly higher than placebo at 4 hours (*P*<0.01) but not at 2 hours.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			acceptability of study medication	Eletriptan also showed a significantly greater pain-free response at 2 hours (35% vs. 18%; *P*<0.001) as well as lower use of rescue medication (15% vs. 27%; *P*<0.01) and higher sustained headache response at 24 hours (38%) compared with naratriptan (27%; *P*<0.05) and placebo (19%; *P*<0.01). Among patients who achieved a 2-hour headache response, headache recurrence rates were consistently low for eletriptan (29%), naratriptan (26%), and placebo (28%), with no significant differences among the 3 treatment groups. The proportion of patients taking a second dose of study medication for headache recurrence was lower for eletriptan and naratriptan (19% and 18%, respectively) than for placebo (26%). The proportion of patients reporting sustained headache response at 24 hours was significantly higher for eletriptan (38%) compared with both naratriptan (27%; *P*<0.05) and placebo (19%; *P*<0.01). The difference in sustained response was not significant for naratriptan vs. placebo. The proportion of patients reporting a sustained pain-free response at 24 hours was significantly higher for eletriptan (22%) compared with both naratriptan (11%; *P*<0.05) and placebo (12%; *P*<0.05). Patients treated with eletriptan showed significantly better functional improvement at 2 hours compared with both naratriptan (60% vs. 52%; *P*=0.014) and placebo (44%; *P*<0.001). The difference in functional status was not significantly different for naratriptan vs. placebo. Patient ratings of treatment acceptability (recorded at 24 hours for current vs. prior migraine treatments) were significantly higher for eletriptan compared to both naratriptan (68% vs. 50%; *P*<0.001) and placebo (31%; *P* < 0.0001). Naratriptan also showed significantly higher acceptability compared to placebo (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The proportion of patients reporting treatment to be 'good-to excellent' was significantly higher for eletriptan (70%) compared to both naratriptan (53%; *P*<0.001) and placebo (33%; *P*<0.0001). Naratriptan also showed significantly higher global ratings compared to placebo (*P*<0.001).
Sheftell et al.[33] (2003) Eletriptan 20 mg vs. eletriptan 40 mg vs. eletriptan 80 mg vs. placebo	MC, R, DB, PC, PG Men and women over 18 years of age with a history of at least one typical attack of migraine with or without aura every 6 weeks	N=1334 3 migraine attacks	Primary: 2-hour headache response for the first attack Secondary: Incidence of associated symptom relief, and pain-free, sustained pain-free, and consistency of response	Primary: Eletriptan 20 mg, 40 mg, and 80 mg achieved significantly (*P*<0.001) better headache response rates than placebo at 2 hours (47%, 62%, and 59%, respectively, versus 22%) and 4 hours (64%, 76%, and 79%, respectively, versus 25%). Secondary: Two-hour pain-free response rates for eletriptan 20 mg, 40 mg, and 80 mg were 14%, 27%, and 27%, respectively, compared with 4% for placebo (*P*<0.001). Sustained pain-free response rates were significantly better for eletriptan 20 mg (10%), 40 mg (20%), and 80 mg (18%) compared with placebo (3%) (*P*<0.001). Eletriptan had a higher consistency of intra-patient response than placebo in two of three (68% to 82%) and three of three attacks (32% to 60%) versus 16% and 8%, respectively (*P* value not reported). All eletriptan doses yielded significant functional improvement at 2 hours (*P*<0.001).
Diener et al.[34] (2002) Eletriptan 40 mg vs eletriptan 80 mg	MC, DB, R, PC, PG Male or female patients aged 18–65 years, who experienced migraine with or without aura for at least 1 year; frequency of migraine attacks had to be at least 1 every 6 weeks but	N=733 24 hours	Primary: Headache response (improvement from severe or moderate to mild or no pain) at 2 hours Secondary: Headache response at	Primary: Significantly more eletriptan-treated patients (80 mg, 68%; 40 mg, 54%) than Cafergot®-treated patients (33%; *P*< 0.001) reported headache response (improvement from moderate-to-severe to mild or no pain) at 2 hours. Substantially more eletriptan recipients reported no pain (80 mg, 38%; 40 mg, 28%; Cafergot®, 10%; placebo, 5%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. ergotamine tartrate 2mg, caffeine 200 mg (Cafergot®) vs. placebo	not more than 6 per month		1 hour, pain-free rates at 1 and 2 hours, functional hour impairment, functional response, and presence of migraine-associated symptoms or absence of nausea, vomiting, photophobia and phonophobia	Secondary: Eletriptan headache response rates at 1 hour were significantly higher (80 mg, 39%; 40 mg, 29%; Cafergot®, 13%; placebo, 13%; *P*< 0.002 for each comparison). Both doses of eletriptan were significantly more effective than Cafergot® 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 2 hours.
Steiner et al.[35] (2003) Eletriptan 40 mg vs. eletriptan 80 mg vs. zolmitriptan 2.5 mg vs. placebo	R, DB, PC, PG Male or female patients aged 18-65 years with migraine with or without aura	N=1,312 Single migraine attack	Primary: Headache response within 2 hours of taking the first dose of study medication Secondary : Headache-response rates at 0.5, 1 and 1.5 hours, pain-free rates at 0.5, 1, 1.5 and 2 hours, absence of associated symptoms at 0.5, 1, 1.5 and 2 hours, functional recovery at 1 and 2 hours, headache-recurrence rate, use of rescue medication, sustained headache response, sustained pain-free, patient's global evaluation of study medication at 24 hours on a 7-point Likert scale,	Primary: On the primary efficacy end-point of headache response at 2 hours, eletriptan 80 mg (265/360, 74%) was significantly better than zolmitriptan 2.5 mg (224/376, 60%; P<0.0001) and placebo (30/135, 22%; *P*<0.0001). Eletriptan 40 mg was more efficacious than placebo (*P*< 0.0001) at 2 hours (229/359, 64%) and 1 hour (101/361, 28%) but not significantly better than zolmitriptan 2.5 mg at any time point. Eletriptan 80 mg was significantly better (*P*<0.01) than eletriptan 40 mg in headache response at 2 hours. Secondary: On the secondary efficacy endpoint of 1 hour response rates, eletriptan 80 mg (149/369, 40%) was more efficacious than zolmitriptan 2.5 mg (93/371, 25%; *P*<0.0001) and placebo (7/134, 5%; *P*<0.0001). Pain-free rates for eletriptan 80 mg were better at both 2 hours (157/360, 44%) and 1 hour (44/369, 12%) compared to zolmitriptan (99/376, 26%: *P*<0.0001; 21/371, 6%: *P*<0.01) and placebo (8/135, 6%: *P*<0.0001; 1/134, <1.0%: *P*<0.01). Eletriptan 40 mg was significantly better than placebo at 2 hours (115/359, 32%: *P*<0.0001) and 1 hour (21/361, 6%:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			acceptability of study medication	*P*<0.05) but not zolmitriptan 2.5 mg. Eletriptan 80 mg was significantly better (*P*<0.01) than eletriptan 40 mg in headache response and pain-free rates at 2 hours. Eletriptan 80 mg was significantly better (*P*<0.01) than eletriptan 40 mg in pain-free rates at 2 hours. In the subsets with severe or moderate functional impairment at baseline (3 or 2 on the scale 0-3), all active treatments were better than placebo (*P*<0.0001) at bringing improvement. Patients on eletriptan 80 mg (response rates: 194/285, 68% at 2 hours; 100/296, 34% at 1 hour) did better than those on zolmitriptan 2.5 mg (171/303, 56% at 2 hours: *P*<0.05; 73/303, 24% at 1 hour: *P*<0.05). Eletriptan 40 mg (181/296, 61%; 73/300, 24%) was not significantly different from zolmitriptan on this measure. In the subsets of patients achieving headache response by 2 hours, headache-recurrence rates were numerically lower for patients on eletriptan 80 mg (84/253,33%:*P*=0.271) and significantly lower for patients on eletriptan 40 mg (65/225, 29%: *P*<0.05) than for those on zolmitriptan (83/218, 38%). Both doses of eletriptan had significantly lower recurrence rates than placebo (16/31, 52%: *P*<0.05). Significantly fewer patients used rescue medication after eletriptan 80 mg (53/390, 14%) than after zolmitriptan (101/395, 26%: *P*<0.0001) or placebo (81/140, 58%: *P*<0.0001). This was true of those taking eletriptan 40 mg also (76/387, 20%: *P*< 0.05 vs. zolmitriptan; *P*<0.0001 vs. placebo). More patients achieved headache response by 2 hours and continued to 24 hours without recurrence or use of rescue medication (sustained headache response) on eletriptan 80 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(160/338, 47%: *P*<0.001) and 40 mg (151/345, 44%: *P*<0.01) than on zolmitriptan (125/362, 35%). Eletriptan 80 mg (*P*<0.0001) and 40 mg (*P*<0.0001), as well as zolmitriptan (*P*<0.0001), were all significantly better than placebo (14/131, 11%). Sustained-pain-free rate was higher for eletriptan 80 mg (100/343, 29%) than for zolmitriptan (61/367, 17%: *P*<0.001). Eletriptan 80 mg (*P*<0.0001) and 40 mg (75/349, 22%: *P*<0.0001), as well as zolmitriptan (*P*<0.01), were better than placebo (6/134, 5%). Patients' ratings of treatment acceptability ('would use again') showed preferences for eletriptan 80 mg (232/381, 61%: *P*<0.05) and 40 mg (244/379, 64%: *P*<0.01) over zolmitriptan 2.5 mg (205/389, 53%). All active treatments were rated significantly better than placebo (26/137, 19%: *P*<0.0001). On the 7-point global rating of study medication, analysis was of the percentage of patients in each group recording either "excellent" or "good". Eletriptan 80 mg (254/387, 66%) and 40 mg (243/380, 64%) were both rated more highly than zolmitriptan (214/389, 55%: *P*<0.01). All active treatments scored significantly better than placebo (24/139, 17%: *P*< 0.0001).
Goadsby et al.[36] (2000) Eletriptan 20 mg vs. eletriptan 40 mg vs.	R, DB, PG Male and female subjects, 18 years of age and older, who met the International Headache Society (IHS) criteria for migraine with or without aura	N=692 Single migraine attack 24 hours	Primary: Percentage of responders, operationally defined as any patient who, within 2 hours after ingesting study drug, reported improvement in headache intensity to	Primary: Headache response rates 2 hours after dosing were 24% (30/126) for placebo, 55% (63/115) for sumatriptan 100 mg, 54% (70/129) for eletriptan 20 mg, 65% (76/117) for eletriptan 40 mg, and 77% (91/118) for eletriptan 80 mg. There was a difference compared with placebo (*P*<0.001) for all doses of eletriptan. There was a difference between sumatriptan 100 mg, and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
eletriptan 80 mg vs. sumatriptan 100 mg vs. placebo			mild or pain-free levels from a pretreatment level of moderate or severe	eletriptan 80 mg (*P*<0.001) at 2 hours. Headache-free rates at 2 hours were better than placebo (6%; *P*<0.001) for both the 80-mg dose of eletriptan (37%) and the 40-mg dose (29%), with the 80-mg dose of eletriptan also being more efficacious than the 100-mg dose of sumatriptan (23%; *P*<0.05).
Mandema et al.[37] (2005) Eletriptan 20 mg vs. eletriptan 40 mg vs. eletriptan 80 mg vs. sumatriptan 25 mg vs. sumatriptan 50 mg vs. sumatriptan 100 mg vs.	MA, PC For inclusion in the analysis, each trial had to meet the following criteria: (1) randomized double-blind placebo controlled trial; (2) treatment of moderate or severe migraine in adults within 8 hours of onset; (3) measurement of relief from migraine pain on a four point categorical scale of none, mild, moderate, severe; (4) includes efficacy results for the first attack; (5) no re-medication or rescue before 2 hours	N≅11,400 N/A	Primary: Proportion of patients that achieved migraine pain relief up to 4 hours after treatment and proportion of patients that became pain free	Primary: The results of this analysis show a significant difference for eletriptan 40 mg compared to sumatriptan 100 mg at any point in time up to 4 hours after treatment. The benefit of eletriptan 40 mg is greatest around 1.5–2 hours after treatment with an absolute difference at 2 hours of 9.1% (7.4%–11.5%) more patients achieving pain relief and 7.3% (5.8%–8.6%) more patient achieving pain free when compared to sumatriptan 100 mg. An absolute benefit of more than 5% of patients is maintained from 45 minutes up to 4 hours after treatment for pain relief and from 1.5 hours up to 4 hours for pain-free response. 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. The benefit of eletriptan 20 mg when compared to sumatriptan 50 mg is greatest around 1.5–2 hours after treatment with an absolute difference at 2 hours of 5.0% (2.9%–8.1%) more patients achieving pain relief. An absolute benefit of more than 3% of patients was maintained from 1 hour up to 3 hours after treatment. No significant difference was found between eletriptan 20 mg and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sumatriptan 200 mg vs. sumatriptan 300 mg vs. placebo				sumatriptan 50 mg for the fraction of patients that became pain free. No significant effect of encapsulation of sumatriptan was found on the time course of response up to 4 hours after treatment when compared to commercial sumatriptan.
Mathew et al.[38] (2003) Eletriptan 40 mg vs. sumatriptan 100 mg vs. placebo	R, DB, PG, PC Men and women, aged 18 to 65 years, who met the IHS (NAÏVE) criteria for migraine with or without aura	N=2113 24 hours	Primary: The primary endpoint was 2-hour headache response Secondary: Headache response rates at 1 hour, pain-free rates, absence of associated symptoms, functional response at 1 and 2 hours, and sustained headache response	Primary: Headache response rates at 2 hours postdose were significantly higher for eletriptan 40 mg (67%) than for sumatriptan 100 mg (59%; $P<0.001$) and placebo (26%; $P<0.0001$). Secondary: Eletriptan 40 mg consistently showed significantly better ($P<0.01$) efficacy over sumatriptan 100 mg across secondary clinical outcomes, including 1-hour headache response; 2-hour pain-free response; absence of nausea, photophobia, and phonophobia; functional improvement; use of rescue medication; treatment acceptability; and sustained headache response ($P<0.05$).
Schoenen et al.[39] (2005) Eletriptan 80 mg vs. sumatriptan 6 mg SC	R, OL, XO Male and female patients 18–65 years of age that met the IHS criteria for migraine with or without aura, and suffered at least one acute attack every 6 weeks	N=311 3 migraine attacks	Primary: Patient preference for eletriptan versus sumatriptan SC Secondary: Change from pretreatment baseline in headache intensity; change from pretreatment baseline in a 5-point patient-rated Global	Primary: Fifty-one percent of patients preferred or greatly preferred eletriptan, while 43% preferred sumatriptan SC. 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 extension-phase attacks ($P < 0.05$). Secondary: Secondary efficacy measures showed comparable efficacy for each study medication, except for faster headache response

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			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 2 and 24 hours after ingestion of study medication; time to use of rescue medication; sustained relief; acceptability of study medication	and pain-free rates in favor of sumatriptan SC, and a significantly lower recurrence rate on eletriptan (25% vs. 40%; *P*<0.05).
Sandrini et al.[40] (2002) Eletriptan 40 mg vs. eletriptan 80 mg vs. sumatriptan 50 mg vs. sumatriptan 100 mg	MC, DB, DD, PC, PG RCT Men and women >18 years of age who were expected to have at least one attack of migraine with or without aura, every 6 weeks	N=1008 3 attack study	Primary: Early headache response (at 1 hour) was the primary endpoint, 2-hour headache response Secondary: Headache response rates, functional improvement, patient acceptability	Primary: Headache response rates were 12% at 1 hour and 31% at 2 hours for placebo; 24% at 1 hour and 50% at 2 hours for sumatriptan 50 mg; 27% at 1 hour and 53% at 2 hours for sumatriptan 100 mg; 30% at 1 hour and 64% at 2 hours for eletriptan 40 mg; and 37% at 1 hour and 67% at 2 hours for eletriptan 80 mg. More patients receiving eletriptan 80 mg achieved a 1-hour headache response than did patients receiving sumatriptan 50 mg (*P*<0.05). All doses of eletriptan were more efficacious than sumatriptan at 2 hours for headache response and complete pain relief (*P*<0.05). Secondary: Significantly, more patients on eletriptan 80 mg achieved

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				headache response in all attacks than did patients receiving either sumatriptan dose. Eletriptan 40 mg was more efficacious than both sumatriptan doses in functional improvement ($P<0.005$). The higher efficacy of both eletriptan doses was associated with higher rates of patient acceptability than sumatriptan 50 mg ($P<0.05$).
Ryan et al.[41] (2002) Frovatriptan 2.5 mg vs. placebo	MA, PC, DB, PG	N=2,676 24 hours (up to 3 migraine attacks)	Primary: Headache response at 2 hours Secondary: Time to headache recurrence, incidence of patients with 24-hour headache recurrence	Primary: In all three studies, headache response 2 hours after frovatriptan dosing was significantly greater than that seen with placebo ($P\leq0.001$) with approximately a two-fold measure of effect over placebo for headache response at 2 and 4 hours postdosing. Time to headache response occurred within 1.5 hours in a substantial proportion of patients. The incidence of 24-hour headache recurrence with frovatriptan was low (10% to 25%).
Cady et al.[42] (2004) Frovatriptan 2.5 mg early use Dose 1: frovatriptan Dose 2: placebo vs. Frovatriptan 2.5 mg late use Dose 1: placebo Dose 2: frovatriptan	MC, DB, PC, XO Patients had migraine history >1 year with 2 to 8 migraines in the previous 2 months	N=165 2 migraine attacks	Primary: The incidence of no migraine headache 2 hours post dose Secondary: Comparison of early vs. later use of frovatriptan	Primary: Twenty-eight percent and 20% of early frovatriptan users and placebo users, respectively, were headache free at 2 hours ($P=0.04$). Secondary: Fifty percent of early users were pain free at 3 hours. Early use of frovatriptan prevented mild migraine headaches from progressing to moderate or severe headaches (*P* value not reported). Migraine recurrence was low, 4%-6%, regardless of treatment group (*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 with 48% of patients when placebo was used early ($P<0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Stark et al.[43] (2000) Naratriptan 2.5 mg vs. sumatriptan 50 mg vs. placebo	Single blind for attack 1, R, DB, PG, PC for attack 2 Self-described poor sumatriptan responders, had history of migraine >1 year	N=347 2 migraine attacks	Primary: Conversion from moderate or severe pain to mild or no pain at 4 hours after the use of the double-blind test medication for the treatment of attack 2 Secondary: Headache relief at 2 hours and complete pain relief at 4 hours, which include relief of other components of migraine syndrome	Primary: For attack 2, naratriptan was statistically more efficacious than placebo for the relief of headache pain (defined as mild or no pain) at 4 hours (P<0.001). Secondary: Naratriptan was more efficacious than placebo at 2 hours for relief of headache (P=0.005), but statistical significance was not shown for pain-free response (P>0.05).
Klassen et al.[44] (1997) Naratriptan 0.1 mg vs. naratriptan 0.25 mg vs. naratriptan 1 mg vs. naratriptan 2.5 mg vs.	R, DB, PC, PG Men and women 18 to 65 years of age with at least a 1-year history of migraine with or without aura	N=613 Single migraine attack	Primary: Percentage of patients who experienced headache relief (moderate or severe pain at dosing reduced to mild or no pain) 4 hours after the first dose of study medication Secondary: Examined at each measured time point through 4 hours postdose, included the proportions of patients with	Primary: Headache relief 4 hours postdose was reported in 60% of patients receiving naratriptan 2.5 mg compared with 50%, 35%, 32%, and 34% of patients receiving naratriptan 1 mg, 0.25 mg, 0.1 mg, and placebo, respectively (P<0.05 naratriptan 2.5 mg and 1 mg vs. placebo, 1 mg vs. 0.1 mg, and 2.5 mg vs. 0.1 mg and 0.25 mg). Secondary: Clinical disability 4 hours postdose was reported as mild or none for 70% of patients receiving naratriptan 2.5 mg compared with 63%, 47%, 48%, and 48% of patients receiving naratriptan 1 mg, 0.25 mg, 0.1 mg, or placebo, respectively (P<0.05 naratriptan 2.5 mg and 1 mg vs. placebo, 1 mg vs. 0.1 mg, and 2.5 mg vs. 0.1 mg and 0.25 mg). Four-hour efficacy for absence of nausea, photophobia, and phonophobia was similar to efficacy for headache relief at each dose.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			headache relief, proportions of patients with meaningful relief, proportions with headache relief 8, 12, and 24 hours postdose, the proportion taking rescue medication within 24 hours of initial dosing, and the proportion experiencing headache recurrence within 24 hours of initial dosing	The adverse event profile of each dose of naratriptan was similar to that of placebo. No clinically relevant change in any safety measure was reported.
Gobel et al.[45] (2000) Naratriptan 2.5 mg vs. sumatriptan 100 mg	R, DB, CO Men and women 18-65 years old with >1 year history of migraine with or without aura, randomly assigned to treat 1 moderate or severe migraine attack in a nonclinical setting with one naratriptan 2.5 tablet and 1 attack with 1 sumatriptan 100 mg tablet	N=253 24 hours	Primary: Percent of patients with headache recurrence, percent of patients with 24-hour maintenance of headache relief Secondary: Percentage of patients experiencing headache relief, the percent of patients using rescue medication during the 24 hours after dosing, and the percentage of patients that took a second dose of study	Primary: Headache recurrence for naratriptan was 45% and recurrence with sumatriptan was 57% (no significant statistical difference). After 2 attacks, headache recurrence for naratriptan was 41% and for sumatriptan was 57%. The odds ratio for not experiencing recurrence after treatment with naratriptan relative to sumatriptan was 1.97 (*P*=0.005; 95%CI, 1.24-3.15). Twenty-four hour maintenance of headache relief was reported by 39% of patients given naratriptan and 34% of patients treated with sumatriptan (OR=1.26; 95%CI, 0.86-1.85; NS). Secondary: Percentage of patients experiencing headache relief was 76% for patients treated with naratriptan 2.5 mg, and 84% in patients who received sumatriptan 100 mg (not significantly different).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			drug	The percent of patients who received rescue medications for inadequate relief up to 24 hours after dosing did not differ significantly between naratriptan-treated patients (21%) and sumatriptan-treated patients (16%) (OR=1.47; 95% CI, 0.94-2.30). The percent of patients that took a second dose of study drug did differ significantly. Forty percent of patients treated with naratriptan used a second dose of study medication after initial treatment, compared with 57% for sumatriptan (*P*<0.001;OR=0.51; 95% CI, 0.37-0.71).
Ashcroft et al.[46] (2004) Naratriptan 2.5 mg vs. naratriptan 1 mg vs. rizatriptan 10 mg vs. sumatriptan 100 mg vs. placebo	MA Patients suffering from moderate or severe migraine attacks	N= 449 Single migraine attack	Primary: Response rate ratios for headache relief, pain-free response and sustained relief (4-24 hours) Secondary: Adverse events were estimated with the rate ratio (RR), risk difference and number needed to harm	Primary: Pooled RRs relative to placebo for pain-free response at 2 and 4 hours for naratriptan 2.5 mg were 2.52 (95% CI: 1.78-3.57) and 2.58 (1.99-3.35), respectively. Naratriptan 2.5 mg was more effective than naratriptan 1mg; the corresponding RRs for pain-free response at 2 and 4 hours were 1.54 (95% CI: 1.28-1.86) and 1.35 (1.20-1.51), respectively. Naratriptan 2.5 mg was less effective in pain-free response than either rizatriptan 10 mg at 4 hours (RR: 0.68; 95% CI: 0.55-0.85) or sumatriptan 100 mg at 4 hours (RR: 0.79; 95% CI: 0.67-0.93). Secondary: Significantly fewer patients experienced adverse effects with naratriptan 2.5 mg than with rizatriptan 10 mg (RR: 0.73; 95% CI: 0.56-0.97) or sumatriptan 100 mg (RR: 0.68; 95% CI: 0.55-0.86).
Mathew et al.[47] (2004) Rizatriptan 10 mg	R, PC Patients aged 20 to 64 years with migraine and a history of headache progressing to	N=112 3 migraine attacks	Primary: Percentage of migraine attacks in which treatment produced a pain-free	Primary: Pain-free response at 2 hours after early treatment occurred in 151 of 216 attacks (70%) in the rizatriptan group and 24 of 109 attacks (22%) in the placebo group (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. placebo	moderate or severe pain when no intervention was used		response at 2 hours after study drug administration Secondary: Pain-free response at 1 hour after administration, percentage of migraine attacks in which treatment provided a sustained pain-free response lasting between 2 and 24 hours after administration	Secondary: Pain-free response at 1 hour occurred in 97 attacks (45%) in the rizatriptan group, compared with 9 (8%) in the placebo group (*P*<0.01). When the attacks were categorized by headache severity at the time of treatment, the pain-free response at 2 hours was higher for mild attacks than for moderate or severe attacks (*P*<0.01). Sustained pain-free response after treatment was significantly higher for attacks treated with rizatriptan (60%) than for those treated with placebo (17%) (*P* <0.001).
Ferrari et al.[48] (2001) Rizatriptan 5 mg vs. rizatriptan 10 mg vs. placebo	MA of R, DB Outpatients who had at least a 6-month history of migraine	N=4,816 Single migraine attack	Primary: Pain relief, associated migraine symptoms and functional disability (all measured immediately before dosing and at 0.5, 1, 1.5 and 2 hours), headache recurrence	Primary: At 2 hours, rizatriptan 10 mg was significantly more effective than placebo for pain relief (71% vs. 38%, *P*<0.001), and for elimination of pain, nausea, photophobia, phonophobia and functional disability. The benefit was maintained over 24 hours; 37% of patients on rizatriptan 10 mg had sustained pain relief vs. 18% for placebo (*P*<0.001). Rizatriptan 10 mg was also more effective than rizatriptan 5 mg, with a significant difference at 2 hours on all measures except for elimination of nausea. The benefit was maintained over 24 hours; 38% of patients on rizatriptan 10 mg had sustained pain relief vs. 32% for rizatriptan 5 mg (*P*=0.001).
Oldman et al.[49] (2006)	MA	N=2,626	Primary: Headache response at	Primary: Headache response (moderate to severe pain reduced to mild

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rizatriptan 5 mg vs. rizatriptan 10 mg vs. placebo	Men and women in good health aged >18 years with moderate or severe migraine with or without aura	Single dose	2 hours, headache response at 1 hour, pain-free response at 2 hours, sustained relief over 24 hours	or none) at 2 hours were reported as follows: Rizatriptan 5 mg: RB 1.8 (1.6 to 2.0); NNT 3.9 (3.3 to 4.7); n=1646 Rizatriptan 10 mg: RB 2.2 (2.0 to 2.4); NNT 2.7 (2.4 to 2.9); n=2770 Headache response at one hour was reported as follows: Rizatriptan 5 mg: RB 1.6 (1.4 to 1.9); NNT 7.2 (5.4 to 10); n=1646 Rizatriptan 10 mg: RB 1.9 (1.6 to 2.1); NNT 4.9 (4.2 to 6.0); n =2770 Pain-free response (moderate to severe pain reduced to none) at two hours was noted as follows: Rizatriptan 5 mg: RB 3.4 (2.6 to 4.4); NNT 4.7 (4.0 to 5.7); n=1646 Rizatriptan 10 mg: RB 4.8 (3.8 to 5.9); NNT 3.1 (2.9 to 3.4); n=2770 Sustained relief over 24 hours (headache response at 2 hours, sustained for 24 hours with no rescue medication and no second dose of study medication) was noted as follows: Rizatriptan 5 mg: RB 1.5 (1.3 to 1.8); NNT 8.3 (6.0 to 14); n=1450 Rizatriptan 10 mg: RB 1.7 (1.5 to 2.0); NNT 5.6 (4.5 to 7.4); n=1677
Kolodny et al.[50] (2004) Rizatriptan 5 mg vs. rizatriptan 10 mg vs.	R, DB, PC, CO, two-attack study Men and women in good health aged >18 years with at least 6-month history of migraine with or without aura	N=1,447 5 days	Primary: Time to pain relief during the 2 hours after taking study drug Secondary: 2-hour pain relief status and the presence of associated symptoms	Primary: The primary efficacy variable, expressed as the hazard ratio of rizatriptan 10 mg vs. sumatriptan 50 mg, was 1.10 (95% CI 0.96, 1.26; *P*=0.161). Rizatriptan 5 mg was statistically (*P*=0.007) more efficacious than sumatriptan 25 mg; the hazard ratio of rizatriptan 5 mg vs. sumatriptan 25 mg was 1.22 (95% CI 1.06, 1.41). Secondary: Rizatriptan 10 mg-treated patients had significantly less

