

Antiemetics

Drug Class Review

Meclizine
Metoclopramide
Nabilone
Prochlorperazine
Promethazine
Scopolamine
Trimethobenzamide

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Executive Summary

Introduction: A number of pharmacologic agents belong to the drug class referred to as antiemetic agents. This review focuses on a group of the phenothiazine, anticholinergic and antihistamine agents with a primary indication for treatment or prevention of nausea and vomiting including: meclizine, metoclopramide, nabilone, prochlorperazine, promethazine, scopolamine and trimethobenzamide. The agents are available in oral, injectable and transdermal formulations.

Many varied receptors are implicated in the complex process of nausea and vomiting (muscarinic, histamine, neurokinin, dopamine, serotonin) and combination therapy with antiemetic agents with differing mechanisms of action may be used together in the treatment of nausea and vomiting. The American Society of Clinical Oncology recommends a three-drug antiemetic combination therapy including a NK1 receptor antagonist, a 5-HT₃ receptor antagonist and dexamethasone in patients receiving highly emetogenic antineoplastic regimens. Guidelines for the Prevention and Management of PONV/PDNU recommend serotonin 5-HT₃ receptor antagonists and antihistamines as first line treatment options. The American College of Obstetricians and Gynecologists recommend vitamin B₆ alone or in combination with doxylamine in patients with nausea and vomiting in pregnancy.

Clinical Efficacy: Evaluation of the clinical efficacy of antiemetic agents is limited by the lack of comparative clinical trials. One systematic review of 30 randomized trials evaluating nabilone, metoclopramide and prochlorperazine in the treatment of chemotherapy-related nausea and vomiting reported reduced rates of nausea and vomiting but increased frequency of adverse events with nabilone therapy. Two comparative clinical trials evaluating the antiemetic agents in the treatment of nausea and vomiting of pregnancy suggest metoclopramide, prochlorperazine, and promethazine are efficacious but the rate of adverse effects with the agents is inconsistent across the trials. Three comparative clinical trials evaluating the use of antiemetic agents in the emergency department suggest metoclopramide, promethazine and prochlorperazine are effective treatment options for nausea and vomiting in the ED. Overall, the comparative clinical data are limited and rates of adverse events are inconsistent across trials.

Adverse Drug Reactions: The most common adverse events reported with the antiemetic agents include dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention. The antiemetic agents are also associated with extrapyramidal side effects including acute dystonic reactions involving facial and skeletal muscle spasms. Extrapyramidal effects are seen most frequently with the phenothiazines and metoclopramide. Nabilone is also associated with euphoria, dysphoria, hallucinations, and increased appetite. Metoclopramide has a FDA Black Box warning for increased risk of tardive dyskinesia. Prochlorperazine has an FDA Black Box Warning for increased risk of death in elderly patients with dementia-related psychosis. Promethazine has an FDA Black Box Warning for risk of severe tissue injury and is contraindicated in children <2 years due to increased risk of respiratory failure.

Summary: Overall, the agents appear to be efficacious in the treatment of nausea and vomiting. There may be differences in safety between the agents but the available clinical evidence is

inconsistent. In general the agents should be used at the lowest effective dose for the shortest duration possible. Antiemetic therapy should be guided by etiology, patient history and comorbidities, and current guideline recommendations.

Introduction

A number of pharmacologic agents belong to the drug class referred to as antiemetic agents. Antiemetic agents work within a neuronal region to counteract the complex act of vomiting through interactions with cranial nerves and neural networks.^{1,2} Drug classes which have been labeled for use as an antiemetic in the United States include serotonin 5-HT₃ antagonists, neurokinin receptor antagonists, phenothiazines, butyrophenones, benzamides, corticosteroids, benzodiazepines, antihistamines, anticholinergic agents, muscarinic receptor antagonists and cannabinoids.^{1,2} This review focuses on the phenothiazine, anticholinergic and antihistamine agents with a primary indication for treatment or prevention of nausea and vomiting. In total, seven agents are included in this review: meclizine, metoclopramide, nabilone, prochlorperazine, promethazine, scopolamine, and trimethobenzamide. The agents are available in oral, injectable and transdermal formulations.^{3,4} Table 1 compares the antiemetic agents included in this review.

