Antivertigo Agents
Therapeutic Class Review (TCR)

February 16, 2018

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Anticholinergics		
scopolamine (Transderm Scop®)[1]	generic, Novartis/ Baxter	▪ Prevention of nausea/vomiting (N/V) associated with motion sickness ▪ Prevention of postoperative N/V associated with recovery from anesthesia and/or opiate analgesia and surgery
Antihistamines[2]		
dimenhydrinate (Dramamine®)	generic, MedTech	▪ Treatment and prevention of motion sickness ▪ Treatment of N/V
diphenhydramine (Benadryl®, Naramin™, Vanamine PD™)	generic, McNeil, National, GM Pharm	▪ Treatment and prevention of N/V associated with motion sickness
meclizine [3] (Bonine®, Dramamine® Less Drowsy)	generic, Insight/MedTech	▪ Treatment of vertigo associated with diseases affecting the vestibular system
Phenothiazines[4]		
prochlorperazine (Compazine®, Compro®)	generic, PBM; Perrigo	▪ Control of severe N/V ▪ Preoperative nausea control ▪ Treatment of N/V
promethazine (Phenergan®)	generic, West-Ward, Prestium/ Mylan	▪ Treatment and prevention of N/V associated with motion sickness ▪ Prevention and control of N/V associated with certain types of anesthesia and surgery

OVERVIEW

Motion sickness is the result of a conflict between the various senses related to motion.[5] The overall incidence of dizziness, vertigo, and imbalance is 5% to 10%.[6] There are multiple causes of vertigo, such as head trauma, cerebellar lesions, vestibular disease, or migraine. The semicircular canals and otoliths in the inner ear sense angular and vertical motion, while the eyes and the proprioceptors determine the body's position in space.[7] When signals received by the eyes or the proprioceptors do not match those being transmitted by the inner ear, motion sickness occurs. It can occur in either the presence or absence of actual motion, such as when viewing a slide through a microscope. Symptoms include nausea, vomiting, pallor, sweating, and often a sense of impending doom. There are both non-pharmacologic and pharmacologic interventions for the prevention or management of motion sickness. None are ideal, and the medications typically cause drowsiness or similar adverse effects. Symptomatic treatment of motion sickness generally includes the use of antihistamines, benzodiazepines, or antiemetics. Vestibular rehabilitation in select patients may be used with a goal of treating the underlying cause.[8]

Nausea and vomiting (N/V) are common symptoms with a wide variety of underlying causes.[9] Nausea, the perception that emesis may occur, can be judged only by the patient. Nausea and vomiting can lead to several adverse events, such as nutrient depletion, metabolic imbalances, erosion of self-care, anorexia, diminished performance and mental status, wound dehiscence, and tears in the esophagus.[10] The goal of antiemetic therapy is to prevent N/V completely. Even though vomiting can often be

prevented or reduced significantly with prophylactic antiemetic medications, nausea is often much harder to control.[11,12]

The American Society of Anesthesiologists has published recommendations on the prevention of postoperative nausea and vomiting (PONV) within their guidelines on postanesthetic care.[13] They recommend routine assessment and monitoring for N/V. For prophylaxis and treatment of N/V, they evaluated the following classes of medication and rated them based on the quality of evidence (range of A to C, from randomized controlled trials to informal opinion and determination of beneficial [B] or equivocal [E]): antihistamines (Category A3-B evidence), 5-HT_3 receptor antagonists (Category A1-B evidence as a class), tranquilizers/neuroleptics (e.g., droperidol [Category A1-B evidence], haloperidol [Category A2-B evidence], hydroxyzine [Category A3-B evidence], perphenazine [Category A3-B evidence], prochlorperazine [Category A1-E evidence]). For prophylaxis of PONV using multiple agents, the society determined that multiple agents may be used when needed (Category A2-B evidence). They further note that pharmacologic treatment of N/V is recommended as it improves patient satisfaction, comfort, and reduces time to discharge.

PHARMACOLOGY[14,15]

Anticholinergics (scopolamine [Transderm Scop])

It is suggested that scopolamine (Transderm Scop) exerts its activity in the central nervous system (CNS) by blocking activity to the vomiting center and vestibular nuclei.

Antihistamines (dimenhydrinate [Dramamine], diphenhydramine [Benadryl, Naramin, Vanamine PD], meclizine [Bonine, Dramamine Less Drowsy])

Histaminergic (H1) antagonists act on the vomiting center and vestibular pathways making them effective in the prevention and treatment of motion sickness induced N/V.

Phenothiazines (promethazine [Phenergan], prochlorperazine [Compazine, Compro])

The phenothiazines block postsynaptic dopaminergic receptors in the brain, including the chemoreceptor trigger zone (CTZ). This mechanism contributes to depression of the reticular activating system and affects basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis. Promethazine also has both antihistaminic and anticholinergic properties.