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sumatriptan 25 mg vs. sumatriptan 50 mg vs. placebo			at 2 hours	nausea (*P*=0.004) compared with those treated with sumatriptan 50 mg. For all other secondary measures at 2-hours, rizatriptan 10 mg was not statistically different than sumatriptan 50 mg.
Lainez et al.[51] (2006) Rizatriptan 10 mg vs. eletriptan 40 mg	MC, OL, XO Patients aged 18–65 years with a history of at least 6 months of migraine, with or without aura	N=372 Single migraine attack	Primary: Patient preference was analyzed for all patients who treated both attacks and who expressed a preference for one medication over the other	Primary: Significantly more ($P \leq 0.001$) patients preferred rizatriptan 10 mg wafer (61.1%; 95% confidence interval [CI] 55.7-66.3) to eletriptan 40-mg tablet (38.9%; 95% CI 33.7-44.3). The most common reason given for preference of either treatment was speed of headache relief. At 2 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; $P \leq 0.001$).
Adelman et al.[52] (2001) Rizatriptan 10 mg vs. naratriptan 2.5 mg vs. zolmitriptan 2.5 mg vs. sumatriptan 25 mg vs.	PC, DB 5 trials Outpatients who had at least a 6-month history of migraine with or without aura	N=4,064 24 hours	Primary: Pain-free response at 2 hours, symptom-free response at 2 hours, 24-hour sustained pain-free response Secondary: Adverse events	Primary: Pain-free rates at 2 hours were significantly higher for rizatriptan than for all other triptans included in the studies. Percent of patients who were pain-free ranged from 38%-45% for rizatriptan 10 mg and 21%-36% for all other triptans. The statistical significance of these differences are noted below. Rizatriptan 10 mg vs. sumatriptan 100 mg (*P*=0.019) Rizatriptan 10 mg vs. sumatriptan 50 mg (*P*=0.009) Rizatriptan 10 mg vs. sumatriptan 25 mg (*P*<0.001) Rizatriptan 10 mg vs. naratriptan 2.5 mg (*P*<0.001) Rizatriptan 10 mg vs. zolmitriptan 2.5 mg (*P*=0.041). Two hours after the dose, significantly more patients taking rizatriptan 10 mg were symptom free than were patients taking other triptans. The percentage of patients with freedom from pain and associated symptoms ranged from 30% to 33% for rizatriptan 10 mg and from 11% to 28% for the other triptans. The statistical significance is noted below. Rizatriptan 10 mg vs. sumatriptan 100 mg (*P*=0.002)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sumatriptan 50 mg vs. sumatriptan 100 mg				Rizatriptan 10 mg vs. sumatriptan 50 mg (*P*=0.003) Rizatriptan 10 mg vs. sumatriptan 25 mg (*P*<0.001) Rizatriptan 10 mg vs. naratriptan 2.5 mg (*P*<0.001) Rizatriptan 10 mg vs. zolmitriptan 2.5 mg (*P*=0.042) More patients taking rizatriptan had a 24-hour sustained pain-free response than did patients taking other triptans. The statistical significance is noted below. Rizatriptan 10 mg vs. sumatriptan 100 mg (*P*=0.112) Rizatriptan 10 mg vs. sumatriptan 50 mg (*P*=0.015) Rizatriptan 10 mg vs. sumatriptan 25 mg (*P*=0.005) Rizatriptan 10 mg vs. naratriptan 2.5 mg (*P*=0.004) Rizatriptan 10 mg vs. zolmitriptan 2.5 mg (*P*=0.013) Secondary: Incidence 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) Rizatriptan 10 mg vs. zolmitriptan 2.5 mg=25% vs. 28% (*P*=0.410).
Bomhof et al.[53] (1999) Rizatriptan 10 mg vs. naratriptan 2.5 mg vs.	R, MC, double-masked, DD, PC Patients aged 18-65 years who met IHS criteria for migraine with or without aura, a 6-month history of migraine and usually experienced 1-8 attacks per month	N=552 Single migraine attack	Primary: Time to headache relief within 2 hours Secondary: Headache relief and pain free up to 2 hours, associated symptoms, functional disability, satisfaction with	Primary: Rizatriptan 10 mg was more effective than naratriptan 2.5 mg on the primary efficacy measure of time to headache relief within 2 hours. HR=1.62 (95% CI, 1.26-2.09, *P*<0.001). Secondary: Headache relief at 2 hours was 68.7% with rizatriptan and 48.4% with naratriptan (*P*<0.001). In patients with migraine associated symptoms at baseline, rizatriptan gave earlier relief than naratriptan from nausea,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			medication at 2 hours, need for additional medication from 2 to 24 hours, 24-hour quality of life, safety	photophobia, and phonophobia within 2 hours, with HR of 1.53 (95% CI, 1.11-2.11, *P*=0.009), 1.57 (95% CI, 1.13-2.19, *P*=0.007), and 1.61 (95% CI, 1.15-2.27, *P*=0.006) respectively. Rizatriptan was better than naratriptan with regard to time to no functional disability, with HR of 1.96 (95% CI, 1.36-2.82, *P*<0.001). Patients on rizatriptan were more satisfied with their medication than those on naratriptan at 2 hour means scores 3.55 vs. 4.21, *P*<0.001. Fewer patients in both active treatment groups needed additional medications than those taking placebo (*P*<0.001), while there was no statistically significant difference between active agents (*P*=0.068). The overall incidence of any clinical adverse event was significantly higher in the rizatriptan group than in the naratriptan and placebo groups (*P*<0.05). Rizatriptan and naratriptan were significantly better than placebo on all five quality-of-life domains (*P*<0.01). Both active treatments were effective compared to placebo. Both active treatments were well tolerated.
Lipton et al.[54] (2001) Rizatriptan 10 mg vs. sumatriptan 100 mg vs.	MA of 5 trials Men and women in good health aged >18 years with history of migraine with or without aura	N=4,097 Single dose	Primary: Relief of nausea in those who had it at baseline and emergence of nausea in those who were free of it at baseline	Primary: Approximately 60% of patients in each treatment group had nausea at baseline. In those patients with nausea at baseline, significantly more patients treated with rizatriptan 10 mg were free of nausea at 2 hours compared with sumatriptan 100 mg (66% versus 58%, *P*=0.043), sumatriptan 50 mg (68% versus 57%, *P*=0.010), sumatriptan 25 mg (68% versus 59%, *P*=0.017), and naratriptan 2.5 mg (59% versus 45%, *P*=0.014).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sumatriptan 50 mg vs. sumatriptan 25 mg vs. naratriptan 2.5 mg vs. zolmitriptan 2.5 mg vs. placebo				Averaging over the four post treatment time points in the first 2 hours, significantly more patients treated with rizatriptan 10 mg were free of nausea compared with sumatriptan 100 mg (*P*=0.004), sumatriptan 50 mg (*P*=0.001), and naratriptan 2.5 mg (*P*=0.015). No significant differences in nausea relief were seen between rizatriptan 10 mg and zolmitriptan 2.5 mg, either at 2 hours (65% versus 61%, *P*=0.210) or over the first 2 hours (*P*=0.781). Rates of treatment-emergent nausea at 2 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.
Cady et al.[55] (1991) Sumatriptan 6 mg SC vs. placebo	R, PC Adult patients with history of migraine with or without aura	N=1,104	Primary: 1-hour headache response rate Secondary: Complete relief of headache, clinical disability, and reduction in other migraine symptoms	Primary: Sumatriptan 6 mg SC produced a response (defined as mild pain or no pain) rate of 70%, compared with 22% for placebo (*P*<0.001) and was more effective than placebo in totally eliminating migraine headache at 60 minutes (49% versus 9%; *P*<0.001). Secondary: Clinical disability improved more with sumatriptan (76%) than with placebo (34%; *P*<0.001). Sumatriptan 6 mg SC was effective in reducing other symptoms such as nausea, vomiting, and photophobia.
SC Sumatriptan International Study Group[56] (1991) Sumatriptan 6 mg SC	R, DB, PG, PC Adult patients with history of migraine with or without aura	N=639	Primary: Severity of headache at 60 minutes and 120 minutes	Primary: After 60 minutes, the severity of headache pain declined in 72% of the 422 patients given 6 mg of sumatriptan, 79% of the 109 patients given 8 mg of sumatriptan, and 25% of the 105 patients who received placebo (3 patients were not evaluable) (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. sumatriptan 8 mg SC vs. placebo				Compared with patients receiving placebo, 47% more patients who received 6 mg of sumatriptan and 54% more patients who received 8 mg of sumatriptan had less severe headaches (*P*<0.001). After 120 minutes, 86% to 92% of the 511 patients receiving sumatriptan felt headache severity improve, compared with 37% of the 104 patients who were given placebo once or twice (*P*<0.001).
Oral Sumatriptan International Multi-Dose Study Group[57] (1991) Sumatriptan 100 mg PO vs. placebo One tablet at onset of headache, one tablet 2 hours later if migraine, and one tablet if the headache came back within 24 hours	PC, DB, PG Adult patients with history of migraine with or without aura	N=233	Primary: Headache relief at 2 and 4 hours Secondary: Pain free at 2 hours, improvement in headache severity at 1 hour postdose, number of patients needing two or three doses	Primary: Sumatriptan was significantly more effective than placebo at 2 hours (50% versus 19%; *P*<0.001) and at 4 hours (75% versus 30%; *P*<0.001). Secondary: In the sumatriptan group, 59% of the patients opted to take a second dose compared with 80% of the placebo arm (*P*<0.001). More patients treated with sumatriptan than with placebo were pain free by 2 hours (26% versus 5%; *P*<0.001) and by 4 hours (48% versus 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).
Cutler et al.[58] (1995) Sumatriptan 25 mg PO vs.	R, DB, PG, PC Adult patients with history of migraine with or without aura	N=259 Single attack study	Primary: Headache relief by 2 hours Secondary: Headache relief by 4 hours	Primary: By 2 hours, 50% to 56% of the patients who had received sumatriptan (any dosage) and 26% of the patients receiving placebo experienced relief (*P*<0.05). Secondary: By 4 hours, 68% to 71% of the patients treated with sumatriptan and 38% of the patients who received placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sumatriptan 50 mg PO vs. sumatriptan 100 mg PO vs. Placebo				experienced relief (*P*<0.05).
Salonen et al.[59] (1994) Sumatriptan 1 mg IN vs. sumatriptan 5 mg IN vs. sumatriptan 10 mg IN vs. sumatriptan 20 mg IN vs. sumatriptan 40 mg IN vs. placebo	Two DB, PC, PG, MC, Adult patients with history of migraine with or without aura	N=245 N=210 Single attack study	Primary: Headache relief at 2 hours	Primary: In both studies, headache severity had significantly improved at 120 minutes after doses of 10-40 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 with 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Study medication was taken as a single dose through one nostril in the first study, and as a divided dose through two nostrils in the second study.				
Winner et al.[60] (2005) Sumatriptan 50 mg PO vs. sumatriptan 100 mg PO vs. placebo	MA of 6 R, DB, PC trials Patients between 18 and 65 years of age, had at least a 1-year history of migraine with or without aura	N=2,297 Single attack study	Primary: Proportion of patients reporting a pain free result 2 hours postdose Secondary: Migraine-free 2 hours postdose, worsening pain 2 hours postdose, sustained pain-free results from 2-24 hours postdose	Primary: A pain-free result 2 hours postdose was reported by significantly more patients who took either dose of sumatriptan tablets compared with placebo and by significantly more patients who took the 100-mg dose compared with the 50-mg dose (50 mg, 49%; 100 mg, 58%; placebo, 24%; *P*<0.001, both sumatriptan doses vs. placebo, and 100 mg vs. 50 mg). Secondary: The proportion of patients who were migraine-free at 2 hours postdose was 42% for sumatriptan 50 mg, 47% for sumatriptan 100 mg, and 20% for placebo (*P*<0.05 for both sumatriptan doses vs. placebo). The proportion of patients reporting worsening of pain 2 hours postdose was 26% for sumatriptan 50 mg, 21% for sumatriptan 100 mg and 46% for placebo (*P*<0.05 for both sumatriptan doses vs. placebo). Sustained pain-free results from 2 through 24 hours postdose were 30% for sumatriptan 50 mg, 35% for sumatriptan 100 mg, and 12% for placebo (*P*<0.05 for both sumatriptan doses vs. placebo).
Gershovich et al.[61] (2006) Sumatriptan to	RETRO Patients aged 18 years and older	N=457 initiated conversion from sumatriptan to rizatriptan ODT; 315 were randomly	Primary: Successful conversion rate, medication preference	Primary: The total number of successful conversions from sumatriptan to rizatriptan ODT (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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
rizatriptan orally disintegrating tablet (ODT)		sampled for a satisfaction questionnaire 180 day medication conversion period; 180 day follow-up period		Among the patients that were successfully converted to rizatriptan ODT and responded to the questionnaire, 68% preferred the rizatriptan ODT compared to the sumatriptan; whereas 8.5% of patients who failed conversion rated rizatriptan ODT as their preferred medication (*P*<0.001). Successfully-converted patients reported faster and more complete headache relief with rizatriptan ODT (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).
Loder et al.[62] (2001) Sumatriptan 50 mg tablet vs. rizatriptan orally disintegrating tablet (ODT) 10 mg Patients treated first migraine with ODT and second with sumatriptan	MC, RCT, OL, XO Patients aged 18 years and older	N=524 7 days	Primary: Patient preference Secondary: Head pain severity, functional disability, headache recurrence	Primary: No preference for either therapy was reported in 10 of 386 patients (2.6%). Of the remaining 374 patients 57% preferred rizatriptan ODT 10 mg and 43% preferred sumatriptan 50 mg tablet (*P*=0.009). Secondary: A significant greater percentage of patients reported pain relief after taking ODT than sumatriptan at 45 and 60 minutes post dose (38% vs. 29% and 58% vs. 49%, respectively; *P*<0.01) A significantly greater percentage of patients taking ODT reported a pain-free status at 60 and 120 minutes post dose (23% vs. 17% [*P*<0.05] and 60% vs. 52% [*P*<0.01), respectively. Significantly more patients reported normal function following treatment with ODT than with sumatriptan 60 minutes (36% vs. 27%, *P*=0.004) and 120 minutes (70% vs. 64%, *P*=0.029) postdose. The overall rate of headache recurrence was similar in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
McCrory et al.[63] (2006) Sumatriptan 100 mg vs. sumatriptan 50 mg vs. sumatriptan 25 mg vs. placebo	MA, PC Adult patients with history of migraine with or without aura	N=16,200 Single attacks	Primary: 2-hour pain-free response, headache relief/headache intensity, and functional disability, headache recurrence, adverse events	Primary: Sixteen trials were placebo comparisons and showed that sumatriptan in doses of 100 mg (14 trials), 50 mg (five trials), and 25 mg (three trials) provided significantly better pain-free response (100 mg and 25 mg only), headache relief, and relief of disability at 2 hours than placebo. Numbers-needed-to-treat (NNTs) for pain-free response at 2 hours were 5.1 (3.9 to 7.1) for the 100-mg dose (n=2,221) and 7.5 (2.7 to 142) for the 25-mg dose (n=131); there was no significant difference between the 50-mg dose and placebo for this outcome (n=127). For headache relief at 2 hours, NNTs were 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 mg (n=2,940), 50 mg (n=420), and 25 mg (n=226), respectively. Adverse events were more common with sumatriptan 100 mg than with placebo (risk difference [RD]=0.14 [0.09 to 0.20]; number-needed-to-harm [NNH]=7.1 [5.0 to 11.1]; n=3172). RDs for the 50- and 25-mg vs. placebo comparisons were not statistically significant.
Cady et al.[64] (2000) Sumatriptan 25 mg PO vs. sumatriptan 50 mg PO vs. sumatriptan 100 mg PO	MA, DB, PC Patients with ≥1 headache which was treated early when pain was mild	N=92 118 headaches Single attack	Primary: Pain-free response 2 and 4 hours after dosing Secondary: Use of a second dose of medication, clinical disability migraine-associated symptoms, meaningful pain relief (patient-defined), time to meaningful relief,	Primary: Pain-free response was higher 2 hours after dosing with sumatriptan 50 mg (51%) or 100 mg (67%; $P<0.05$) compared with placebo (28%), and were higher with early treatment of mild pain compared with treatment of moderate/severe pain at 2 hours (sumatriptan 50 mg: mild pain, 51%; moderate/severe pain, 31%; $P<0.05$; sumatriptan 100 mg: mild pain 67%; moderate/severe pain, 36%) and 4 hours (50 mg: 75% vs. 56%; 100 mg: 90% vs. 6 1%; $P<0.05$). Secondary: Early intervention also resulted in less re-dosing than when moderate/severe pain was treated (50 mg: 21% vs. 32%; 100 mg: 20% vs. 29%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. ergotamine 2 mg plus caffeine 200 mg vs. aspirin 900 mg plus metoclopramide 10 mg vs. placebo			sustained pain-free response, and proportion of attacks in which pain had worsened 2 and 4 hours after dosing, all of which were compared in headaches treated during mild versus moderate/severe pain	More attacks treated early with sumatriptan 50 or 100 mg were associated with normal function 4 hours after dosing compared with placebo (70% and 93% vs. 46%, respectively). Sustained pain-free response rates 2 to 24 hours after early dosing with sumatriptan 50 or 100 mg were also higher (34% and 53%, respectively) compared with treatment of moderate/severe pain (19% and 24%, respectively). Early treatment with sumatriptan 100 mg produced significantly higher pain-free rates at 2 hours after dosing (*P*<0.001) than did ergotamine plus caffeine (69% vs. 34%, respectively) or aspirin plus metoclopramide 73% vs. 25%, respectively).
Geraud et al.[65] (2000) Zolmitriptan 5 mg vs. sumatriptan 100 mg vs. placebo Use of escape medication was permitted 2 hours postdose if symptoms persisted.	R, MC, DB, PC Treatment naïve migraine patients 18-65 years old with established diagnosis of migraine with or without aura for >1 year	N=1,058 24 hours	Primary: Complete headache response rates in acute treatment (defined as a reduction in headache pain from moderate/severe at baseline to mild or no pain 2 hours after taking study drug with no moderate or severe recurrences at 24 hours Secondary: Compare headache responses at 1, 2 and 4 hours postdose	Primary: Complete headache response (2-24 hours) was 39% for zolmitriptan, 38% for sumatriptan and 32% for placebo (no statistical difference). In patients with moderate headache, response was greater with zolmitriptan (48%) than placebo (27%) (*P*=0.01). In patients with moderate headache, there was no significant difference in complete response with zolmitriptan (48%) vs. sumatriptan (40%). In patients with moderate headache, response was not statistically different with zolmitriptan (48%) vs. sumatriptan (40%). For patients with severe baseline headache, there was no significant difference in complete response rates between placebo (44%) and either active treatment (27% for zolmitriptan and 35% sumatriptan). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Active treatment groups were significantly more effective than placebo for 1-, 2-, and 4-hour headache response; (*P*<0.05 vs. placebo).
Diener et al.[66] (2005) Zolmitriptan 2.5 mg orally disintegrating tablet (ODT)	OS Patients aged 9-95 years with migraines	N=14,543 2 years	Primary: Efficacy evaluation	Primary: Headache pain improved in 96% of patients after taking zolmitriptan ODT, 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).
Spierings et al.[67] (2004) Zolmitriptan 5 mg orally disintegrating tablet (ODT) vs. placebo One dose was used to treat migraine headache; if there was inadequate relief or if the headache returned, a second dose was allowed 2-24 hours later	RCT, DB, MC, PG, PC Patients aged 18-65 years with at least 2 migraine headaches per month of moderate to severe intensity in addition to less than 10 days of non-migraine headaches per month for the 3 months prior to enrollment	N=656 6 weeks	Primary: Migraine headache response at 30 minutes Secondary: Speed of onset of headache response, duration of response	Primary: The percentages of zolmitriptan and placebo patients with reduced migraine headache intensity (decreased from "moderate" or "severe" to "mild" or "no pain," as assessed at 30 minutes) were 16.5% (102/620 headaches) and 12.5% (81/647), respectively (*P*=0.048). Secondary: At the 1-hour interval, the difference in the percentages of zolmitriptan and placebo patients with reduced migraine headache intensity (from "moderate" or "severe" to "mild" or "no pain") was statistically significant, with 41.1% (253/615) in the zolmitriptan group and 22.9%(147/642) in the placebo group (*P*<0.0001). This difference was also consistent at the 2-hour mark: 59.0% (347/588) for zolmitriptan and 30.6% (193/631) (*P*<0.0001). A greater number of patients achieved sustained headache response (defined as a response maintained for 24 hours) with zolmitriptan compared to placebo, with rates of 42.5% and 16.4%, respectively (*P*<0.0001). The percentage of patients that returned to normal activities was greater for the zolmitriptan group compared to placebo, with rates of 51.8% and 25.7%, respectively, at the 2-hour mark (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Loder et al.[68] (2005) Zolmitriptan 2.5 mg orally disintegrating tablet (ODT) (studies A and B) or zolmitriptan 5 mg orally disintegrating tablet (ODT) (study C) vs. placebo	3 RCT, DB, PC, MC 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= 470 (study A); 565 (study B); 670 (study C) 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 2 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 2-hour interval was achieved in 40.1% of the zolmitriptan patients and 19.8% of the placebo group ($P<0.001$). At the 24-hour mark, this was maintained in 31.1% of the zolmitriptan patients and 14.6% of placebo patients ($P<0.001$). In study C, the percentage of zolmitriptan 5 mg ODT and placebo patients with reduced migraine headache intensity from “moderate” or “severe” to “mild” or “no pain” at 30 minutes were 16% and 13%, respectively ($P<0.05$). Secondary: In study A, the percentage of zolmitriptan 2.5 mg ODT and placebo patients with reduced migraine headache intensity from “moderate” or “severe” to “mild” or “no pain” at 30 minutes were 16% and 10%, respectively ($P=0.054$). Collective results data from studies A and B showed a greater reduction of headache intensity (excluding mild-intensity attacks) at 30 minutes for the zolmitriptan ODT group compared to placebo (20.1% vs. 12.7%; $P<0.005$). In study A, pain-free status at the 2-hour interval was achieved in 27% of the zolmitriptan 2.5mg 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 2 hours post-treatment in study B in 55.8% of the zolmitriptan ODT-treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 2 hours post-treatment in the zolmitriptan group compared to placebo (51.8% vs. 25.7%; $P<0.0001$).
Dowson et al.[69] (2005) Zolmitriptan 2.5 mg orally disintegrating tablet (ODT) vs. sumatriptan 50 mg tablet or rizatriptan 10 mg ODT or placebo	RCT, PC (vs. placebo); RCT, OL, XO Patients with migraines	N=470 (vs. placebo); N=168 (vs. sumatriptan); N=171 (vs. rizatriptan ODT) 12 weeks (vs. sumatriptan)	Primary: Patient preference	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, there was a greater percentage of patients that preferred the zolmitriptan ODT compared to sumatriptan (60.1% vs. 39.9%; $P=0.013$). Patients also found zolmitriptan ODT to be more efficacious compared to sumatriptan (76.7% vs. 63.4%; $P=0.006$). Patient preference for zolmitriptan ODT was greater than that of rizatriptan ODT (70% vs. 27%; $P<0.001$).
Charlesworth et al.[70] (2003) Zolmitriptan 0.5 mg IN vs. zolmitriptan 1.0 mg IN vs.	DB, DD, MC, PC, PG, RCT Patients aged 18-65 years with migraine with or without aura (defined by IHS), minimum 1-year history of migraine symptoms, with an age of onset of migraine <50 years and an average of 1-6 migraine attacks per month during the 2 months	N=1,547	Primary: 2-hour headache response Secondary: Early headache response at 15, 30, and 45 minutes, headache response at 1 and 4 hours postdose, pain-free rates at 15, 30 and 45	Primary: The 2-hour headache response was reported to be the following: placebo 31% and zolmitriptan IN 70% ($P\leq0.01$), 59% ($P\leq0.01$), 55% ($P\leq0.01$), and 42% ($P\leq0.0008$) for 5.0, 2.5, 1.0, and 0.5 mg, respectively. Zolmitriptan IN 5.0 mg was more effective than zolmitriptan 2.5 mg oral tablet (61%; $P<0.05$). Comparisons of the other doses of zolmitriptan IN to the oral tablet were not statistically significant. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
zolmitriptan 2.5 mg IN vs. zolmitriptan 5.0 mg IN vs. zolmitriptan 2.5 mg oral tablet vs. placebo	preceding the study		minutes and 1, 2 and 4 postdose	The nasal spray at doses of 5.0 and 2.5 mg showed a rapid onset of action, with a significant difference in headache response compared with placebo from 15 minutes through 4 hours after administration. At 15 minutes, early headache response was 5% for placebo, 11% for zolmitriptan 5.0 mg IN (*P*=0.0115), and 8% for zolmitriptan 2.5 mg IN (*P*=0.0261). Zolmitriptan 5.0 mg IN produced a significantly faster headache response than the 2.5 mg oral tablet from 15 minutes through 2 hours. The other nasal spray doses were not statistically different than the 2.5 mg oral tablet. Zolmitriptan IN resulted in pain-free rates that were dose dependent. While all doses ≥1.0 mg produced significant pain-free outcomes from 30 minutes vs. placebo, only the 5.0 mg dose produced pain-free rates significantly better than the 2.5 mg oral tablet.
Dowson et al.[71] (2003) Zolmitriptan 5.0 mg IN	DB, PG, RCT, XO Patients 18-65 years with migraine with or without aura, previous participation in a dose-ranging study, 1-year history of migraine symptoms, with an age of onset of migraine <50 years and an average of 1-6 migraine attacks per month during the 2 months preceding the study	N=1,093 (783 XO) 1 year	Primary: Tolerability (incidence and nature of all serious and non-serious adverse events) Secondary: Efficacy measured at 90-day intervals (2-hour headache response, pain-free response rate)	Primary: Adverse events occurred in 22.1% of attacks treated with zolmitriptan 5.0 mg IN, and the majority were of short duration and mild or moderate intensity. Unusual taste and nasopharyngeal events were reported in 11.0% and 5.5% of attacks, respectively. Only 1.9% of patients withdrew from the 12-month 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 2-hour headache response rates of 73%, 74%, 75% and 74% during the four 90-day periods. Long-term usage of zolmitriptan 5 mg IN was associated with a consistently effective response, with 58% of patients experiencing a 2-hour headache response in over 75% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				attacks. Pain-free response rates were also consistent over each 90-day period (52% to 56%).
Ferrari et al.[72] (2002) Almotriptan 12.5 mg vs. eletriptan 20 mg vs. eletriptan 40 mg vs. eletriptan 80 mg vs. frovatriptan 2.5 mg vs. naratriptan 2.5 mg vs. rizatriptan 5 mg vs. rizatriptan 10 mg	MA of 53 RCT Randomized, double blind, controlled clinical trials which included the treatment of moderate or severe migraine attacks within 8 hours of onset in migraine patients aged 18-65 years, treated with an oral triptan at a recommended clinical dose	N=24,089	Primary: Headache response at 2 hours, pain-free results at 2 hours, sustained pain-free response Secondary: Adverse events	Primary: Headache response results at 2 hours (mean % [95% CI]) for sumatriptan 100 mg are 59 (57.3-60.8). 5-HT_1 agonists with better efficacy than sumatriptan 100 mg are: rizatriptan 10 mg: 68.6 (66.9-70.4) eletriptan 80 mg: 65.8 (63.6-68.3). 5-HT_1 agonists with similar efficacy to sumatriptan 100 mg almotriptan 12.5 mg: 61.2 (57.6-64.8) eletriptan 40 mg: 60.2 (58.0-62.4) zolmitriptan 2.5 mg: 63.5 (60.8-66.2) zolmitriptan 5 mg: 62.8 (60.0-65.6) rizatriptan 5 mg: 62.4 (60.2-64.5). 5-HT_1 agonists with lower efficacy to sumatriptan 100 mg sumatriptan 25 mg: 56.0 (53.1-58.9) naratriptan 2.5 mg: 48.6 (45.7-51.4) eletriptan 20 mg: 48.9 (44.5-53.3) frovatriptan 2.5 mg: 41.5 (39.3-43.8). Pain-free results at 2 hours (mean % [95% CI]) for sumatriptan 100 mg are 28.9 (27.2-30.5). 5-HT_1 agonists with higher rates than sumatriptan 100 mg are: almotriptan 12.5 mg: 61.2 (NA) eletriptan 80 mg: 33.0 (30.5-35.4) rizatriptan 10 mg: 40.1 (38.3-42.0). 5-HT_1 agonists with lower rates than sumatriptan 100 mg are: sumatriptan 25 mg: 23.4 (21.0-25.9) naratriptan 2.5 mg: 22.4 (20.0-24.7)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. sumatriptan 25 mg vs. sumatriptan 50 mg vs. zolmitriptan 2.5 mg vs. zolmitriptan 5 mg vs. sumatriptan 100 mg vs. placebo				eletriptan 20 mg: 16.4 (13.2-19.7). All other triptans did not differ from sumatriptan 100 mg. Sustained pain-free results (mean % [95% CI]) for sumatriptan 100 mg are 20.0 (18.2-21.3). 5-HT_1 agonists with higher rates than sumatriptan 100 mg are: almotriptan 12.5 mg: 25.9 (22.7-29.1) rizatriptan 10 mg: 25.3 (23.7-26.9) eletriptan 80 mg: 25.0 (22.8-27.2). 5-HT_1 agonists with lower rates than sumatriptan 100 mg are: eletriptan 20 mg: 10.6 (7.7-13.5) sumatriptan 25 mg: 16.7 (14.5-18.9) naratriptan 2.5 mg: 15.9 (13.4-18.5). No differences were found with other triptan doses. Secondary: Adverse effects – placebo subtracted adverse effects (mean [95% CI]) for sumatriptan 100 mg: 13.2 (8.6-17.8). 5-HT_1 agonists with lower rates than sumatriptan 100 mg are: almotriptan 12.5 mg: 1.8 (-2.5-6.2) naratriptan 2.5 mg: 2.4 (-2.2-7.0) CNS Adverse effects-placebo subtracted adverse effects (mean [95% CI]) for sumatriptan 100 mg: 6.3 (3.2-9.5). 5-HT_1 agonist with higher CNS adverse effect rates than sumatriptan 100 mg was: eletriptan 80 mg: 14.6 (10.2-19.0) Rates for all other triptans and doses largely overlap. 5-HT_1 agonist with lower CNS adverse effect rates than sumatriptan 100 mg was:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				almotriptan 12.5 mg: -1.5 (-3.9-1.0). Rates for all other triptans and doses largely overlap.
Mathew et al.[81] (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 Acute treatment of 3 migraines	Primary: Pain free with no supplemental pain and/or anti-emetic meds at 2 hours post-dose for the first headache. Secondary: Pain free at 0.5, 1, 4, and 24 hours with no supplemental pain and/or anti-emetic meds Modified pain relief with no supplemental pain and/or anti-emetic meds at 0.5, 1, 2, 4, and 24 hours; Sustained pain free with no recurrence of moderate/severe headache pain over 2 to 24 hours, and with no supplemental pain and/or anti-emetic meds through 24 hours post-dose	Almotriptan group showed significantly greater number of patients achieving 2-hour pain free (37.0% vs 23.9%, *P*=0.010), 2-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 1 hour. At 2 to 4 hours and 4 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 2 hours post-dose (54.4% vs 38.1%, *P*= 0.007) and 4 hours post-dose (74.5% vs 54.3%, *P* <0.001). The percentage of patients experiencing 1 or more treatment-emergent adverse events (AE) was 9.8% for almotriptan and 6.4% for placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Use of rescue medication; level of migraine-associated symptoms of phonophobia, photophobia, nausea at baseline and at 0.5, 1, 2, 4, and 24 hours; Level of functional disability, ranging from performance of normal activity to requiring ED visit or hospitalization.	
Goadsby et al.[82] (2007) Almotriptan12.5 mg vs. zolmitriptan 2.5 mg	DB, MC, PG, RCT Patients aged 18–65 years with at least a 12-month history of migraine with onset before age 50, and 2-6 migraine attacks per month in the 2 months preceding the trial.	N=1062 Single dose	Primary: sustained pain free plus no adverse events (SNAE) - the proportion of patients having no pain 2 hours post-dose and no recurrence, use of rescue meds or AE 2-24 hours post-dose Secondary: Pain relief and pain free at several time points; sustained pain free, Headache recurrence and use of rescue	Primary: No significant difference was seen in SNAE (almotriptan 29.2% vs zolmitriptan 31.8%) Secondary: Incidence of triptan-associated AE and triptan-associated central nervous system AE was significantly lower for patients receiving almotriptan compared to zolmitriptan. (X^2= 4.8, P = 0.03) No significant differences indicated among other efficacy endpoints measured.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			medication Functional impairment; time lost due to migraine, Treatment acceptability and overall satisfaction.	
Winner et al.[83] (2007) Eletriptan 40 mg vs. placebo	DB,MC, PC, PG, RCT Patients 12 to 17 years of age with history of migraine at least every 6 weeks with mean duration of 4 hours minimum	N=267 Single dose	Primary: 2-hour headache response - change from moderate/severe pain to mild/no pain 2 hours post-dose Secondary: Headache response at 1-hour post-dose Absence of headache pain at 1 and 2 hours Absence of nausea, photophobia or phonophobia) Change in functional impairment 2 hours post-dose, measured on a 4-point scale Time to use of rescue meds	Primary: No significant difference in 2-hour headache response for eletriptan 40 mg vs. placebo (57% vs 57%) Secondary: No significant improvements were observed for any of the outcomes at 1 or 2 hours post-dose. 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 statistically 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Headache recurrence/time to headache recurrence 2-24 hours post-dose Sustained headache response/ pain-free response within 2 hours post-dose, without recurrence or use of rescue meds within 24 hours following the first dose of study med were analyzed post hoc.	
Cady et al.[85] (2006) Rizatriptan 10 mg vs. placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with at least a 6-month history of 1-4 migraine attacks per month that were typically mild at onset	N=1030 in 2 parallel studies (TAME1 and TAME2) Single dose	Primary: Pain freedom at 2 hours post-dose Secondary: Sustained pain freedom at 24 hours post-dose	Primary/Secondary: TAME1: 57.3% vs. 31.1% of patients reported pain freedom at 2 hours post-dose and 42.6% vs. 23.2% reported 24-hour sustained pain freedom with rizatriptan vs. placebo, respectively. (P <0.001 for both). TAME2: 58.9% vs. 31.1% of patients reported pain freedom at 2 hours post-dose and 48.0% vs.24.6% reported 24-hour sustained pain freedom with rizatriptan vs. placebo, respectively (P <0.001 for both).
Winner et al.[87] (2006) Sumatriptan 6mg SC vs. placebo	DB,PC,PG, RCT Patients 18 to 65 years of age with history of migraine with moderate or severe pain on awakening	N=584 in 2 parallel groups Single dose	Primary: Pain free at 2 hours post-dose Secondary: Onset of efficacy and mean time to efficacy	Primary: Sumatriptan groups reported 48% and 57% pain free at 2 hours post-dose vs. 18% and 19% for placebo groups (both P < 0.001). Secondary: Onset of efficacy vs. control (first time point with statistical significance of pain relief) was observed beginning 10

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				minutes post-dose ($P < 0.05$ sumatriptan injection vs. placebo across pooled studies). Mean time to efficacy in the sumatriptan group was 10 minutes ($P < 0.05$ vs controls).
Smith et al.[94] (2005) Sumatriptan/naproxen sodium 50 mg/500 mg vs. sumatriptan 50 mg vs. naproxen sodium 500mg vs. placebo	DB, PC, MC, RCT Patients ≥ 18 years of age with history of migraine	N=972 in 2 parallel groups Single dose	Primary: 24-hour pain relief response Secondary: 2-hour headache response;2-hour pain free; sustained pain free (2-24 hours); incidence of photophobia nausea at 2 hours; adverse events	Primary: 46% of sumatriptan/ naproxen sodium group, achieved 24-hour pain relief response, significantly more than sumatriptan alone (29%), naproxen sodium alone (25%), or placebo (17%) ($P < 0.001$). Secondary: Two-hour headache response significantly favored sumatriptan/naproxen sodium 500 mg therapy (65%) vs. sumatriptan (49%), naproxen sodium (46%), or placebo (27%) ($P < 0.001$). A similar pattern of between-group differences was observed for 2-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 sodium group (29%) vs. sumatriptan alone (41%; $P = 0.048$), vs. naproxen sodium alone (47%; $P= 0.0035$), and versus placebo (38%; $P= 0.08$). Incidences of photophobia, phonophobia or nausea were significantly lower at 2 hours following sumatriptan/ naproxen sodium 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.
Smith et al.[89] (2007) Sumatriptan/naproxen	OL, MC Patients 18 to 65 years of age who had experienced	N=565 12 months	Primary: Pain measures: Pain severity, as recorded on 4-point	Primary: 70% of the 24,485 moderate or severe migraine attacks were treated with a single dose of study drug, and 98% of these attacks did not require any rescue meds.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sodium 85 mg/500 mg taken at onset of migraine and repeated after at least 2 hours from initial dose if response was unsatisfactory or incomplete	first migraine prior to age 50, with average migraine frequency of 2 to 8 moderate or severe attacks per month in the previous 6 months		scale, at baseline, 2 hours post-dose and just prior to any rescue meds Pain relief, defined as mild or no pain at 2 hours, without rescue or a second dose Satisfaction, determined using Patient Perception of Migraine Questionnaire (PPMQ) Health-Related Quality of Life (HRQOL), measured using Migraine-Specific Quality of Life Questionnaire (MSQ)	30% of the total were treated with a second dose of study drug; 93% of these attacks did not require use of additional rescue meds. Overall, only 3% of all attacks required additional rescue meds. Pain relief at 2 hours was reported for 81% of attacks, and 60% of attacks were pain-free at 2 hours post-dose. After 3 months of therapy, the percentage of patients satisfied/very satisfied increased from 52% at screening to 90% at 3 months on 7 of 8 PPMQ items and remained high (86%) through the 12 months of the study. The 3-month and 12- month ratings were significantly higher than at screening ($P < 0.001$). Mean MSQ domain scores increased by 13 - 15 points following 3 months therapy, exceeding a clinically relevant improvement on each of the 3 domains in the questionnaire; these improvements were maintained through the 12 months of the study. Both 3 and 12 month scores were significantly improved from screening scores ($P < 0.001$).
Silberstein et al.[90] (2008) Sumatriptan/naproxen sodium 85 mg/500 mg vs. placebo	DB, PC, PG, RCT Patients 18 to 65 years of age, with 6-month history of migraine and 2 - 6 migraine attacks per month in the 3 months prior to screening.	N=1111 in 2 parallel groups Single dose	Primary: Pain free at 2 hours post-dose Secondary: Percentage pain-free at 0.5, 1, and 4 hours post-dose; percentage of patients with	Primary: 52% of patients in Study 1 and 51% in Study 2 were pain free at 2 hours post-dose, vs. 17% and 15% in placebo groups, respectively ($P<0.001$) Secondary: Significant differences in pain-free response rates in favor of sumatriptan/naproxen were observed as early as 30 minutes after dosing and were maintained at 1, 2, and 4 hours across studies.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			sustained pain-free response from 2 to 24 hours post-dose; percentage with migraine-free response at 2 and 4 hours post-dose; percentage of patients using rescue meds within 24 hours post-dose; percentage of patients with migraine-associated symptoms at 2 and 4 hours post-dose; percentage of patients with neck pain or discomfort and sinus pain or pressure at 2 and 4 hours post-dose	In both studies, significantly more patients experienced a sustained pain-free response 2 to 24 hours after dosing with sumatriptan/naproxen (Study 1: 45%; Study 2: 40%) compared with placebo (Study 1: 12%; Study 2: 14%). Incidence of nausea, photophobia, and phonophobia at 2 and 4 hours was significantly lower after treatment with sumatriptan/naproxen compared with placebo in both studies. There were no significant differences in incidence of vomiting at 2 and 4 hours. Significantly fewer patients treated with sumatriptan/naproxen used rescue medication within 24 hours vs. placebo-treated patients in both studies ($P < 0.001$). Significantly more patients treated with sumatriptan/naproxen (Study 1: 45%; Study 2: 46%) were migraine-free at 2 hours vs. placebo groups (Study 1: 15%; Study 2: 14%). Similar results were observed for migraine-free at 4 hours (sumatriptan/naproxen, Study 1: 63%; Study 2: 64%; placebo, Study 1: 24%; Study 2: 25%; $P < 0.05$). The incidence of neck pain/discomfort and sinus pain/pressure at 2 and 4 hours were also significantly lower after treatment with sumatriptan/naproxen vs. placebo in both studies.
Brandes et al.[92] (2007) Sumatriptan/naproxen sodium 85 mg/500 mg vs. sumatriptan 85mg	DB, MC, PC, PG, RCT Patients between 18 and 65 years of age, with a ≥ 6-month history of migraine and 2 to 6 moderate or severe migraine episodes monthly during the 3 months preceding the screening visit	N=2956 in 2 parallel groups Single dose	Primary: Percentages of patients pain free 0.5, 1, 1.5 and 2 hours post-dose; absence of photophobia, phonophobia or nausea 2 hours post-dose; percentage of patients with sustained pain-free	Primary: Sumatriptan/naproxen sodium was more effective than placebo for headache relief at 2 hours post-dose (study 1, 65% vs 28%; $P<0.001$ and study 2, 57% vs 29%; $P<0.001$); absence of photophobia at 2 hours (58% vs 26%; $P<0.001$ and 50% vs 32%; $P<0.001$); absence of phonophobia at 2 hours (61% vs 38%; $P<0.001$ and 56% vs 34%; $P<0.001$). Absence of nausea 2 hours post-dose was higher with sumatriptan/naproxen sodium than placebo in study 1 (71% vs 65%; $P = 0.007$), but in study 2 rates of absence of nausea did

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. naproxen sodium 500 mg vs. placebo			response from 2 to 24 hours post-dose; Secondary: Use of rescue medication thru 24 hours post-dose; headache recurrence within 24 hours of dosing among patients with headache relief 2 hours post-dose; incidence of vomiting thru 24 hours post-dose; clinical safety	not differ between sumatriptan/naproxen sodium and placebo (65% vs 64%; *P* = 0.71). For 2- to 24-hour sustained pain-free response, sumatriptan/naproxen sodium was more effective (25% and 23% in studies 1 and 2, respectively; *P*<0.01) than sumatriptan monotherapy (16% and 14% in studies 1 and 2, respectively), naproxen sodium monotherapy (10% and 10% in studies 1 and 2, respectively), and placebo (8% and 7% in studies 1 and 2, respectively). Secondary: Incidence of pain-free response 2 hours post-dose with sumatriptan/naproxen sodium was 34% in study 1 and 30% in study 2 compared with 9% and 10% in the respective placebo groups (*P*<0.001). In both studies, sumatriptan/naproxen sodium was significantly more effective than placebo for all measures of sustained efficacy, including sustained headache relief (*P*<0.001), sustained freedom from nausea, photophobia and phonophobia (all *P*<0.001), and the occurrence of any vomiting through 24 hours after dosing (*P*<0.005). Fewer patients treated with sumatriptan/naproxen sodium vs. placebo used rescue medication or had headache recurrence in either study. Sumatriptan/naproxen sodium was more effective than sumatriptan monotherapy for sustained headache relief, sustained freedom from photophobia and phonophobia, and use of rescue medication in both studies and, in study 1, for sustained freedom from nausea. Percentages of patients with at least 1 adverse event in study 1 were 27%, 24%, 13%, and 12% in patients treated with sumatriptan/naproxen sodium, sumatriptan monotherapy,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				naproxen monotherapy, and placebo, respectively. The corresponding values for study 2 were 26%, 28%, 14%, and 10%.
Landy et al.[93] (2007) Sumatriptan/naproxen sodium 85 mg/500 mg vs. sumatriptan 85mg vs. naproxen sodium 500mg vs. placebo	DB,MC, PC, PG, RCT Patients 18 to 65 years of age, with 6-month history of migraine, first migraine before age 50 and 2 - 6 migraine attacks per month in the 3 months prior to screening	N=3512 in 2 parallel groups Single dose	Primary: Ability to function; productivity-related impairment; patient satisfaction	Primary: Significantly more patients in the sumatriptan/naproxen sodium group reported no impairment vs. naproxen and placebo groups. Median time to first report of normal function in Study 1 was 4 hours for the sumatriptan/naproxen sodium group compared with 4, 7, 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 sodium group compared with 5, 5, 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 sodium 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 with the naproxen group (5.6 and 5.4 hours; P=0.016) for studies 1 and 2, respectively. In Study 2, the sumatriptan/naproxen sodium group was 20% lower compared with the sumatriptan group (5.6 hours; P = 0.002). For workplace productivity, the sumatriptan/naproxen sodium group reported a mean of 3.2 hours of lost work productivity compared with 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 sodium group reported losing 3.7 hours compared with 5.4 hours reported by the placebo group (P < 0.001) in Study 1, and a loss of 3.6 hours compared with 4.7 for the placebo group (P =0.005) in Study 2.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Menstrual Migraine				
Allais et al.[73] (2006) Almotriptan 12.5 mg vs. zolmitriptan 2.5 mg	Retrospective analysis of MC, R, DB, PC Patients with 12-month history of migraine and 2-6 migraine attacks in each of the two moths preceding the trial	N=255 24 hours	Primary: Pain relief (from severe or moderate to mild or no pain) at 0.5, 1, 1.5, and 2 hours; pain free at 0.5, 1,1.5 and 2 hours; sustained pain free 2 hours with no recurrence and no rescue medication over 24 hours); recurrence within 24 hours of treatment; and level of functional impairment before intake and after 0.5, 1, 1.5, and 2 hours Secondary: Tolerability defined as the number of patients reporting adverse events within 24 hours after dosing	Primary: In the intent-to-treat group, almotriptan did not differ significantly from zolmitriptan for any of the variables tested. Two hours after dosing, 67.9% of the 136 women who took almotriptan and 68.6% of the women who took zolmitriptan (*P*=0.900) had obtained pain relief. Evolution of pain from “moderate/severe” to “mild/no pain” was also similar in both groups, 14.9% of almotriptan-treated women vs. 11.9% of zolmitriptan-treated women had improved at 0.5 hours (*P*=0.477). A pain-free state at 2 hours was reported by 44.9% of women on almotriptan and 41.2% on zolmitriptan (*P*=0.554); 24 hours after dosing 56.6% and 64.7% of patients, respectively, were pain free (*P*=0.187). Recurrences 2-24 hours postdose were reported in 32.8% and 34.7% of patients respectively (*P*=0.833). Use of rescue medication 2-24 hours after dose was reported by 21.8% of almotriptan and 25.4% of zolmitriptan (*P*=0.499). A sustained pain-free response was reported by 29.3% of almotriptan patients and 27.1% of zolmitriptan patients (*P* =0.698). Secondary: Adverse effects in the 24 hours postdosing were reported in 19.8% of almotriptan group and 23.1% of zolmitritpan group;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				13.2% and 17.6% (*P*=0.328) respectively, were considered to be triptan-related.
Silberstein et al.[74] (2004) Frovatriptan 2.5 mg daily vs. frovatriptan 2.5 mg twice daily vs. placebo	PC, MC, DB, XO Women migraineurs aged >18 years, >1-year history of migraine, and an attack frequency of at least 3 to 4 (perimenstrual period)	N= 443 3 perimenstrual periods	Primary: Efficacy of frovatriptan in menstrual migraine given for 6 days (2 days before menses) in comparison with placebo	Primary: The incidence of menstrual migraine was 67% (n=468) in the placebo treated group compared with 52% (n=484; *P* <0.0001) and 41% (n=483; *P*<0.0001) in the frovatriptan 2.5 daily and twice daily groups, respectively. Significant reductions in headache severity were observed in frovatriptan-treated patients (*P*<0.0001). Frovatriptan administered twice daily was more efficacious than once-daily administration (*P*<0.0001).
Mannix et al.[84] (2007) Naratriptan 1mg BID vs. placebo BID, beginning 3 days before the predicted onset of MRM for a total of 6 days for 4 PMPs/ 6 months, whichever sooner	DB,MC, PC, PG, RCT Female patients ≥ 18 years of age with at least a 1-year history of migraine, a reported history of MRM (defined as a migraine attack starting from 2 days before thru 4 days after onset of menstrual flow), regular and predictable menstrual cycles and at least 1 MRM during the last menstrual cycle before the screening visit	N=633 total in 2 identical studies 4-6 months	Primary: Mean percentage of treated PMP with MRM per patient. Secondary: Percentage of patients who were free of MRM during all treated PMPs Median number of days with MRM over 4 PMPs, and Patient satisfaction Safety and tolerability measures, including AE,	Primary: Mean percentage of PMPs without MRM per patient was 38% and 34% in naratriptan groups, significantly higher than 29% and 24% in placebo groups (*P* < 0.05 naratriptan vs placebo for both studies). More patients in naratriptan groups reported attacks post-treatment compared to patients in placebo groups. Secondary: Among patients treating at least 1 PMP, the percentage of patients with no MRM in any treated PMP was significantly (*P*=0.006) higher in the naratriptan group than the placebo group in study 2 only. Number of MRM days per patient across 4 PMPs was significantly lower in naratriptan group than in placebo group in both studies (median 5.0 days vs. 6.5 days in study 1 [*P*=0.005] and 5.3 days vs 6.0 days in study 2 [*P* = 0.018]). At visit 5, significantly more naratriptan- treated patients reported greater overall