Disease Overview

Nausea is the sensation of the need to vomit.^{1,2} Vomiting is an autonomic response resulting in contractions of gut and expulsion of gastrointestinal contents. In general, vomiting is a protection against harmful ingested substances but may also be a manifestation of other conditions including infection, pregnancy, vestibular disturbance, adverse effects from chemotherapy and other medications or gastrointestinal obstruction. Nausea and vomiting can have a negative impact on quality of life and, in the United States, an estimated \$3.4 billion annually is spent on nausea and vomiting associated with acute gastrointestinal infections. This does not take into account the costs spent on other common causes of nausea and vomiting including chemotherapy and pregnancy or the costs associated with post-operative nausea and vomiting. Postoperative nausea and vomiting (PONV), for example, is one of the most frequent adverse effects reported with anesthesia and each year up to 12 million Americans will experience PONV.⁵ When added all together, the medical costs related to nausea and vomiting in the US are substantial.^{1,2}

The mechanism of nausea is thought to take place in the cerebral cortex.^{1,2,6} The mechanism of vomiting involves communication between the brainstem and the gut, pharynx, and thoracoabdominal wall. The "vomiting center" in the brainstem is a neuronal complex which coordinates the multifaceted act of vomiting through interactions between cranial nerves, neural networks and muscarinic M₁, histamine H₁, neurokinin 1 (NK₁), dopamine D₂ and serotonin 5-HT₃ receptors. The identification of the different receptors and neurotransmitters involved in the processes of nausea and vomiting has led to the development of a diverse group of antiemetic agents which work on various receptors including serotonin 5-HT₃ antagonists, neurokinin receptor antagonists, antihistamines, anticholinergic agents, muscarinic receptor antagonists and cannabinoids. The mechanism of action of the antihistamines (meclizine) and anticholinergic agents (scopolamine) tend to be the most useful in motion sickness and inner ear disorders. The dopamine antagonists (metoclopramide) are useful for metabolic etiologies and the serotonin antagonists (ondansetron) are useful in postoperative vomiting, radiation therapy, and chemotherapy.⁷ Often, 2-3 agents with differing mechanisms of action will be used together in

the treatment of complicated or ongoing cases of nausea and vomiting. Overall, treatments will vary depending on the etiology of the nausea and vomiting and other comorbid conditions.^{1, 2}

The American Society of Clinical Oncology recently updated the clinical practice guidelines for antiemetics in patients receiving radiation or chemotherapy (2011).⁸ A three-drug antiemetic combination therapy including a NK1 receptor antagonist, a 5-HT₃ receptor antagonist and dexamethasone is recommended for highly emetogenic antineoplastic regimens. A two-drug antiemetic combination therapy including palonosetron (or granisetron or ondansetron) and dexamethasone is recommended for moderately emetogenic antineoplastic regimens. For low emetogenic antineoplastic regimens, dexamethasone before the chemotherapy is recommended to prevent nausea and vomiting. Lorazepam and diphenhydramine are recommended as adjuncts to antiemetic therapies, if needed. In patients with refractory nausea and vomiting, the guidelines recommend substituting high-dose intravenous metoclopramide for the 5-HT₃ receptor antagonist or adding lorazepam, alprazolam, olanzapine or a dopamine antagonist to the regimen. A 5-HT₃ receptor antagonist before and during radiation therapy is recommended for all patients receiving high, moderate or low emetic risk radiation therapies. Combination therapy with dexamethasone may also be considered in patients receiving high and moderate emetic risk radiation therapies.⁸

The American Society of PeriAnesthesia Nurses published evidence-based clinical practice guidelines for the Prevention and Management of Postoperative and Postdischarge Nausea and Vomiting (PONV/PDNV; 2009).⁹ Agents recommended as first-line PONV rescue therapy include the serotonin 5-HT₃ receptor antagonists and antihistamines. Other options include droperidol, metoclopramide, low-dose promethazine, prochlorperazine, and the neurokinin-1 (NK1) antagonists. Agents recommended for PDNV include ondansetron, promethazine or scopolamine. According to the guidelines, dexamethasone, a serotonin 5-HT₃ receptor antagonist, an antihistamine, or the scopolamine patch may be used for prophylaxis of PONV in high-risk patients. Droperidol and the NK1 antagonists are listed as potential second line prophylaxis agents. Risk factors for experiencing PONV/PDNV including female gender, nonsmoker, use of volatile anesthetics or nitrous oxide, postoperative use of opioids and a history of PONV or motion sickness.⁹

The American College of Obstetricians and Gynecologists published guidelines for Nausea and Vomiting of Pregnancy (2004).¹⁰ Recommended first-line treatment of nausea and vomiting of pregnancy includes vitamin B₆ (pyridoxine) alone or in combination with doxylamine. A pyridoxine/doxylamine combination agent (Bendectin) was previously available for use in the United States but was voluntarily removed from the market due to reports of birth defects with its use.¹¹ Since then, the FDA has concluded there is no association between the combination agent and birth defects. A new pyridoxine/doxylamine combination agent is now available (Diclegis) for use in the US. According to the guidelines, ginger may be considered a non-pharmacologic treatment option. In patients with refractory nausea and vomiting treatment options include antihistamines (hydroxyzine, meclizine), phenothiazines (prochlorperazine, promethazine) or benzamides (metoclopramide, trimethobenzamide). In severe cases, methylprednisolone may be used, although this should be considered a last-line treatment option. Taking multivitamins at the time of conception, eating small meals and avoiding spicy or fatty foods are other non-pharmacological therapies to avoid nausea and vomiting in pregnancy.¹⁰