PHARMACOKINETICS[16,17]

Drug	Bioavailability (%)	Half life ($t_{1/2}$) (hr)	Metabolites	Excretion (%)
Anticholinergics				
scopolamine (Transderm Scop)	--	--	yes	urine: 34
Antihistamines				
dimenhydrinate (Dramamine)	--	3.5	yes, active	--
diphenhydramine (Benadryl, Naramin, Vanamine PD)	65–100	2.4–9.3	yes, 5 active	urine: 50–75
meclizine (Bonine, Dramamine Less Drowsy)	--	6	yes, 1 active	--
Phenothiazines				
prochlorperazine (Compazine, Compro)	12.5	6–10 (single dose) 14–22 (repeat dosing)	yes; 1 active	--
promethazine (Phenergan)	low	10-14	yes, 1 active	--

hr = hours

CONTRAINDICATIONS/WARNINGS[18,19]

Promethazine (Phenergan) and prochlorperazine (Compazine, Compro) are contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to phenothiazines. Promethazine tablets and prochlorperazine should be used cautiously in persons with cardiovascular disease or with impairment of liver function. Prochlorperazine should be used cautiously in patient populations with pheochromocytoma as prochlorperazine-induced buildup of neurotransmitters can result in a cardiotoxic effect.

Dimenhydrinate (Dramamine), diphenhydramine (Benadryl, Naramin, Vanamine PD), meclizine (Bonine, Dramamine Less Drowsy) should not be used in patients with known hypersensitivity to their active or inert ingredients. These agents may cause excessive drowsiness; patients should use caution operating heavy machinery and driving, as well as avoid use with other medications and substances that can cause CNS depression. Due to their anticholinergic effects, these agents should be avoided or only used cautiously in patients with bladder obstruction, constipation, ileus or gastrointestinal (GI) obstruction, seizure disorders, cardiac conditions, or patients with respiratory conditions (e.g. asthma, chronic obstructive pulmonary disease), as it may thicken bronchial secretions in this latter population. Older patients may be more susceptible to these anticholinergic effects. Paradoxical reactions (e.g., CNS stimulation, seizures) have been reported in patients use these agents, particularly in children.

Dimenhydrinate can mask the symptoms of ototoxicity and should be used cautiously with ototoxic drugs. Select dimenhydrinate formulations contain tartrazine (chewable formulations); these products should not be used in in patients with tartrazine dye hypersensitivity or other sensitive individuals,

such as patients who are sensitive to aspirin (salicylate hypersensitivity). Likewise, some chewable formulations contain phenylalanine and should not be used in patients with phenylketonuria.

Scopolamine (Transderm Scop) is contraindicated in persons who are hypersensitive to the drug scopolamine or to other belladonna alkaloids, or to any ingredient or component in the formulation or delivery system, or in patients with angle-closure (narrow angle) glaucoma. Reactions have included generalized rash and erythema. As an anticholinergic agent, it should be used cautiously in patients with open angle glaucoma as it can increase intraocular pressure. It may also cause temporary pupil dilation. Scopolamine may exacerbate psychosis or cause other psychiatric reactions (e.g., acute toxic psychosis, including confusion, agitation, speech disorder, hallucinations, paranoia, and delusions) and should be used cautiously in patients with a history of seizures or psychosis as it can exacerbate these conditions. Due to its anticholinergic properties, scopolamine can decrease GI motility and cause urinary retention; discontinue if urinary retention occurs. Discontinuation after several days of use may result in withdrawal symptoms (e.g., dizziness, nausea, vomiting, abdominal cramps, sweating, headache, mental confusion, muscle weakness, bradycardia, and hypotension). Remove the scopolamine patch before undergoing magnetic resonance imaging (MRI) since skin burns have been reported at the application site.

DRUG INTERACTIONS[20,21]

Anticholinergics

The absorption of oral medications may be decreased during the concurrent use of scopolamine (Transderm Scop) because of decreased gastric motility and delayed gastric emptying. Scopolamine should be used with care in patients taking other drugs that are capable of causing CNS effects, such as sedatives, tranquilizers, or alcohol. Special attention should be paid to potential interactions with drugs having anticholinergic properties (e.g., other belladonna alkaloids, antihistamines [including meclizine], tricyclic antidepressants, and muscle relaxants).

Antihistamines

Dimenhydrinate (Dramamine), diphenhydramine (Benadryl, Naramin, Vanamine PD), and meclizine (Bonine, Dramamine Less Drowsy) may enhance the toxic effects of CNS depressants and anticholinergics. Diphenhydramine moderately inhibits CYP2D6; therefore, therapy with tramadol, codeine, tamoxifen, and nebivolol should be monitored.