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			standard clinical laboratory tests, and vital signs.	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.[86] (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 MRM, regular and predictable menstrual cycles and at least 1 MRM during 2 of 3 previous menstrual cycles before the screening visit	N=707 in 2 parallel studies (MM1=357; MM2=350) Single dose	Primary: Pain freedom at 2 hours post-dose Secondary: Sustained pain freedom at 24 hours post-dose	Primary/Secondary: MM1: 70% vs. 53% of patients reported pain freedom at 2 hours post-dose (*P* =0.001) and 46% vs. 33% reported 24-hour sustained pain freedom (*P*=0.016) with rizatriptan vs. placebo, respectively. MM2: 73% vs. 50% of patients reported pain freedom at 2 hours post-dose (*P* <0.001) and 46.0% vs.33% reported 24-hour sustained pain freedom (*P* = 0.024) with rizatriptan vs. placebo, respectively.
Cluster Headache				
Siow et al.[75] (2004) Frovatriptan 2.5-5.0 mg daily for up to 3 weeks	OL Median age=43 Cluster headache history 1-38 years	N=17 3 weeks	Primary: Headache occurrence in patients with episodic and chronic cluster headaches for preventative and transitional therapy	Primary: 8 of 9 patients with episodic cluster headache reported at least 75% improvement, with 100% relief within 48 hours of treatment. 3 of 8 patients with chronic cluster headaches had complete relief.
Gobel et al.[76] (1998) Sumatriptan SC 6 mg	MC, OL Patients 18-65 years of age with a diagnosis of cluster headache or episodic cluster headache	N=52 1 year	Primary: Efficacy of therapy defined by freedom from pain within 15 minutes in more than 90% of attacks Secondary:	Primary: Therapy was successful in 88% of all attacks (*P* value not reported). Freedom from pain within 15 minutes in more than 90% of attacks was reported by 42% of patients (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Tolerability defined by adverse effects reported by patients	Secondary: Adverse events were reported by 62% of patients (*P* value not reported).
Ekbom et al.[77] (1993) Sumatriptan 6 mg SC vs. sumatriptan 12 mg SC vs. placebo	MC, DB, PC, R, XO Patients 18-65 years with a diagnosis of cluster headache or episodic cluster headache	N=134 Single dose study	Primary: Headache improvement to mild or no pain at 5, 10 and 15 minutes	Primary: At 10 minutes, headache relief was reported by 25% (placebo), 49% (6 mg), and 63% (12 mg) of patients. At 15 minutes headache relief was reported by 35% (placebo), 75% (6 mg), and 80% (12 mg). *P*<0.001 for all comparisons vs. placebo. *P* was not significant for 6 mg vs. 12 mg.
Rapoport et al.[88] (2007) Zolmitriptan 5mg intranasally vs. zolmitriptan 10mg intranasally vs. placebo	DB, MC, RCT, XO (three-period) 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 with 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.
Cardiovascular Safety				
Elkind et al.[78]	RC, DB, PC, PG, MC	N=75	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2004) Frovatriptan 2.5 mg daily vs. placebo	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 1-6 moderate or severe migraines per month	Single migraine attack (follow-up at 36 hours)	Cardiovascular effects assessed by a 24-hour Holter monitor in patients administered frovatriptan 2.5 mg for the acute relief of migraine headache	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.
Fleishaker et al.[79] (2002) Almotriptan 12.5 mg vs. almotriptan 25 mg vs. placebo	R, DB, SD, 3-way, XO Patients with mild-to-moderate hypertension controlled by medications	N=20 Single dose	Primary: Assess cardiovascular effects of almotriptan in patients with mild-to-moderate hypertension controlled by antihypertensive medication Secondary: Plasma concentrations and cardiovascular effects	Primary: Almotriptan produced a dose-related change in systolic blood pressure (SBP) for both 4 and 12 hours postdose. Mean changes from baseline from 0-4 hours were 1.59 ± 3.88, 1.85 ± 5.94, and 4.84 ± 5.99 mm Hg for SBP and 1.38 ± 6.95, 6.25 ± 9.54, and 11.0 ± 10.6 mm Hg for diastolic blood pressure (DBP) 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: QD=once daily, BID=twice daily, IN=intranasal, SC=subcutaneous PO=oral, PRN=as needed,
Study abbreviations: CI=confidence interval, CS=comparative study, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, XO=crossover, NNT=numbers needed to treat
Miscellaneous abbreviations: AE = adverse effects, CAD=coronary artery disease, MRM=menstrually-related migraine, PMP=perimenstrual period, RB=relative benefit

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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
Almotriptan	tablet	Axert®	$$$$-$$$$$	N/A
Eletriptan	tablet	Relpax®	$$$$-$$$$$	N/A
Frovatriptan	tablet	Frova®	$$$$$	N/A
Naratriptan	tablet	Amerge®	$$$$-$$$$$	N/A
Rizatriptan	tablet, orally disintegrating tablet	Maxalt®, Maxalt MLT®	$$$-$$$$$	N/A
Sumatriptan	tablet, nasal spray, subcutaneous injection	Imitrex®*	$$$$-$$$$$	$$$$$
Sumatriptan/ naproxen	tablet	Treximet®	$$$$	N/A
Zolmitriptan	tablet, orally disintegrating tablet, nasal spray	Zomig®, Zomig ZMT®	$$$$-$$$$$	N/A

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

X. Conclusions

The selective serotonin agonists are indicated for the treatment of acute migraines with or without aura. The subcutaneous formulation of sumatriptan is also indicated for cluster headache. Numerous clinical trials have been conducted comparing the efficacy and safety of the selective serotonin agonists to placebo, as well as to each other. Several studies have found similar efficacy among the selective serotonin agonists.[25,28,29,43,45,50,65,82] However, other studies have demonstrated greater efficacy with one selective serotonin agonist over another.[32,35-38,40,52,53] There is insufficient clinical evidence to conclude that one selective serotonin agonist is safer or more efficacious than another when administered at equivalent doses. While these agents have different pharmacokinetic properties, these differences have not resulted in different clinical outcomes. Recent clinical guidelines suggest that a triptan can be efficacious even if another triptan was not.[9]

The fixed-dose combination product containing sumatriptan and naproxen sodium (Treximet®) has been evaluated in several migraine clinical trials.[90,92-93] These studies demonstrate greater efficacy with sumatriptan/naproxen sodium compared to placebo or the monotherapy components.[90,92-93] There were no published head-to-head clinical trials comparing sumatriptan/naproxen sodium to other selective serotonin agonists found in the medical literature.

Therefore, all brand selective serotonin agonists within the class reviewed are comparable to each other and to the generics and OTC 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. Adelman JU, Adelman RD. Current options for the prevention and treatment of migraine. Clin Ther. 2001;23(6):772-788.
2. Lance JW. 5-hydroxytryptamine and its role in migraine. Eur Neurol. 1991;31:279-281.
3. Bateman DN. Sumatriptan. Lancet. 1993;341 221-224.
4. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000.55;754-762.
5. 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;2215-2224.
6. 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.
7. Matchar DB, Young WB, Rosenberg JH, Pietrzak MP, Silberstein SD, Lipton RB, et al. Evidence-based guidelines for migraine headache in the primary care setting; pharmacologic management of acute attacks. Available at: http://www.aan.com/professionals/practice/pdfs/gl0087.pdf. Accessed December, 2008.
8. Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. Available at: https://www.aan.com/professionals/practice/pdfs/gl0090.pdf. Accessed December, 2008.
9. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. Eur J Neurol. 2006 Jun;13(6):560-572.
10. Frova® [package insert]. Chadds Ford, PA: Endo Pharmaceuticals Inc.; June 2006.
11. Imitrex® Tablets and Imitrex® Nasal Spray [package inserts]. Research Triangle Park, NC: GlaxoSmithKline; June 2006.
12. Imitrex® Injection [package insert]. Research Triangle Park, NC: GlaxoSmithKline; November 2006.
13. Amerge® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; June 2006.
14. Axert® [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc.; June 2005.
15. Maxalt®, Maxalt-MLT ® Tablets and Orally Disintegrating Tablets [package inserts]. Whitehouse Station, NJ: Merck & Co, Inc.; June 2006.
16. Relpax® [package insert]. New York, NY: Pfizer, Inc.; April 2006.
17. Zomig®, Zomig-ZMT® Tablets and Orally Disintegrating Tablets, Zomig® Nasal Spray [package inserts]. Wilmington, DE: AstraZeneca; 2005-2006.
18. Jhee SS, Shiovtz T, Crawford AW, Cutler NR. Pharmacokinetics and pharmacodynamics of the triptan antimigraine agents: a comparative review. Clin Pharmacokinet. 2001;40(3)189-205,
19. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November, 2008.
20. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November, 2008.
21. Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan: drug information. In: Rose BD, ed. UpToDate, Waltham, MA, 2008.
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. 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; 45:874-882.
24. 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 Neurol. 2001; 45:206-13.
25. 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):453-461.
26. 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):1811-1817.
27. 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; 26:400-408.

28. 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):127-145.
29. 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):944-950.
30. Olesen J, Diener HC, Schoenen J, Hettiarachchi J. No effect of eletriptan administration during the aura phase of migraine. Eur J Neurol. 2004; 11:671-677.
31. 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; 23:463-471.
32. 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; 23:869–876.
33. 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; 43:202-213.
34. 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.
35. 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; 23:942-952.
36. 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):156-161.
37. 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; 25:715-725.
38. Mathew NT, Schoenen J, Winner P, Muirhead N, and Sikes CR. Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. Headache. 2003; 43:214-222.
39. Schoenen J, Pascual J, Rasmussen S, Sun W, Sikes C, Hettiarachchi J. Patient preference for eletriptan 80 mg versus subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. Eur J Neurol. 2005; 25:108-117.
40. 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; 59:1210–1217.
41. Ryan R. Geraud G, Goldstein J, Cady R, Keywood C. Clinical efficacy of frovatriptan: placebo-controlled studies. Headache. 2002; (42 Suppl 2):S84-92.
42. Cady R, Elkind A, Goldstein J, Keywood C. Randomized, placebo-controlled comparison of early use of frovatriptan in a migraine attack versus dosing after the headache has become moderate or severe. Curr Med Res Opin. 2004; 20:1465-1472.
43. 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; 40:513-520.
44. 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; 37:640-645.
45. Gobel H, Winter P, Boswell D, et al. Comparison of naratriptan and sumatriptan in recurrence-prone migraine patients. Clin Ther. 2000; 22(8):981-989.
46. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. Pharmacoepidemiol Drug Saf. 2004; 13(2):73-82.
47. Mathew NT, Kailasam J, Meadors L. Early treatment of migraine with rizatriptan: a placebo-controlled study. Headache. 2004; 44:669-673.
48. Ferrari MD, Loder E, McCarroll KA, Lines CR. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. Cephalalgia. 2001; 21:129-136.
49. 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.
50. 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; 24:540-546.
51. 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; 26:246–256.

52. 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; 57:1377-1383.
53. 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; 42:173-179.
54. 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):754-763.
55. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous sumatriptan. JAMA. 1991; 265(21):2831-2835.
56. 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):316-321.
57. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. Sumatriptan Auto-Injector Study Group. Eur Neurol. 1991; 31:323-331.
58. 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.
59. Salonen R, Ashford E, Dahlöf C, et al. Intranasal sumatriptan for the acute treatment of migraine. J Neurol. 1994; 241:463-469.
60. 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; 27:1785-1794.
61. 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; 12:246-253.
62. 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):745-753.
63. McCrory, DC. Gray, RN. Oral sumatriptan for acute migraine. Cochrane Database of Systematic Reviews. 4, 2006.
64. 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; 22:1035-1048.
65. 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; 20:30-38.
66. 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.
67. Spierings ELH, Rapoport AM, Dodick DW, et al. Acute treatment of migraine with zolmitriptan 5 mg orally disintegrating tablet. CNS Drugs. 2004; 18:1133-1141.
68. 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.
69. 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.
70. 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 randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. CNS Drugs. 2003; 17:653-667.
71. 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; 17:839-851.
72. 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; 22:633-658.
73. Allais G, Acuto G, Cabarrocas X, Esbri R, Benedetto G, Bussone G. Efficacy and tolerability of almotriptan versus zolmitriptan for the acute treatment of menstrual migraine. Neurol Sci. 2006; 27:S193-197.
74. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. Neurology. 2004; 63:261-269.
75. Siow HC, Pozo-Rosich P and Silberstein SD. Frovatriptan for the treatment of cluster headaches. Cephalagia. 2004; 24:1045-1048.

76. 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):908-911.
77. 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):63-69.
78. Elkind AH, Satin LZ, Nila A, Keywood C. Frovatriptan use in migraineurs with or at high risk of coronary artery disease. Headache. 2004; 44:403-410.
79. Fleishaker JC, McEnroe JD, Azie NE, Francom SF, Carel BJ. Cardiovascular effect of almotriptan in treated hypertensive patients. Clin Pharmacol Ther. 2002; 71;169-175.
80. Lipton RB, Stewart WF, Diamond S et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001; 41:646-657.
81. 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
82. 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
83. 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):511-18
84. 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
85. 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
86. 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
87. 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
88. 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): 821-26
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. 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
91. Treximet® [package insert]. Research Triangle Park, NC: GlaxoSmithKline;
92. Brandes J, Kudrow D, Stark S et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. JAMA 2007 Apr 04; 297:1443-1454
93. 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.
94. 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.
95. Sumatriptan succinate tablets [package insert]. Bridgewater NJ: Dr. Reddy's Laboratories, Inc.; November 2008.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, Antihistamines
AHFS Class 562208
February 11, 2009

I. Overview

The pathophysiology of nausea and vomiting is complex and involves multiple neurotransmitters and organ systems. Five neurotransmitter receptor sites play a key role in the vomiting reflex. These receptor sites include M1 (muscarinic), D2 (dopamine), H1 (histamine), 5-HT_3 (serotonin), and NK1 (substance P).[2] 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 to the 5-HT_3 receptor antagonists and the miscellaneous antiemetic, aprepitant.[3]

The antihistamine antiemetics are FDA-approved for the treatment of postoperative nausea and vomiting, general nausea and vomiting, motion sickness, and vertigo.[4-9] These agents can be divided into two categories: antihistaminic-anticholinergic agents and phenothiazines. The antihistaminic-anticholinergic agents consist of dimenhydrinate, meclizine and trimethobenzamide. They interrupt various visceral afferent pathways that stimulate nausea and vomiting. Prochlorperazine is the only phenothiazine in this AHFS class. Phenothiazines block dopamine receptors most likely located in the chemoreceptor trigger zone (CTZ). Phenothiazines are most useful in patients with simple nausea and vomiting or those receiving mildly emetogenic chemotherapy.

The antihistamine antiemetics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents are available in a generic formulation. Dimenhydrinate and meclizine are also available over-the-counter.

Table 1. Antihistamine Antiemetics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dimenhydrinate	tablet, injection	Dramamine®*‡	dimenhydrinate
Meclizine	tablet	Antivert®*‡	meclizine
Prochlorperazine edisylate	injection	N/A	prochlorperazine edisylate
Prochlorperazine maleate	tablet, rectal suppository	N/A	prochlorperazine maleate
Trimethobenzamide	capsule, injection	Tigan®*	trimethobenzamide

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available
‡ Product is available over-the-counter

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 (NCCN): **Clinical Practice Guidelines in Oncology: Antiemesis[13] (2009)**	• Prochlorperazine may be given at a dose of 10 mg orally (PO) or intravenously (IV) every 4-6 hours in patients receiving low and minimal emetic risk chemotherapy • Prochlorperazine may be given as 25 mg rectally or 10 mg PO or IV every 4-6 hours as breakthrough treatment for chemotherapy-induced nausea and vomiting.
American Society of Clinical Oncology (ASCO):	• Prochlorperazine may be used in patients receiving minimal emetic risk radiation therapy on an as needed basis.

Clinical Guideline	Recommendation(s)
Guideline for Antiemetics in Oncology: Update 2006 [12] **(2006)**	• Prochlorperazine may be added to the antiemetic regimen in patients experiencing emesis despite proper prophylaxis. • Prochlorperazine may be used in patients receiving intermediate emetic risk radiation therapy, specifically craniospinal radiation or radiation to the lower half of the body.
Multinational Association of Supportive Care in Cancer (MASCC): **Prevention of Chemotherapy- and Radiotherapy-Induced Emesis: The Results of the 2004 Perugia International Antiemetic Consensus Conference**[14] **(2006)**	• Prochlorperazine may be used as rescue therapy in patients receiving minimal emetic risk radiation therapy.
American Gastroenterological Association Institute: **Technical Review of the Use of Gastrointestinal Medications in Pregnancy**[18] **(2006)**	• Prochlorperazine is considered a low risk drug based on studies in pregnant women and can be used for nausea and vomiting and for hyperemesis gravidarum.
American College of Obstetricians and Gynecologists: **ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy**[16] **(2004)**	• Treatment of nausea and vomiting of pregnancy with vitamin B6 or vitamin B6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy. • In refractory cases of nausea and vomiting of pregnancy, the following medications have been shown to be safe and efficacious in pregnancy: antihistamine H_1 receptor blockers, phenothiazines, and benzamides (trimethobenzamide).
The International Anesthesia Research Society: **Consensus Guidelines for Managing Postoperative Nausea and Vomiting**[19] **(2003)**	• Dimenhydrinate, an antihistaminic, has been reviewed systematically. Its degree of efficacy seems to be similar to that of the 5-HT_3 receptor antagonists and droperidol. • The role of prochlorperazine in the treatment of PONV is still poorly understood. • Prochlorperazine 5–10 mg IV, administered at the end of surgery, has been shown to be effective. However, use of phenothiazines is limited in the ambulatory setting because of the resulting sedation.
American Gastroenterological Association (AGA): **Technical Review: Nausea and Vomiting**[15] **(2001)**	• In clinical studies, dimenhydrinate and meclizine, among others, have shown efficacy in the prevention 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. • 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. • For more severe cases of hyperemesis gravidarum, parenteral prochlorperazine may be used. • 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.
American Gastroenterological	• Severe intractable nausea and vomiting episodes require parenteral

Clinical Guideline	Recommendation(s)
Association Institute: **American Gastroenterological Association Medical Position Statement: Nausea and Vomiting[10]** **(2001)**	administration of such agents as phenothiazines • Motion sickness and related disorders are treated primarily with histamine H_1 and muscarinic, cholinergic M_1-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[4-6,9,21,36]

Generic Name	Motion Sickness	Peripheral Vertigo	Nausea and Vomiting	Postoperative Nausea and Vomiting
Dimenhydrinate	✔			
Meclizine	✔	✔		
Prochlorperazine edisylate*			✔	
Prochlorperazine maleate*			✔	
Trimethobenzamide			✔	✔

* Indicated for schizophrenia and non-psychotic anxiety

IV. Pharmacokinetics

The pharmacokinetic parameters of the antihistamine antiemetics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antihistamine Antiemetics[4-6,9,21,36]

Drugs(s)	Onset	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Dimenhydrinate	15-30 minutes	3	0	No	1-4
Meclizine	1 hour	8-24	0	Yes	6
Prochlorperazine edisylate	10-20 minutes	12	60	Yes	6-9
Prochlorperazine maleate	Tablet: 30-40 minutes Rectal: 60 minutes	3-4	80-85	Yes	6-9
Trimethobenzamide	2-4 hours	16-24	50	Yes	10

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Antihistamine Antiemetics[21]

Generic Name	Significance Level	Interaction	Mechanism
Prochlorperazine	1	Cisapride	Concurrent use may possibly cause additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias, including torsades de pointes.

Generic Name	Significance Level	Interaction	Mechanism
Prochlorperazine	1	Dofetilide	Prochlorperazine may decrease renal elimination of dofetilide, elevating plasma concentrations, which may increase the risk of ventricular arrhythmias.
Prochlorperazine	1	Quinolones	Although the exact mechanism is unknown, the risk of life-threatening arrhythmias, including torsades de pointes, may be increased.
Prochlorperazine	2	Anticholinergics	Anticholinergics probably antagonize phenothiazines by direct central nervous system (CNS) 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.
Prochlorperazine	2	Paroxetine	Concurrent administration may result in decreased metabolism of prochlorperazine via CYP 2D6 enzyme inhibition.

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.

Table 6. Adverse Drug Events (%) Reported with the Antihistamine Antiemetics[4-6,9,21,36]

Adverse Event(s)	Dimenhydrinate	Meclizine	Prochlorperazine	Trimethobenzamide
Cardiovascular				
Cardiac arrest	-	-	✔	-
Hypertension	✔	<10	✔	-
Hypotension	-	-	✔	✔
Migraine	✔	<10	✔	-
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	1-10	1-10	✔	✔
Drowsiness	>10	>10	✔	✔
Excitability	✔	✔	✔	-

Adverse Event(s)	Dimenhydrinate	Meclizine	Prochlorperazine	Trimethobenzamide
Fatigue	1-10	1-10	-	-
Hallucination	✔	✔	-	-
Headache	1-10	1-10	✔	✔
Hyperactivity	-	-	✔	-
Hyperpyrexia	-	-	✔	-
Impaired cognition	✔	-	-	-
Insomnia	✔	✔	✔	-
Nervousness	1-10	1-10	-	-
NMS	-	-	✔	-
Paresthesia	-	<1	-	-
Restlessness	✔	✔	✔	-
Sedation	-	<1	-	-
Vertigo	✔	✔	-	-
Dermatological				
Angioedema	-	<1	✔	-
Contact dermatitis	-	-	✔	-
Discoloration of skin	-	-	✔	-
Eczema	-	-	✔	-
Epithelial keratopathy	-	-	✔	-
Erythema	-	-	✔	-
Exfoliative dermatitis	-	-	✔	-
Itching	-	-	✔	-
Photosensitivity	✔	<1	✔	-
Porphyria cutanea tarda	✔	-	-	-
Rash	✔	<1	✔	✔
Sweating	-	-	✔	-
Urticaria	✔	✔	✔	-
Endocrine and Metabolic				
Amenorrhea	-	-	✔	-
Breast enlargement	-	-	✔	-
Cholestatic jaundice	-	✔	✔	✔
Galactorrhea	-	-	✔	-
Glucosuria	-	-	✔	-
Gynecomastia	-	-	✔	-
Hepatitis	-	<1	-	-
Hepatoxicity	-	-	✔	-
Hyperglycemia	-	-	✔	-
Hyperprolactinemia	-	-	✔	-
Hypoglycemia	-	-	✔	-
Menstrual irregularity	-	-	✔	-
SIADH	-	-	✔	-
Gastrointestinal				
Abdominal pain	1-10	1-10	-	-
Anorexia	✔	✔	-	-
Atonic colon	-	-	✔	-
Constipation	✔	✔	✔	-
Diarrhea	1-10	1-10	-	✔
Dyspepsia	✔	-	-	-
Ileus	-	-	✔	-
Nausea	1-10	1-10	✔	-
Proctocolitis	-	-	✔	-
Taste alteration	1-10	1-10	-	-
Vomiting	✔	✔	-	-
Genitourinary				

Adverse Event(s)	Dimenhydrinate	Meclizine	Prochlorperazine	Trimethobenzamide
Dysuria	✔	✔	-	-
Ejaculating dysfunction	-	-	✔	-
Impotence	-	-	✔	-
Incontinence	-	-	✔	-
Polyuria	-	-	✔	-
Porphyria	✔	-	-	-
Priapism	-	-	✔	-
Urinary retention	✔	<1	✔	-
Hematologic				
Agranulocytosis	-	-	✔	✔
Aplastic anemia	-	-	✔	-
Blood dyscrasias	-	-	-	✔
Eosinophilia	-	-	✔	-
Hemolytic anemia	✔	-	✔	-
Leukopenia	-	-	✔	✔
Pancytopenia	-	-	✔	-
Thrombocytopenia	-	-	✔	-
Musculoskeletal				
Arthralgia	1-10	1-10	-	-
Ataxia	✔	-	-	-
Dystonias	-	-	✔	-
Extrapyramidal symptoms	-	-	✔	-
Muscle cramps	-	-	-	✔
Myalgia	-	<1	-	-
Respiratory				
Asthma	-	-	✔	-
Bronchospasm	-	<1	-	-
Laryngeal edema	-	-	✔	-
Nasal congestion	-	-	✔	-
Pharyngitis	1-10	1-10	-	-
Wheezing	✔	-	-	-
Other				
Blurred vision	✔	<1	✔	✔
Epistaxis	-	<1	-	-
Fever	-	-	✔	✔
Hypersensitivity reaction	-	-	-	✔
Malaise	✔	-	-	-
Opisthotonos	✔	-	-	✔
Parkinson-like syndrome	-	-	-	✔
Retinopathy	-	-	✔	-
Seizure	✔	✔	-	✔
Thickening of bronchial secretions	>10	>10	-	-
Tinnitus	✔	✔	✔	-
Tremor	-	<1	✔	✔
Weight alteration	1-10	1-10	-	-
Withdrawal	-	-	✔	-
Xerophthalmia	✔	-	-	-
Xerostomia	1-10	1-10	✔	-

NMS=neuroleptic malignant syndrome, SIADH=syndrome of inappropriate antidiuretic hormone secretion
✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the antihistamine antiemetics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Antihistamine Antiemetics[4-6,9,21,36]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Dimenhydrinate	Motion Sickness: 50-100 mg orally every 4-6 hours Maximum: 400 mg per day	Motion Sickness: 6-12 years : 25-50 mg orally every 6-8 hours Maximum: 150 mg per day 2-5 years: 12.5-25 mg orally every 6-8 hours Maximum: 75 mg per day	Injection: 50 mg/mL Tablet: 50 mg
Meclizine	Motion Sickness: 25-50 mg every 24 hours Vertigo: 25 – 100 mg daily, in divided dosage, depending on clinical response	Safety and efficacy have not been established in children <12 years of age.	Tablet: 12.5 mg, 25 mg, 50 mg
Prochlorperazine	Severe Nausea and Vomiting: Oral: 5-10 mg 3-4 times daily Rectal: 25 mg twice daily IV: 2.5 – 10 mg as a single dose (maximum daily dose of 40 mg)	Severe Nausea and Vomiting: 2 years and older: 20-29 pounds: 2.5 mg orally or rectally 1-2 times per day (maximum: 7.5 mg/day) 30-39 pounds: 2.5 mg orally or rectally 2-3 times per day (maximum: 10 mg/day) 40-85 pounds: 2.5 mg orally or rectally 3 times a day or 5 mg orally or rectally 2 times per day (maximum: 15 mg/day) IM: 0.06 mg of drug per pound of body weight.	Injection: 5 mg/mL Rectal Suppository: 25 mg Tablet: 5 mg, 10 mg, 25 mg
Trimethobenzamide	PONV; Nausea and Vomiting: Intramuscular: 200 mg 3-4 times daily Oral: 300 mg 3-4 times daily	Safety and efficacy have not been established in children.	Injection: 100 mg/mL Capsule: 300 mg

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials with the Antihistamine Antiemetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting (CINV)				
Lindley et al.[22] (2005) Prochlorperazine SR 15 mg BID vs. ondansetron 8 mg BID vs. dexamethasone 8 mg BID All patients received ondansetron 24 mg and dexamethasone 20 mg orally before chemotherapy	RCT, MC Chemotherapy-naive 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 2 through 5	Primary: The treatment regimen for delayed CINV did not affect the percentage of patients reporting 1 or more vomiting episodes on days 2 through 5 (prochlorperazine 24%; ondansetron 22%; and dexamethasone 21%; *P*=0.86). The average severity of nausea during days 2 through 5 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 1 or more vomiting episodes also experienced some degree of nausea.
Hickok et al.[24] (2005) Day 1: Any 5-HT_3 receptor antagonist with dexamethasone (or equivalent dose of methylprednisolone)	RCT, OL Patients >18 years old scheduled to receive their first treatment with a chemotherapy regimen containing doxorubicin and antiemetic	N=691 3 days	Primary: Mean severity of delayed nausea Secondary: Severity of acute nausea, frequency of acute and delayed nausea, frequency of acute	Primary: 519 (77%) of the 671 evaluable patients had delayed nausea. Delayed nausea was reported in 71% of patients treated with prochlorperazine every 8 hours and 79% of patients treated with 5-HT_3 receptor antagonist and 82% of patients treated with prochlorperazine as needed. Groups did not differ in mean severity of delayed nausea.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Days 2 and 3: prochlorperazine PO 10 mg every 8 hours vs. Day 1: any 5-HT_3 receptor antagonist with dexamethasone (or equivalent dose of methylprednisolone) Day 2 and 3: ondansetron 8 mg BID, granisetron 1 mg BID, dolasetron 100 mg QD or 50 mg BID vs. Day 1: any 5-HT_3 receptor antagonist with dexamethasone (or equivalent dose of methylprednisolone) Day 2 and 3: prochlorperazine 10 mg as needed	prophylaxis with ondansetron, granisetron, or dolasetron plus dexamethasone or equivalent methyl-prednisolone		and delayed vomiting, compliance	Patients treated with prochlorperazine every 8 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: Severity of acute nausea did not differ between groups. Frequency of acute vomiting or delayed vomiting did not differ between groups.
Friedman et al.[23] (2000) Prochlorperazine SR 10 mg BID	MC, DB, PG, CS Patients ≥18 years old and scheduled to receive first cycle of	N=230 5-11 days	Primary: Proportion of patients with no emesis, no nausea, moderate or severe	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. granisetron 1 mg BID All medications given 1 hour prior to and 12 hours after chemotherapy	moderately emetogenic chemotherapy		nausea and no antiemetic rescue at 48 hours Secondary: Safety and tolerability	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%).
General Nausea and Vomiting				
Braude et al.[25] (2006) Prochlorperazine 10 mg vs. droperidol 1.25 mg	RCT, PRO, DB Patients 18-65 years of age admitted to emergency department complaining of moderate to severe nausea of any etiology	N=97 24 hours	Primary: Reduction in visual analog scale (VAS) scores for nausea at 30 minutes Secondary: Change in VAS scores for sedation and anxiety, need	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-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. metoclopramide 10 mg vs. saline placebo			for rescue antiemetic administration, adverse medication effects, patient satisfaction	hour follow up. 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.
Motion Sickness				
Paul et al.[26] (2005) Dimenhydrinate 50 mg vs. meclizine 50 mg vs. promethazine 25 mg vs. promethazine 25 mg plus pseudoephedrine 60 mg vs. promethazine 25 mg plus dextroamphetamine 10 mg vs.	RCT Aircrew personnel 22-59 years of age	N=21 7 hours	Primary: Serial reaction time (SRT), logical reasoning time (LRT), serial subtraction time (SST), multitask (MT)	Primary: SRT 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 SRT (P<0.901), but the addition of pseudoephedrine to promethazine did not abolish the effect on SRT (P<0.00001). Impairment on LRT 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 LRT (P<0.77) but pseudoephedrine did not (P<0.007). Impairment on SST was significant for promethazine (P<0.001) and meclizine (P<0.006). The addition of dextroamphetamine to promethazine abolished the effect on SST (P<0.99), but the addition of pseudoephedrine did not (P<0.006). Impairment on MT 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 MT (P<0.25), but the addition of pseudoephedrine did not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				(*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.
Postoperative Nausea and Vomiting (PONV)				
Jamil et al.[32] (2005) Prochlorperazine 0.1-0.2 mg/kg IM vs. metoclopramide 0.1-0.2 mg/kg IV vs. placebo (2 ml D5NS) All injected IV 10 minutes before induction of general anesthesia	RCT, PC Young adult patients 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 0.1-0.2 mg/kg IV)	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.
Turner et al.[28] (2004) Dimenhydrinate long-acting (LA) capsule pre-operatively and IV placebo before induction vs.	RCT, DB Women 27-40 years old scheduled for elective outpatient gynecologic laparoscopic surgery	N=141 Until lunchtime the day after discharge	Primary: Complete treatment failure (CTF) defined as the administration of rescue medication in post anesthesia care unit (PACU) or nausea, vomiting, or retching at any	Primary: CTF was not significantly different among the three treatment groups. Secondary: TFV was significantly less in the combination group versus droperidol (*P*=0.007). The TFV in patients receiving dimenhydrinate alone was less than with droperidol (35% versus 25%), but was not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo capsule and IV droperidol vs. dimenhydrinate LA* capsule and IV droperidol 0.625 mg			time during the study Secondary: Treatment failure for vomiting (TFV) defined as the administration of rescue medication in PACU or vomiting or retching at any time point during the study	
Eberhart et al.[27] (2000) Dimenhydrinate 1 mg/kg vs. metoclopramide 0.3 mg/kg vs. dimenhydrinate 1 mg/kg and 0.3 mg/kg metoclopramide vs. placebo (saline) Administered after induction of	RCT, DB Men undergoing endonasal surgery (e.g., septoplasty, rhinoplasty, septorhinoplasty)	N=160 24 hours	Primary: Number of men free from nausea and vomiting (= "no PONV"); severity of PONV during the 24 hour observation interval categorized into four degrees: "no PONV" "mild PONV" "moderate PONV" "severe PONV"; 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 with placebo treatment (*P*=0.017). Secondary: The incidence of side effects was the same in all four groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
anesthesia, and 6 hours later				
Kothari et al.[30] (2000) Dimenhydrinate 50 mg IV vs. ondansetron 4 mg IV All medications administered before induction of anesthesia	PRO, RCT, DB Consecutive patients undergoing laparoscopic cholecystectomy	N=128 24 hours after discharge	Primary: Frequency of PONV, need for rescue antiemetics, need for overnight hospitalization secondary to persistent nausea and vomiting, frequency PONV 24 hours after discharge	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 2 patients in the dimenhydrinate group required overnight hospitalization for persistent nausea and vomiting (*P*=NS). Rates of postoperative nausea and vomiting 24 hours after discharge were similar between the ondansetron and dimenhydrinate groups (10% and 14%, *P*=0.397 and 2% and 5%, *P*=0.375, respectively).
McCall et al.[31] (1999) Dimenhydrinate 0.5 mg/kg vs. ondansetron 0.1 mg/kg vs. placebo Study drugs were given at the end of	RCT, DB, PRO, PC 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	Primary: Statistically significant reductions in the incidence of PONV in the patients who received ondansetron or dimenhydrinate were found, as compared with 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
surgery and again 4 hours later				
Hamid et al.[29] (1998) Dimenhydrinate 0.5 mg/kg vs. ondansetron 0.1 mg/kg IV vs. placebo All given at induction of anesthesia	RCT, DB, PC, PRO Children 2-10 years of age scheduled for adenotonsillectomy	N=47 24 hours	Primary: Incidence of retching and vomiting observed first 24 hours post surgery	Primary: The incidence of postoperative vomiting (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, $P<0.04$)
Chen et al.[34] (1998) Prochlorperazine maleate 10 mg IM vs. ondansetron 4 mg IV All administered at end of surgical procedure	RCT, DB Patients greater than 17 years old 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 with 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[33] (1996)	RCT, DB, PRO	N=148	Primary: Incidence of	Primary: Nausea alone during the first 24-hour postoperative period was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prochlorperazine 0.2 mg/kg IM vs. prochlorperazine 0.2 mg/kg IV vs. ondansetron 0.06 mg/kg IV vs. placebo All given with induction of anesthesia	Patients from 9-61 years of age received standardized general anesthesia for tympanoplasty	24 hours	retching and vomiting in the PACU during first 24 hours post surgery Secondary: Postoperative headache	infrequent in each treatment group with a similar incidence (3%-8%). The incidence of vomiting alone (without accompanied nausea) during this time was also similar between groups (11%-24%). The incidence of vomiting or retching immediately after extubation or during recovery occurred in 16% of placebo patients, 5% of patients in the IM prochlorperazine group, and 8% in the prochlorperazine and ondansetron IV groups, but the differences between groups was not significant (P>0.05 for all groups). The incidence of nausea accompanied by vomiting occurred in 53% of the placebo group and 16% and 19% in those given prochlorperazine IM and ondansetron IV, respectively (P<0.0005), and 30% in those given prochlorperazine IV (P<0.05). The study was not powered to detect a difference between groups. The percent of patients who experienced no nausea or vomiting was 27% for placebo, 57% for prochlorperazine IM, 43% for prochlorperazine IV, and 62% for ondansetron IV. Only the prochlorperazine IM and ondansetron IV groups achieved significance compared to placebo (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.[35] (1986) Meclizine (oral) vs. scopolamine (transdermal)	RCT, DB, XO Healthy subjects	N=12 7 days	Primary: Effect on vertigo symptoms Secondary: Side effects	Primary: Vertigo symptoms on day 1 of treatment were significantly less with transdermal scopolamine than oral meclizine or placebo and on day 7 were significantly less with both scopolamine and meclizine compared to placebo. On day 1, meclizine did not reduce vertigo symptoms significantly when compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. placebo Crossover separated by 1 week intervals				Secondary: Drowsiness was greater with use of oral meclizine than transdermal scopolamine.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, SB=single-blind, DB=double-blind, TB=triple-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, 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 study by Chen et al. evaluated the impact on hospital stays and cancellations of physical therapy visits in patients undergoing total hip or total knee replacement surgeries.[34] Patients were randomized to receive ondansetron 4 mg intravenously or prochlorperazine 10 mg intramuscularly (and matching placebo to maintain blinding) 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 cancelled 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). Other primary and secondary endpoints of this study were reported in the previous section.