Table 1. Comparison of the Antiemetic Agents^{3,4}

Agent	Dosage Form	Indications	Dosing Recommendations	Generic Availability
Meclizine (Dramamine Less Drowsy [OTC]; Medi-Meclizine [OTC]; Travel Sickness [OTC]; UniVert; Vertin-32 [OTC])	Chewable tablet: 25 mg Oral tablet: 12.5 mg, 25 mg, 32 mg	Prevention and treatment of symptoms of motion sickness; management of vertigo with diseases affecting the vestibular system	Motion sickness: Oral: 25-50 mg 1 hour before travel, repeat dose every 24 hours if needed Vertigo: Oral: 25-100 mg daily in divided doses Children ≥12 years: Refer to adult dosing.	Yes
Metoclopramide (Metozolv ODT; Reglan)	Injection Solution: 5 mg/mL Injection Solution [preservative free]: 5 mg/mL Oral Solution: 5 mg/5 mL; 10 mg/10 mL Oral Tablet: 5 mg; 10 mg Oral Tablet; Dispersible: 5 mg	Oral: Symptomatic treatment of diabetic gastroparesis; gastroesophageal reflux I.V., I.M.: Symptomatic treatment of diabetic gastroparesis; postpyloric placement of enteral feeding tubes; prevention and/or treatment of nausea and vomiting associated with chemotherapy, or postsurgery; to stimulate gastric emptying and intestinal transit of barium during radiological examination of the stomach/small intestine Unlabeled: Management of gastroparesis (regardless of etiology)	Gastroesophageal reflux: Oral: 10-15 mg up to 4 times daily 30 minutes before meals or food and at bedtime. Treatment >12 weeks is not recommended. Gastroparesis: Oral: 10 mg up to 4 times daily 30 minutes before meals or food and at bedtime for 2-8 weeks. Treatment >12 weeks is not recommended. I.M., I.V. (for severe symptoms): 10 mg over 1-2 minutes. Chemotherapy-induced emesis prophylaxis: I.V.: 1-2 mg/kg 30 minutes before chemotherapy and repeated every 2 hours for 2 doses, then every 3 hours for 3 doses (manufacturer labeling); pretreatment with diphenhydramine will decrease risk of extrapyramidal reactions Postpyloric feeding tube placement, radiological exam: I.V.: 10 mg as a single dose	Yes
Nabilone (Cesamet)	Oral Capsule: 1 mg	Treatment of refractory nausea and vomiting associated with cancer chemotherapy	1-2 mg twice daily (maximum: 6 mg divided in 3 doses daily). Children >4 years (unlabeled use): <18 kg: 0.5 mg every 12 hours 18-30 kg: 1 mg every 12 hours >30 kg: 1 mg every 8-12 hours	No

Agent	Dosage Form	Indications	Dosing Recommendations	Generic Availability
Prochlorperazine (Compazine; Compro)	Injection Solution: 5 mg/mL Oral Tablet: 5 mg, 10 mg Rectal Suppository: 25 mg	<p>Management of nausea and vomiting; psychotic disorders, including schizophrenia and anxiety; nonpsychotic anxiety</p> <p>Unlabeled: Behavioral syndromes in dementia; psychosis/agitation related to Alzheimer's dementia</p>	<p>Antiemetic: Oral: 5-10 mg 3-4 times/day I.M. (as edisylate): 5-10 mg every 3-4 hours I.M. (as mesylate): 5-10 mg 2-3 times/day I.V. (as edisylate): 2.5-10 mg Rectal: 25 mg twice daily</p> <p>Antipsychotic: Oral: 5-10 mg 3-4 times/day I.M.: 10-20 mg; if necessary repeat initial dose every 2-4 hours to gain control</p> <p>Pediatric Use is contraindicated in children <9 kg or <2 years.</p> <p>Antiemetic: Oral, rectal: 9-13 kg: 2.5 mg 1-2 times/day as needed >13-18 kg: 2.5 mg 2-3 times/day as needed >18-39 kg: 2.5 mg 3 times/day or 5 mg 2 times/day as needed I.M.: 0.13-0.14 mg/kg/dose</p> <p>Antipsychotic: Children 2-12 years: Oral, rectal: 2.5 mg 2-3 times/day I.M.: 0.13-0.14 mg/kg/dose</p>	Yes