Phenothiazines

Prochlorperazine (Compazine, Compro) may diminish the effect of dopamine agonists (antiparkinson's agents). Prochlorperazine may enhance the toxic effects of antipsychotics and enhance CNS depressant effects of opioids, barbiturates, and other CNS agents. Promethazine (Phenergan) is a major substrate of CYP2D6; therefore, monitor therapy with CYP2D6 inhibitors or inducers. Avoid combination with metoclopramide (Reglan®, Metozolv® ODT) or serotonin modulators.

Phenothiazines have been reported to prolong the QT interval. Taking phenothiazines with other medications known to prolong QT intervals should be avoided.

Caution should be used when phenothiazines are used with other drugs with antimuscarinic activity as side effects may be potentiated.

Caution should be used when phenothiazines are used with CNS depressants such as anxiolytics, sedatives, and hypnotics, as additive depressive CNS effects could occur.

Phenothiazines can lower the seizure threshold and dose adjustments of anticonvulsants may be needed.

ADVERSE EFFECTS[22,23]

Drug	Drowsiness	Xerostomia	Tachycardia	Rash	Blurred Vision	Urinary Retention
Anticholinergics						
scopolamine (Transderm Scop)	17	67	reported	reported	reported	reported
Antihistamines						
dimenhydrinate (Dramamine)	reported	reported	reported	reported	reported	reported
diphenhydramine (Benadryl, Naramin, Vanamine PD)	reported	reported	reported	reported	reported	reported
meclizine (Bonine, Dramamine Less Drowsy)	31	16.7	reported	nr	reported	reported
Phenothiazines						
prochlorperazine (Compazine, Compro)	reported	reported	reported	nr	reported	reported
promethazine (Phenergan)	reported	reported	reported	nr	reported	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive.

nr = not reported.

SPECIAL POPULATIONS[24,25]

Pediatrics

Dimenhydrinate (Dramamine) and diphenhydramine (Benadryl, Naramin, Vanamine PD) have been used to prevent and treat N/V associated with motion sickness in pediatric populations. Use of meclizine (Bonine, Dramamine Less Drowsy) in children less than 12 years of age is not recommended.

Promethazine (Phenergan) and prochlorperazine (Compazine, Compro) should not be used in pediatric patients less than 2 years of age.

Safety and effectiveness of scopolamine (Transderm Scop) in children have not been established.

Pregnancy

The antihistamines in this class, dimenhydrinate (Dramamine), diphenhydramine (Benadryl, Naramin, Vanamine PD), and meclizine (Bonine, Dramamine Less Drowsy), are Pregnancy Category B.

Promethazine (Phenergan) and prochlorperazine (Compazine, Compro) are Pregnancy Category C. Product labeling for scopolamine (Transderm Scop) was updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and states that available data have not identified a drug associated risk of adverse fetal outcomes.

DOSAGES[26,27]

Drug	Adult	Pediatric	Availability
Anticholinergics			
scopolamine (Transderm Scop)	Transdermal: 1 disc applied behind the ear 4 hours prior to antiemetic need; disc may stay in place for up to 3 days (If repeat dose needed, apply to skin behind opposite ear)		transdermal: 1.5 mg per 72 hours (delivers 1 mg over 72 hours) (Rx only)
Antihistamines			
dimenhydrinate (Dramamine, Motion Sickness)	Adults and children ≥ 12 years old: Oral: 1 to 2 tablets every 4 to 6 hours (do not exceed 8 tablets in 24 hours) Injection: 50 to 100 mg IM or IV every 4 hours (do not exceed 300 mg in 24 hours)	Children ages 6 to 12 years: Oral: ½ to 1 tablet every 6 to 8 hours (do not exceed 3 tablets in 24 hours) Children ages 2 to 6 years: Oral: ¼ to ½ tablet every 6 to 8 hours (do not exceed more than 1.5 tablets in 24 hours) Children ages 2 to 12 years: Injection: 1.25 mg/kg or 37.5 mg/m^2 BSA IM or IV every 6 hours (do not exceed 300 mg in 24 hours)	tablets: 50 mg (OTC) chewable tablets: 25 mg, 50 mg (OTC) injection: 50 mg/mL in 1 mL multi-dose vials (Rx)
diphenhydramine (Benadryl, Naramin, Vanamine PD)	Injection: 10 mg IV or IM initially then 20 to 50 mg every 2 to 3 hours as needed (do not exceed 400 mg in 24 hours) Oral: 25 to 50 mg every 4 to 6 hours in adults and children ages ≥12 years old (do not to exceed 300 mg in 24 hours)	Ages 6 to 12 years: Injection: 1 to 1.5 mg per kg IV or IM every 6 hours, not to exceed 300 mg per day Ages 6 to 12 years: Oral: 12.5 mg to 25 mg every 4 to 6 hours (do not exceed 150 mg in 24 hours) Ages < 6 years: Oral and injection: safety and efficacy have not been established	tablets: 25 mg, 50 mg (OTC) capsules: 25 mg, 50 mg (OTC) softgels/gelcaps: 25 mg (OTC) chewable tablet: 12.5 mg (OTC) injection: 50 mg/mL in 1 mL single-use vials and 10 mL multi-dose vials (Rx) oral dissolving film: 25 mg (OTC) oral dissolving tablet: 12.5 mg, 25 mg (OTC) oral solution: 12.5 mg/5 mL (OTC and Rx), 50 mg/30 mL (OTC) oral drops: 6.25 mg/mL (OTC)