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Antihistamine Antiemetics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Dimenhydrinate	tablet, injection	Dramamine®*‡	$	$
Meclizine	tablet	Antivert®*‡	$-$$$	$
Prochlorperazine edisylate	injection	N/A	$-$$$	$
Prochlorperazine maleate	tablet, rectal suppository	N/A	$-$$$	$
Trimethobenzamide	capsule, injection	Tigan®*	$-$$$	$$

*Generic is available in at least one dosage form or strength.
N/A=Not available
‡ Product is available over-the-counter

X. Conclusions

The antihistamine antiemetics are effective treatment options for the management of nausea and vomiting. Current guidelines recommend these agents for the treatment of nausea and vomiting associated with motion sickness, vertigo and other related disorders.[10,12,13-16,18-19] Although there are limited head-to-head clinical trials using the antihistamine antiemetics, available studies show no significant differences in terms of relative efficacy and safety of these agents. Antihistamine antiemetics may also be considered in the management of acute or breakthrough episodes of nausea and vomiting of pregnancy.[16-18] While antihistamine antiemetics are not recommended as first-line therapy for the prevention of postoperative nausea and vomiting, several studies have reported that dimenhydrinate was as effective as 5-HT_3 receptor antagonists and droperidol.[19,30,31]

Current guidelines recommend the use of multiple antiemetic agents for the management of nausea and vomiting associated with chemotherapy and radiation.[12-14] The selection of a pharmacologic agent generally depends on the relative emetogenic potential of the chemotherapy regimen. Prochlorperazine is an accepted treatment option to prevent emesis in patients receiving low and minimal emetic risk chemotherapy.[12-13] Prochlorperazine is also a treatment option for the management of radiation-induced emesis.[14]

Therefore, all brand antihistamine antiemetics within the class reviewed are comparable to each other and to the generics and OTC 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. Stahl SM. The ups and downs of novel antiemetic drugs, part 1:substance P, 5-HT, and the neuropharmacology of vomiting. J Clin Psychiatry. 2003;64(5):498-499.
2. Longstreth GF, Hesketh PJ. Characteristics of antiemetic drugs. In: UpToDate, Talley NJ, (Ed), UpToDate, Waltham, MA, 2008.
3. Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. Am Fam Physician.2004;1169-1174.
4. Dimenhydrinate injection [package insert]. Schaumburg, IL: APP; 2003.
5. Antivert® [package insert]. New York, NY: Pfizer, Inc.; October, 2006.
6. Compazine® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2004.
7. Compazine® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2002.
8. Torecan® [package insert]. Ridgefield, CT: Boehringer Ingelheim; 1995.
9. Tigan® [package insert]. Rochester, MI: JHP Pharmaceuticals, LLC. January 2008.
10. American Gastroenterological Association Medical Position Statement: Nausea and Vomiting. Gastroenterology. 2001 Jan;120(1):261-262.
11. DiPiro CV, Taylor AT. Nausea and Vomiting. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 6th ed. New York, NY: McGraw-Hill Companies, Inc.; 2005:665-676.
12. 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.
13. National Comprehensive Cancer Network (NCCN) Guidelines. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed December 2008.
14. The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncology. 2006;17:20-28.
15. Quigley EMM, Hasler WL, Parkman HP. American Gastroenterological Association (AGA) technical review: nausea and vomiting. In: Rose, BD, ed. UpToDate. Waltham, MA: UpToDate; 2006.
16. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2004;103(4):803-815.
17. Arsenault MY, Lane CA. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2002;24(10):817-833.
18. Mahadevan U, Kane S. American Gastroenterological Association Institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology. 2006;131(1):278-282.
19. Gan T, Meyer T, Apfel C, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg. 2003;97:62-71.
20. Tatro DS, ed. Drug Interaction Facts. St. Louis, MO: Wolters Kluwer Health, Inc.; 2006.
21. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed December 2008.
22. 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):270-276.
23. 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;5:136-143.
24. Hickok JT, Roscoe JA, Marrow GR, et al. 5-Hydroxytryptamine-receptor antagonists versus prochlorperazine for control of delayed nausea caused by doxorubicin: a URCC CCOP randomized controlled trial. Lancet Oncol. 2005;6(10):765-772.
25. 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):177-182.
26. Paul MA, MacLellan M, Gray G. Motion-sickness medications for aircrew: impact on psychomotor performance. Aviat Space Environ Med. 2005;76(6):560-565.
27. 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):780-785.

28. 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):1660-1664.
29. 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.
30. Kothari SN, Boyd WC, Bottcher PJ. Antiemetic efficacy of prophylactic dimenhydrinate (Dramamine®) vs. ondansetron (Zofran®). Surg Endosc. 2000;14:926-929.
31. 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 versus dimenhydrinate. J Burn Care Rehabil. 1999;20(4):309-315.
32. 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(4):40-44.
33. 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):939-945.
34. 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):2124-2128.
35. 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.
36. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed December, 2008.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, 5-HT_3 Receptor Antagonists
AHFS Class 562220
February 11, 2009

I. Overview

The pathophysiology of nausea and vomiting is complex and involves multiple neurotransmitters and organ systems. Five neurotransmitter receptor sites play a key role in the vomiting reflex. These receptor sites include M1 (muscarinic), D2 (dopamine), H1 (histamine), 5-HT_3 (serotonin), and NK1 (substance P).[2] 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 to 5-HT_3 receptor antagonists and the miscellaneous antiemetic, aprepitant.[3]

The 5-HT_3 receptor antagonists are FDA-approved for the treatment of chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), and radiation-induced nausea and vomiting (RINV). These agents block the 5-HT_3 receptors in both the gastric area and the chemoreceptor trigger zone, thereby disrupting the signal to vomit and reduce the sensation of nausea.[4, 21,23]

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.

Table 1. 5-HT_3 Receptor Antagonists Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dolasetron	tablet, injection	Anzemet®	none
Granisetron	tablet, solution, injection	Kytril®*, Granisol®	granisetron
Ondansetron	orally disintegrating tablet, tablet, solution, injection	Zofran®*, Zofran ODT®*	ondansetron
Palonosetron	injection	Aloxi®	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 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 (NCCN): **Practice Guidelines in Oncology: Antiemesis[21] (2009)**	• A 5-HT_3 receptor antagonist should be administered prior to each days 1st dose of moderately or highly-emetogenic chemotherapy. • For highly emetogenic chemotherapy, the combination of aprepitant (or fosaprepitant), dexamethasone and a 5-HT_3 receptor antagonist, with or without lorazepam is recommended. • The antiemetic regimen for moderately emetogenic drugs on day 1 includes dexamethasone and a 5-HT_3 receptor antagonist with or without lorazepam. Any one of the 5-HT_3 receptor antagonists can be used. The regimens on days 2 to 3 may include a 5-HT_3 receptor antagonist, such as ondansetron, granisetron, or dolasetron (palonosetron is not given on days 2-3). • Intravenous palonosetron may be used prior to the start of a three day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT_3 receptor antagonists.

Clinical Guideline	Recommendation(s)
	• Possibly switching to a different 5-HT_3 receptor antagonist although not necessarily likely to effective, anecdotal and limited investigational trial data suggest it may sometimes be efficacious when managing breakthrough emesis. • All four 5-HT_3 receptor antagonists are considered to have similar effectiveness for control of acute emesis. • 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 2 or 3) is not supported by the scientific literature. • The NCCN panel recommends the use of 5-HT_3 receptor antagonists as one of several options to prevent delayed emesis for moderately emetogenic agents. • Ondansetron and granisetron are options for RINV.
American Society of Clinical Oncology (ASCO): **Guideline for Antiemetics in Oncology: Update 2006[20] (2006)**	High (> 90%) emetic risk • The three-drug combination of a 5-HT3 serotonin receptor antagonist, dexamethasone, and aprepitant is recommended before chemotherapy. In all patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant is recommended. The Update Committee no longer recommends the combination of a 5-HT3 serotonin receptor antagonist and dexamethasone on days 2 and 3. Moderate (> 30% to 90%) emetic risk • The three-drug combination of a 5-HT3 receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving anthracycline and cyclophosphamide (AC). For patients receiving chemotherapy of moderate emetic risk other than AC, we recommend the two-drug combination of a 5-HT3 receptor serotonin antagonist and dexamethasone. In patients receiving AC, aprepitant as a single agent is recommended on days 2 and 3. For all other chemotherapies of moderate emetic risk, single-agent dexamethasone or a 5-HT3 serotonin receptor antagonist is suggested for the prevention of emesis on days 2 and 3. Low (10% to 30%) emetic risk • Dexamethasone 8 mg is suggested. No routine preventive use of antiemetics for delayed emesis is suggested. Minimal (<10%) emetic risk • No antiemetic should be administered routinely before or after chemotherapy. Combination chemotherapy • Patients should be administered antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk. 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 2 days after, if appropriate. Special Emetic Problems: • The combination of a 5-HT3 antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. • For radiation-induced emesis: a 5-HT_3 receptor antagonist should be administered with or without a corticosteroid before each fraction • The guidelines do not designate a preferred 5-HT_3 receptor antagonist.
Multinational Association of	High Emetogenic Risk

Clinical Guideline	Recommendation(s)
Supportive Care in Cancer (MASCC): **Consensus Conference on Antiemetic Therapy[22]** **(2006)**	• To prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT3-receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended. • The principles of 5-HT3-receptor antagonist use to prevent acute vomiting and nausea induced by chemotherapy of high emetogenic risk are the following: (i) use the lowest tested fully effective dose, (ii) no schedule is better than a single dose given before chemotherapy, (iii) the antiemetic efficacy and adverse effects of these agents are comparable in controlled trials, (iv) intravenous and oral formulations are equally effective and safe; always use in combination with dexamethasone and administered before chemotherapy. <u>Moderate Emetogenic Risk</u> • The standard antiemetic therapy for acute emesis in patients receiving chemotherapy of moderate emetic risk is a combination of a 5-HT3-receptor antagonist plus dexamethasone. • Women receiving a combination of an anthracycline plus cyclophosphamide should receive a three-drug regimen including single doses of a 5-HT3-receptor antagonist, dexamethasone and aprepitant given before chemotherapy • In patients receiving cisplatin treated with a combination of aprepitant, a 5-HT3-receptor antagonist and dexamethasone to prevent acute vomiting and nausea, the combination of dexamethasone and aprepitant is suggested to prevent delayed emesis, on the basis of its superiority to dexamethasone alone. • Patients who receive chemotherapy of moderate emetic risk known to be associated with a significant incidence of delayed nausea and vomiting should receive antiemetic prophylaxis for delayed emesis. Oral dexamethasone is the preferred treatment while the 5-HT3-receptor antagonists may be used as an alternative. <u>Prevention of Emesis Induced by Multiple-day Chemotherapy</u> • Patients receiving multiple-day cisplatin should receive a 5-HT3-receptor antagonist plus dexamethasone for acute nausea and vomiting and dexamethasone. <u>Antiemetics in Children Receiving Chemotherapy</u> • All pediatric patients receiving chemotherapy of high or moderate emetogenic potential should receive antiemetic prophylaxis with a combination of a 5-HT3-receptor antagonist and dexamethasone.
American College of Obstetricians and Gynecologists: **ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy [26]** **(2004)**	• Evidence is limited on the safety or efficacy of the 5-hydroxytryptamine 3 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.
The International Anesthesia Research Society: **Consensus Guidelines for Managing PONV[25]** **(2003)**	• There is no evidence of any difference in the efficacy and safety profiles of the serotonin (5-HT3) receptor antagonists—ondansetron, dolasetron, granisetron, and tropisetron—in the prophylaxis of PONV. • Because the 5-HT_3 antagonists as a group have greater efficacy in the prevention of vomiting than nausea, they are the drugs of first choice for prophylaxis in children. • If a patient has received no prophylaxis, therapy with small-dose 5-HT_3 receptor antagonists should be initiated on the first signs of PONV.

Clinical Guideline	Recommendation(s)
	• When prophylaxis with dexamethasone fails to prevent PONV, treatment with a small-dose 5-HT_3 receptor antagonist has been recommended. • When prophylaxis with a 5-HT_3 antagonist is inadequate to prevent PONV, a 5-HT_3 antagonist should not be initiated as rescue therapy within the first 6 h after surgery because it confers no additional benefit. • When PONV occurs more than 6 h after surgery, repeat dosing of 5-HT_3 antagonists and droperidol can be considered.
American Gastroenterological Association (AGA): **Technical Review: Nausea and Vomiting[23]** **(2001)**	• 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. • The various 5-HT3 antagonists appear to be of similar efficacy and have a comparable incidence of side effects. • For postoperative nausea and vomiting (PONV), the use of 5-HT_3 receptor antagonists and droperidol have proven most effective in comparisons both with 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.
American Gastroenterological Association Institute: **American Gastroenterological Association Medical Position Statement: Nausea and Vomiting[24]** **(2001)**	• 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 serotonergic 5-HT3–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[27-30,65-68]

Generic Name	Chemotherapy-Induced Nausea and Vomiting (CINV)	Radiation-Induced Nausea and Vomiting (RINV)	Postoperative Nausea and Vomiting (PONV)
Dolasetron	✔		✔
Granisetron	✔	✔ [a]	✔ [b]
Ondansetron	✔	✔ [a]	✔
Palonosetron	✔		✔

[a] Oral formulation only
[b] Injection only

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[27-30,65-68]

Drugs(s)	Onset (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
Dolasetron	0.6 – 1	No data	45 – 68	Hydro-dolasetron	8

Drugs(s)	Onset (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
Granisetron	0.5 – 2	24	12	None	9
Ondansetron	0.5 – 2	9	44 – 60	None	4
Palonosetron	0.5 – 2	>24	80 – 93	None	37 – 48

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[31]

Generic Name	Significance Level	Interaction	Mechanism
Dolasetron	1	Ziprasidone	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Ondansetron	2	Rifamycins (rifabutin, rifampin, rifapentine)	Rifamycins may decrease the half-life and increase the clearance of ondansetron through induction of hepatic metabolism.

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[27-30,65-68]

Adverse Event(s)	Dolasetron	Granisetron	Ondansetron	Palonosetron
Cardiovascular				
Bradycardia	4-5	-	-	-
Hypertension	2-3	2	2	-
Hypotension	5	-	3-5	-
Tachycardia	2-3	-	-	-
Central Nervous System				
Anxiety	-	-	6	-
Chills/shivering	1-2	5	7	-
Dizziness	2-4	-	7	1
Drowsiness	1-2	-	8	-
Headache	7-24	14-21	9-27	9
Insomnia	-	-	-	<1
Malaise/fatigue	2-5	-	9-13	<1
Paresthesia	-	-	2	-
Dermatological				
Pruritus	3	-	2-5	-
Endocrine and Metabolic				
Increased AST and ALT	3	3	3	-
Gastrointestinal				
Abdominal pain	3	6	3	<1
Constipation	-	18	6-9	5
Diarrhea	2-12	8	6	1
Dyspepsia	2	-	-	-
Xerostomia	-	-	2	-
Genitourinary				
Oliguria	2	-	-	-
Urinary retention	2	-	5	-

Adverse Event(s)	Dolasetron	Granisetron	Ondansetron	Palonosetron
Musculoskeletal				
Asthenia	-	14	-	-
Other				
Cold sensation	-	-	2	-
Fever/pyrexia	3-4	-	2-8	-
Gynecological disorder	-	-	7	-
Hypoxia	-	-	9	-
Injection site reaction	-	-	4	-
Pain	<3	2	2	-
Weakness	-	-	2	-

ALT=alanine aminotransferase, AST=aspartate aminotransferase
- 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[27-30,65-68]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Dolasetron	CINV: 100 mg orally within one hour before chemotherapy or 1.8 mg/kg or 100 mg IV 30 minutes before chemotherapy 100 mg PO QD, days 2-4 or 1.8 mg/kg or 100 mg IV QD, days 2-4 PONV: 100 mg orally within two hours before surgery or 12.5 mg IV 15 minutes before cessation of anesthesia or as soon as nausea or vomiting presents	Age 2-16 years CINV: 1.8 mg/kg up to 100 mg orally within one hour before chemotherapy or 1.8 mg/kg up to 100 mg IV 30 minutes before chemotherapy PONV: 1.2 mg/kg up to 100 mg orally within two hours before surgery or 0.35 mg/kg up to 12.5 mg IV 15 minutes before cessation of anesthesia or as soon as nausea or vomiting presents	Tablet: 50 mg, 100 mg Injection: 12.5 mg/ 0.625 ml, 20 mg/ml
Granisetron	CINV: 2 mg orally up to one hour before chemotherapy or 1 mg orally up to one hour before chemotherapy and 1 mg 12 hours after the first dose or 10mcg/kg IV within 30 minutes before chemotherapy PONV: 1 mg IV before induction of anesthesia or immediately before reversal of anesthesia	CINV: Age 2-16 years: 10mcg/kg IV The safety and efficacy of the oral formulation have not been established in children.	Tablet: 1 mg Solution: 6 mg/30 mL Injection: 100 mcg/ml, 1 mg/ ml

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	RINV: 2 mg orally within 1 hour of radiation		
Ondansetron	CINV: 24 mg orally 30 minutes prior to chemotherapy (highly emetogenic chemotherapy) or 8 mg orally BID (moderately emetogenic chemotherapy) or 32 mg IV up to 30 minutes prior to chemotherapy or three 0.15 mg/kg IV doses (first dose prior to chemotherapy, then repeated 4 and 8 hours after first dose) PONV: 16 mg orally 1 hour before induction of anesthesia or 4 mg IV immediately before induction of anesthesia, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery RINV: 8 mg orally TID	CINV: Ages >12 years: 8 mg orally BID Ages 4-11 years: 4 mg orally TID Ages 6 months-18 years: three 0.15 mg/kg IV doses (first dose prior to chemotherapy, then repeated 4 and 8 hours after first dose) PONV: Age 1 month to 12 years: • weight ≤40 kg: 0.1 mg/kg IV • weight >40 kg: 4 mg IV	Tablet: 4 mg, 8 mg, 24 mg Orally disintegrating tablet: 4 mg, 8 mg Solution: 4 mg/5 mL Injection: 2 mg/ml, 4 mg/2 ml Injection premixed: 32 mg/50 ml in 5% dextrose
Palonosetron	CINV: 0.25 mg IV 30 minutes prior to chemotherapy PONV: 0.075 mg IV immediately before the induction of anesthesia	Safety and efficacy in children have not been established.	Injection: 0.075 mg/1.5 ml, 0.25 mg/5 ml

QD=once daily, BID=twice daily, TID=three times daily, IV=intravenous

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)				
Aapro et al.[75] (2006) Palonosetron 0.25 mg IV vs. palonosetron 0.75 mg IV vs. ondansetron 32 mg IV	MC, RCT, DB, DD, PG 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 1	N=673 5 days	Primary: Complete response (no emetic episodes and no rescue medication use) during the acute phase (0-24 hours post-chemotherapy) Secondary: Complete response for the delayed (24-120 hour post-chemotherapy) and overall (0-120 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 with 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.
Abali et al.[76] (2007)	PRO, OL, OBS Patients receiving	N=158 5 days	Primary: Emesis control and nausea control in	Primary: During the acute period, there were no significant differences between the treatment groups with respect to the following outcomes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ondansetron 8 mg IV vs. granisetron 3 mg IV vs. tropisetron† 5 mg IV *dexamethasone 8 mg IV coadministered with all treatments	highly and moderately emetogenic chemotherapy		acute (within 24 hours of chemotherapy) and delayed periods (between 25 and 120 hours); nausea Complete response (CR) = no emetic episodes; Major response (MR) = ≤2 emetic episodes; Minor response (mR) = 2-5 emetic episodes; Failure (Fa) = ≥5 emetic episodes or rescue medication	(p=0.877): Tropisetron: CR (80.4%), MR (13.7%), mR (3.9%) Ondansetron: CR (72.1%), MR (18%), mR (4.9%) Granisetron: CR (71.7%), MR (21.7%), mR (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: CR (68.6%), MR (19.6%), mR (7.8%) Ondansetron: CR (68.9%), MR (11.5%), mR (6.6%) Granisetron: CR (76.1%), MR (10.9%), mR (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%)
Meiri et al.[77] (2007) <u>Day 2 (fixed dose)</u> Dronabinol 2.5 mg PO QID vs. ondansetron 8 mg PO BID vs.	RCT, DB, PC, PG Patients ≥18 years old with malignancy that did not involve the bone marrow and be undergoing chemotherapy including a moderately to highly emetogenic regimen	N=64 (out of planned 464 patients) 5 days *Early termination of study and insufficient patient enrollment due to presence of placebo group	Primary: Total response 2-5 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	Primary: Total response during active treatment did not differ between treatment groups (p=NS) due to small sample size. Improvement (range 47-58%) in three active treatment groups compared to placebo (20%) implies clinically relevant improvement (days 2-5 LOCF). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dronabinol 2.5 mg PO QID + ondansetron 8 mg PO BID vs. placebo Days 3-5 (flexible dose) dronabinol 2.5-5 mg PO QID vs. ondansetron 4-8 mg PO BID vs. dronabinol 2.5-5 mg PO QID + ondansetron 4-8 mg PO BID vs. placebo *Day 1 (prechemotherapy) regimen consisted of dexamethasone 20 mg and ondansetron 16 mg administered to all study participants.			rate, nausea status, episodes of vomiting and/or retching, duration of nausea and vomiting and/or retching, intensity of nausea, ECOG, and QoL	combination therapy, 58% with ondansetron, and 20% with placebo (p<0.005 vs. placebo). All active treatments reduced the intensity of nausea versus placebo (p<0.05). No significant difference ws 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 4 and 5. Active treatment reduced the duration of vomiting/retching to 0 hours in all groups by days 4 and 5. Duration of nausea was comparable among all groups. Changes from baseline in ECOG 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 MSDS (QoL) 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
Dronabinol 2.5 mg was also administered on day 1 in the 3 active treatment arms.				
Jordan et al.[78] (2007) Granisetron vs. ondansetron granisetron vs. tropisetron ondansetron vs. tropisetron ondansetron vs. dolasetron	MA Randomized trials of four 5-HT_3-receptor antagonists to identify differences in efficacy for 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	Primary: Granisetron vs. ondansetron: Pooled odds ratios (including all dose schedules) revealed an overall equivalence of granisetron and ondansetron (OR 1.033; 95% CI, 0.93-1.142). 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, 0.916-1.211). 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, 1.069-2.002). Ondansetron was similar in efficacy to tropisetron (OR 1.103; 95% CI, 0.835-1.458). 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).
Mandanas et al.[79] (2005) Dolasetron 100 mg IV prior to chemotherapy, then 100 mg PO 8-12	R, MC, OL	N=197	Primary: Total response (no emetic episodes and no nausea); complete response (no emetic	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%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours afterward on each day of chemotherapy vs. ondansetron 32 mg IV prior to chemotherapy, then 8 mg PO 8-12 hours afterward on each day of chemotherapy *Other antiemetic medications were allowed			episodes with no rescue antiemetic medication); major response (1-2 emetic episodes with no rescue antiemetic medications; failure (≥2 emetic episodes in any 24-hour period)	Major response: Dolasetron (26.5%) vs. ondansetron (25.9%) Treatment failure: Dolasetron (27.7%) vs. ondansetron (27.2%)
Eisenberg et al.[37] (2003) Dolasetron 100 mg IV vs. palonosetron 0.25 mg IV vs. palonosetron 0.75 mg IV	RCT, DB, MC, PG Patients receiving moderately emetogenic chemotherapy, study drug given 30 minutes before chemotherapy, dexamethasone could be added 15 minutes before chemotherapy	N=592 5 days	Primary: Complete response (no emetic episodes and no need for rescue medication) during the first 24 hours after chemotherapy Secondary: Complete response during hours 24 to 120	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%, 21.9%, *P*=0.049)], [palonosetron 0.75 mg 57.1% vs. dolasetron 100 mg 52.9% (97.5% CI, -7.7%, 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 mg and 0.25 mg were significantly higher in the delayed phase (hours 24-120) 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 3 groups.
Lofters et al.[38] (1997) Dolasetron 2.4 mg/kg IV followed by oral	DB, RCT, PG Patients receiving 7 days of moderately emetogenic	N=696 7 days	Primary: Control of nausea and vomiting in the first 24 hours, complete response	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dolasetron (200 mg) (arm 1) vs. dolasetron 2.4 mg/kg IV and dexamethasone 8 mg IV followed by dexamethasone 8 mg PO (arm 2) vs. dolasetron 2.4 mg/kg IV and dexamethasone 8 mg IV followed by dexamethasone 8 mg PO and dolasetron 200 mg PO (arm 3) vs. ondansetron 32 mg IV or 8 mg PO BID without dexamethasone followed by ondansetron 8 mg PO BID (arm 4) vs. ondansetron 32 mg IV or 8 mg PO BID with dexamethasone 8 mg IV followed by ondansetron 8 mg PO	chemotherapy		was no episode of emesis Secondary: Mean nausea score (MNS) based on a visual analog scale, rates of complete protection after 7 days of treatment	MNS was more pronounced on the dolasetron arm, but the difference did not reach statistical significance (*P*=0.051). MNS was significantly reduced with the addition of dexamethasone to either dolasetron or ondansetron (*P*=0.001). Complete protection rates over 7 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 7 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
BID and dexamethasone 8 mg PO (arm 5) vs. ondansetron 32 mg IV or 8 mg PO BID with dexamethasone 8 mg IV followed by dexamethasone 8 mg PO (arm 6)				
del Giglio et al.[39] (2000) Granisetron various IV and PO regimens vs. ondansetron various IV and PO regimens	MA, RCT CINV	14 studies which included 6,467 patients with >25 patients per arm	Primary: Comparison of prophylaxis of acute or delayed nausea and vomiting in highly or moderately emetogenic chemotherapy	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 (*P* value not given). 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 (*P* value not given).
Jaing et al.[40] (2004) Granisetron 0.5-1 mg PO vs. ondansetron 0.15 mg/kg IV for 2 doses (1 hour prior to chemotherapy and 4 hours later) and then a single PO dose (8	PRO, RCT, OL, XO Patients 3-18 years old	N=33 24 hours	Primary: Number of emetic episodes within 24 hours of chemotherapy (complete efficacy was defined as no emetic episodes and no need for rescue medication) Secondary: Therapeutic success (defined as	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours after first dose)			0-2 emetic episodes), therapeutic failure (defined as 3 or more vomiting episodes)	
Dempsey et al.[41] (2004) Granisetron 10 mcg/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	Data from 6 centers in the United States N=224 (N=68 for ondansetron 8 mg IV, N=76 for ondansetron 32 mg IV, N=80 for granisetron 10 mcg/kg or 1 mg IV) 72 hours	Primary: Incidence of acute nausea or vomiting (occurring within 24 hours of completion of chemotherapy) Secondary: Incidence of delayed emesis (occurring 25-72 hours after chemotherapy), total control of CINV with or without dexamethasone	Primary: 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. Incidence of acute emesis was not different amongst the three groups (*P* value not given). Secondary: Incidence of delayed nausea was 6% for ondansetron 8 mg IV, 9% for ondansetron 32 mg, and 9% for granisetron, which were not statistically different for any group (*P* value not given). Incidence of delayed emesis was not different amongst the three groups (*P* value not given). 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 amongst the three groups (*P* value not given).
Lacerda et al.[42] (2000) Granisetron 3 mg IV vs. ondansetron 16 mg IV	DB, RCT, PG Patients undergoing autologous or allogenic stem cell transplantation received daily IV doses of 5-HT_3 antagonist during	N=100	Primary: Complete response (CR) (no episodes of nausea or vomiting) Secondary: Major response (MajR) (one	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 (*P*