Agent	Dosage Form	Indications	Dosing Recommendations	Generic Availability
Promethazine (Phenadoz; Phenergan; Promethegan)	Injection Solution: 25 mg/mL, 50 mg/mL Oral Solution: 6.25 mg/5 mL Oral Syrup: 6.25 mg/5 mL Oral Tablet: 12.5 mg, 25 mg, 50 mg Rectal Suppository: 12.5 mg, 25 mg, 50 mg	Symptomatic treatment of various allergic conditions; antiemetic; motion sickness; sedative; adjunct to postoperative analgesia and anesthesia Unlabeled: Treatment of nausea and vomiting of pregnancy (NVP)	Allergic conditions: Oral, rectal: 25 mg at bedtime or 12.5 mg before meals and at bedtime I.M., I.V.: 25 mg, may repeat in 2 hours when necessary Antiemetic: Oral, I.M., I.V., rectal: 12.5-25 mg every 4-6 hours as needed Motion sickness: Oral, rectal: 25 mg 30-60 minutes before departure, then every 12 hours as needed Obstetrics (labor) analgesia adjunct: I.M., I.V.: Early labor: 50 mg; Established labor: 25-75 mg Pre-/postoperative analgesia/hypnotic adjunct: I.M., I.V.: 25-50 mg in combination with analgesic or hypnotic Sedation: Oral, I.M., I.V., rectal: 12.5-50 mg/dose Pediatric Allergic conditions: Children ≥2 years: Oral, rectal: 0.1-0.5 mg/kg/dose Antiemetic: Children ≥2 years: Oral, I.M., I.V., rectal: 0.25-1 mg/kg 4-6 times/day as needed Motion sickness: Children ≥2 years: Oral, rectal: 0.5 mg/kg/dose 30 minutes to 1 hour before departure, then every 12 hours as needed Preoperative analgesia/hypnotic adjunct: Children ≥2 years: I.M., I.V.: 1.1 mg/kg Sedation: Children ≥2 years: Oral, I.M., I.V., rectal: 12.5-25 mg at bedtime or preoperatively	Yes
Scopolamine (Transderm-Scop)	Injection Solution: 0.4 mg/mL Transdermal Patch; 72 Hour: 1.5 mg	Transdermal: Prevention of nausea/vomiting associated with motion sickness and recovery from anesthesia and surgery Injection: Preoperative medication to produce amnesia, sedation, tranquilization, antiemetic effects, and decrease salivary and respiratory secretions Unlabeled: Transdermal: Breakthrough treatment of nausea and vomiting associated with chemotherapy	Preoperative: Patch: Apply 1 patch behind ear the night before surgery or 1 hour prior to cesarean section and remove 24 hours after surgery I.M., I.V., SubQ: 0.3-0.65 mg Motion sickness: Patch: Apply 1 patch behind the ear at least 4 hours prior to exposure and every 3 days as needed Antiemetic: SubQ: 0.6-1 mg Sedation, tranquilization: I.M., I.V., SubQ: 0.6 mg 3-4 times/day Pediatric Antiemetic: SubQ: 0.006 mg/kg Preoperative: I.M., I.V., SubQ: Children 6 months to 3 years: 0.1-0.15 mg Children 3-6 years: 0.2-0.3 mg	May be product dependent
Trimethobenzamide (Tigan)	Intramuscular Solution: 100 mg/mL (2 mL, 20 mL) Oral Capsule: 300 mg	Treatment of postoperative nausea and vomiting; treatment of nausea associated with gastroenteritis	Oral: 300 mg 3 or 4 times daily I.M.: 200 mg 3 or 4 times daily	Yes

Mechanism of Action

In general, the antiemetic agents work within a neuronal region to counteract the complex act of vomiting through interactions with cranial nerves and neural networks. Each of the individual agents has varying mechanisms of action.¹⁻⁴ Antihistamines, for example, work by directly inhibiting histamine at the histamine1-receptor and indirectly inhibiting histamine in the vestibular system. These two actions combine to produce decreased stimulation in the vomiting center. Phenothiazines inhibit vomiting by blocking both central D2 receptors in the chemoreceptor trigger zone and gastrointestinal D2 receptors. Similar to the phenothiazines, metoclopramide acts in the central chemoreceptor trigger zone and in the gastrointestinal tract.¹² Nabilone is a 9-tetrahydrocannabinol (THC) derivative which is the major psychoactive chemical in marijuana. Nabilone has action as an appetite stimulant and as an antiemetic, but the mechanisms for these effects are not well understood. The specific mechanism of action for trimethobenzamide is unknown but it is believed to affect the chemoreceptor trigger zone (CTZ) without impact on the serotonergic, dopaminergic, or histaminergic systems.^{1,2}

Table 2. Pharmacokinetic and Pharmacodynamic Properties of the Antiemetic Agents¹⁻⁴