OTC = over the counter; Rx = prescription required

Dosages (continued)

Drug	Adult	Pediatric	Availability
Antihistamines (*continued*)			
meclizine (Bonine, Dramamine Less Drowsy)	**Motion Sickness:** Adults and children ≥ 12 years old (OTC Dramamine Less Drowsy): 25 to 50 mg taken 1 hour prior to travel; may repeat dose every 24 hours as needed **Vertigo:** Adults and children ≥ 12 years old: 25 to 100 mg daily in divided doses	--	Chewable tablets: 25 mg (OTC) Tablets: 12.5 mg (Rx and OTC), 25 mg (Rx and OTC)
Phenothiazines			
prochlorperazine (Compazine, Compro)	Immediate release tablets: 5 to 10 mg 3 to 4 times daily Sustained release capsules: 10 or 15 mg every 12 hours Rectal suppositories: 25 mg twice daily IV or IM: 5 to 10 mg repeated every 3 to 4 hours as needed (max dose is 40 mg/day)	Oral or rectal: Children 2 to 12 years (weight 18 to 39 kg): 2.5 mg 3 times per day or 5 mg twice per day (max: 15 mg/day) Children 2 to 12 years (weight 14 to 17 kg): 2.5 mg 2 to 3 times per day (max: 10 mg/day) Children 2 to 12 years (weight 9 to 13 kg): 2.5 mg once or twice per day (max: 7.5 mg/day) Children < 2 years of age and infants (weight < 9 kg): Dosage not established IV or IM: Children 2 to 12 years (weight 18 to 39 kg): 0.132 mg per kg deep IM injection given 3 to 4 times per day, not to exceed 10 mg per day on the first day of treatment (max: 15 mg per day on subsequent days) Children 2 to 12 years (weight 14 to 17 kg): 0.132 mg per kg deep IM injection given 3 to 4 times per day (max: 10 mg per day) Children 2 to 12 years (weight 9 to 13 kg): 0.132 mg per kg deep IM injection given 3 to 4 times per day (max: 7.5 mg per day) Children < 2 years and infants (weight < 9 kg): Dosage not established	tablets: 5 mg, 10 mg suppositories: 25 mg injection: 5 mg/mL in 2 mL and 10 mL vials (all Rx only)
promethazine (Phenergan)	**Motion Sickness:** Adults: 25 mg (oral or rectal) 30 to 60 minutes prior to departure, then every 12 hours as needed **N/V:** Adults: 12.5 to 25 (oral, rectal, IV, IM) mg every 4 to 6 hours as needed	**Motion Sickness:** Children > 2 years of age: 12.5 to 25 mg (oral or rectal) twice daily as needed with first dose given 30 to 60 minutes prior to departure **N/V:** Children > 2 years of age: 0.5 mg per pound (oral or rectal), max 25 mg per dose, every 4 to 6 hours as needed Children > 2 years of age: 6.25 to 12.5 mg (IM or IV) every 4 to 6 hours as needed (max: 25mg/dose)	tablets: 12.5 mg, 25 mg, 50 mg oral solution: 6.25 mg/5 mL suppositories: 12.5 mg, 25 mg, 50 mg injection: 25 mg/mL, 50 mg/mL in 1 mL ampules or vials (all Rx only)

OTC = over the counter; Rx = prescription required

CLINICAL TRIALS

The literature review of significant trials comparing agents within this therapeutic class is complete as of March 20, 2019.

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Antivertigo agents used in the prevention and treatment of N/V associated with motion sickness are included in this review. There is a paucity of clinical trial data available related to motion sickness, and the primary treatment option for this condition involves the use of older medications including the more sedating antihistamines. Therefore, no clinical trials are included at this time related to vertigo and motion sickness prophylaxis and treatment.

SUMMARY

There are both non-pharmacologic and pharmacologic interventions for the prevention or management of motion sickness. None are ideal, and the medications used, including antihistamines, phenothiazines, and anticholinergics, typically cause drowsiness or similar adverse effects.

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