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. ondansetron 24 mg IV vs. tropisetron 5 mg IV†	days of chemotherapy		episode), minimal response (MinR) (2-4 episodes) and failure (F) (more than 4 episodes of nausea or vomiting)	value not given). Secondary: There was a trend in the MajR of ondansetron 24 mg versus 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 (*P* values not given).
Walsh et al.[43] (2004) Granisetron 10 mcg/kg IV daily vs. ondansetron 0.15 mg/kg IV every 8 hours	RCT, PG, DB, PRO 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 3 and for the ondansetron arm was 1 (*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 1, 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.[44] (1999) Granisetron 7.5 mcg/kg/dose (≥18 years) or 10 mcg/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	DB, PRO, RCT Patients 2-65 years old 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 1-2 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 (1.17) and ondansetron (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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bolus then 0.03 mg/kg/hour (< 18 years)				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).
Kalaycio et al.[45] (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: Incidence of nausea was no different between ondansetron and granisetron (*P*=0.86). Secondary: Incidence of emesis was not statistically different between granisetron and ondansetron (*P*=0.67). There was no statistical difference between the groups in regards 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 granisetron and ondansetron.
Gralla et al.[46] (2003) Ondansetron 32 mg IV vs. palonosetron 0.25 mg IV vs. palonsetron 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 (CR)] during the 24 hour period after chemotherapy (acute period) Secondary: Efficacy in treatment of delayed CINV (≤ 5 days post chemotherapy),	Primary: CR rates were significantly higher for palonosetron 0.25 mg (81.0%) than ondansetron (68.6%) during the acute period (*P<0.01*). Secondary: CR rates were significantly higher for palonosetron than ondansetron at 24-120 hours (74.1% vs. 55.1%, *P<0.01*) and overall 0-120 hours (69.3% vs. 50.3%, *P<0.01*). CR 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			overall tolerability	
Aapro et al.[47] (2005) Palonosetron 0.25 mg IV vs. ondansetron 32 mg IV or dolasetron 100 mg IV	RETRO post hoc analysis of studies by Eisenberg et al.[37] and Gralla et al.[46] Patients ≥ 65 years receiving moderately emetogenic chemotherapy	N=171 5 days	Primary: Complete response during the acute period (0-24 hours after chemotherapy), delayed period (24-120 hours), and over all period (0-120 hours) with significance *P*≤ 0.025	Primary: During the overall post chemotherapy period, complete response rate was significantly higher in the palonosetron group than in the ondansetron /dolasetron group (70.9% vs. 51.2%, *P*=0.011). The proportion of patients with complete response during the acute time period was not significantly different between the palonosetron and ondansetron/dolasetron groups (84.8% vs. 74.4%, *P*>0.025). Complete response was significantly higher in the palonosetron group compared to the ondansetron/dolasetron group during the delayed period (72.2% vs. 53.5%, *P*=0.016).
Davidson et al.[48] (1999) Ondansetron 8 mg oral tablet (OT) BID for 3 days vs. Ondansetron 8 mg orally disintegrating tablet (ODT) BID for 3 days	DB, RCT, PRO, MC Patients receiving cyclophosphamide	N=427 3 days	Primary: Complete or major control of emesis on their worst of days 1 through 3	Primary: Complete or major control of emesis was achieved by 80% of OT patients and 78% of ODT patients (90% CI -8.6% to 4.4% with ±15% limit for equivalence). Complete control of emesis for days 1 through 3 was not significantly different between the treatment groups with 63% of OT and 64% of ODT patients. There was no significant difference in overall incidence of adverse effects between the 2 formulations. The most common adverse effects reported and those most frequently assessed as drug-related were headache (OT 11% vs. ODT 9%) and constipation (both 10%).
Radiation-Induced Nausea and Vomiting (RINV)				
Spitzer et al.[49] (2000) Granisetron 2 mg PO vs. ondansetron 8 mg PO vs.	DB, RCT, PRO, PG Patients ≥ 18 years 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 0 emetic episodes over 4 days Secondary: Percent of patients with 0 emetic episodes and no	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
historical control			rescue medication over 24 hours and 4 days	Within the first 4 days, fewer patients in the granisetron (27.8%) and ondansetron groups (26.7%) had 0 emetic episodes and needed no rescue medication compared to historical controls (0%) (*P*<0.01).
Postoperative Nausea and Vomiting (PONV)				
Erhan et al.[80] (2008) 0.9% NaCl (Control) vs. ondansetron 4 mg IV vs. granisetron 3 mg IV vs. dexamethasone 8 mg IV	RCT, DB, PC Patients 21-75 years old (ASA I-II) scheduled for laparoscopic cholecystectomy	N=80 24 hours	Primary: Incidence of nausea and vomiting at intervals 0-6 hours, 6-12 hours, and 12-24 hours; rescue antiemetic use	Primary: <u>0-6 hour Nausea/Vomiting:</u> Control 70%, ondansetron 30%, granisetron 20%, dexamethasone 15% (p<0.05 for all treatment groups vs. control) <u>0-6 hour Rescue Antiemetic:</u> Control 55%, ondansetron 15%, granisetron 10%, dexamethasone 10% (p<0.05 for all treatment groups vs. control) <u>6-12 hour Nausea/Vomiting:</u> Control 20%, ondansetron 5%, granisetron 10%, dexamethasone 15% <u>6-12 hour Rescue Antiemetic:</u> Control 15%, ondansetron 5%, granisetron 0%, dexamethasone 10% <u>12-24 hour Nausea/Vomiting:</u> Control 10%, ondansetron 0%, granisetron 0%, dexamethasone 0% <u>12-24 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.
Bhatnagar et al.[81] (2007) Granisetron 2 mg PO	RCT, DB Hospitalized female patients 18-65 years	N=90 24 hours	Primary: Complete response (no nausea, vomiting/retching,	Primary: Complete response (0-2 hours): Placebo (43%), granisetron (63%), ondansetron (90%); Ondansetron was found to be significantly better than granisetron (p value not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. ondansetron 4 mg PO vs. placebo	old (ASA I-II) scheduled for modified radical mastectomies		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);	given). Rescue medication use (0-2 hours): Placebo (40%), granisetron (17%), ondansetron (7%); Ondansetron was found to be significantly better than granisetron (p value not given). 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.
Oksuz et al.[82] (2007) Metoclopramide 10 mg IV vs. granisetron 40 mcg/kg IV vs. ondansetron 15 mcg/kg IV	PRO, RCT, DB Patients 21 – 72 years old and weighing 52-102 kg (ASA I-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=womiting); nausea/vomiting incidence, and antiemetic rescue	Primary: Prophylactic antiemetic treatment with granisetron resulted in a lower incidence (0%) of PONV than with ondansetron (3%) and metoclopramide (3%) during the first 3 hours. Granisetron resulted in a lower incidence (1%) of PONV in the 4-24 hour period than with ondansetron (3%) or metoclopramide (11%). Nausea and vomiting scores in the first 3-hour period revealed that each of the drugs had a similar antiemetic effect (p>0.05). Scores between 4-24 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.
White et al.[71] (2007) <u>Laparoscopic surgery study:</u> Transdermal scopolamine (TDS) 1.5 mg vs.	RCT, DB, PC Patients aged 18-65 years scheduled to undergo major laparoscopic (e.g., bariatric surgery) or plastic (e.g., abdominoplasty, reduction mammoplasty) surgery procedures	N=77 72 hours	Primary: Postoperative nausea and vomiting / retching; need for rescue antiemetics, complete response rates (i.e., absence of protracted nausea or repeated episodes of emesis requiring	Primary: There were no differences between the TDS 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 TDS and ondansetron treatment groups (51% and 47%, respectively). The requirement for rescue antiemetics was not significantly reduced in the TDS group compared to the ondansetron group during the 24-48 hour period (21% vs. 40%, p=0.07)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron 4 mg			antiemetic rescue medication)	
Diemunsch et al.[72] (2007) Aprepitant 40 mg PO vs. aprepitant 125 mg PO vs. ondansetron 4 mg IV	RCT, DB, MC, PC Patients aged ≥18 years old, ASA I-III, 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 0-24 hours after surgery; no vomiting over 0-24 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 non-inferiority of the aprepitant treatment compared to ondansetron treatment. The percentage of patients with no vomiting over 0-24 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). The percentage of patients with no vomiting over 0-48 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 PO vs. aprepitant 125 mg PO vs. ondandetron 4 mg IV	RCT, DB, PC, MC Patients ≥18 years old scheduled to undergo open abdominal surgery requiring an overnight hospital stay, met criteria of ASA physical status of I-III, 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 0-24 hours; no vomiting 0-48 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 0-24 hours, the treatments did not differ significantly in terms of no 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 0-48 hour time interval compared with 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).
Candiotti et al.[74] (2007) Granisetron 0.1 mg IV	RCT, DB, SC Patients aged 18-64 years with ASA I-II	N=88 24 hours	Primary: Complete response (no further PONV and no requests for	Primary: Complete response occurred in 57%, 60%, and 68% of patients in the ondansetron 4 mg, granisetron 1 mg, and granisetron 0.1 mg groups, respectively (p=0.773).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. granisetron 1 mg IV vs. ondansetron 4 mg IV	status who were scheduled to undergo nonemergency surgery, requiring general anesthesia of at least 30 min; women who developed PONV following surgery were enrolled		further medication)	There were no significant differences between the treatment groups for nausea scores, breakthrough rate of vomiting with or without nausea in the 30 min after rescue, and efficacy between rescue arms relating to vomiting.
Birmingham et al.[70] (2006) Dolasetron 12.5 mg IV vs. ondansetron 4 mg IV	RCT, BD, PRO Patients >18 years of age at high risk for PONV undergoing general anesthesia	N=100 24 hours	Primary: Satisfaction with medication (VAS score, 0-100 mm); Overall satisfaction (VAS score, 0-100 mm) Secondary: Complete response; emetic episodes; post-discharge emesis; delay in PACU 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 PACU discharge attributable to PONV (41 minutes vs. 21 minutes) were not different in patients receiving dolasetron compared to ondansetron (p=0.36, p=0.32, p=0.79, p=0.12, respectively).
Olutoye et al.[50] (2003) Dolasetron 45 mcg/kg IV vs. dolasetron 175 mcg/kg	RCT, DB, PRO, PG Patients 2-12 years old receiving day surgery	N=204	Primary: Complete response (no postoperative emetic symptoms)	Primary: There were no significant differences in complete response between ondansetron 100 mcg/kg, dolasetron 700 mcg/kg and dolasetron 350 mcg/kg. Ondansetron, dolasetron 700 mcg/kg and dolasetron 350 mcg/kg were all statistically better than dolasetron 175 mcg/kg and dolasetron 45 mcg/kg (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV vs. dolasetron 350 mcg/kg IV vs. dolasetron 700 mcg/kg IV vs. ondansetron 100 mcg/kg IV				
Meyer et al.[51] (2005) Dolasetron 12.5 mg IV vs. ondansetron 4 mg IV	RCT, DB, PRO Patients undergoing day surgery	N=92	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 PACU	Primary: The need for rescue antiemetic in the dolasetron group was 40% compared to the ondansetron group which was 70% (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 PACU was similar between groups (P=0.99).
Walker[52] (2001) Dolasetron 12.5 mg IV vs.	RETRO Medical charts of patients who underwent total abdominal	N=59 24 hours	Primary: Number of recorded episodes of PONV in 24 hours after surgery, time to occurrence	Primary: PONV occurred in 44% patients receiving dolasetron and 53% patients receiving ondansetron. Four patients (36%) receiving dolasetron experienced PONV in the first 2 hours after surgery, compared with 7 patients (39%) receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ondansetron 4 mg IV	hysterectomy or laparoscopic cholecystectomy		of PONV	ondansetron. Differences in primary endpoints did not reach statistical significance (*P* value not reported).
Karamanlioglu et al.[53] (2003) Dolasetron 1.8 mg/kg PO vs. ondansetron 0.15 mg/kg PO vs. placebo Medications were given 1 hour before induction of surgery	PRO, RCT, DB Children undergoing elective strabismus surgery, middle ear surgery, adenotonsillectomy or orchiopexy	N=150	Primary:	Primary: Over the 0-24 hour period, both dolasetron and ondansetron were significantly better than placebo (nausea 16% vs. 26% vs. 40%), vomiting 8% vs. 16% vs. 30%), and total nausea and vomiting scores (32% vs. 48% vs. 78%) (*P*<0.05 compared to placebo). There were no significant differences between dolasetron and ondansetron (no *P* values reported). There were no important adverse events.
White et al.[54] (2006) Granisetron 1 mg PO one hour before surgery vs. ondansetron 4 mg IV at the end of surgery	PRO, RCT, DB, MC Patients undergoing laparoscopic surgery	N=220 24 hours post surgery	Primary: Postoperative episodes of emesis, patient report of nausea, need for rescue antiemetic medication	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 4-24 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 (*P* values not given).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gan et al.[55] (2005) Granisetron 0.1 mg IV and dexamethasone 8 mg IV vs. ondansetron 4 mg IV and dexamethasone 8 mg IV	PRO, RCT, DB, PG, MC Patients undergoing abdominal hysterectomy, medications given 15 minutes prior to end of surgery	N=176 24 hours post surgery	Primary: Proportion of patients with no vomiting during 0-2 hours post surgery Secondary: Proportion of patients with no vomiting during 0-6 hours and overall 0-24 hours post surgery	Primary: From 0-2 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; -8.5-3.8). Secondary: From 0-6 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; -14.6-2.8). From 0-24 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; -14.4-6.9). There were no differences in adverse effects between the groups.
Gan et al.[56] (2002) Ondansetron ODT 8 mg before discharge and 12 hours later vs. placebo	PC, PRO, RCT, DB Patients undergoing outpatient gynecological laparoscopy	N=60 24 hours post surgery	Primary: Incidence of PONV, severity of nausea, rescue antiemetic, side effects, satisfaction PONV manage-ment assessed at 2 and 24 hours post surgery	Primary: Ondansetron ODT patients had significantly less post discharge emesis (3% vs. 23%), and less severe nausea after discharge compared to placebo patients (P <0.05). The ondansetron ODT group was more satisfied with PONV control than placebo (90% vs. 63%, P <0.05). Ondansetron ODT was less acceptable to patients although they would use it again (P<0.01).
Loewen et al.[57] (2000) 5-HT_3 antagonists (dosages and routes were not specified) vs. traditional agents	MA Review of randomized, double-blind, controlled clinical trials published in English and in MEDLINE or EMBASE from	41 trials met criteria 5-HT_3 antagonists N=2855, traditional agents N=3783	Primary: Postoperative nausea and vomiting that occurred within 48 hours after surgery 5-HT_3 receptor antagonists compared to	Primary: 5-HT_3 receptor antagonists showed a 46% reduction in the odds of PONV (OR 0.54, 95% CI 0.42-0.71, P<0.001). 5-HT_3 receptor antagonists showed a 39% reduction in PONV over droperidol (OR 0.61, 95% CI 0.42-0.89, P<0.001). 5-HT_3 receptor antagonists showed a 56% reduction in PONV over metoclopramide (OR 0.44, 95% CI 0.31-0.62, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol)	1966-October 1999		traditional antiemetics and specifically compared to droperidol and metoclopramide Secondary: 5-HT3 receptor antagonists compared to traditional antiemetics for rates of vomiting	Secondary: 5-HT_3 receptor antagonists showed a 38% reduction in vomiting compared to traditional antiemetics (OR 0.62, 95% CI 0.48-0.81, *P*<0.001). 5-HT_3 antagonists showed a beneficial effect over droperidol in rate of vomiting (OR 0.56, 95% CI 0.41-0.76, *P*<0.001). 5-HT_3 antagonists showed a beneficial effect over metoclopramide in rate of vomiting (OR 0.50, 95% CI 0.32-0.77, *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 0.32-0.64, *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 1.35-2.02, *P*<0.001).
Eberhart, et al.[58] (2004) Dolasetron 12.5 mg IV vs. droperidol 10 mcg/kg IV vs. dolasetron 12.5 mg and droperidol 10 mcg/kg IV vs. placebo	DB, RCT, PG Patients undergoing vitreoretinal surgery received study medication 5-10 minutes before the end of surgery	N=304	Primary: Mean PONV score (0-3, with 0 being no nausea or vomiting) with a significance level of *P*=0.01 Secondary: Complete prevention of PONV	Primary: Droperidol was statistically better than placebo (*P*<0.0001) in reduction of mean PONV score. Dolasetron was numerically better but not statistically better than placebo (*P*=0.017). Combination therapy was statistically better than placebo (*P*<0.0001) in reduction of mean PONV score. Droperidol and dolasetron were not statistically different from each other (*P*=0.096), although droperidol was numerically better in the reduction of mean PONV score. Secondary: Droperidol was statistically better than placebo (*P*<0.0006) in complete prevention of PONV. Dolasetron was numerically better but not statistically better than placebo (*P*=0.038). Combination therapy was statistically better than placebo (*P*<0.0001) in complete prevention of PONV. Droperidol and dolasetron were not statistically different from each other (*P*=0.17) although droperidol was numerically better in complete prevention of PONV.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hamid et al.[59] (1998) Dimenhydrinate 0.5 mg/kg vs. ondansetron 0.1 mg/kg IV vs. placebo All given at induction of anesthesia	RCT, DB, PC, PRO Children 2-10 years of age scheduled for adenotonsillectomy	N=47 24 hours	Primary: Incidence of retching and vomiting observed first 24 hours post surgery	Primary: The incidence of postoperative vomiting (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)
Kothari et al.[60] (2000) Dimenhydrinate 50 mg IV vs. ondansetron 4 mg IV All medications administered before induction of anesthesia	PRO, RCT, DB Consecutive patients undergoing laparoscopic cholecystectomy	N=128 24 hours after discharge	Primary: Frequency of PONV, need for rescue antiemetics, need for overnight hospitalization secondary to persistent nausea and vomiting, frequency PONV 24 hours after discharge	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 2 patients in the dimenhydrinate group required overnight hospitalization for persistent nausea and vomiting (*P*=NS). Rates of postoperative nausea and vomiting 24 hours after discharge were similar between the ondansetron and dimenhydrinate groups (10% and 14%, *P*=0.397 and 2% and 5%, *P*=0.375, respectively).
McCall et al.[61] (1999)	RCT, DB, PRO, PC Patients with a	N=100 8 hours	Primary: Incidence of PONV, POV	Primary: Statistically significant reductions in the incidence of PONV in the patients who received ondansetron or dimenhydrinate were found, as

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dimenhydrinate 0.5 mg/kg vs. ondansetron 0.1 mg/kg vs. placebo Study drugs were given at the end of surgery and again 4 hours later	mean age of 11.8 years undergoing reconstructive burn surgery with general anesthesia			compared with 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.
Van den Berg[62] (1996) Prochlorperazine 0.2 mg/kg IM vs. prochlorperazine 0.2 mg/kg IV vs. ondansetron 0.06 mg/kg IV vs. placebo All given with	RCT, DB, PRO Patients from 9-61 years of age received standardized general anesthesia for tympanoplasty	N=148 24 hours	Primary: Incidence of retching and vomiting in the PACU 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%-8%). The incidence of vomiting alone (without accompanied nausea) during this time was also similar between groups (11%-24%). The incidence of vomiting or retching immediately after extubation or during recovery occurred in 16% of placebo patients, 5% of patients in the IM prochlorperazine group, and 8% in the prochlorperazine and ondansetron IV groups, but the differences between groups was not significant (P>0.05 for all groups). The incidence of nausea accompanied by vomiting occurred in 53% of the placebo group and 16% and 19% in those given prochlorperazine IM and ondansetron IV, respectively (P<0.0005), and 30% in those given prochlorperazine IV (P<0.05). The study was not powered to detect a difference between groups. The percent of patients who experienced no nausea or vomiting was 27% for placebo, 57% for prochlorperazine IM, 43% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
induction of anesthesia				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.[63] (1998) Prochlorperazine maleate 10 mg IM vs. ondansetron 4 mg IV All administered at end of surgical procedure	RCT, DB Patients greater than 17 years old 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 with 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).

Drug regimen abbreviations: QD=once daily, BID=twice daily, IM=intramuscular, IV=intravenous, PO=oral
Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OBS=observational, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=crossover
Miscellaneous abbreviations: CINV=chemotherapy-induced nausea and vomiting, CR=complete response, MajR=major response, MNS=mean nausea score, MinR=minimal response, ODT=orally disintegrating tablet, PACU=post anesthesia care unit, 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Dolasetron	tablet, injection	Anzemet®	$$$$$	N/A
Granisetron	tablet, solution, injection	Kytril®*, Granisol®	$$$$$	$$$$$
Ondansetron	orally disintegrating tablet, tablet, solution, injection	Zofran®*, Zofran ODT®*	$$$$-$$$$$	$-$$$$
Palonosetron	injection	Aloxi®	$$$$$	N/A

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

X. Conclusions

The 5-HT_3 receptor antagonists are very effective for the treatment of CINV, RINV, and PONV. Treatment of CINV generally involves the use of multiple agents that affect different receptor types. Selection of the pharmacologic agent depends upon the relative emetogenic potential of the chemotherapy regimen. The 5-HT_3 receptor antagonists are considered first-line therapy for the prevention of acute emesis associated with moderately or highly emetogenic chemotherapy.[20-22] A large number of clinical trials have demonstrated similar efficacy and safety among the 5-HT_3 receptor antagonists for the treatment of CINV.[37,39-40,43-45,75-76,78-79] Guidelines do not give preference to one 5-HT_3 receptor antagonist over another for CINV.[20-22] If breakthrough emesis or nausea occur, adding an agent with a different mechanism of action may be appropriate.[1,4,6,14,17]

Granisetron and ondansetron are indicated for the treatment of RINV and have demonstrated similar efficacy in one clinical trial.[49] All 5-HT_3 receptor antagonists are indicated for the treatment of PONV, and clinical trials

have demonstrated similar efficacy among the agents for this indication.[50,52-55,70,74,80] According to current guidelines, there is no evidence of any difference in the efficacy and safety profiles of the 5-HT_3 receptor antagonists in the prophylaxis of PONV.[25]

Therefore, all brand 5-HT_3 receptor antagonists within the class reviewed are comparable to each other and to the generics and OTC 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. Pasricha PJ. Antiemetics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's the Pharmacologic Basis of Therapeutics. 11th ed. New York: McGraw Hill; 2006:1000-1003.
2. Longstreth GF, Hesketh PJ. Characteristics of antiemetic drugs. In: UpToDate, Talley NJ, (Ed), UpToDate, Waltham, MA, 2008.
3. Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. Am Fam Physician. 2004;1169-1174.
4. Mannix K. Palliation of nausea and vomiting in malignancy. Clin Med. 2006;6:144-147.
5. Gralla RJ, de Wit R, Herrstadt J, et al. Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5-HT_3 antagonist and a corticosteroid in patients receiving anthracycline or cyclophosphamide in addition to high-dose cisplatin. Cancer. 2005;104:864-868.
6. Longstreth GF. Approach to the adult patient with nausea and vomiting. In: Rose, BD, ed. UpToDate. Waltham, MA: UpToDate, 2007.
7. Aapro M. 5-HT_3-receptor antagonists in the management of nausea and vomiting in cancer and cancer treatment. Oncology. 2005:69;97-109.
8. Herrstedt J, Koeller JM, Roila F, et al. Acute emesis: moderately emetogenic chemotherapy. Support Care Cancer. 2005;13:97-103.
9. Roila F, Feyer P, Maranzano E, et al. Antiemetics in children receiving chemotherapy. Support Care Cancer. 2005;13:129-131
10. Einhorn LH, Rapoport B, Koeller J, et al. Antiemetic therapy for multiple-day chemotherapy and high-dose chemotherapy with stem cell transplant: review and consensus statement. Support Care Cancer. 2005;13:112-116.
11. Habib AS, El-Moalem HE, Gan TJ. The efficacy of the 5-HT_3 receptor antagonists combined with droperidol for PONV prophylaxis is similar to their combination with dexamethasone. A meta-analysis of randomized controlled trials. Can J Anesth. 2004;51(4):311-319.
12. Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. Can J Anesth. 2004;51(4):326-341.
13. Peterson K, McDonagh MS, Carson S, et al. Drug class review on newer antiemetics, final report. http://www.ohsu.edu/drugeffectiveness/reports/documents/Antiemetics%20Final%20Report.pdf (Accessed 8/5/06).
14. Jordan K, Kasper C, Schmoll H. Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment. Eur J Cancer. 2005;41:199-205.
15. Kris MG, Hesketh PJ, Herrstedt J, et al. Consensus proposals for the prevention of acute and delayed vomiting and nausea following high-emetic risk chemotherapy. Support Care Cancer. 2005;13:85-96.
16. Hickok JT, Roscoe JA, Morrow GR, et al. 5-hydroxytryptamine-receptor antagonists versus prochlorperazine for control of delayed nausea caused by doxorubicin: a URCC CCOP randomized controlled trial. Lancet Oncol. 2005;6:765-772.
17. Hesketh PJ. Prevention and treatment of chemotherapy-induced nausea and vomiting. In: UpToDate, Drews, RE (Ed), UpToDate, Waltham, MA, 2008.
18. Kirkbride P. Radiation-induced emesis. In: UpToDate, Rose, BD (Ed), UpToDate. Waltham, MA, 2006.
19. Feyer PC, Maranzano E, Molassiotis A. Radiotherapy-induced nausea and vomiting (RINV): antiemetic guidelines. Support Care Cancer. 2005;13:122-128.
20. 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.
21. National Comprehensive Cancer Network (NCCN) guidelines. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed December 2008.
22. The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncology. 2006;17:20-28.
23. Quigley EMM, Hasler WL, Parkman HP. American Gastroenterological Association (AGA) technical review: nausea and vomiting. In: Rose, BD, ed. UpToDate. Waltham, MA. UpToDate. 2006.
24. American Gastroenterological Association medical position statement: nausea and vomiting. Gastroenterology.2001;120(1):261-262.
25. Gan T, Meyer T, Apfel C, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg. 2003;97:62-71.

26. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2004;103(4):803-815.
27. Aloxi® [package insert]. Woodcliff Lake, NJ: Eisai Inc.; August 2008.
28. Anzemet® tablets [package insert]. Bridgewater, NJ: Sanofi-Aventis Pharmaceuticals; June 2006.
29. Kytril® [package insert]. Nutley, NJ: Roche Laboratories, Inc.; November 2005.
30. Zofran® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; February 2006.
31. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November 2008.
32. de Wit R, Aapro M, Blower PR. Is there a pharmacological basis for differences in 5-HT_3-receptor antagonist efficacy in refractory patients? Cancer Chemother Pharmacol. 2005;56:231-238.
33. Gridelli C, Aapro M. Factors influencing the choice of 5-HT_3-receptor antagonist antiemetics: focus on elderly cancer patients. Support Care Cancer. 2004;12:487-496.
34. Janicki PK. Cytochrome P450 2D6 metabolism and 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. Med Sci Monit. 2005;11(10):RA322-328.
35. Janicki PK, Schuler HG, Jarzembowski TM, et al. Prevention of postoperative nausea and vomiting with granisetron and dolasetron in relation to CYP2D6 genotype. Anesth Analg. 2006;102:1127-1133.
36. Tatro DS, ed. Drug Interaction Facts. St. Louis, Mo: Wolters Kluwer Health, Inc.; 2006.
37. 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;98:2473-2482.
38. 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;15:2966-2973.
39. 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;89:2301-2308.
40. Jaing T, Tsay P, Hung I, et al. Single-dose oral granisetron versus multidose intravenous ondansetron for moderately emetogenic cyclophosphamide-based chemotherapy in pediatric outpatients with acute lymphoblastic leukemia. Pediatr Hemato Onc. 2004;21:227-235.
41. 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;61:781-786.
42. 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;32:2680-2681.
43. 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;34:963-968.
44. 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;386-393.
45. 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;124:265-269.
46. 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;14:1570-1577.
47. Aapro MA, Macciocchi A, Gridelli C. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting in elderly patients. J Supp Oncology. 2005:3(5):369-374.
48. Davisdon 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.
49. 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;26:203-210.
50. 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;97:390-396.

51. Meyer TA, Roberson CR, Rajab MH, et al. Dolasetron versus ondansetron for the treatment of postoperative nausea and vomiting. Anesth Analg. 2005;100:373-377.
52. Walker JB. Efficacy of single-dose intravenous dolasetron versus ondansetron in the prevention of postoperative nausea and vomiting. Clin Ther. 2001;23(6):932-938.
53. 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;20:831-835.
54. White PF, Tang J, Hamza MA, et al. The use of oral granisetron versus intravenous ondansetron for antiemetic prophylaxis in patients undergoing laparoscopic surgery: the effect on emetic symptoms and quality of recovery. Anesth Analg. 2006;102:1387-1393.
55. Gan TJ, Coop A, Philip BK, et al. A randomized, double-blind study of granisetron plus dexamethasone versus ondansetron plus dexamethasone to prevent postoperative nausea and vomiting in patients undergoing abdominal hysterectomy. Anesth Analg. 2005;101:1323-1329.
56. Gan TJ, Franiak R, Reeves J. Ondansetron orally disintegrating tablet versus placebo for the prevention of post-discharge nausea and vomiting after ambulatory surgery. Anesth Anal. 2002;94:1199-1200.
57. 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;47:1008-1018.
58. 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;111:1569-1575.
59. 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.
60. Kothari SN, Boyd WC, Bottcher PJ. Antiemetic efficacy of prophylactic dimenhydrinate (Dramamine®) vs. ondansetron (Zofran®). Surg Endosc. 2000;14:926-929.
61. 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 versus dimenhydrinate. J Burn Care Rehabil. 1999;20(4):309-315.
62. 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):939-945.
63. 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):2124-2128.
64. de Wit R, de Boer AC, vd Linden GHM, et al. Effective cross-over to granisetron after failure to ondansetron, a randomized double blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy. Brit J Cancer. 2001;85:1099-1101.
65. Anzemet® injection [package insert]. Bridgewater, NJ: Sanofi-Aventis Pharmaceuticals; June 2006.
66. Granisol® [package insert]. Madison, MN: Hawthorn Pharmaceuticals, Inc. December 2007.
67. Kytril® injection [package insert]. Nutley, NJ: Roche Laboratories, Inc.; November 2005.
68. Zofran® injection [package insert]. Research Triangle Park, NC: GlaxoSmithKline; February 2006.
69. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 2008.
70. Birmingham S, Mecklenburg B, Lujan E, et al. Dolasetron versus ondansetron as single-agent prophylaxis for patients at increased risk for postoperative nausea and vomiting: a prospective, double-blind, randomized trial. Military Medicine 2006;171:913-916.
71. 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;104:92-96.
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 antagnoist, aprepitant, versus ondansetron fro the prevention of postoperative nausea and vomiting. Anesth Analg 2007;104:1082-9.
74. Candiotti K, Nhuch F, Kamat A, et al. Granisetron versus ondansetron treatment for breakthrough postoperative nausea and vomiting after prophylactic ondansetron failure: a pilot study. Anesth Analg 2007;104:1370-3.
75. Aapro M, Grunberg S, Manikhas G, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Annals of Oncology 2006;17:1441-1449.

76. 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;25:135-139.
77. Meiri E, Jhangiani H, Vredenburgh J, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin 2007;23:533-543.
78. 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.
79. Mandanas R, Beveridge R, Rifkin R, et al. A randomized, multicenter, open-label comparison of the antiemetic efficacy of dolasetron versus ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy. Support Cancer Therapy 2005;2:114-21.
80. 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;22:1487-1492.
81. Bhatnagar S, Gupta D, Mishra S, et al. Preemptive antiemesis in patients undergoing modified radical mastectomy: oral granisetron versus oral ondansetron in a double-blind, randomized, controlled study. J Clin Anesth 2007;19:512-516.
82. 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.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiemetics, Miscellaneous
AHFS Class 562292
February 11, 2009

I. Overview

The pathophysiology of nausea and vomiting is complex and involves multiple neurotransmitters and organ systems. Five neurotransmitter receptor sites play a key role in the vomiting reflex. These receptor sites include M1 (muscarinic), D2 (dopamine), H1 (histamine), 5-HT_3 (serotonin), and NK1 (substance P).[6] 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 to the 5-HT_3 receptor antagonists and aprepitant.[36]

The miscellaneous antiemetics are FDA-approved for a variety of disorders, including the treatment of chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), motion sickness, and AIDs-related anorexia.[1,3-5,41-42] Aprepitant is a selective, high-affinity NK1 receptor antagonist; fosaprepitant is a prodrug of aprepitant. Dronabinol and nabilone are orally active cannabinoids, which have complex effects on the central nervous system. 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.

The miscellaneous antiemetics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Dronabinol is available in a generic formulation.

Table 1. Miscellaneous Antiemetics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aprepitant	capsule, capsule dose pack	Emend®	none
Dronabinol	capsule	Marinol®*	dronabinol
Fosaprepitant	injection	Emend®	none
Nabilone	capsule	Cesamet®	none
Scopolamine	tablet, transdermal patch	Scopace®, Transderm-Scop®	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 (NCCN): **Clinical Practice Guidelines in Oncology: Antiemesis[8] (2009)**	• For highly emetogenic chemotherapy on day 1, the combination of aprepitant (or fosaprepitant), dexamethasone and a 5-HT_3 receptor antagonist, with or without lorazepam is recommended. The regimen and doses are often modified on days 2-4 after chemotherapy. • For moderate emetogenic chemotherapy on day 1, aprepitant should be added (to dexamethasone and a 5-HT_3 receptor antagonist) for select patients receiving other chemotherapies of moderate emetic risk (carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate) because these agents are more emetogenic than the other moderately emetogenic agents. • For moderate emetogenic chemotherapy, post-chemotherapy

Clinical Guideline	Recommendation(s)
	prevention depends on what antiemetics were used before chemotherapy; treatment options include aprepitant continued on days 2-3 with or without dexamethasone or lorazepam. • Aprepitant may be used for multi-day chemotherapy regimens likely to be highly-emetogenic and associated with significant risk for delayed nausea and emesis. • Dronabinol, nabilone, and aprepitant are treatment options for breakthrough nausea and vomiting.
American Society of Clinical Oncology (ASCO): **Guideline for Antiemetics in Oncology: Update 2006[2]** **(2006)**	<u>High (> 90%) emetic risk</u> • The three-drug combination of a 5-HT_3 serotonin receptor antagonist, dexamethasone, and aprepitant is recommended before chemotherapy. In all patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant is recommended. <u>Moderate (> 30% to 90%) emetic risk</u> • The three-drug combination of a 5-HT_3 receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving anthracycline and cyclophosphamide (AC). In patients receiving AC, aprepitant as a single agent is recommended on days 2 and 3. <u>Multiple consecutive days of chemotherapy</u> • 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 2 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-HT_3 serotonin receptor antagonists, dexamethasone, and aprepitant.
Multinational Association of Supportive Care in Cancer (MASCC): **Prevention of Chemotherapy- and Radiotherapy-Induced Emesis: The Results of the 2004 Perugia International Antiemetic Consensus Conference[9]** **(2006)**	<u>High Emetogenic Risk</u> • To prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended. <u>Moderate Emetogenic Risk</u> • Women receiving a combination of an anthracycline plus cyclophosphamide should receive a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy. • 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 prevent delayed emesis, on the basis of its superiority to dexamethasone alone.
American College of Obstetricians and Gynecologists: **ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy [13]** **(2004)**	• There are no specific recommendations about the use of the miscellaneous antiemetics in this guideline.
The International Anesthesia Research Society: **Consensus Guidelines for Managing Postoperative**	• Transdermal scopolamine applied the evening before surgery or 4 hours before the end of anesthesia has an antiemetic effect. Its limitations are a 2- to 4-hour onset of effect, as well as its medical contraindications and age-related considerations.

Clinical Guideline	Recommendation(s)
Nausea and Vomiting[14] (2003)	• An emetic episode more than 6 hours after surgery can be treated with any of the drugs used for prophylaxis except dexamethasone and transdermal scopolamine. • Cannabinoids (nabilone and dronabinol), although promising in the control of chemotherapy-induced sickness, have not shown antiemetic efficacy in the PONV setting.
American Gastroenterological Association (AGA): **Technical Review: Nausea and Vomiting[10] (2001)**	• Scopolamine is used principally for prophylaxis and treatment of motion sickness. • 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. • 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 Institute: **American Gastroenterological Association Medical Position Statement: Nausea and Vomiting[11] (2001)**	• Motion sickness and related disorders are treated primarily with histamine H_1 and cholinergic receptor antagonists (e.g., scopolamine). • There are no specific recommendations about the use of the other miscellaneous antiemetics in this guideline.

III. Indications

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

Table 3. FDA-Approved Indications for the Miscellaneous Antiemetics[1,3-5,41-42]

Generic Name	Chemotherapy-Induced Nausea and Vomiting (CINV)	Postoperative Nausea and Vomiting (PONV)	Motion Sickness Nausea	Anorexia (AIDS-related)
Aprepitant	✔	✔		
Dronabinol	✔			✔
Fosaprepitant	✔			
Nabilone	✔ [a]			
Scopolamine*		✔ [b]	✔	

AIDS=acquired immune deficiency syndrome
[a] In patients who have failed to respond adequately to conventional antiemetic treatments. Not intended to be used on as needed basis or as a first antiemetic product prescribed for a patient.
[b] Transdermal formulation.
* Scopolamine tablets are also indicated for use as an anticholinergic central-nervous system depressant; in the symptomatic treatment of postencephalitic parkinsonism and paralysis agitans; in spastic states; and, locally as a substitute for atropine in ophthalmology. Scopolamine tablets inhibit excessive motility and hypertonus of the gastrointestinal tract in such conditions as the irritable colon syndrome, mild dysentery, diverticulitis, pylorospasm, and cardiospasm.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antiemetics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Miscellaneous Antiemetics[1,3-5,41-44]

Drugs(s)	Peak Concentration (hours)	Onset (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Aprepitant	3-4	No data	No data	0	7 metabolites	9-13
Dronabinol	2-4	0.5-1	4-6	10-15	1 metabolite	19-36
Fosaprepitant	No data	No data	No data	57	aprepitant	9-13
Nabilone	2	1-1.5	8-12	20-24	Isomeric carbinol	2 (parent) 35 (metabolites)
Scopolamine, oral	1-2	1	8	<1	0	No data
Scopolamine, transdermal	24	4	72	<5	0	9.5

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Miscellaneous Antiemetics[1,3-5,41-43]

Generic Name	Significance Level	Interaction	Mechanism
Aprepitant	1	Cisapride	Aprepitant may inhibit the metabolism of cisapride, increasing the risk of life-threatening cardiac arrhythmias.
Aprepitant	1	Pimozide	Aprepitant may inhibit the metabolism of pimozide, increasing the risk of life-threatening cardiac arrhythmias.
Fosaprepitant	1	Cisapride	Aprepitant (active metabolite of fosaprepitant) may inhibit the metabolism of cisapride, increasing the risk of life-threatening cardiac arrhythmias.
Fosaprepitant	1	Pimozide	Aprepitant (active metabolite of fosaprepitant) may inhibit the metabolism of pimozide, increasing the risk of life-threatening cardiac arrhythmias.
Aprepitant	2	Dexamethasone, hydrocortisone, methylprednisolone	Aprepitant's inhibition of first pass and systemic metabolism via cytochrome P450 3A4 may result in elevated plasma concentrations of dexamethasone, hydrocortisone, and methylprednisolone.
Scopolamine	2	Anticholinergics	The anticholinergic activity of scopolamine may predispose the patient to excessive anticholinergic activity.

Generic Name	Significance Level	Interaction	Mechanism
Scopolamine	2	Phenothiazines	Scopolamine may antagonize the effects of phenothiazines by direct central nervous system pathways involving cholinergic mechanisms. An acceleration of phenothiazine gut metabolism has also been postulated.
Scopolamine	2	Haloperidol	The coadministration of scopolamine and haloperidol has lead to decreased serum concentrations of haloperidol and development of tardive dyskinesia.

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 Table 6.