Agents	Mechanism	Route	Action	Half-life	Distribution	Metabolism
Meclizine	Anticholinergic action by blocking chemoreceptor trigger zone	Oral	Onset of action: ~1 hour Duration: ~24 hours Time to peak: 3 hours	5 hours	7 L/kg	Hepatic to norchlorcyclizine Excretion: Urine and feces as unchanged drug and metabolites
Metoclopramide	Blocks dopamine receptors in chemoreceptor trigger zone of the CNS	Oral, IV, IM	Onset of action: Oral: 30-60 minutes; I.V.: 1-3 minutes; I.M.: 10-15 minutes Duration: 1-2 hours, regardless of route Time to peak; oral: 1-2 hours	Children: ~4 hours; Adults: 5-6 hours (may be dose dependent)	~3.5 L/kg	Metoclopramide is metabolized by CYP2D6 and is a reversible inhibitor, but not inactivator, of CYP2D6 Excretion: Urine (~85%)
Nabilone	Effect on cannabinoid receptors (CB1) within the central nervous system	Oral	Onset of action: 1 – 1.5 hours Duration: 8 – 12 hours Time to peak: Within 2 hours	Parent compound: ~2 hours Metabolites: ~35 hours	~12.5 L/kg	Extensively metabolized to several active metabolites by oxidation and stereospecific enzyme reduction; CYP450 enzymes may also be involved Excretion: Feces (~60%); renal (~24%)
Prochlorperazine	Blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain, including the chemoreceptor trigger zone	Oral, Rectal, IV, IM	Onset of action: Oral: 30-40 minutes; I.M.: 10-20 minutes; Rectal: ~60 minutes Duration: Rectal: 3-12 hours; I.M., Oral: 3-4 hours	Oral: 6-10 hours (single dose), 14-22 hours (repeated dosing) I.V.: 6-10 hours	~12.9 L/kg	Primarily hepatic; N-desmethyl prochlorperazine (major active metabolite) Excretion: Mainly in feces

Agents	Mechanism	Route	Action	Half-life	Distribution	Metabolism
Promethazine	blocks postsynaptic mesolimbic dopaminergic receptors in the brain	Oral, Rectal, IV, IM	Onset of action: Oral, I.M.: ~20 minutes; I.V.: ~5 minutes Duration: Usually 4-6 hours (up to 12 hours) Time to peak: Suppositories: 6.7-8.6 hours; Syrup: 4.4 hours	I.M.: ~10 hours; I.V.: 9-16 hours; Suppositories, syrup: 16-19 hours	Syrup: 98 L/kg	Hepatic; hydroxylation via CYP2D6 and N-demethylation via CYP2B6; significant first-pass effect Excretion: Urine
Scopolamine	Blocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands and the CNS	Transdermal, IV, IM	Onset of action: Oral, I.M.: 0.5-1 hour; I.V.: 10 minutes; Transdermal: 6-8 hours Duration: I.M., I.V., SubQ: 4 hours Time to peak: I.M.: ~20 minutes, SubQ: ~15 minutes; Transdermal: 24 hours	IV, IM: ~1-4 hours; Transdermal: 9.5 hours	Not available	Hepatic Excretion: Urine (<10%, as parent drug and metabolites)
Trimethobenzamide	Inhibits the medullary chemoreceptor trigger zone	Oral, IM	Onset of action: Oral: 10-40 minutes; IM: 15-35 minutes Duration: Oral: 3-4 hours; IM: 2-3 hours Time to peak: Oral: ~45 minutes; I.M.: ~30 minutes	7-9 hours	0.49 L/kg	Via oxidation, forms metabolite trimethobenzamide N-oxide Excretion: Urine (30% to 50%, as unchanged drug)

Methods

A literature search was conducted to identify articles addressing clinical safety and efficacy of the antiemetic agents searching the MEDLINE database (1993 – 2014), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE prior to 1/2014, evaluating efficacy of the agents are included. Comparative trials of monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens or agents which are not available in the US were excluded.¹³⁻²⁵

Clinical Efficacy

Evaluation of the efficacy of antiemetics in the treatment of nausea and vomiting associated with any of the numerous etiologies is limited by the lack of comparative clinical trials. One systematic review found very little data available to assess the efficacy of the antiemetic agents.¹² Another non-comparative meta-analysis reported doxylamine/pyridoxine, antihistamines and phenothiazines are effective antiemetic drug therapies but did not evaluate whether one agent was more effective than another.^{12, 22} Overall, one comparative systematic review and five randomized, controlled trials are available for evaluation of the antiemetic agents. See the Evidence Table in the Appendix of this document for a summary of the clinical trials.

A systematic review of 30 randomized trials evaluated cannabinoid agents (including nabilone) compared to other antiemetic agents (including metoclopramide and prochlorperazine) in the treatment of chemotherapy-related nausea and vomiting.²⁶ Overall, 1366 patients were included in the analysis. Cannabinoid agents, like nabilone, demonstrated reduced rates of nausea and vomiting compared to antiemetic agents. However, cannabinoid agents were associated with increased frequency of adverse events, including sedation, euphoria, dizziness, depression, hallucinations, paranoia, and arterial hypotension. This review suggests nabilone is an effective treatment option for nausea and vomiting in cancer treatment but is associated with an increased rate of adverse events.