Table 6. Adverse Drug Events (%) Reported with the Miscellaneous Antiemetics[1,3-5,41-44]

Adverse Event(s)	Aprepitant	Dronabinol	Fosaprepitant	Nabilone	Scopolamine
Cardiovascular					
Bradycardia	-	-	>3	-	-
Hypotension	-	-	-	8	-
Orthostatic hypotension	-	>10	-	5-42	-
Tachycardia	-	>10	-	✔	✔ [a]
Central Nervous System					
Anxiety	-	>10	-	✔	-
Asthenia	-	-	✔	8	-
Ataxia	-	4	-	13-14	-
Confusion	-	30	-	-	-
Delusional disorder	-	-	-	✔	-
Depersonalization	-	-	-	2	-
Depression	-	7	-	14	-
Derealization	-	-	-	✔	-
Detachment	-	>10	-	-	-
Difficulty concentrating	-	>10	-	12	-
Dizziness	3-7	21	7	36	-
Drowsiness	-	48	-	-	✔ [a] 67[b]
Dysphoric mood	-	-	-	9	-
Dyssomnia	-	-	-	11	-
Euphoria	-	-	-	11-38	-
Hallucinations	-	5	-	✔	-
Headache	-	1-10	3	6-7	-
Impaired cognition	-	-	-	✔	-
Impulse control disorder	-	-	-	✔	-
Insomnia	-	-	-	✔	-
Malaise/fatigue	18-22	-	-	-	-
Memory lapse	-	4	-	✔	-
Mood change	-	>10	-	-	-
Panic	-	-	-	✔	-
Paresthesia	-	-	-	✔	-
Psychotic disorder	-	-	-	✔	-
Sedation	-	53	-	-	-
Somnolence	-	-	-	62-66	-

Adverse Event(s)	Aprepitant	Dronabinol	Fosaprepitant	Nabilone	Scopolamine
Vertigo	-	1-10	-	52-59	-
Dermatological					
Angioedema	-	-	✔	-	-
Contact dermatitis	-	-	-	-	✔ [b]
Flushing	3	-	3	-	✔ [a]
Injection site induration	-	-	1	-	-
Injection site pain	-	-	8	-	-
Stevens-Johnson Syndrome	-	-	✔	-	-
Urticaria	-	-	✔	-	-
Gastrointestinal					
Abdominal pain	5	-	5	-	-
Constipation	10-12	-	-	-	-
Diarrhea	6-10	<1	10	-	-
Dyspepsia	8	-	-	-	-
Epigastric discomfort	4	-	4	-	-
Gastritis	4	-	4	-	-
Indigestion	-	-	8	-	-
Loss of appetite	-	-	10	8	-
Mucous membrane disorder	3	-	-	-	-
Nausea	7-13	-	13	-	-
Stomatitis	5	-	5	-	-
Throat pain	3	-	-	-	-
Xerostomia	-	-	-	22-36	✔ [a] 67[b]
Hematologic					
Hemoglobin decreased	5	-	-	-	-
Leukopenia	9	-	-	-	-
Neutropenia	3-9	-	3	-	-
Laboratory Test Abnormalities					
Elevated ALT	6	-	-	-	-
Elevated AST	3	-	-	-	-
Elevated BUN	5	-	-	-	-
Elevated serum creatinine	4	-	-	-	-
Proteinuria	7	-	-	-	-
Musculoskeletal					
Myalgia	-	<1	-	-	-
Paresthesia	-	1-10	-	-	-
Weakness	3-18	1-10	-	-	-
Other					
Alopecia	24	-	-	-	-
Blurred vision	-	-	-	-	✔
Dehydration	6	-	6	-	-
Diaphoresis	<1	-	-	-	-
Hiccups	11	-	11	-	-
Mydriasis	-	-	-	-	✔
Tinnitus	-	<1	-	-	-
Urinary retention	-	-	-	-	✔ [a]
Visual disturbance	-	-	-	13	-

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood nitrogen urea, PO=oral, TD=transdermal
[a] Oral formulation.
[b] Transdermal formulation.
✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antiemetics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Miscellaneous Antiemetics[1, 3-5,41-42]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Aprepitant	CINV Given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist, the recommended dose is 125 mg orally 1 hour prior to chemotherapy treatment (day 1) and 80 mg once daily in the morning on days 2 and 3 PONV 40 mg orally within 3 hours prior to induction of anesthesia	Safety and efficacy in children have not been established.	Capsule: 40 mg, 80 mg, 125 mg Dose pack: two 80 mg capsules and one 125 mg capsule
Dronabinol	CINV Initial: 5 mg/m^2 given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses/day If 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 Maximum: 15 mg/m^2 per dose Appetite Stimulation: Initial: 2.5 mg orally twice daily, before lunch and dinner. If adverse effects occur and do not resolve in 1 to 3 days with continued use, the dose may be reduced to 2.5 mg before dinner or at bedtime. Maximum: 20 mg daily	CINV Initial: 5 mg/m^2 given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses/day If 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 Maximum: 15 mg/m^2 per dose Dronabinol should be used with caution in pediatric patients because it has not been studied in this patient population. Caution is recommended in prescribing dronabinol for children because of the psychoactive effects.	Capsule: 2.5 mg, 5 mg, 10 mg
Fosaprepitant	CINV Fosaprepitant (115 mg) may be substituted for oral aprepitant (125 mg) 30 minutes prior to chemotherapy on Day 1 in addition to a corticosteroid and a 5-HT3 antagonist	Safety and efficacy in children have not been established.	Injection: 115 mg/10 ml
Nabilone	CINV 1 or 2 mg twice daily on the day of chemotherapy, the initial dose should be given 1 to 3 hours before the chemotherapeutic agent is administered. A dose of	Safety and effectiveness have not been established in patients younger than 18 years of age. Caution is recommended in prescribing nabilone to children because of psychoactive effects.	Capsule: 1 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	1 or 2 mg the night before may be useful. The maximum recommended daily dose is 6 mg given in divided doses three times daily. Nabilone may be administered 2 or 3 times daily 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	Motion Sickness Oral: 0.4 – 0.8 mg Transdermal: Apply one patch behind one ear at least 4 hours before antiemetic effect is required PONV Transdermal: Apply patch the evening before scheduled surgery Maximum: 1 patch at any time	Safety and efficacy of scopolamine soluble tablets or the transdermal system in children have not been established.	Oral: 0.4 mg tablet Patch: 1.5 mg/72 hours

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials with the Miscellaneous Antiemetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting (CINV)				
Meiri et al.[49] (2007) <u>Day 2 (fixed dose)</u> Dronabinol 2.5 mg PO QID vs. ondansetron 8 mg PO BID vs. dronabinol 2.5 mg PO QID + ondansetron 8 mg PO BID vs. placebo <u>Days 3-5 (flexible dose)</u> dronabinol 2.5-5 mg PO QID vs.	RCT, DB, PC, PG Patients ≥18 years old with malignancy that did not involve the bone marrow and be undergoing chemotherapy including a moderately to highly emetogenic regimen	N=64 (out of planned 464 patients) 5 days *Early termination of study and insufficient patient enrollment due to presence of placebo group	Primary: Total response 2-5 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, ECOG, and QoL	Primary: Total response during active treatment did not differ between treatment groups (p=NS) due to small sample size. Improvement (range 47-58%) in three active treatment groups compared to placebo (20%) implies clinically relevant improvement (days 2-5 LOCF). 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 versus placebo (p<0.05). No significant difference ws 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 4 and 5. Active treatment reduced the duration of vomiting/retching to 0 hours in all groups by days 4 and 5. Duration of nausea was comparable among all groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ondansetron 4-8 mg PO BID vs. dronabinol 2.5-5 mg PO QID + ondansetron 4-8 mg PO BID vs. placebo *Day 1 (prechemotherapy) regimen consisted of dexamethasone 20 mg and ondansetron 16 mg administered to all study participants. Dronabinol 2.5 mg was also administered on day 1 in the 3 active treatment arms.				Changes from baseline in ECOG 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 MSDS (QoL) was observed only in patients receiving dronabinol vs. combination therapy (+3.6; p=0.033, in favor of dronabinol).
Herrington et al.[48] (2007) Aprepitant 125 mg PO on day 1, then 80 mg PO days 2-3 (Arm A) vs. aprepitant 125 mg PO day 1, then placebo days 2-3 (Arm B)	RCT, DB, PC Patients ≥18 years old with histologically or cytologically confirmed malignant disease and an ECOG performance status of 0-2	N=75 5 days	Primary: Proportion of patients without emesis in the acute (day 1) and delayed (days 2-5) phases after chemotherapy Secondary: Assessment of prevention of acute	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
*All patients received dexamethasone 12 mg PO and palonosetron 0.25 mg IV before chemotherapy			and delayed nausea and the use of breakthrough antiemetics	The frequency of rescue Antiemetics was similar among the treatment groups (p=NS).
Herrstedt et al.[16] (2005) Aprepitant (APR) day 1: APR 125 mg, ondansetron (OND) 8 mg, and dexamethasone (DEX) 12 mg before chemotherapy and OND 8 mg 8 hrs later; days 2-3: APR 80 mg QD vs. control regimen day 1: OND 8 mg and DEX 20 mg before chemotherapy and OND 8 mg 8 hrs later; days 2-3: OND 8 mg BID	RCT, DB, PRO, MC, DD, PG Patients with breast carcinoma naive to emetogenic chemotherapy and treated with cyclophosphamide alone or 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 (CR; no emesis or use of rescue therapy) in cycle 1, efficacy end points for the multiple-cycle extension were the probabilities of a CR in cycles 2-4 and a sustained CR rate across multiple cycles	Primary: 744 (85.9%) entered the multiple-cycle extension, and 650 (75.1%) completed all 4 cycles. Overall, the CR was greater with the APR regimen over the 4 cycles: 50.8% versus 42.5% for cycle 1, 53.8% versus 39.4% for cycle 2, 54.1% versus 39.3% for cycle 3, and 55.0% versus 38.4% for cycle 4. The cumulative percentage of patients with a sustained CR over all 4 cycles was greater with the APR regimen (*P*=0.017). The APR regimen was more effective than a control regimen for the prevention of nausea and emesis induced by moderately emetogenic chemotherapy over multiple chemotherapy cycles.
Gralla et al.[17] (2005) APR 125 mg plus OND 32 mg and DEX 12 mg on day 1; APR 80 mg and DEX 8 mg QD on days 2-3; and	RCT, DB, PG Pooled data from two identically designed studies Cisplatin-naive patients >18 years	N=1,043 4 days of treatment and looking at a response 120 hours after chemotherapy	Primary: Complete response (CR) defined as no vomiting and no rescue therapy on days 1-5	Primary: In the total combined study population regardless of treatment group or use of concomitant chemotherapy, CR was achieved in 58% (n=602) of patients. Analysis by treatment group showed 20% greater efficacy with the aprepitant regimen (68% vs. 48%; *P*<0.001). Among the approximately 13% (n=142) of patients (n=81 for APR; n=80 for control) who received additional emetogenic chemotherapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DEX 8 mg on day 4 vs. control regimen of OND 32 mg intravenously (IV) and DEX 20 mg PO on day 1; DEX 8 mg BID on days 2-4	old receiving their first cisplatin-based chemotherapy			(doxorubicin or cyclophosphamide), the aprepitant regimen provided a 33% improvement in the complete response rate compared with the control regimen (*P*<0.001).
Warr et al.[18] (2005) Day 1, APR 125 mg, OND 8 mg, and DEX 12 mg before chemotherapy and OND 8 mg 8 hours later; days 2 through 3, APR 80 QD vs. control regimen day 1, OND 8 mg and DEX 20 mg before chemotherapy and OND 8 mg 8 hours later; days 2 through 3, OND 8 mg BID	RCT, PRO, DB, DD, PG Breast cancer patients naive to emetogenic chemotherapy and treated with a regimen of cyclophosphamide alone, cyclophosphamide plus doxorubicin, or cyclophosphamide plus epirubicin	N=857 3 days of treatment, patients observed for 120 hours after initiation of chemotherapy in cycle 1	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 1 Secondary: Proportion of patients with an average item score higher than 6 of 7 on the Functional Living Index-Emesis questionnaire	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.
De Wit et al.[20] (2004) APR 125 mg, OND 32 mg IV, DEX 12 mg on day 1, APR 80 mg and	RCT, DB, MC Cancer patients receiving a first cycle of cisplatin-based (> or = 70	N=1,038 4 days of treatment and looking at a response 120	Primary: Combined exploratory endpoint of no emesis and no significant nausea	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 (n=516) and 46% in the standard therapy group (n=522), and thereafter, rates for the aprepitant regimen remained higher throughout

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DEX 8 mg on days 2-3, DEX 8 mg on day 4 vs. standard group received OND 32 mg IV and DEX 20 mg on day 1, DEX 8 mg BID on days 2-4	mg/m^2) chemotherapy	hours after chemotherapy	(i.e., nausea which interfered with a patient's normal activities) over the 5 days following cisplatin, for up to six cycles of chemotherapy	(59% [n=89] versus 40% [n=78] for the standard therapy, by cycle 6). 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.
Hesketh et al.[19] (2003) APR plus OND and DEX on day 1; APR and DEX on days 2 to 3; DEX on day 4 vs. standard therapy of OND and DEX on day 1; DEX on days 2 to 4	MC, RCT, DB, PG Patients receiving cisplatin > or =70 mg/m^2 for the first time	N=530 4 days of treatment, patients observed 120 hours after chemotherapy	Primary: Complete response (no emesis and no rescue therapy) on days 1 to 5 post cisplatin	Primary: The percentage of patients with complete response on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n = 260] vs. 52.3% in the standard therapy group [n=260]), as were the percentages on day 1, and especially on days 2 to 5 (P<0.001 for all three comparisons). Compared with standard dual therapy, addition of aprepitant was generally well tolerated and provided consistent protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy.
Poli-Bigelli et al.[21] (2003) APR 125 mg, OND 32 mg IV, and DEX 12 mg PO on day 1; APR 80 mg and DEX 8 mg PO QD on days 2-3; and DEX 8 mg PO on day 4 vs. standard therapy:	RCT, MC, DB, PG Patients with cancer who were scheduled to receive treatment with high-dose cisplatin chemotherapy	N=1,091 4 days of treatment and looking at a response 120 hours after chemotherapy	Primary: Primary endpoint was complete response (no emesis and no rescue therapy) during the 5-day period post cisplatin	Primary: During the 5 days after chemotherapy, the percentages of patients who achieved a complete response were 62.7% in the aprepitant group (163 of 260 patients) versus 43.3% in the standard therapy group (114 of 263 patients, P< 0.001). For day 1, the complete response rates were 82.8% for the aprepitant group and 68.4% for the standard therapy group (P<0.001); for days 2-5, 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 2 treatment groups (72.8% in the aprepitant group [206 of 283 patients] and 72.6% in the standard therapy group [207 of 285 patients]) as were rates of serious adverse events, discontinuations due to adverse events,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
OND 32 mg IV and DEX 20 mg PO on day 1, and DEX 8 mg PO BID on days 2-4				and deaths. In patients with cancer who were receiving high-dose cisplatin-based chemotherapy, therapy consisting of aprepitant (125 mg on day 1 and 80 mg on days 2-3) plus a standard regimen of ondansetron and dexamethasone provided greater antiemetic protection compared with standard therapy alone and was generally well tolerated.
Martin et al.[22] (2003) APR and DEX plus OND on day 1 and APR and DEX on days 2-5 vs. standard antiemetic therapy of DEX and OND on day 1 and DEX on days 2-5	RCT, DB Patients treated with cisplatin	N=381 5 days of treatment, FLIE was completed on day 6	Primary: The Functional Living Index-Emesis (FLIE)	Primary: Compared with 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 FLIE total score (84% vs. 66%, *P*<0.01). Use of the FLIE demonstrated that improved control of emesis was highly effective in reducing the impact of CINV on patients' daily activities.
Gilbert et al.[23] (1995) Metoclopramide (80 mg/m^2 IV loading dose followed by 20 mg/m^2/hour) each with either dronabinol 5 mg/m^2 or placebo capsules for two doses before carmustine on the last day of chemotherapy; all subjects received scheduled lorazepam and diphenhydramine	RCT, DB Patients with cancer receiving high dose cisplatin, cyclophosphamide, and carmustine with autologous bone marrow support	N=126 4-day study period	Primary: Efficacy was measured by the Emetic Process Rating Scale and the Rhodes Index of Nausea and Vomiting (INV) Form 2	Primary: The median number of emetic episodes on the metoclopramide study arm were: 1 (0-7, day 6), 1 (0-6, day 5), 2 (0-9, day 4), and 2 (0-10, with dronabinol day 3) or 2 (0-7, no dronabinol day 3) and on the prochlorperazine study arm were: 4 (0-12, day 6), 0 (0-8, day 5), 0 (0-12, day 4) and 2.5 (0-9, with dronabinol day 3) or 2 (0-12, no dronabinol day 3). Metoclopramide was significantly better on the first day of therapy (day 6, *P*<0.002) and prochlorperazine was significantly better on the third day of therapy (day 4, *P*<0.002). There was no significant difference among any of the four arms on the last day of chemotherapy (day 3), or when the median number of emetic episodes over the total study period were compared.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
throughout the 4-day study period vs. 4-day continuous infusion prochlorperazine (6 mg/m^2 IV loading dose followed by 1.5 mg/ m^2/hour)				
Lane et al.[24] (1991) Dronabinol 10 mg every 6 hours plus placebo (group 1) vs. placebo plus prochlorperazine 10 mg every 6 hours (group 2) vs. dronabinol and prochlorperazine, each 10 mg every 6 hours (group 3)	RCT, DB, PG, MC Individuals 18-69 years of age, being treated for cancer with 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 versus 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).
Niiranen et al.[50] (1985) Nabilone 2 mg every 12 hours	RCT, DB, XO Lung cancer patients receiving chemotherapy with cisplatinum,	N=24 Two consecutive chemotherapy cycles	Primary: Reduction of vomiting episodes; adverse events; patient preference	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. Prochlorperazine 15 mg every 12 hours	vincristine, cyclophosphamide, adriamycin, vindesine, and etoposide			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.
Einhorn et al.[51] (1981) Nabilone vs. prochlorperazine	R, PRO, DB Patients receiving chemotherapy	N=80 Two consecutive chemotherapy cycles	Primary: Relief of nausea and vomiting; adverse events	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 were more pronounced with nabilone.
Postoperative Nausea and Vomiting (PONV)				
White et al.[45] (2007) <u>Laparoscopic surgery study:</u> Transdermal scopolamine (TDS) 1.5 mg vs. ondansetron 4 mg	RCT, DB, PC Patients aged 18-65 years scheduled to undergo major laparoscopic (e.g., bariatric surgery) or plastic (e.g., abdominoplasty, reduction mammoplasty) surgery procedures	N=77 72 hours	Primary: Postoperative nausea and vomiting / retching; need for rescue antiemetics, complete response rates (i.e., absence of protracted nausea or repeated episodes of emesis requiring antiemetic rescue medication)	Primary: There were no differences between the TDS 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 TDS and ondansetron treatment groups (51% and 47%, respectively). The requirement for rescue antiemetics was not significantly reduced in the TDS group compared to the ondansetron group during the 24-48 hour period (21% vs. 40%, p=0.07)
Diemunsch et al.[46] (2007) Aprepitant 40 mg PO vs. aprepitant 125 mg PO	RCT, DB, MC, PC Patients aged ≥18 years old, ASA I-III, undergoing open abdominal surgery requiring at least one overnight	N=922 48 hours	Primary: Complete response (no vomiting and no use of rescue therapy) over 0-24 hours after surgery; no vomiting over 0-24 hours after	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 0-24 hours was 84% with aprepitant 40 mg, 86% with aprepitant 125 mg, and 71% with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. ondansetron 4 mg IV	hospital stay and receiving volatile-agent-based general anesthesia including nitrous oxide		surgery Secondary: No vomiting in the first 48 hours after surgery	ondansetron 4 mg (p<0.001 for both doses of aprepitant vs. ondansetron). The percentage of patients with no vomiting over 0-48 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.[47] (2007) Aprepitant 40 mg PO vs. aprepitant 125 mg PO vs. ondandetron 4 mg IV	RCT, DB, PC, MC Patients ≥18 years old scheduled to undergo open abdominal surgery requiring an overnight hospital stay, met criteria of ASA physical status of I-III, 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 0-24 hours; no vomiting 0-48 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 0-24 hours, the treatments did not differ significantly in terms of no 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 0-48 hour time interval compared with 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.[25] (2006) Prophylactic oral dronabinol 5 mg and rectal prochlorperazine 25 mg (after anesthesia) vs. standard preoperative care (which does not include routine	RETRO Patients who were operated on before 09/02 with standard preoperative care were designated as “old cohort” (OC). Patients operated on after 09/02 who received prophylactic oral dronabinol 5 mg and rectal	N=242 RETRO review of all patients between July 2001 and November 2002	Primary: Rate and severity of PONV	Primary: The rate of nausea and vomiting were significantly better in the patients treated prophylactically with dronabinol and prochlorperazine (59% vs. 15%, *P*<0.001 and 29% vs. 3%, *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prophylaxis with antiemetics)	prochlorperazine 25 mg were designated as "new cohort" (NC)			
Jones et al. [26] (2006) Scopolamine transdermal patch vs. placebo All patients received prophylactic intravenous ondansetron.	RCT, DB, PC, PRO Patients 18 years or older at high risk for PONV	N=56 Patients were administered a patch prior to surgery and monitored for 72 hours following surgery	Primary: Incidence and severity of PONV, side effects, antiemetic requirements	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 with the placebo group.
Tarkkila et al.[27] (1995) Combination of promethazine and transdermal scopolamine (1.5 mg) vs. oral diazepam (5-15 mg) plus oral promethazine (10 mg)	PRO, DB Patients scheduled for arthroplasty surgery of the lower extremity were anaesthetized with spinal anesthesia with a combination of isobaric bupivacaine 20 mg and morphine 0.3 mg	N=60 24-hour study period	Primary: The effect of different premedications on postoperative emetic sequelae induced by intrathecal morphine	Primary: 60% of the patients with both promethazine and transdermal scopolamine were totally free from postoperative nausea and vomiting (PONV) symptoms compared to those premedicated with diazepam (40%) or promethazine alone (30%). Promethazine together with transdermal scopolamine significantly reduced the number of patients with vomiting (to 25%) and also vomiting episodes. This combination was also more efficient in reducing the incidence of nausea (to 25%) and nausea episodes than promethazine alone (*P*<0.05). PONV occurred in a majority of patients during the first 12 hours of the 24-hour study period and the need for additional analgesics thereafter.
Motion Sickness – Nausea				
Spinks et al.[29] (2004)	MA	12 trials	Primary: Prevention of onset	Scopolamine was more effective than placebo in the prevention of motion sickness symptoms. (Pooled OR 0.25, 95% CI 0.12-0.54).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Scopolamine transdermal patches, tablets, capsules, oral solutions vs. placebo, other drugs (calcium channel antagonists, meclizine, dimenhydrinate, methscopolamine)	Review of RCT, published in MEDLINE (1966-March 2004), EMBASE (1974-2004), CINAHL (1982-March 2004)	N=901	of clinically defined motion sickness Secondary: Task ability and psychological tests, changes in physiological parameters and adverse effects	Transdermal scopolamine was more effective than methscopolamine in preventing sickness (OR 0.17, 95% CI 0.03-0.92). Compared to meclizine, scopolamine showed a greater decrease in mean motion sickness score (89%) than meclizine (59%) (no *P* value reported). Transdermal scopolamine was equivalent to dimenhydrinate in preventing motion sickness with global assessment reported 'good' or 'very good' for 7 (out of 10) and 8 (out of 10) participants, respectively (no *P* value reported). Secondary: Scopolamine was no more likely to induce drowsiness, blurring of vision or dizziness compared to other agents.
Dahl et al.[28] (1984) Scopolamine transdermal patch (0.5 mg) vs. meclizine 25 mg tablet vs. placebo	DB, DD, PC, RCT, XO Individuals between the ages of 20 to 39 years, no concomitant medication use that could influence trial outcome, no 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	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 (no *P* values provided). However there was a statistical difference between meclizine and placebo for the last half of the trial period (no *P* value provided). The number of patients experiencing dry mouth was 21 for the scopolamine groups, 8 for placebo, and 6 for meclizine (*P* value not provided).
Anorexia (Acquired Immune Deficiency Syndrome-Related)				
Jatoi et al.[32] (2002) Dronabinol 2.5 mg BID plus placebo vs.	MC, DB, RCT Adult patients (>18 years of age) with histologic evidence of an incurable malignancy other than brain, breast,	N=469 Patients completed a baseline questionnaire and at least one weekly	Primary: Binary end points of whether patients' appetite improved and whether patients gained 10% of their baseline	Primary: A greater percentage of megestrol acetate-treated patients reported appetite improvement and weight gain compared with dronabinol-treated patients: 75% versus 49% (*P*=0.0001) for appetite and 11% versus 3% (*P*=0.02) for > or = 10% baseline weight gain. Combination treatment resulted in no significant differences in appetite or weight compared with megestrol acetate alone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
megestrol acetate 800 mg/day liquid suspension plus placebo vs. dronabinol 2.5 mg BID and megestrol acetate 800 mg/day liquid suspension	ovarian, or endometrial cancer	questionnaire in the first follow up	weight at some point during the study	
Timpone et al.[33] (1997) Dronabinol 2.5 mg BID (D) vs. megestrol acetate 750 mg/ day (M750) vs. dronabinol 2.5 mg BID and megestrol acetate 750 mg/day (M750+D) vs. dronabinol 2.5 mg BID and megestrol acetate 250 mg/day (M250+D)	RCT, MC	N=52 12 weeks	Primary: Occurrence of adverse events, drug discontinuation, new AIDS-defining conditions, CD4+ T lymphocyte, mean weight change, C_{max}, AUC, and visual analog scale for hunger (VASH) score	Primary: Occurrence of adverse events, drug discontinuation, new AIDS-defining conditions, or CD4+ T lymphocyte changes was not statistically significantly different among arms. Serious adverse events assessed as related to dronabinol included CNS events and those assessed as related to megestrol acetate included dyspnea, liver enzyme changes, and hyperglycemia. The mean weight change +/- SE over 12 weeks was as follows: D, -2.0 +/- 1.3 kg; M750, +6.5 +/- 1.1 kg; M750+D, +6.0 +/- 1.0 kg; and M250+D, -0.3 +/- 1.0 kg (difference among treatment arms, *P*=0.0001). Pharmacokinetic parameters measured after 2 weeks of therapy for M750 were C_{max}=985 ng/ml and AUC=22,487 ng x hr/mL, and for dronabinol and its active metabolite (HO-THC), respectively, were C_{max}=2.01; 4.61 ng/mL and AUC=5.3; 23.7 ng x hr/ml. For megestrol acetate, but not dronabinol, there was a positive correlation at week 2 between both C_{max} and AUC with each of the following: (1) weight change, (2) breakfast visual analog scale for hunger (VASH) score, and (3) dinner VASH score.
Beal et al.[30] (1995)	MC, DB, PG, PC	N=139	Primary: Patients rated	Primary: Dronabinol was associated with increased appetite above baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dronabinol 2.5 mg BID vs. placebo	AIDS-related anorexia and ≥ 2.3 kg weight loss	6 weeks	appetite, mood, and nausea by using a 100-mm visual analogue scale 3 days weekly Secondary: Side effects	(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 with 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.[31] (1993) Dronabinol 5 mg bid for 5 weeks followed by a two week washout period vs. placebo for 5 weeks followed by a two week washout period	RCT, DB, PC HIV-infected patients who had at least a 2.25 kg weight loss	N=12 7 weeks	Primary: Caloric intake, weight, percent body fat, serum prealbumin, and symptom distress	Primary: During dronabinol treatment, subjects experienced increased percent body fat (one percent, *P*=0.04); decreased symptom distress (*P*=0.04); and 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).

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, SB=single-blind, DB=double-blind, TB=triple-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PM=post marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Miscellaneous Antiemetics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Aprepitant	capsule, capsule dose pack	Emend®	$$$$-$$$$$	N/A
Dronabinol	capsule	Marinol®*	$$$$$	$$$$$
Fosaprepitant	injection	Emend®	$$$$$	N/A
Nabilone	capsule	Cesamet®	$$$$$	N/A
Scopolamine	tablet, transdermal patch	Scopace®, Transderm-Scop®	$-$$$	N/A

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

X. Conclusions

The miscellaneous antiemetics are effective in a variety of disorders, including CINV, PONV, motion sickness, and AIDs-related anorexia. However, there is a lack of head-to-head clinical trials with agents in this class.

Treatment of CINV generally involves the use of multiple agents that affect different receptor types. Aprepitant (or fosaprepitant) is considered first-line therapy in combination with a 5-HT_3 receptor antagonist and dexamethasone for the prevention of acute emesis associated with moderately or highly emetogenic chemotherapy.[2,8-9] Several clinical trials have demonstrated greater efficacy using a triple therapy regimen (aprepitant, 5-HT_3 receptor antagonist, and dexamethasone) compared to a dual therapy regimen (5-HT_3 receptor antagonist and dexamethasone).[16-22] Dronabinol, nabilone, and aprepitant are also effective treatment options for breakthrough nausea and vomiting.[8]

Aprepitant and scopolamine are indicated for the treatment of PONV. Although there are no head-to-head clinical trials comparing the miscellaneous antiemetics in PONV, scopolamine and aprepitant have demonstrated similar efficacy compared to ondansetron.[45-47]

Scopolamine is the only miscellaneous antiemetic indicated 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.[28-29]

Dronabinol is the only miscellaneous antiemetic indicated for the treatment of AIDS-related anorexia. Clinical trials have shown that dronabinol increases appetite in AIDS patients, but does not consistently produce weight gain.[30,33] Megestrol acetate, which is available in a generic formulation, was shown to be more effective than dronabinol for improving appetite and producing weight gain.[32,33] Adding dronabinol to megestrol acetate produced no additional clinical benefits.[32,33]

Therefore, all brand miscellaneous antiemetics within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Aprepitant is considered first-line therapy in certain clinical settings, such as in patients receiving moderately or highly emetogenic chemotherapy. Therefore, patients with a cancer diagnosis should be allowed approval for aprepitant through the medical justification portion of the prior authorization process, as well as automatic approval through the electronic prior authorization process.

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.

XII. References

1. Emend® capsules [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; April, 2008.
2. 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;24:2932-2947.
3. Marinol® [package insert]. Marietta, GA: Solvay Pharmaceuticals; March 2008.
4. Transderm Scop® [package insert]. Parsippany, NJ: Novartis Consumer Health, Inc.; February, 2006.
5. Scopace® [package insert]. Scottsdale, AZ: Hope Pharmaceuticals; February, 2007. Available at http://www.motionsickness.net/prescrib.html. Accessed December 2008.
6. Longstreth GF, Hesketh PJ. Characteristics of antiemetic drugs. In: UpToDate, Talley NJ, (Ed), UpToDate, Waltham, MA, 2008.
7. Harris SN, Sevarino FB, Sinatra RS. Nausea prophylaxis using transdermal scopolamine in the setting of patient-controlled analgesia. Obstetrics & Gynecology. 1991;78(4):673-677.
8. National Comprehensive Cancer Network (NCCN) guidelines. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed December 2008.
9. The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncology. 2006; 17:20-28.
10. Quigley EMM, Hasler WL, Parkman HP. American Gastroenterological Association (AGA) technical review: Nausea and vomiting. In: Rose, BD, ed. UpToDate. Waltham, MA, UpToDate; 2006.
11. American Gastroenterological Association medical position statement: nausea and vomiting. Gastroenterology. 2001; 120(1):261-262.
12. Arsenault MY, Lane CA. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2002; 24(10):817-833.
13. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2004; 103(4):803-815.
14. Gan T, Meyer T, Apfel C, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg. 2003; 97:62-71.
15. Tatro DS, ed. Drug Interaction Facts. St. Louis, Mo: Wolters Kluwer Health, Inc.; 2006.
16. 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):1548-1555.
17. 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):864-868.
18. 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):2822-2830.
19. 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):4112-4119.
20. 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):403-410.
21. 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):3090-3098.
22. 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):1395-1401.
23. Gilbert C, Ohly K. Randomized, double-blind comparison of a prochlorperazine-based versus a metoclopramide-based antiemetic regimen in patients undergoing autologous bone marrow transplantation. Cancer. 1995; 76(11):2330-2337.
24. 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):352-359.

25. Layeeque R, Siegel E, et al. Prevention of nausea and vomiting following breast surgery. The American Journal of Surgery. 2006; (191): 767-772.
26. 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):127-132.
27. 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):983-986.
28. Dahle E, Offer-Ohlsen D, Lillevold PE, et al. Transdermal scopolamine, oral meclizine, and placebo in motion sickness. Clin Pharmacol Ther. 1984; 36:116-120.
29. Spinks AB, Wasiak J, Villanueva EV, Bernath V. Scopolamine for preventing and treating motion sickness. Cochrane Database of Systematic Reviews. 2004, Issue 3. Art. No.:CD002851.
30. 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.
31. Struwe M, Kaempfer S, et al. Effect of dronabinol on nutritional status in HIV infection. Annals of Pharmacotherapy. 1993; 27(7-8):827-831.
32. Jatoi A, Windschitl H, Loprinzi CL. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: A North Central Cancer Treatment Group study. J Clin Obcol. 2002; 20(2): 567-573.
33. 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): 305-315.
34. Pasricha PJ. Antiemetics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York: McGraw-Hill; 2006:1000-1003.
35. Longstreth GF, Hesketh PJ. Characteristics of antiemetic drugs. In: UpToDate, Talley NJ, (Ed), UpToDate, Waltham, MA, 2008.
36. Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. Am Fam Physician. 2004; 1169-1174.
37. Mannix K. Palliation of nausea and vomiting in malignancy. Clin Med. 2006;6: 144-147.
38. Longstreth GF. Approach to the adult patient with nausea and vomiting. In: Rose, BD, ed. UpToDate. Waltham, MA: UpToDate, 2007.
39. Jordan K, Kasper C, Schmoll H. Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment. Eur J Cancer.2005; 41:199-205.
40. Hesketh PJ. Prevention and treatment of chemotherapy-induced nausea and vomiting. In: UpToDate, Drews, RE (Ed), UpToDate, Waltham, MA, 2008.
41. Emend® injection [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; April, 2008.
42. Cesamet® [package insert]. Costa Mesa, AC: Valeant Pharmaceuticals, Inc.; July, 2006
43. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed December 2008.
44. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed December 2008.
45. 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; 104:92-96.
46. 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.
47. Gan T, Apfel C, Kovac A, et al. A randomized, double-blind comparison of the NK_1 antagnoist, aprepitant, versus ondansetron fro the prevention of postoperative nausea and vomiting. Anesth Analg 2007; 104:1082-9.
48. 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.
49. Meiri E, Jhangiani H, Vredenburgh J, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin 2007; 23:533-543.
50. 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.
51. Einhorn L, Nagy C, Furnas B, et al. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. J Clin Pharmacol 1981; 21:64S-69S

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Proton-pump Inhibitors
Single Entity Agents
AHFS Class 562836
February 11, 2009

I. Overview

Dyspepsia is a common symptom which can be caused by a number of acid-related disorders, including peptic ulcer disease and gastroesophageal reflux disease (GERD). Inhibiting gastric acid secretion and reducing the acidity of gastric juice helps improve symptoms and may resolve the underlying disorder. Proton-pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally recognized as the most potent acid suppressants available.[1] 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. PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. PPIs will only inhibit proton pumps that are actively secreting acid.[1] Following a meal, approximately 70%-80% of the proton pumps will be active.[2] Thus, single doses of PPIs will not completely inhibit acid secretion and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. With regular dosing, maximal acid suppression occurs in 3-4 days.[1-3]

PPIs are substituted benzimidazole derivatives and are structurally related. Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole contains only the *S*-isomers of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer. Primary differences between the PPIs occur in their pharmacokinetic and pharmacodynamic properties along with formulation availability.

The single entity proton-pump inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Omeprazole and pantoprazole are available in generic formulations. Omeprazole is also available over-the-counter.

Table 1. Single Entity Proton-pump Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Esomeprazole	delayed-release capsule, delayed-release powder for suspension, injection	Nexium®, Nexium I.V.®	none
Lansoprazole	delayed-release capsule, delayed-release orally disintegrating tablet, delayed-release granules for suspension, injection	Prevacid®, Prevacid IV®	none
Omeprazole	delayed-release capsule, delayed-release tablet	Prilosec®*‡	omeprazole†
Omeprazole magnesium	delayed-release tablet	Prilosec OTC®‡	Prilosec OTC®‡
Omeprazole and sodium bicarbonate	capsule, powder for suspension	Zegerid®	Zegerid®
Pantoprazole	delayed-release tablet, delayed-release granules for suspension, injection	Protonix®*, Protonix IV®	none†
Rabeprazole	delayed-release tablet	Aciphex®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
‡Product is available over-the-counter
†Omeprazole (OTC) is available on the PDL. Omeprazole (RX) and pantoprazole require prior authorization.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the single entity proton-pump inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines using the Single Entity Proton-pump Inhibitors

Clinical Guideline	Recommendation(s)
American Gastroenterological Association: **Medical Position Statement on the Management of Gastroesophageal Reflux Disease**[55] **(2008)**	• Antisecretory drugs for the treatment of patients with esophageal GERD syndromes (healing esophagitis and symptomatic relief). In these uses, proton pump inhibitors (PPIs) are more effective than histamine$_2$ receptor antagonists (H2RAs), which are more effective than placebo. • Twice-daily PPI therapy 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 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 H2RAs, which are more effective than placebo. • Long-term use of PPIs 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.
American College of Gastroenterology: **Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease (GERD)**[13] **(2005)**	• Antacids and OTC acid suppressants are options for patient-directed therapy for heartburn. Patients should be evaluated if symptoms persist and they require continuous therapy. • Acid suppression is the mainstay of GERD therapy. • PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients. • Although less effective than PPIs, histamine2-receptor blockers given in divided doses may be effective in some patients with less severe GERD. • Because GERD is a chronic condition, continuous therapy to control symptoms and prevent complications is appropriate.
Canadian Association of Gastroenterology GERD Consensus Group: **Canadian Consensus Conference on the Management of GERD in Adults–Update**[14] **(2004)**	• PPIs are superior to H_2RAs for the reduction of heart burn and healing of 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.
North American Society for Pediatric Gastroenterology and	• Proton pump inhibitors (PPIs), the most effective acid suppressant medications, are superior to H2RAs in relieving symptoms and healing

Clinical Guideline	Recommendation(s)
Nutrition: **Guidelines for Evaluation and Treatment of Gastroesophageal Reflux in Infants and Children**[15] **(2001)**	esophagitis.
American College of Gastroenterology: **Guideline on the Management of *Helicobacter pylori* Infection**[16] **(2007)**	• 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 10–14 days.
Canadian Helicobacter Study Group Consensus Conference: **Update on the Management of *Helicobacter pylori***[17] **(2004)**	• A quadruple combination of a PPI, bismuth, tetracycline, and metronidazole for 10-14 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.
European *Helicobacter pylori* Study Group: **Current Concepts in the Management of *H. pylori* Infection–The Maastricht 2-2000 Consensus Report**[18] **(2002)**	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should use quadruple therapy with a PPI, bismuth, metronidazole, and tetracycline. • When bismuth is not available, second-line therapy should be triple therapy with a proton-pump inhibitor.
Canadian Dyspepsia Working Group: **An Evidence-Based Approach to the Management of Uninvestigated Dyspepsia in the Era of *Helicobacter pylori***[19] **(2000)**	• PPIs are considered a first-line therapy choice in patients on NSAIDs with dyspepsia who cannot discontinue NSAID therapy. • For the management of patients with GERD, PPIs are listed as first choice over H_2-RAs based on efficacy data. • In accordance with the recommendations of the Canadian *Helicobacter pylori* Consensus Conference, first-line eradication therapies for *H. pylori* are triple therapies of a PPI plus 1000 mg of amoxicillin plus 500 mg of clarithromycin (PPI + AC), or a PPI plus 500 mg of metronidazole plus 250 or 500 mg of clarithromycin (PPI + MC), twice daily for 1 week; or ranitidine bismuth citrate plus either AC or MC • If the first eradication therapy has failed, the action recommended by the Canadian *Helicobacter pylori* Consensus Conference is to use a different first-line therapy than that used initially (e.g., switch from PPI + AC to PPI + MC). • An alternative therapy is a 14-day quadruple regimen of a PPI (twice daily) plus bismuth (subsalicylate, 2 tablets 4 times daily) plus metronidazole (250 mg 4 times daily) plus tetracycline (500 mg 4 times daily) (PPI + BMT). • For the management of patients negative for *H. pylori*, a PPI is the first-line therapy choice.
American College of Gastroenterology: **Guidelines for the Management of Dyspepsia**[20] **(2005)**	• In patients aged 55 yr or younger with no alarm features, the clinician may consider two approximately equivalent management options: (i) 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 or (ii) an empiric trial of acid suppression with a proton pump inhibitor (PPI) for 4–8 wk. • 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.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the single entity 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 Single Entity Proton-pump Inhibitors[4-5,7-12,54]

Indication	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Duodenal ulcer		✔ [1]	✔ [3,6]		✔
Duodenal ulcer associated with *H. pylori* (combination with antibiotics)	✔	✔ [1,2]	✔ [3,4]		✔
Gastric ulcer		✔ [1]	✔ [3,6]		
Gastric ulcer associated with NSAID use	✔	✔ [1]			
Erosive esophagitis	✔	✔	✔ [3,6]	✔	✔
Symptomatic GERD	✔	✔ [1]	✔ [3,6]		✔
Hypersecretory conditions (e.g., Zollinger-Ellison syndrome)	✔	✔ [1]	✔ [3]	✔	✔
Treatment of frequent heartburn			✔ [5]		
Reduction of risk of upper GI bleeding in critically ill patients			✔ [6]		

GERD=gastroesophageal reflux disease, NSAID=Non-steroidal anti-inflammatory drugs, GI=gastrointestinal
[1]Oral administration only.
[2]Lansoprazole as dual therapy with amoxicillin is indicated for the treatment of *H. pylori* infection and duodenal ulcer disease.
[3]RX only.
[4]Omeprazole as dual therapy with clarithromycin is indicated for the treatment of *H. pylori* infection and duodenal ulcer disease
[5]OTC product.
[6]Omeprazole/sodium bicarbonate product.

IV. Pharmacokinetics

The pharmacokinetic parameters of the single entity proton-pump inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Single Entity Proton-pump Inhibitors[4-5,7-12,54]

Generic Name	Onset (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
Esomeprazole	1-2	17	80	No	1-1.5
Lansoprazole	1-3	>24	14-25	Yes (sulfonamide and disulfide metabolites)	1.3-1.5
Omeprazole	≤2	72	77	No	0.5-1
Omeprazole magnesium	No data	>24	No data	No	0.5-1
Omeprazole and sodium bicarbonate	1-2.5	No data	77	No	0.5-1
Pantoprazole	No data	>24	71-82	No data	1
Rabeprazole	≤1	No data	90	No data	1-2

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Single Entity Proton-pump Inhibitors [4-5,7-12,54]

Generic Name	Significance Level	Interaction	Mechanism
PPIs	1	Protease inhibitors (atazanavir, indinavir, nelfinavir, saquinavir)	PPIs may reduce the dissolution of certain protease inhibitors, reducing GI absorption and antiviral activity. Dose adjustment of some protease inhibitors may be required with concurrent administration. Concomitant use of atazanavir and PPIs is not recommended.
PPIs	2	Azole antifungals (itraconazole, ketoconazole)	Oral tablet dissolution may be reduced due to higher gastric pH. Concurrent use should be avoided. If concurrent use is necessary, administer the oral azole antifungal with an acidic beverage.
Lansoprazole	2	Clarithromycin	The metabolism of lansoprazole may be inhibited resulting in elevated plasma levels. Patients should be monitored for an increase in adverse reactions during concurrent administration.
Omeprazole	2	Cilostazol	Omeprazole may inhibit the metabolism (CYP2C19) of cilostazol. A dose decrease of cilostazol to 50 mg twice daily may be required during concurrent administration with omeprazole.
Omeprazole	3	Benzodiazepines	Omeprazole may decrease the oxidative metabolism of benzodiazepines. Reduced clearance, prolonged half-life, and increased serum levels of certain benzodiazepines may occur. Certain actions, especially sedation or ataxia, may be enhanced.

Significance Level 1 = major severity
Significance Level 2 = moderate severity
Significance Level 3 = minor severity

VI. Adverse Drug Events

The most common adverse drug events reported with the single entity proton-pump inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Single Entity Proton-pump Inhibitors[4-5,7-12,54]

Adverse Event(s)	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Cardiovascular					
Flushing	<1	-	-	-	-
Hypertension	<1	-	-	-	-
Tachycardia	<1	-	-	-	-
Central Nervous System					
Anxiety	-	-	-	≥1	-
Apathy	<1	-	-	-	-
Asthenia	<1	-	1.1	-	-

Adverse Event(s)	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Confusion	<1	-	-	-	-
Depression	<1	-	-	-	-
Dizziness	<1	-	1.5	≥1	-
Fatigue	<1	-	-	-	-
Headache	5.5	-	6.9	2-9	2.4
Hypertonia	<1	-	-	-	-
Insomnia	<1	-	-	<1	-
Migraine	<1	-	-	≥1	-
Nervousness	<1	-	-	-	-
Paresthesia	<1	-	-	-	-
Somnolence	<1	-	-	-	-
Vertigo	<1	-	-	-	-
Dermatological					
Acne	<1	-	-	-	-
Angioedema	<1	-	-	-	-
Dermatitis	<1	-	-	-	-
Pruritus	<1	-	-	-	-
Rash	<1	-	1.5	<1-2	-
Stevens-Johnson syndrome	-	-	-	✔	-
Sweating	<1	-	-	-	-
Urticaria	<1	-	-	-	-
Endocrine and Metabolic					
Hyponatremia	-	-	-	<1	-
Liver function abnormalities	<1	-	-	2	-
Weight decrease	<1	-	-	-	-
Weight increase	<1	-	-	-	-
Gastrointestinal					
Abdomen enlarged	<1	-	-	-	-
Abdominal pain	✔	2.8	2.4	1-4	-
Anorexia	<1	-	-	-	-
Constipation	✔	1	1.1	≥1	-
Diarrhea	4.3	3.8	3	2-6	-
Dry mouth	✔	-	-	-	-
Dyspepsia	<1	-	-	≥1	-
Dysphagia	<1	-	-	-	-
Epigastric pain	<1	-	-	-	-
Flatulence	✔	-	-	2-4	-
Nausea	✔	1.3	2.2	2	-
Vomiting	<1	-	1.5	2	-
Genitourinary					
Dysuria	<1	-	-	-	-
Impotence	<1	-	-	-	-
Polyuria	<1	-	-	-	-
Urinary tract infection	-	-	-	≥1	-
Hematologic					
Anemia	<1	-	-	-	-
Leukopenia	<1	-	-	-	-
Thrombocytopenia	<1	-	-	-	-
Laboratory Test Abnormalities					

Adverse Event(s)	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Elevated alkaline phosphatase	<1	-	-	-	-
Elevated creatinine	<1	-	-	-	-
Elevated SGOT	<1	-	-	-	-
Elevated SGPT	<1	-	-	≥1	-
Musculoskeletal					
Arthralgia	<1	-	-	≥1	-
Asthenia	-	-	-	≥1	-
Back pain	-	-	1.1	≥1	-
Respiratory					
Asthma	<1	-	-	-	-
Bronchitis	-	-	-	≥1	-
Cough	<1	-	1.1	≥1	-
Dyspnea	<1	-	-	≥1	-
Pharyngitis	<1	-	-	-	-
Rhinitis	<1	-	-	-	-
Sinusitis	-	-	-	≥1	-
Upper respiratory tract infection	-	-	1.9	≥1	-
Other					
Anaphylaxis	<1	-	-	✔	-
Blurred vision	<1	-	-	-	-
Flu-like syndrome	-	-	-	≥1	-
Ocular pain	<1	-	-	-	-
Tinnitus	<1	-	-	-	-
Tremor	<1	-	-	-	-

BUN=blood nitrogen urea, SGOT=serum glutamic-oxaloacetic transaminase, SGPT= serum glutamic-pyruvic transaminase
✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the single entity proton-pump inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Single Entity Proton-pump Inhibitors[4-5,7-12,54]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Esomeprazole	Erosive esophagitis: Treatment: 20 mg or 40 mg once daily for 4 to 8 weeks (intravenous formulation is indicated for use up to 10 days) Maintenance: 20 mg once daily Symptomatic GERD: 20 mg once daily for 4 weeks; an additional 4 weeks may be considered if symptoms do not completely resolve NSAID-associated gastric ulcer: 20 mg or 40 mg once daily for up to 6 months *H. pylori* eradication:	12 – 17 years of age Symptomatic GERD: 20 mg or 40 mg once daily for up to 8 weeks 1 – 11 years of age Symptomatic GERD: 10 mg once daily for up to 8 weeks Healing of erosive esophagitis: • weight <20 kg: 10 mg once daily for 8 weeks • weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks	Delayed-release capsule: 20 mg, 40 mg Delayed-release powder for suspension: 10 mg, 20 mg, 40 mg Injection: 20 mg, 40 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	40 mg once daily for 10 days (triple therapy with amoxicillin 1,000 mg twice daily and clarithromycin 500 mg twice daily) Pathological hypersecretory conditions: 40 mg twice daily (individual dose; doses up to 240 mg have been administered)		
Lansoprazole	Duodenal ulcer: Treatment: 15 mg once daily for 4 weeks Maintenance: 15 mg once daily *H. pylori* eradication: Dual therapy: 30 mg lansoprazole plus 1 g amoxicillin both taken 3 times/day (every 8 hours) for 14 days for patients intolerant or resistant to clarithromycin. Triple therapy: 30 mg lansoprazole plus 500 mg clarithromycin and 1 g amoxicillin all taken twice daily (every 12 hours) for 10 or 14 days. Erosive esophagitis: Treatment: 30 mg once daily up to 8-16 weeks (intravenous formulation is indicated for use up to 7 days) Maintenance: 15 mg once daily Gastric ulcer treatment: 30 mg once daily up to 8 weeks NSAID-associated gastric ulcer: Healing: 30 mg once daily up to 8 weeks Risk reduction: 15 mg once daily up to 12 weeks Symptomatic GERD: 15 mg once daily for up to 8 weeks Pathological hypersecretory conditions: 60 mg once daily (doses up to 90 mg twice daily have been given)	12 to 17 years of age: Erosive esophagitis: Treatment: 30 mg once daily up to 8 weeks GERD: 15 mg once daily for up to 8 weeks 1 to 11 years of age: Erosive esophagitis and GERD • weight ≤ 30 kg: 15 mg once daily for up to 12weeks • weight >30 kg: 30 mg once daily for up to 12 weeks Dose increases of up to 30 mg twice daily have been used if patients remain symptomatic after 2 weeks	Delayed-release orally disintegrating tablet: 15 mg, 30 mg Delayed-release capsule: 15 mg, 30 mg Delayed-release granules for oral suspension: 15 mg, 30 mg Injection: 30 mg
Omeprazole	Erosive esophagitis: Treatment: 20 mg once daily for 4-8 weeks Maintenance: 20 mg once daily Symptomatic GERD:	1 – 16 years of age: GERD and healing of erosive esophagitis: • 5 kg to <10 kg: 5 mg daily • 10 kg to <20 kg: 10mg	Delayed-release capsule: 10 mg, 20 mg, 40 mg Delayed-release

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	20 mg once daily for 4 weeks Duodenal ulcer disease: 20 mg once daily for 4-8 weeks Gastric ulcer: 40 mg once daily for 4-8 weeks *H. pylori* eradication: Triple therapy: 20 mg twice daily for 10 days (with amoxicillin 1000 mg and clarithromycin 500 mg BID) Dual therapy: 40 mg once daily for 14 – 28 days (with clarithromycin 500 mg TID) Pathological hypersecretory conditions: 60 mg once daily up to 120 mg three times daily	daily • ≥20 kg: 20 mg daily	tablet: 20 mg
Omeprazole magnesium	Heartburn: 20 mg once daily for 14 days	Safety and efficacy in children have not been established	Delayed-release tablet: 20 mg
Omeprazole and sodium bicarbonate	Erosive esophagitis: Treatment: 20 mg once daily for 4-8 weeks Maintenance: 20 mg once daily Symptomatic GERD: 20 mg once daily for 4 weeks Duodenal ulcer: 20 mg once daily for 4-8 weeks Gastric ulcer: 40 mg once daily for 4-8 weeks Reduction of risk of upper GI bleeding in critically ill patients: 40 mg initially followed by 40 mg 6 to 8 hours later and 40 mg daily thereafter for 14 days	Safety and efficacy in children have not been established	Immediate-release capsule: 20 mg omeprazole/ 1,100 mg sodium bicarbonate; 40 mg omeprazole/ 1,100 mg sodium bicarbonate Powder for oral suspension: 20 mg omeprazole/ 1,680 sodium bicarbonate; 40 mg omeprazole/ 1,680 sodium bicarbonate
Pantoprazole	Erosive esophagitis: Treatment: 40 mg once daily for 8-16 weeks (IV formulation is indicated for use up to 7-10 days) Maintenance: 40 mg once daily Pathological hypersecretory conditions: Oral: 40 mg BID up to 240 mg daily IV: 80 mg BID up to 240 mg daily for up to 6 days	Safety and efficacy in children have not been established	Delayed-release tablet: 20 mg, 40 mg Delayed-release suspension: 40 mg Injection: 40 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Rabeprazole	Erosive esophagitis: Treatment: 20 mg once daily for 4-8 weeks Maintenance: 20 mg once daily Symptomatic GERD: 20 mg once daily for 4-8 weeks Duodenal ulcer: 20 mg once daily for 4 weeks *H. pylori* eradication: 20 mg twice daily for 7 days (with amoxicillin 1,000 mg twice daily and clarithromycin 500 mg twice daily) Pathological hypersecretory conditions: 60 mg once daily up to 100 mg once daily or 60 mg twice daily	≥12 years of age: GERD: 20 mg once daily for up to 8 weeks The safety and efficacy have not been established for pediatric patients less than 12 years of age.	Delayed-release tablet: 20 mg

BID=twice daily; TID=three times daily; IV=intravenous; GI=gastrointestinal

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity proton-pump inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Single Entity 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.[23] (2001) Lansoprazole 30 mg QD vs. omeprazole 20 mg QD	MA Randomized double-blind trials in patients with endoscopically diagnosed erosive esophagitis where healing rates had to be reported after 4 and/or 8 weeks	N=2,040 (6 trials) 4-8 weeks	Primary: Differences in pooled healing rates at 4 and 8 weeks per protocol and intention-to-treat data	Primary: Pooled healing rates after 4 weeks were 77.7% for lansoprazole and 74.7% for omeprazole (absolute benefit increase 3.1%; 95% confidence interval [CI] =-1.1-7.3) in the per protocol analysis. After 4 weeks, pooled healing rates were 72.7% for lansoprazole and 70.8% for omeprazole (absolute benefit increase 2.0%; 95% CI=-2.0-6.0) for the intention-to-treat analysis. After 8 weeks, pooled healing rates were 88.7% for lansoprazole and 87.0% for omeprazole (absolute benefit increase 1.7%; 95% CI=-1.5-5.0) in the per protocol analysis. After 8 weeks, pooled healing rates were 83.3% for lansoprazole and 81.8% for omeprazole (absolute benefit increase 1.5%; 95% CI=-1.9-4.9) in the intention-to-treat analysis. Lansoprazole and omeprazole healing rates were not statistically different.
Caro et al.[24] (2001) Lansoprazole, pantoprazole, or rabeprazole vs. omeprazole, ranitidine or placebo	MA Randomized trials for GERD acute and maintenance therapy (placebo arm included)	41 trials Duration varied	Primary: Healing and relapse rates	Primary: Compared to omeprazole 20 mg daily, the healing rate ratios (RR) after 8 weeks were as follows: lansoprazole 30 mg daily RR=1.02 (95% CI=0.98-1.06); rabeprazole 20 mg daily, RR=0.93 (95% CI=0.87-1.00); and pantoprazole 40 mg daily, RR=0.98 (95% CI=0.90-1.07). Relapse rates after 6 months were as follows: lansoprazole 30 mg daily 6%-29%; rabeprazole 20 mg daily 9%; and omeprazole 20 mg daily 7%-42%. (No maintenance trials with pantoprazole were included.)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Edwards et al.[25] (2001) Omeprazole 20 mg daily vs. esomeprazole 20-40 mg daily, lansoprazole 30 mg daily, pantoprazole 40 mg daily, or rabeprazole 20 mg daily	MA Randomized trials comparing omeprazole to other PPIs for acute treatment for GERD	12 trials 4-8 weeks	Primary: Healing rates	Primary; Compared to omeprazole 20 mg daily, esomeprazole 40 mg daily had significantly greater healing rates at week 4 (RR=1.14, 95% CI=1.10-1.18) and at week 8 (RR=1.08, 95% CI=1.05-1.10). Compared to omeprazole 20 mg daily, there was no significant difference in healing rates at 4 or 8 weeks with lansoprazole 30 mg daily, pantoprazole 40 mg daily, and rabeprazole 20 mg daily.
Klok et al.[26] (2003) Direct comparison of short-term PPI therapy under the same clinical conditions	MA Randomized trials of PPI use in GERD, PUD, or *H. pylori* eradication were included	41 trials	Primary: Success rates (defined as endoscopically determined cure for GERD and PUD or absence of *H. pylori*)	Primary: Comparisons between PPI treatment for GERD included the following: esomeprazole 40 mg vs. omeprazole 20 mg daily; esomeprazole 20 mg vs. omeprazole 20 mg daily; lansoprazole 30 mg daily vs. omeprazole 20 mg daily; lansoprazole 30 mg daily vs. omeprazole 40 mg daily; lansoprazole 15 mg daily vs. omeprazole 20 mg daily; lansoprazole 30 mg daily vs. pantoprazole 40 mg daily. pantoprazole 40 mg daily vs. omeprazole 20 mg daily; pantoprazole 20 mg daily vs. omeprazole 20 mg daily; rabeprazole 20 mg daily vs. omeprazole 20 mg daily; and rabeprazole 10 mg daily vs. omeprazole 20 mg daily For GERD treatment, one statistically significant difference was noted. After 4 weeks of 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=1.14-1.23). For all other comparisons in GERD, no significant difference was found. Comparisons between PPI treatment for ulcer healing included the following: esomeprazole 40 mg vs. omeprazole 20 mg daily;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				lansoprazole 30 mg daily vs. omeprazole 20 mg daily; pantoprazole 40 mg daily vs. omeprazole 20 mg daily; rabeprazole 20 mg daily vs. omeprazole 20 mg daily. For PUD treatment, one statistically significant difference was noted. After 4 weeks of 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=1.02-1.13). For all other comparisons, no significant difference was found. No significant differences were found in *H. pylori* eradication rates between PPIs.
Tsai et al.[27] (2004) Esomeprazole 20 mg on-demand therapy (PRN) vs. lansoprazole 15 mg QD All patients received esomeprazole 20 mg QD for 2-4 weeks for acute treatment of GERD, then proceeded into the maintenance phase and were randomized into the above treatment groups.	RCT, MC, SB, PG Patients 18-80 years of age with >6 month history of GERD without esophageal mucosal breaks and reported symptoms in >4 out of the previous 7 days Patients excluded if they received >10 days of PPI therapy in the previous 28 days, were on anticholinergics, cisapride, prostaglandin analogues, NSAIDs, or salicylates	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 PRN compared to lansoprazole QD (*P*=0.001). At 6 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 (*P* value not reported). 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 1 month of treatment (*P*=0.02). At 3 and 6 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 1, 3, and 6 months (*P* value not reported).
Castell et al.[28] (2002)	RCT, MC, DB, PG Adult patients with	N=5,241 8 weeks	Primary: Healing rates at 8 weeks	Primary: Esomeprazole demonstrated significantly higher healing rates at 8 weeks compared to lansoprazole (92.6% vs. 88.8%, *P*=0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Esomeprazole 40 mg QD in the morning vs. lansoprazole 30 mg QD in the morning	endoscopically documented erosive esophagitis Patients excluded if they had GI bleeding, history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders, esophageal stricture, Barrett's esophagitis, upper GI malignancy, or other severe concomitant disease		Secondary: Healing rates at week 4, resolution of investigator-recorded heartburn at week 4, time to first and time to sustained relief of heartburn and proportion of heartburn-free days and nights	Secondary: Esomeprazole demonstrated higher healing rates at 4 weeks compared to lansoprazole (79.4% vs. 75.1%, *P* value not reported). Resolution of heartburn at week 4 was significantly higher with esomeprazole compared to lansoprazole (62.9% vs. 60.2%, $P \leq 0.05$). No significant difference was observed in time to first resolution of heartburn (median of 2 days for both treatment groups); however, time to sustained relief was significantly less with esomeprazole (7 vs. 8 days, $P \leq 0.01$). There was no significant difference in the proportion of heartburn-free days between treatment groups; however, heartburn-free nights were significantly higher with esomeprazole (87.1% vs. 85.8%, $P \leq 0.05$).
Howden et al.[29] (2002) Esomeprazole 40 mg QD vs. lansoprazole 30 mg QD	RCT, MC, DB Adult patients with endoscopically documented erosive esophagitis Exclusion criteria not specified	N=284 8 weeks	Primary: Healing rates at 8 weeks Secondary: Healing rates at week 4, proportion of patients reporting heartburn-free days and nights, and rate of healing or improvement of esophagitis by 2 grades	Primary: Comparable healing rates at week 8 were observed between esomeprazole compared to lansoprazole (89.1% vs. 91.4% respectively; *P* value not reported). Secondary: Healing rates at week 4 were comparable between the two treatment groups (77.0% for lansoprazole and 78.3% for esomeprazole; *P* value not reported). The percentage of patients reporting heartburn-free days and nights were comparable between treatment groups. Healing or improvement of esophagitis by 2 grades was observed in 90% of patients taking lansoprazole and 81% taking esomeprazole.
Chey et al.[30] (2003)	RCT, MC, DB Adult patients with	N=3,034 2 weeks	Primary: Average symptom severity after day 3	Primary: No statistically significant differences were noted between the two treatment groups in symptom severity after day 3 (*P* value not

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	symptomatic GERD Exclusion criteria not specified		Secondary: Percentage of patients without daytime and nighttime heartburn after day 1, symptom relief after day 1, and symptom severity after day 1, day 7, and day 14	reported). Secondary: No statistically significant differences were noted for any of the secondary endpoints (*P* value not reported).
Devault et al.[31] (2006) Esomeprazole 20 mg QD vs. lansoprazole 15 mg QD	RCT, MC, PG, DB Patients 18-75 years with erosive esophagitis (LA grades A, B, C or D) who were treated and healed	N=1026 6 months	Primary: Remission rates (defined as no detectable erosive esophagitis and no study discontinuation due to reflux symptoms) estimated by Kaplan-Meier at 6 months Secondary: Observed remission rate at 3 months and 6 months	Primary: Estimated endoscopic/symptomatic remission rate during a period of 6 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 3 months (92.8% vs. 86.8%, *P*<0.0001) and 6 months (86.2% vs. 77.6%, *P*<0.0001) were significantly higher in the esomeprazole group compared with the lansoprazole group. There was no significant difference between esomeprazole and lansoprazole at 6 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.[32] (2005) Esomeprazole 40 mg QD	RCT, MC, DB Patients with moderate-severe erosive esophagitis (Los Angeles Grade	N=999 8 weeks	Primary: Healing rates at week 8 Secondary: Resolution of	Primary: Healing rates at week 8 were significantly greater in patients taking esomeprazole compared to lansoprazole (82.4% vs. 77.5%; *P*=0.007). Secondary: Significantly more patients taking esomeprazole had resolution of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. lansoprazole 30 mg QD	C or D) Patients excluded if they had GI bleeding, history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders, inflammatory bowel disease, esophageal stricture, Barrett's esophagitis, duodenal or gastric ulcer, upper GI malignancy, or other severe concomitant disease		heartburn symptoms at week 4	heartburn symptoms at week 4 than lansoprazole (72.0% vs. 63.6%, *P*=0.005).
Lauritsen et al.[33] (2003) Esomeprazole 20 mg QD vs. lansoprazole 15 mg QD	RCT, MC, DB Patients with healed esophagitis Patients excluded if they had GI bleeding, history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders, inflammatory bowel disease, esophageal stricture, Barrett's	N=1,391 6 months	Primary: Remission rates at 6 months	Primary: Remission rates at 6 months were significantly higher with esomeprazole compared to lansoprazole (83% vs. 74%; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	esophagitis, duodenal or gastric ulcer, upper GI malignancy, or other severe concomitant disease			
Richter et al.[34] (2001) Esomeprazole 40 mg QD vs. omeprazole 20 mg QD	RCT, MC, DB, PG Adult patients with erosive esophagitis Patients excluded if they tested positive for *H. pylori*, had GI bleeding, history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders, esophageal stricture, Barrett's esophagitis, duodenal or gastric ulcer, inflammatory bowel disease, upper GI malignancy, unstable diabetes or other severe concomitant disease	N=2,425 8 weeks	Primary: Healing rates at 8 weeks Secondary: Healing rates at 4 weeks, and resolution of heartburn symptoms at week 4, 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 8 weeks compared to those taking omeprazole (93.7% vs. 84.2%; $P<0.001$). Secondary: Significantly more patients taking esomeprazole were healed at 4 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 1 (45.3% vs. 32.0%; $P\leq0.0005$) and day 7 (85.6% vs. 81.6%; $P\leq0.0005$) compared to omeprazole. Time to sustained resolution with esomeprazole was significantly greater at day 1, 14, and 28 compared to omeprazole ($P\leq0.0005$). Esomeprazole resulted in greater heartburn-free days (74.9% vs. 69.7%) and nights (90.8% vs. 87.9%) (both $P<0.001$).
Armstrong et al.[35] (2004) Esomeprazole 40 mg QD	3 RCT, MC, DB, PG Patients with heartburn for >6	N=2,645 4 weeks	Primary: Complete resolution of heartburn at 4 weeks	Primary: Complete resolution of heartburn at 4 weeks was comparable for all treatment arms throughout the 3 studies. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. esomeprazole 20 mg QD vs. omeprazole 20 mg QD In study A, patients received either esomeprazole 40 mg QD, esomeprazole 20 mg QD, or omeprazole 20 mg QD. In study B patients received esomeprazole 40 mg QD or omeprazole 20 mg QD and in study C, patients received esomeprazole 20 mg QD or omeprazole 20 mg QD	months with a normal endoscopy were included in one of 3 trials Exclusion criteria not specified		Secondary: Complete resolution of heartburn at 14 days, adequate control of heartburn, relief of other reflux and GI symptoms, and relief of heartburn (assessed by patient diary)	Complete resolution of heartburn at 2 weeks was comparable for all treatment arms throughout the 3 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 (*P* value not reported). In study B, 73.5% taking esomeprazole 40 mg, and 72.8% on omeprazole 20 mg reported adequate heartburn control (*P* value not reported). In study C, 67.9% taking esomeprazole 20 mg, and 65.3% on omeprazole 20 mg reported adequate heartburn control (*P* value not reported). After 4 weeks, relief of other reflux and gastrointestinal symptoms was comparable in all treatment arms throughout the 3 studies. In study A, relief of heartburn reported by patients was higher with esomeprazole 20 mg (*P* value not reported). No differences were detected throughout the other 2 studies.
Kahrilas et al.[36] (2000) Esomeprazole 40 mg QD vs. esomeprazole 20 mg QD vs.	RCT, MC, DB, PG Patients with endoscopically documented reflux esophagitis Patients excluded if they had GI bleeding, history of gastric or esophageal surgery, had Zollinger-	N=1,960 8 weeks	Primary: Healing rates after 8 weeks Secondary: Resolution of heartburn symptoms at week 4, time to first and time to sustained relief of heartburn, and proportion of heartburn-free days	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 for patients taking esomeprazole 40 mg compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
omeprazole 20 mg QD	Ellison syndrome, esophageal motility disorders, esophageal stricture, Barrett's esophagitis, upper GI malignancy, or other severe concomitant disease		and nights	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 (5 days) compared to omeprazole (9 days; *P*=0.0006). There were no significant differences between omeprazole 20 mg and esomeprazole 20 mg (8 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%).
Labenz et al.[37] (2005) Esomeprazole 40 mg QD vs. pantoprazole 40 mg QD	RCT, MC, DB, Adult patients with erosive esophagitis confirmed by endoscopy Patients were excluded if they had peptic ulcers, Zollinger-Ellison syndrome, esophageal stricture, or Barrett's esophagitis	N=3,170 8 weeks	Primary: Healing rates at 8 weeks Secondary: Healing rates at 4 and 8 weeks by baseline esophagitis severity, time to sustained symptom relief, and proportion of heartburn-free days	Primary: At 8 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 4 and 8 weeks, healing rates for esomeprazole 40 mg QD was statistically higher than for pantoprazole 40 mg QD for erosive esophagitis grades B-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 (6 days) compared to pantoprazole (8 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).
Scholten et al.[38] (2003) Esomeprazole 40 mg	RCT, MC, DB, PG Adult patients with GERD grade B and	N=217 4 weeks	Primary: GERD-related symptoms reported	Primary: Both treatment groups reported similar relief of gastrointestinal symptoms (*P*> 0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs. pantoprazole 40 mg QD	C (Los Angeles classification system) Patients excluded if they had peptic ulcers, Zollinger-Ellison syndrome, pyloric stenosis and esophageal and/or GI surgery		Secondary: Relief rates of GERD-related symptoms, GI symptom rating scale (GSRS) score, and time to first symptom relief	Secondary: At 4 weeks, the proportion of patients reporting no or mild heartburn was 99% with pantoprazole and 98% with esomeprazole. There were no significant differences in GSRS 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).
Richter et al.[39] (2001) Lansoprazole 30 mg QD vs. omeprazole 20 mg QD	RCT, MC, DB Adult patients with endoscopically documented erosive esophagitis Patients excluded if they had GI bleeding, history of gastric or esophageal surgery, esophageal motility disorders, esophageal stricture, or duodenal or gastric ulcers	N=3,510 8 weeks	Primary: Percentage of heartburn-free days and nights following 1-3 days and 1 week of treatment; and the frequency and severity of day- and nighttime heartburn	Primary: The percentage of heartburn-free days was significantly higher with lansoprazole compared to omeprazole after 1-3 days of treatment and after 1 week of treatment (*P*<0.0001). The percentage of heartburn-free nights was significantly higher with lansoprazole compared to omeprazole after 1-3 days of treatment and after 1 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 no heartburn compared to omeprazole at anytime during the first 14 days (*P*<0.001). At 8 weeks, patients reporting no heartburn throughout the entire study was also significantly higher for lansoprazole (*P*<0.05).
Bardhan et al.[40] (2001) Omeprazole 20 QD vs. pantoprazole 20 mg QD	RCT, PG, OL, PG Adult patients with grade I GERD Patients were excluded if they had grade II, III, IV GERD, GI bleeding,	N=327 8 weeks	Primary: Rate of symptom relief at weeks 2 and 4 and healing rates at week 4 and 8	Primary: At 2 and 4 weeks, the rate of symptom relief was similar for pantoprazole (70% and 77%) and omeprazole (79% and 84%; *P* value not reported). Healing rates at 4 weeks were comparable between pantoprazole (84%) and omeprazole (89%; *P* value not reported). Healing rates at 8 weeks were comparable between pantoprazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders, pyloric stenosis, esophageal stricture, or duodenal or gastric ulcers			(90%) and omeprazole (95%; *P* value not reported).
Delcher et al.[41] (2000) Omeprazole 20 mg QD vs. rabeprazole 20 mg QD vs. rabeprazole 10 mg BID	RCT, PG, DB, PG Adult patients with ulcerative or erosive GERD Patients excluded if they had grade I GERD, history of gastric or esophageal surgery, esophageal motility disorders, or pyloric stenosis	N=310 8 weeks	Primary: Healing rates Secondary: Improvement of GI symptoms, number of hours missed from normal daily activity, the use of antacids, and physical well-being	Primary: At 4 weeks, the rates of healing were comparable among rabeprazole 20 mg QD (94%), rabeprazole 10 mg BID (93%), and omeprazole (98%; *P* value not reported). At 4 weeks, the rates of healing were comparable among rabeprazole 20 mg QD (97%), rabeprazole 10 mg BID (98%), and omeprazole (100%; *P* value not reported). Secondary: At 4 and 8 weeks, improvements in GI symptoms were comparable among all treatment groups (*P* value not reported). Use of antacid tablets was comparable between all treatment groups (*P* value not reported). 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.[42] (2005) Omeprazole 20 mg QD vs.	RCT, DB Patients with grade I-III GERD Exclusion criteria not specified	N=560 8 weeks	Primary: Healing rates Secondary: Time to first day with satisfactory relief	Primary: After 8 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rabeprazole 20 mg QD				
Glatzel et al.[56] (2006) Esomeprazole 40 mg QD vs. pantoprazole 40 mg QD	RCT, DB, MC, PG Patients >18 y/o with endoscopically-confirmed GERD grades A-D (Los Angeles Classification)	N=585 42 days	Primary: GERD symptoms using the Request-GI patient-oriented self-assessment subscale during the pretreatment phase (7 days), treatment phase (28 days), and post-treatment phase (7 days)	Primary: Pretreatment phase: The median values of the mean ReQuest-GI 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. Treatment phase: The median of the mean ReQuest-GI score of the last 3 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 1) to 0.7 (week 4) and the maximum ReQuest-GI scores from 3.2 and 3.7 (pantoprazole and esomeprazole, respectively, week 1) to 1.0 and 1.1 (pantoprazole and esomeprazole, respectively, week 4). 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-GI 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 versus 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).
Gralnek et al.[57]	MA	N=15,316	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Esomeprazole vs. omeprazole, lansoprazole, or pantoprazole	Randomized clinical trials in patients with erosive esophagitis	(10 trials) 4-8 weeks	Relative risk of erosive esophagitis healing, symptom relief, and adverse events	At 4 and 8 weeks, there was 10% (RR, 1.10; 95% CI, 1.05–1.15) and 5% (RR, 1.05; 95% CI, 1.02–1.08) relative increase in the probability of healing, respectively, with esomeprazole versus alternative PPIs. At 8 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–D) were 50, 33, 14, and 8, respectively. At 4 weeks, esomeprazole was associated with an 8% relative increase in the probability of GERD symptom relief (RR, 1.08; 95% CI 1.05 – 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.
Pilotto et al.[58] (2007) Omeprazole 20 mg QD vs. lansoprazole 30 mg QD vs. pantoprazole 40 mg QD vs.	R, OL, SC Age 65 years or over and (2) endoscopic 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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rabeprazole 20 mg QD				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). All four PPIs were well tolerated. Adverse events were reported only by four patients (1.3%).
Goh et al.[59] (2007) Pantoprazole 20 mg QD vs. esomeprazole 20 mg QD	RCT, DB, MC, PG Patients ≥years 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.	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 6 months. Combined endoscopic and symptomatic remission was independent of Helicobacter pylori status. Both treatments were well tolerated and no safety concerns arose over the 6-month maintenance phase. Adverse events occurred in 22% of pantoprazole-treated patients and 23% of esomeprazole-treated patients.
Bardhan et al.[60] (2007) Pantoprazole 40 mg QD vs. Esomeprazole 40 mg QD	RCT, DB, MC, PG Patients at least 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 4- and 8-weeks; endoscopically confirmed healing rates at 4-, 8- and 12-weeks; symptom relief rates at 4-, 8- and 12-weeks; endoscopically confirmed healing	Primary: Complete remission rates at 12 weeks were similar with pantoprazole and esomeprazole (93% and 90%, respectively). Secondary: The complete remission rates after 4 and 8 weeks were similar with pantoprazole and esomeprazole (59% and 62% at 4 weeks, and 86% and 84% at 8 weeks, respectively). All complete remission rates were similar at 4, 8 and 12 weeks. Endoscopically confirmed healing rates were similar at 4-8 weeks, and more effective with pantoprazole at 12 weeks (95% CI: 0.02 - 7.27): 4 weeks: 75% for both pantoprazole and esomeprazole 8 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			rates, symptom relief rates and complete remission rates at 4-, 8- and 12-weeks for H. pylori positive & negative patients.	The H. pylori status had no influence on endoscopically confirmed healing rates, symptom relief rates or complete remission rates.
Peptic Ulcer Disease				
Ulmer et al.[43] (2003) *H. pylori* triple therapy with lansoprazole, omeprazole, or pantoprazole with two other antibiotics for 7 days	MA Clinical trials using PPI-based triple therapy for 7 days in *H. pylori* infections Exclusion criteria not specified	N=8,383 (79 trials) 7 days	Primary: Eradication rates	Primary: Eradication rates for all therapies were 71.9%-83.9% in the intention-to-treat population and 78.5%-91.2% for the per-protocol analysis. Pooled data analysis indicated that lansoprazole, omeprazole, or pantoprazole based therapies are comparable in *H. pylori* eradication.
Vergara et al.[44] (2003) *H. pylori* 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 Exclusion criteria not specified	14 trials 7-14 days	Primary: Direct comparison of eradication rates in the intention-to-treat population between PPIs	Primary: Pooled eradication rates with omeprazole (74.7%) were comparable to rates observed with lansoprazole (76%; odds ratio [OR] =0.91, 95% CI 0.69-1.21). Pooled eradication rates with omeprazole (77.9%) were comparable to rates observed with rabeprazole (81.2%; OR=0.81, 95% CI 0.58-1.15). Pooled eradication rates with omeprazole (87.7%) were comparable to rates observed with esomeprazole (89%; OR=0.89, 95% CI 0.58-1.35). Pooled eradication rates with lansoprazole (81%) were comparable to rates observed with rabeprazole (85.7%; OR=0.77, 95% CI 0.48-1.22).
Gisbert et al.[45] (2004) Esomeprazole based *H. pylori* therapies	MA Randomized trials investigating the use of esomeprazole	Number of trials analyzed was not reported	Primary: *H. pylori* eradication rates for esomeprazole therapies	Primary: Dual therapy with esomeprazole and clarithromycin therapy resulted in an eradication rate of 51%-54%. Mean eradication rates following triple therapy with esomeprazole,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. omeprazole based *H. pylori* therapies	based *H. pylori* therapies and other PPI based *H. pylori* therapies were included in the analysis Therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized were included Exclusion criteria not specified		Secondary: Comparison of eradication rates for esomeprazole vs. omeprazole therapy	clarithromycin, and either amoxicillin or metronidazole was 82%-86%. Secondary: Mean eradication rates for esomeprazole-based therapies (85%) were comparable to omeprazole-based therapies (82%, OR=1.19; 95% CI=0.81-1.74).
Bazzoli et al.[46] (1998) Lansoprazole based *H. pylori* therapies vs. omeprazole based *H. pylori* therapies	MA Randomized trials investigating the use of lansoprazole based *H. pylori* therapies and other PPI based *H. pylori* therapies were included in the analysis Therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized were included Exclusion criteria not specified	N=1,354 16 trials	Primary: *H. pylori* eradication rates for lansoprazole therapies Secondary: Comparison of eradication rates for lansoprazole vs. omeprazole therapy	Primary: Eradication rates for lansoprazole monotherapy (6-8 week duration) were comparable to dual therapy with lansoprazole (6-8 week duration) and amoxicillin (2-4 week duration; OR=0.8, 95% CI=0.3-1.9 for gastric ulcers; OR=1.5, 95% CI=0.4-5.7 for duodenal ulcers). 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%2.9-24.5). Secondary: Mean eradication rates for lansoprazole-based therapies (80.6%) were comparable to omeprazole-based therapies (69.6%, OR=0.9; 95% CI=0.6-1.3).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gisbert et al.[47] (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 Exclusion criteria not specified	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 7-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=0.61-1.64). Mean eradication rates for pantoprazole-based therapies (83%) were comparable to omeprazole-based therapies (82%, OR=0.91; 95% CI=0.49-1.69). Mean eradication rates for pantoprazole-based therapies (78%) were comparable to those with lansoprazole-based therapies (75%, OR=1.22; 95% CI=0.68-2.17).
Gisbert et al.[48] (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 Therapies utilizing comparable	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	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 7 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 7 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=0.93-1.42).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	antibiotic regimens and differing only in the PPI utilized were included. Exclusion criteria not specified		rabeprazole 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=0.81-1.32). Mean eradication rates for rabeprazole-based therapies (82%) were comparable to lansoprazole-based therapies (79%, OR=1.17; 95% CI=0.79-1.74).
Ji et al.[61] (2006) Rabeprazole 10 mg QD vs. omeprazole 20 mg QD	R, PRO Patients aged 18 years or older with at least one, but no more than three, active gastric antral or duodenal ulcers with a diameter ≥5 mm to ≤30 mm, when measured by open biopsy forceps.	N=112 6 weeks	Primary: The remaining ratios of the ulcer at 1 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 1 week of treatment were equivalent in the two groups. The remaining ratios of ulcer were 45.5±33.0% in the rabeprazole group and 50.3±35.2% in the omeprazole group (*P*=0.475). Secondary: The healing rates of peptic ulcers observed after 6 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 1 week or the healing rates of peptic ulcers after 6 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 1 week and 6 weeks.
Choi et al.[62] (2007) Omeprazole 20 mg BID vs. pantoprazole 40 mg BID	R, PRO 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	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 ($p<.05$), but the frequencies of individual symptoms were not significantly different among the four groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. rabeprazole 20 mg BID vs. esomeprazole 40 mg BID *all patients also received clarithromycin 500 mg BID and amoxicillin 1 gram BID for 1 week				
Subei et al.[63] (2007) Esomeprazole 20 mg BID, amoxicillin 1 gm BID, and clarithromycin 500 mg BID given for 1 week and followed by 3 weeks of placebo (EAC) vs. omeprazole 20 mg BID, amoxicillin 1 gm BID, and clarithromycin 500 mg BID given for 1 week and followed by 3 weeks of omeprazole 20 mg QD	MC, DB, DD, RCT, PC, PG Patients >18 years of age, active duodenal ulcer of at least 5 mm, and positive for *H. pylori*, assessed by a *Helicobacter* urease test (HUT).	N=382 8 weeks	Primary: 4- and 8-week duodenal ulcer healing rates Secondary: 8-week *H. pylori* eradication rates	Primary: At the end of the 4-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 8-week follow-up period, duodenal ulcer healing rates were similar with EAC compared with OAC (86% in both groups; 95% CI, −8.46% to 5.0%). Secondary: *H. pylori* eradication rates were similar at the end of the 8-week follow-up period for the EAC and OAC treatment groups (74.7% and 78.7%, respectively; 95% CI, −12.6% to 4.6%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
monotherapy (OAC)				
Wu et al.[64] (2007) Esomeprazole 40 mg QD vs. rabeprazole 20 mg BID *all patients also received amoxicillin 1 g BID and clarithromycin 500 mg BID for 1 week)	RCT Patients diagnosed with gastritis or peptic ulcer with *H. pylori* infection.	N=420 12-16 weeks	Primary: *H. pylori* eradication rates, compliance and adverse events	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)
Murakami et al.[65] (2008) Rabeprazole 10 mg BID (RAM) vs. lansoprazole 30 mg BID (LAM) vs. omeprazole 20 mg BID (OAM) *all patients also received amoxicillin 750mg BID and metronidazole 250mg	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 1 week of treatment and 4 weeks of follow-up.	Primary: *H. pylori* eradication rates were not significantly different between the different PPI treatment groups (91.4% with RAM, 91.1% with LAM, and 90.9% with OAM).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID for 1 week.				
Other				
Ramdani et al.[49] (2002) Lansoprazole 30-120 mg/day or omeprazole 20-100 mg/day vs. pantoprazole 40-200 mg/day All patients previously maintained on lansoprazole or omeprazole received pantoprazole for 7-10 days.	OL, PRO Adult patients with Zollinger-Ellison syndrome maintained on omeprazole or lansoprazole Patients excluded if they had a history of gastric or esophageal surgery, GI malignancy, or a significant unstable disease	N=11 7-10 days	Primary: Median 24-hour intragastric pH and percentage of time at or below pH 3, 4, 5, and 6 Secondary: Basal acid output	Primary: Median 24-hour intragastric pH for pantoprazole (5.3) was comparable to the median pH for lansoprazole and omeprazole (4.6 for both agents; *P*=0.90). There were no significant differences in percentage of time at or below pH 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 (*P* value not reported).
Conrad et al.[50] (2005) Immediate-release omeprazole suspension (two 40 mg dose on day 1 then 40 mg daily thereafter) vs. cimetidine IV (300 mg bolus then 50 mg/hr thereafter)	RCT, DB Hospitalized patients > 16 yrs old in ICU with an anticipated stay ≥72 hours with >1 additional risk for upper gastrointestinal bleed Patients were excluded if they had a history of gastric surgery, allergy to cimetidine or	N=359 14 days	Primary: Clinically significant upper gastrointestinal (UGI) bleed Secondary: Median gastric pH on each trial day, percentage of patients with median gastric pH of >4 on each trial day, and the percentage of patients with inadequate gastric	Primary: Clinically significant UGI bleeding was observed in 7 (3.9%) of the patients taking immediate-release omeprazole compared to 10 (5.5%) of the patients taking cimetidine (*P* value not reported). The upper bound of the one-sided 97.5% confidence interval for the difference in bleeding rates was 2.8%, less than the 5% prespecified "noninferiority" 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 1-13, *P*=0.2 on day 14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	omeprazole, active GI bleeding, significant risk of swallowing blood, enteral feeding required for the first 2 days of the trial, admission for upper GI surgery, known upper GI lesions that might bleed, the inability to take a suspension by nasogastric tube, or end-stage liver disease		pH control (2 consecutive pH measurements of ≤4	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.[51] (2005) Immediate-release omeprazole suspension dosed 40 mg daily for 1 week, then 20 or 40 mg twice daily for 1 day vs. pantoprazole 40 mg daily x 1 week, then 40 mg twice daily for 1 day Study participants underwent 8 days of treatment followed by a 10-14 day washout	RCT, OL, XO Adult patients age 18-65 yrs with GERD with recurrent nighttime symptoms for the previous 3 months Patients were excluded if they had current gastrointestinal disease other than GERD, history of gastric surgery, other significant, unstable disease or use of any gastric antisecretory drugs 7 days prior to the	N=36 16 days	Primary: Control of nocturnal gastric acidity measured by the following: percentage of time with gastric pH>4, median gastric pH, and nocturnal acid breakthrough	Primary: Median percentage of time with gastric pH>4 was significantly higher 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
period. Afterwards participants underwent an additional 8 days treatment on the other agent	trial			