Two comparative clinical trials evaluating the antiemetic agents in the treatment of nausea and vomiting of pregnancy are available for evaluation. Bsat et al²⁷ evaluated the efficacy of metoclopramide-pyridoxine, prochlorperazine, and promethazine in 174 patients in their first-trimester of a singleton gestation with nausea and vomiting. The combination therapy of metoclopramide-pyridoxine demonstrated reduced rate of emesis when compared to either of the monotherapy treatment groups (prochlorperazine, promethazine; $p < 0.05$). No differences in adverse effects were reported between the treatment groups; however, one patient withdrew from treatment due to a dystonic reaction and this occurred in the metoclopramide treatment group. Tan et al²⁸ evaluated the efficacy of metoclopramide and promethazine in 149 patients in the hospital for their first case of gravidarum. No differences in the rate of nausea or vomiting were reported between treatment groups. Significantly fewer adverse effects (including drowsiness, dizziness, dystonia) were reported in the metoclopramide treatment group compared to the

promethazine treatment group ($p < 0.05$). Overall, this limited evidence suggests metoclopramide, prochlorperazine, and promethazine are efficacious in the treatment of pregnancy-related nausea and vomiting. Rate of adverse effects is inconsistent across the two trials.

Three comparative clinical trials evaluating the use of antiemetic agents in the emergency department (ED) in the treatment of any etiology are available for evaluation. Ernst et al²⁹ evaluated the efficacy of prochlorperazine and promethazine in 84 adult patients with gastritis. Treatment with prochlorperazine was associated with significantly improved rates of nausea and vomiting and time to symptom resolution compared to treatment with promethazine ($p < 0.05$). Drowsiness was also reported less frequently in the prochlorperazine group compared to the promethazine group ($p < 0.05$). No differences in the rate of extrapyramidal effects were reported between treatment groups. Braude et al³⁰ evaluated the efficacy of droperidol, metoclopramide, prochlorperazine and placebo in 97 patients with moderate to severe nausea and vomiting. Metoclopramide and prochlorperazine were more effective than placebo; however, no differences in nausea/vomiting scores were reported between the agents. Barrett et al³¹ evaluated the efficacy of metoclopramide, ondansetron, promethazine and placebo in 171 adult patients seen in the ED with nausea and vomiting. No differences in reduction of symptoms or rate of adverse effects were reported between treatment groups. Overall, these data suggest metoclopramide, promethazine and prochlorperazine are effective treatment options for nausea and vomiting of any etiology. Based on a single small trial, prochlorperazine may be associated with increased efficacy and reduced rate of adverse events.

Overall, the comparative clinical data available for the antiemetic agents demonstrates efficacy for the agents in the treatment of nausea and vomiting associated with chemotherapy, pregnancy or gastritis. The data is limited and rate of adverse events is inconsistent across trials. Antiemetic therapy should be guided by etiology, patient history and comorbidities, and current guideline recommendations.

Adverse Drug Reactions

The most common adverse events reported with the antiemetic agents are associated with the anticholinergic effects of the drugs and include dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention.^{3,4} Some evidence suggests meclizine may be associated with less sedation.² The muscarinic receptor antagonist, scopolamine, is one of the best agents for the prevention of motion sickness and the rate of anticholinergic effects is reduced with transdermal administration.¹ In addition to anticholinergic effects, the antiemetic agents are associated with extrapyramidal side effects including acute dystonic reactions involving facial and skeletal muscle spasms. Extrapyramidal effects are seen most frequently with the phenothiazines (prochlorperazine, promethazine) and metoclopramide.¹² In addition to dizziness and sedation, nabilone use is also associated with euphoria, dysphoria, hallucinations, and increased appetite. Nabilone also has some autonomic effects that may rarely result in tachycardia, conjunctival injection, and orthostatic hypotension. Because trimethobenzamide does not have effects in the serotonergic, dopaminergic, or histaminergic systems, it may be associated with a reduced rate of adverse effects.^{1,2}

Metoclopramide has an FDA Black Box warning for increased risk of tardive dyskinesia (which may be irreversible) with high-dose and long-term use.^{3,4} Prochlorperazine has an FDA Black Box Warning for increased risk of death when compared to placebo in elderly patients with dementia-related psychosis who are treated with antipsychotics. Promethazine has an FDA Black Box Warning for severe tissue injury (including gangrene) with parental (IV or IM) route of administration.³² Promethazine is also contraindicated in children <2 years due to increased risk of respiratory failure.^{3,4} See Table 3 for a summary of the adverse events associated with the antiemetic agents according to package inserts.