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily, PRN=as needed
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, 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, PRO=prospective, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, RR=rate ratio, SB=single-blind, XO=crossover

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
Nelson et al. conducted an analysis of the impact of converting patients with GERD from omeprazole to lansoprazole through a managed care plan policy.[52] 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 OTC heartburn preparations, diet changes due to heartburn, and patient satisfaction. One hundred and five patients completed both interviews. After the interchange, increased frequency of heartburn while awake was reported in 35% of the patients, 9% reported increased frequency of heartburn that kept them from falling asleep, 33% reported increased frequency of use of any OTC heartburn preparations, and 13% reported increased frequency of diet change 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 conducted a study in 829 patients investigating the long-term effect of health-care consumption when double doses of omeprazole were utilized.[53] Patients with dyspeptic symptoms were randomized to receive omeprazole 40 mg every morning, omeprazole 20 mg every morning, or placebo for 2 weeks. Patients were evaluated on symptom relief. In addition, relapse rates and health-care consumption after 12 months were recorded. Complete symptom relief was comparable between omeprazole 40 mg (66.4%) and omeprazole 20 mg (63.0%). The difference was not significant (95% CI: -4.5%–11.4%). Relapse rates after 12 months were comparable between all treatment arms (67.7% for omeprazole 40 mg, 34.7% for omeprazole 20 mg, and 63.3% for placebo). There was no difference between treatment arms 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Single Entity Proton-pump Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Esomeprazole	delayed-release capsule, delayed-release powder for suspension, injection	Nexium®, Nexium I.V.®	$$$$	N/A

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Lansoprazole	delayed-release capsule, delayed-release orally disintegrating tablet, delayed-release granules for suspension, injection	Prevacid®, Prevacid IV®	$$$$	N/A
Omeprazole	delayed-release capsule, delayed-release tablet	Prilosec®*‡	$$$$	$ - $$$$
Omeprazole magnesium	delayed-release tablet	Prilosec OTC®‡	$	N/A
Omeprazole and sodium bicarbonate	capsule, powder for suspension	Zegerid®	$$$$	N/A
Pantoprazole	delayed-release tablet, delayed-release granules for suspension, injection	Protonix®*, Protonix IV®	$$$ - $$$$	$$$$
Rabeprazole	delayed-release tablet	Aciphex®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=not available
‡ Product is available over-the-counter

X. Conclusions

Proton-pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion available.[1] All PPIs are indicated for the treatment of GERD and pathological hypersecretory conditions.[7-12] Lansoprazole has the greatest number of FDA-approved indications, followed by prescription omeprazole. Esomeprazole, lansoprazole, and prescription omeprazole are approved for use in pediatric patients as young as 1 year of age.[8-10]

PPIs are effective treatment options for a variety of acid-related disorders, including erosive esophagitis and symptomatic GERD. Guidelines recognize that PPIs are more effective than histamine$_2$ receptor antagonists for these indications.[13-15,55] Numerous clinical trials have demonstrated equal efficacy among the various PPIs for the treatment of erosive esophagitis and symptomatic GERD.[23-25,29-30,35,38,40-42,56,59-60] Some studies have demonstrated various degrees of greater efficacy with one PPI over another in the treatment of these disorders[26,28,31-34,36-37,39]; however, close analysis of these studies show that the overall differences are small, often ranging from 3% to 9%. Though 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 FDA-approved doses. However, therapeutically equivalent doses of the PPIs have not been well established. Clinical guidelines do not give preference of one PPI over another for the treatment of erosive esophagitis and symptomatic GERD.[13-15,55]

PPIs are also effective for the treatment of peptic ulcer disease caused by chronic NSAID therapy or *H. pylori* infection when coupled with antibiotics. Several clinical trials and meta analyses have demonstrated similar efficacy among the various PPIs for the treatment of *H. pylori* infection.[43-48,61-65] Guidelines recommend PPIs in combination with antibiotics as first-line therapy for the eradication of *H. pylori* infection, and do not give preference to one PPI over another.[16-19]

Therefore, all brand single entity proton-pump inhibitors within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand single entity 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. 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.
2. 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.
3. Wolfe, MM**.** Overview and comparison of the proton-pump inhibitors for the treatment of acid-related disorders. Waltham, Mass: UpToDate, 2006.
4. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed November, 2008.
5. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November, 2008.
6. McEvoy GK, Ed. American Hospital Formulary Service, AHFS Drug Information. American Society of Health-System Pharmacists. Bethesda. 2006.
7. Aciphex® [package insert].Woodcliff Lake, NJ: Eisai; June 2008.
8. Nexium® [package insert]. Wilmington, DE: AstraZeneca; February 2008.
9. Prevacid® [package insert]. Lake Forest, IL: TAP Pharmaceuticals; August 2008.
10. Prilosec® [package insert]. Wilmington, DE: AstraZeneca; March 2008.
11. Protonix® [package insert].Philadelphia, PA: Wyeth; May 2008.
12. Zegerid® [package insert]. San Diego, CA: Santarus Inc.; January 2008.
13. DeVault KR, Castell DO; American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 2005; 100(1):190-200.
14. Armstrong D, Marshall JK, Chiba N, Enns R, 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.
15. Rudolph CD, Mazur LJ, Liptak GS, Baker RD, et al. North American Society for Pediatric Gastroenterology and Nutrition. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr. 2001;32 (suppl 2):S1-31.
16. Chey W, Wong B. American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. Am J Gastroenterol 2007; 102:1808-1825.
17. Hunt R, 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):547-554.
18. Malfertheiner P, Megraud F, O'Morain C. Hungins A et al. Current Concepts in the Management of Helicobacter pylori Infection. The Maastricht 2-2000 Consensus Report. European Helicobacter Pylori Study Group. Aliment Pharmacol Ther 2002; 16:167-180.
19. Veldhuyzen van Zanten SJ, Flook N, Chiba N, Armstrong D, An evidence-based approach to the management of uninvestigated dyspepsia in the era of Helicobacter pylori. Canadian Dyspepsia Working Group. CMAJ. 2000; 162(suppl 12):S3-23.
20. 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):2324-2337.
21. Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. Members of the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. Am J Gastroenterol. 1998; 93(11):2037-2046.
22. Tatro DS, ed. Drug Interaction Facts. St. Louis, Mo: Wolters Kluwer Health, Inc.; 2006.
23. 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.
24. 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 with omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. Clin Ther. 2001; 23(7):998-1017.
25. 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):1729-1736.

26. 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):1237-1245.
27. Tsai, HH, Chapman, R, 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;20:657-665.
28. Castell, DO, Kahrilas, PJ, Richter, JE, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002;97:575-583.
29. 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.
30. 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.
31. 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;4:852-859.
32. 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):455-463.
33. 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):333-341.
34. Richter, JE, Kahrilas, PJ, Johanson, J, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: A randomized controlled trial. Am J Gastroenterol. 2001;96:656-665.
35. 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.
36. Kahrilas, PJ, Falk, GW, Johnson, DA, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: A randomized controlled trial. Aliment Pharmacol Ther. 2000;14:1249-1258.
37. 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 versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther. 2005;21(6):739-746.
38. 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):587-594.
39. 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;96:3089-3098.
40. 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;15:1585-1591.
41. 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;35:1245-1250.
42. 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;37:741-750.
43. 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.
44. 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;18:647-654.

45. Gisbert JP, Pajares JM. Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis. Dig Liver Dis. 2004;36(4):253-259.
46. 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.
47. 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.
48. Gisbert JP, Khorrami S, Calvet X, Pajares JM. Systematic review: Rabeprazole-based therapies in Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003;17(6):751-764.
49. Ramdani A, Mignon M, Samoyeau R. Effect of pantoprazole versus other proton-pump inhibitors on 24-hour intragastric pH and basal acid output in Zollinger-Ellison syndrome. Gastroenterol Clin Biol. 2002;26(4):355-359.
50. Conrad S, Gabrielli A, Margolis B, Quartin A, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. Crit Care Med. 2005;33(4):760-765.
51. Castell D, Bagin R, 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):1467-1474.
52. 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;160:2491-2496.
53. 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):1050-1058.
54. Protonix IV® [package insert].Philadelphia, PA: Wyeth; December 2007
55. Kahrilas P, Shaheen N, Vaezi M, et al. AGAI medical position statement: management of gastroesophageal reflux disease. Gastroenterology 2008;135:1383-1391.
56. 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 superior regarding the prevention of symptomatic relapse. Digestion 2006;74:145-54.
57. Gralnek I, Dulai G, Fennerty M, et al. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis or randomized clinical trials. Clin Gastroenterol Hepatol 2006;4:1452-58.
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. Goh K, Benamouzig R, Sander P, et al. Efficacy of pantoprazole 20 mg daily compared with 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.
60. 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.
61. 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.
62. 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.
63. 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.
64. Wu I, Wu D, Hsu P, et al. Rabeprazole- versus esomeprazole-based eradication regimens for H. pylori infection. Helicobacter 2007;12:633-7.
65. 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

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Proton-pump Inhibitors Combination Products
AHFS Class 562836
February 11, 2009

I. Overview

Proton-pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally recognized as the most potent acid suppressants available.[1] 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. PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. PPIs will only inhibit proton pumps that are actively secreting acid.[1] Following a meal approximately 70%-80% of the proton pumps will be active.[2] 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. With regular dosing, maximal acid suppression occurs in 3-4 days.[1-3]

Helicobacter pylori (*H. pylori*) is a gram-negative spiral bacteria, which has been found to cause gastric and duodenal ulcers, as well as gastric malignancy.[4-8] Various regimens consisting of a PPI and multiple antibiotics have been approved by the FDA for the eradication of *H. pylori* and prevention of recurrent ulcers. One combination proton-pump inhibitor product is available (Prevpac®), which is supplied as individual daily administration cards, each containing two lansoprazole capsules, four amoxicillin capsules, and two clarithromycin tablets.[9] All components are commercially available in separate formulations and the amoxicillin and clarithromycin components are available generically.

The combination proton-pump inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Combination Proton-pump Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Lansoprazole, amoxicillin, and clarithromycin	combination pack containing capsules and tablets	Prevpac®	none

No generic products are available in this class.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the combination proton-pump inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines using the Combination Proton-pump Inhibitors

Clinical Guideline	Recommendation(s)
American College of Gastroenterology: **Guideline on the Management of *Helicobacter pylori* Infection[10] (2007)**	• 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 10–14 days.
Canadian Helicobacter Study Group Consensus Conference:	• A quadruple combination of a PPI, bismuth, tetracycline, and metronidazole for 10-14 days can be considered first-line therapy for

Clinical Guideline	Recommendation(s)
Update on the Management of *Helicobacter pylori*[11] (2004)	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.
European *Helicobacter pylori* Study Group: **Current Concepts in the Management of *H. pylori* Infection–The Maastricht 2-2000 Consensus Report[13] (2002)**	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should use quadruple therapy with a PPI, bismuth, metronidazole, and tetracycline. • When bismuth is not available, second-line therapy should be triple therapy with a proton-pump inhibitor.
Canadian Dyspepsia Working Group: **An Evidence-Based Approach to the Management of Uninvestigated Dyspepsia in the Era of *Helicobacter pylori*[12] (2000)**	• PPIs are considered a first-line therapy choice in patients on NSAIDs with dyspepsia who cannot discontinue NSAID therapy. • For the management of patients with GERD, PPIs are listed as first choice over H_2-RAs based on efficacy data. • In accordance with the recommendations of the Canadian *Helicobacter pylori* Consensus Conference, first-line eradication therapies for *H. pylori* are triple therapies of a PPI plus 1000 mg of amoxicillin plus 500 mg of clarithromycin (PPI + AC), or a PPI plus 500 mg of metronidazole plus 250 or 500 mg of clarithromycin (PPI + MC), twice daily for 1 week; or ranitidine bismuth citrate plus either AC or MC • If the first eradication therapy has failed, the action recommended by the Canadian *Helicobacter pylori* Consensus Conference is to use a different first-line therapy than that used initially (e.g., switch from PPI + AC to PPI + MC). • An alternative therapy is a 14-day quadruple regimen of a PPI (twice daily) plus bismuth (subsalicylate, 2 tablets 4 times daily) plus metronidazole (250 mg 4 times daily) plus tetracycline (500 mg 4 times daily) (PPI + BMT). • For the management of patients negative for *H. pylori*, a PPI is the first-line therapy choice.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the combination 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 Combination Proton-pump Inhibitors[9]

Generic Name	Indication
Lansoprazole, amoxicillin, and clarithromycin	Treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*

IV. Pharmacokinetics

The pharmacokinetic parameters of the combination proton-pump inhibitors are listed in Table 4. The pharmacokinetics of all three components when co-administered has not been studied. Information regarding the pharmacokinetics of each component is based on studies in which each drug was administered alone.

Table 4. Pharmacokinetic Parameters of the Combination Proton-pump Inhibitors[6]

Generic Name	Tmax (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
Amoxicillin	1-2	No data	60	No	1
Clarithromycin	2-4	No data	30	Yes (14-OH clarithro-mycin)	5-7
Lansoprazole	1.7	>24	14-25	Yes (Cyclic sulfonamide and disulfide metabolites)	1.3-1.5

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Combination Proton-pump Inhibitors[5]

Generic Name	Significance Level	Interaction	Mechanism
Amoxicillin	1	Methotrexate	Amoxicillin may reduce renal clearance of methotrexate. Concurrent use may result in methotrexate toxicity.
Amoxicillin	1	Tetracyclines	Pharmacologic and therapeutic action of amoxicillin could be reduced. The bacteriostatic action of tetracyclines may withhold part of the microorganisms from the bactericidal activity of penicillins.
Clarithromycin	1	Antiarrhythmic agents (class IA and class III)	An additive or synergistic increase in the QT interval may result. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Clarithromycin	1	Carbamazepine	Clarithromycin may inhibit carbamazepine hepatic metabolism, leading to decreased clearance.
Clarithromycin	1	Cisapride	Clarithromycin may inhibit the hepatic metabolism of cisapride.
Clarithromycin	1	Colchicine	Possible inhibition of colchicine metabolism. Increased colchicine serum concentrations with toxicity (including death) may occur.
Clarithromycin	1	Conivaptan	Clarithromycin may inhibit the metabolism (CYP3A4) of conivaptan, increasing the risk of adverse reactions.
Clarithromycin	1	Digoxin	Clarithromycin may inhibit renal tubular *P* glycoprotein excretion of digoxin.
Clarithromycin	1	Diltiazem	Inhibition of clarithromycin metabolism (CYP3A4) by diltiazem, which may increase plasma concentrations of clarithromycin, increasing the risk of cardiotoxicity.

Generic Name	Significance Level	Interaction	Mechanism
Clarithromycin	1	Dihydroergotamine, ergotamine	Clarithromycin may interfere with the hepatic metabolism of ergotamine. Acute ergotism manifested as peripheral ischemia has been reported with concomitant use of these agents.
Clarithromycin	1	Eplerenone	Clarithromycin may inhibit the metabolism (CYP3A4) of eplerenone, which may increase the risk of hyperkalemia and associated serious, sometimes fatal, arrhythmias.
Clarithromycin	1	HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Clarithromycin may inhibit the metabolism of atorvastatin, lovastatin, or simvastatin. Severe myopathy or rhabdomyolysis may occur because of increased HMG-CoA reductase inhibitor levels.
Clarithromycin	1	Pimozide	Clarithromycin may inhibit the hepatic metabolism of pimozide.
Clarithromycin	1	Quinolone antibiotics (gatifloxacin, levofloxacin, moxifloxacin)	Risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Clarithromycin	1	Ranolazine	Clarithromycin may inhibit the metabolism (CYP3A4) of ranolazine, increasing plasma concentrations and the risk of life-threatening cardiac arrhythmias.
Clarithromycin	1	Verapamil	Inhibition of verapamil metabolism (CYP3A4), which may increase the risk of cardiotoxicity.
Clarithromycin	1	Warfarin	Clarithromycin may reduce the total body clearance of warfarin.
Lansoprazole	1	Protease inhibitors (atazanavir, indinavir, nelfinavir, saquinavir)	PPIs may reduce the dissolution of certain protease inhibitors, reducing GI absorption and antiviral activity. Dose adjustment of some protease inhibitors may be required with concurrent administration. The use of PPIs with atazanavir is not recommended.
Amoxicillin	2	Oral contraceptives	Amoxicillin may decrease the enterohepatic circulation of oral contraceptives, reducing their effectiveness.
Amoxicillin	2	Probenecid	Coadministration of probenecid and amoxicillin may cause increases in amoxicillin levels due to decreased renal tubular secretion.
Amoxicillin	2	Warfarin	Amoxicillin may increase the bleeding risk of warfarin through an unknown interaction. International normalized ratio (INR) should be monitored closely.

Generic Name	Significance Level	Interaction	Mechanism
Clarithromycin	2	Aminophylline, oxtriphylline, theophylline	Clarithromycin may inhibit the metabolism of theophylline. Theophylline may reduce bioavailability and increase renal clearance of oral clarithromycin.
Clarithromycin	2	Alprazolam, diazepam, midazolam, triazolam	Clarithromycin may decrease the metabolism of certain benzodiazepines.
Clarithromycin	2	Buspirone	The metabolism of buspirone may be inhibited by clarithromycin.
Clarithromycin	2	Cabergoline	Inhibition of P-glycoprotein and cabergoline metabolism (CYP3A4) is suspected. Cabergoline plasma concentrations may be elevated, increasing the risk of toxicity.
Clarithromycin	2	Cilostazol	Clarithromycin may inhibit the metabolism of cilostazol.
Clarithromycin	2	Cyclosporine	Clarithromycin may interfere with cyclosporine metabolism and may increase rate and extent of absorption or reduce volume of distribution.
Clarithromycin	2	Ixabepilone	Clarithromycin inhibits the metabolism (CYP3A4) of ixabepilone, increasing the risk of toxicity.
Clarithromycin	2	Lapatinib	Clarithromycin inhibits the metabolism (CYP3A4) of lapatinib, increasing the risk of toxicity.
Clarithromycin	2	Methylprednisolone	Clarithromycin may result in an increase in plasma concentrations of methylprednisolone.
Clarithromycin	2	Repaglinide	Clarithromycin may inhibit the metabolism of repaglinide.
Clarithromycin	2	Rifamycins	The metabolism of rifamycin may be inhibited. The metabolism of clarithromycin metabolism may be increased with coadministration of rifampin.
Clarithromycin	2	Sildenafil	Inhibition of sildenafil first-pass metabolism (CYP3A4) by clarithromycin is suspected. Sildenafil plasma concentrations may be elevated, increasing the risk of adverse reactions.
Clarithromycin	2	Tacrolimus	Metabolism of tacrolimus may be inhibited.
Lansoprazole	2	Clarithromycin	The metabolism of lansoprazole may be inhibited and cause increases in plasma levels. Patients should be monitored for an increase in adverse reactions during concurrent administration.
Lansoprazole	2	Azole antifungals (itraconazole, ketoconazole)	Oral tablet dissolution may be reduced due to higher gastric pH. Concurrent use should be avoided.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the combination proton-pump inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Combination Proton-pump Inhibitors[5,6,9]

Adverse Event(s)	Amoxicillin	Clarithromycin	Lansoprazole
Central Nervous System			
Dizziness	✔	-	-
Headache	-	2	-
Hyperactivity	✔	-	-
Dermatological			
Dermatitis	✔	-	-
Pruritus	✔	-	-
Urticaria	✔	-	-
Gastrointestinal			
Abdominal pain	-	2	2.8
Abnormal taste	-	3	-
Anorexia	-	<1	-
Constipation	-	-	1
Diarrhea	✔	3	3.8
Dyspepsia	-	2	-
Nausea	✔	3	1.3
Hematologic			
Anemia	✔	-	-
Thrombocytopenia	✔	-	-
Laboratory Test Abnormalities			
Elevate BUN	-	4	-
Elevated creatinine	-	<1	-
Elevated SGOT	✔	<1	-
Elevated SGPT	✔	<1	-
Other			
Anaphylaxis	✔	-	-
Tooth discoloration	✔	-	-

BUN=blood nitrogen urea, SGOT=serum glutamic-oxaloacetic transaminase, SGPT= serum glutamic-pyruvic transaminase
✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the combination proton-pump inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Combination Proton-pump Inhibitors[9]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Lansoprazole, amoxicillin, and clarithromycin	*H. pylori* eradication: lansoprazole 30 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg administered together twice daily for 10-14 days	Safety and efficacy in children have not been established	Individual dosing cards containing: lansoprazole 30 mg; amoxicillin 500 mg; clarithromycin 500 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the combination proton-pump inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Combination Proton-pump Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Veldhuyzen van Zanten et al.[15] (2003) Lansoprazole 30 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg BID for 7 days vs. placebo	RCT, DB 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 (P value not reported). The proportion of patients requiring additional medication after the 7-day treatment was similar between treatment groups.
Schwartz et al.[16] (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, clarithromycin 500 mg BID or TID, for 14 days	RCT, DB Adult patients positive with *H. pylori* and duodenal ulcers	N=352 4-6 weeks	Primary: *H. pylori* eradication rates Secondary: Recurrence of ulcers at 6 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; 53-77%) and lansoprazole monotherapy (2%). Secondary: Recurrence of ulcers at six months was lower with triple therapy (7%) compared to dual therapies (13-23%) and lansoprazole monotherapy (69%, P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. lansoprazole 30 mg BID or TID with amoxicillin 1,000 mg TID for 14 days				
Lamouliatte et al.[17] (1998) Triple therapy (lansoprazole 30 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg BID) for 14 days vs. dual therapy (lansoprazole 30 mg, amoxicillin 1,000 mg BID) for 14 days	RCT, PRO Adult patients positive with *H. pylori* and dyspepsia	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).
Ulmer et al.[18] (2003) *H. pylori* triple therapy with lansoprazole, omeprazole, or pantoprazole for 7 days	MA All trials that investigated 7-day, triple therapy with lansoprazole, omeprazole, or pantoprazole and two other antibiotics	N=8,383 (79 trials) 7 days	Primary: Eradication rates	Primary: Eradication rates for all therapies were 71.9%-83.9% in the intention-to-treat population and 78.5%-91.2% for the per-protocol analysis. Pooled data analysis indicated that lansoprazole, omeprazole, or pantoprazole based therapies are comparable in *H. pylori* eradication.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vergara et al.[19] (2003) *H. pylori* 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 7-14 days	Primary: Direct comparison of eradication rates in the intention-to-treat population between PPIs S	Primary: Pooled eradication rates with omeprazole (74.7%) were comparable to rates observed with lansoprazole [76%; odds ratio (OR) =0.91, 95% CI 0.69-1.21]. Pooled eradication rates with omeprazole (77.9%) were comparable to rates observed with rabeprazole (81.2%; OR=0.81, 95% CI 0.58-1.15). Pooled eradication rates with omeprazole (87.7%) were comparable to rates observed with esomeprazole (89%; OR=0.89, 95% CI 0.58-1.35). Pooled eradication rates with lansoprazole (81%) were comparable to rates observed with rabeprazole (85.7%; OR=0.77, 95% CI 0.48-1.22).
Bazzoli et al.[20] (1998) Lansoprazole based *H. pylori* therapies vs. omeprazole based *H. pylori* therapies Therapies utilizing comparable antibiotics regimens and differing only in the PPI utilized were included	MA Randomized trials investigating the use of lansoprazole based *H. pylori* therapies and other PPI based *H. pylori* therapies	N=1,354 16 trials	Primary: *H. pylori* eradication rates for lansoprazole therapies Secondary: Comparison of eradication rates for lansoprazole vs. omeprazole therapy	Primary: Eradication rates for lansoprazole monotherapy (6-8 week duration) were comparable to dual therapy with lansoprazole (6-8 week duration) and amoxicillin (2-4 week duration; OR=0.8, 95% CI=0.3-1.9 for gastric ulcers; OR=1.5, 95% CI=0.4-5.7 for duodenal ulcers). 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%2.9-24.5). Secondary: Mean eradication rates for lansoprazole-based therapies (80.6%) were comparable to with omeprazole-based therapies (69.6%, OR=0.9; 95% CI=0.6-1.3).

Study abbreviations: BID=twice daily, DB=double-blind, MA=meta-analysis, PRO=prospective, RCT=randomized controlled trial, TID=three times daily

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Combination Proton-pump Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Lansoprazole, amoxicillin, and clarithromycin	combination pack containing capsules and tablets	Prevpac®	$$$$$	N/A

No generic products are available in this class.
N/A=not available

X. Conclusions

The only combination proton-pump inhibitor product available (Prevpac®) contains lansoprazole capsules, amoxicillin capsules, and clarithromycin tablets as separate dosage forms in an individual daily administration card. It should be administered for 10 – 14 days for the treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*.[9] Each of the individual components are commercially available in separate formulations and the amoxicillin and clarithromycin components are available generically.

Successful treatment of *H. pylori* infection involves the use of a PPI and multiple antibiotics. Clinical trials comparing triple therapy (lansoprazole, amoxicillin, and clarithromycin) to dual therapy (lansoprazole with amoxicillin or clarithromycin) and lansoprazole monotherapy found that triple therapy provides significantly greater eradication rates of *H. pylori*.[16-17] Meta analyses have demonstrated similar efficacy among the various PPI regimens for the treatment of *H. pylori* infection.[18-20] Guidelines recommend PPIs in combination with antibiotics as first-line therapy for the eradication of *H. pylori* infection, and do not give preference to one PPI over another.[10-13]

Therefore, all brand combination proton-pump inhibitors within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand combination 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. Wolfe, MM, Sachs, G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 2000; 118 (Supp 1):S9-S31.
2. 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.
3. Wolfe, MM**.** Overview and comparison of the proton-pump inhibitors for the treatment of acid-related disorders. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2008.
4. Peura DA**.** Pathophysiology of and immune response to Helicobacter pylori infection. Waltham, Mass: UpToDate, 2006.
5. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2008. Available from Wolters Kluwer Health, Inc. Accessed December 2008.
6. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed December 2008.
7. McEvoy GK, Ed. American Hospital Formulary Service, AHFS Drug information. American Society of Health-System Pharmacists. Bethesda. 2006.
8. Eslick GD, Lim LL, Byles JE, Xia HH, Talley NJ. Association of Helicobacter pylori infection with gastric carcinoma: a meta-analysis. Am J Gastroenterol. 1999; 94(9):2373-2379.
9. Prevpac® [package insert]. Lake Forest, IL: Takeda Pharmaceuticals; August 2008.
10. Chey W, Wong B. American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. Am J Gastroenterol 2007; 102:1808-1825.
11. Hunt R, 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):547-554.
12. Veldhuyzen van Zanten SJ, Flook N, Chiba N, Armstrong D. An evidence-based approach to the management of uninvestigated dyspepsia in the era of Helicobacter pylori. Canadian Dyspepsia Working Group. CMAJ. 2000 Jun 13;162(12 Suppl):S3-23.
13. Malfertheiner P, Megraud F, O'Morain C. Hungins A et al. Current Concepts in the Management of Helicobacter pylori Infection. The Maastricht 2-2000 Consensus Report. European Helicobacter Pylori Study Group. Aliment Pharmacol Ther 2002;16:167-180.
14. Tatro DS, ed. Drug Interaction Facts. St. Louis, Mo: Wolters Kluwer Health, Inc.; 2006.
15. 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):1963-1969.
16. Schwartz H, Krause R, Sahba B, Haber M, et al. Triple versus 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):584-590.
17. Lamouliatte H, Cayla R, Zerbib F, Forestier S, de Mascarel A, Joubert-Collin M, Megraud F. Dual therapy using a double dose of lansoprazole with amoxicillin versus 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):1531-15314.
18. 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.
19. 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;18:647-654.
20. 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.