Table 3. Adverse Events Reported with the Antiemetic Agents*^{3,4}

Adverse Event	Meclizine	Metoclopramide	Nabilone	Prochlorperazine	Promethazine	Scopolamine	Trimethobenzamide
Appetite increased	NR	NR	2%	R	NR	NR	NR
Blurred vision	R	R	13%	R	R	R	R
Cardiovascular Effects	NR	R	1-8%	R	R	R	R
Concentration decreased	NR	NR	12%	NR	NR	R	NR
Constipation	NR	NR	R	R	R	R	NR
Depression	NR	NR	14%	NR	NR	NR	R
Dermatologic Reaction	R	R	R	R	R	R	R
Diarrhea	NR	R	R	NR	NR	R	R
Dizziness	NR	1-4%	59%	R	R	R	R
Drowsiness	R	~10-70%	52-66%	R	R	R	R
Drug-induced Parkinson's disease	NR	R	NR	R	R	NR	R
Dystonic reaction	NR	<1-25%	R	R	R	NR	NR
Euphoria	NR	NR	11-38%	NR	R	NR	NR
Fatigue	R	2-10%	R	NR	R	R	NR
Gynecomastia	NR	R	NR	R	R	NR	NR
Headache	R	4-5%	6-7%	R	NR	R	R
Injection-site Reactions	NA	NR	NA	NR	R	NA	R
Leukopenia	NR	R	R	R	R	NR	R
Nausea	NR	4-6%	4%	R	R	R	NR
Neuroleptic Malignant Syndrome	NR	R	NR	R	R	NR	NR
Restlessness	NR	~10%	NR	R	NR	R	NR
Somnolence	NR	2-3%	3%	R	R	R	NR
Tardive dyskinesia	NR	R	NR	R	R	NR	NR
Vertigo	NR	NR	52-59%	NR	NR	R	NR
Vomiting	R	1-2%	R	R	R	R	NR
Xerostomia	R	NR	22-36%	R	R	R	NR

Key: R = reported, NR = not reported, NA = not applicable; *Data is extracted from package inserts and is not meant to be comparative

Summary

A number of pharmacologic agents belong to the drug class referred to as antiemetic agents. This review focuses on a group of the phenothiazine, anticholinergic and antihistamine agents with a primary indication for treatment or prevention of nausea and vomiting. Nausea and vomiting may serve as a protection against harmful ingested substances but may also be a manifestation of other conditions including infection, pregnancy, vestibular disturbance, adverse effects from chemotherapy and other medications or gastrointestinal obstruction. In general, the antiemetic agents work within a neuronal region to counteract the complex act of vomiting through interactions with cranial nerves and neural networks.

Many varied receptors are implicated in the complex process of nausea and vomiting (muscarinic, histamine, neurokinin, dopamine, serotonin). Many of the older phenothiazine, anticholinergic and antihistamine agents reviewed in this report tend to be the most useful in motion sickness and inner ear disorders. The newer serotonin and neurokinin antagonists are more useful in postoperative vomiting, radiation therapy, and chemotherapy. Combination therapy with antiemetic agents with differing mechanisms of action may also be used in the treatment of nausea and vomiting. The American Society of Clinical Oncology, for example, recommends a three-drug antiemetic combination therapy including a NK1 receptor antagonist, a 5-HT₃ receptor antagonist and dexamethasone in patients receiving highly emetogenic antineoplastic regimens. Guidelines for the Prevention and Management of PONV/PDNV recommend serotonin 5-HT₃ receptor antagonists and antihistamines as first line treatment options. The American College of Obstetricians and Gynecologists recommends vitamin B₆ alone or in combination with doxylamine in patients with nausea and vomiting in pregnancy.

Evaluation of the clinical efficacy of antiemetic agents is limited by the lack of comparative clinical trials. One systematic review of 30 randomized trials evaluating nabilone, metoclopramide and prochlorperazine in the treatment of chemotherapy-related nausea and vomiting reported reduced rates of nausea and vomiting but increased frequency of adverse events with nabilone therapy. Two comparative clinical trials evaluating the antiemetic agents in the treatment of nausea and vomiting of pregnancy suggest metoclopramide, prochlorperazine, and promethazine are efficacious in the treatment of pregnancy-related nausea and vomiting. Rate of adverse effects with the agents is inconsistent across the trials. Three comparative clinical trials evaluating the use of antiemetic agents in the emergency department suggest metoclopramide, promethazine and prochlorperazine are effective treatment options for nausea and vomiting in the ED. Overall, the comparative clinical data are limited and rate of adverse events is inconsistent across trials. Antiemetic therapy should be guided by etiology, patient history and comorbidities, and current guideline recommendations.

The most common adverse events reported with the antiemetic agents are associated with the anticholinergic effects of the drugs and include dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention. In addition to anticholinergic effects, the antiemetic agents are associated with extrapyramidal side effects including acute dystonic reactions involving facial and skeletal muscle spasms. Extrapyramidal effects are seen most frequently with the phenothiazines and metoclopramide. Nabilone is also associated with euphoria, dysphoria,

hallucinations, and increased appetite. Metoclopramide has a FDA Black Box warning for increased risk of tardive dyskinesia. Prochlorperazine has an FDA Black Box Warning for increased risk of death in elderly patients with dementia-related psychosis. Promethazine has an FDA Black Box Warning for risk of severe tissue injury and is contraindicated in children <2 years due to increased risk of respiratory failure.

Overall, the agents appear to be efficacious in the treatment of nausea and vomiting. There may be differences in safety between the agents but the available clinical evidence is inconsistent. In general the agents should be used at the lowest effective dose for the shortest duration possible. Therapy should be guided by etiology and the appropriate disease state guideline recommendations.

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Evidence Table. Clinical Trials Evaluating the Agents

Reference/Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes	Adverse Effects
Systematic Reviews					
Tramer et al, 2001 ²⁶ Systematic Review of 30 randomized comparisons of cannabis with placebo or antiemetics	1366	Patients receiving chemotherapy	Cannabinoids (nabilone (16), dronabinol (13), levonantradol(1)) Alizapride (n = 1) Chlorpromazine (n = 2) Domperidone (n =1) Haloperidol (n = 1) Metoclopramide (n = 4) Prochlorperazine (n = 12) Thiethylperazine (n = 1) Placebo (n = 10)	Efficacy Cannabinoids \geq Chlorpromazine or Metoclopramide or Prochlorperazine Safety Cannabinoids \leq Antiemetic Agents	Sedation cannabinoids > antiemetics Euphoria cannabinoids > antiemetics Dizziness cannabinoids > antiemetics Depression cannabinoids > antiemetics Hallucinations cannabinoids > antiemetics Paranoia cannabinoids > antiemetics Arterial hypotension cannabinoids > antiemetics Treatment-related withdrawal rate cannabinoids > antiemetics

Reference/Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes	Adverse Effects
Randomized Controlled Trials					
Barrett et al, 2009 ³¹ Randomized, controlled, double-blind study	171	Adult patients with nausea and vomiting seen in the emergency department	Metoclopramide 10 mg (n = 43) Ondansetron 4 mg (n = 42) Promethazine 12.5 mg (n = 45) Placebo (n = 41)	Metoclopramide = Ondansetron = Promethazine Reduction in VAS score (100-mm visual analog scale) at 30 minutes <ul style="list-style-type: none"> • metoclopramide: -22 (15-32) • ondansetron: -30 (25.5-38) • promethazine: -29 (21-40) • placebo: -16 (3-25) 	Treatment-associated adverse effects metoclopramide = ondansetron = promethazine
Ernst et al, 2000 ²⁹ Randomized, controlled, double-blind, multi-center study	84	Patients 18 years or older with presumed uncomplicated gastritis or gastroenteritis who presented to the emergency department	Prochlorperazine 10 mg (n = 42) Promethazine 25 mg (n = 42)	Prochlorperazine > Promethazine Reduction of symptoms at 30 and 60 minutes: prochlorperazine > promethazine (p < 0.05) Time to complete relief prochlorperazine > promethazine (p < 0.021) Treatment Failures prochlorperazine > promethazine (p < 0.03)	Extrapyramidal effects <ul style="list-style-type: none"> • prochlorperazine: 14% • promethazine: 14% Drowsiness <ul style="list-style-type: none"> • prochlorperazine: 38% • promethazine: 71%, (p < 0.002)

<p>Bsat et al, 2003²⁷</p> <p>Randomized, controlled study</p>	<p>174</p>	<p>Patients with singleton gestations presenting in the first trimester to their obstetrical provider with nausea and/or vomiting</p>	<p>Metoclopramide-pyridoxine (n = 54)</p> <p>Prochlorperazine (n = 50)</p> <p>Promethazine (n = 52)</p>	<p>Metoclopramide-pyridoxine > Prochlorperazine = Promethazine</p> <p>Rate of emesis: Metoclopramide-pyridoxine > Prochlorperazine = Promethazine; p < 0.05</p>	<p>Treatment-related withdrawal rate:</p> <ul style="list-style-type: none"> • metoclopramide: 1 (dystonic reaction) • prochlorperazine: 0 • promethazine: 0
<p>Tan et al, 2010²⁸</p> <p>Randomized, controlled, double-blind study</p>	<p>149</p>	<p>Women at their first hospitalization for gravidarum</p>	<p>Metoclopramide 10 mg (n = 73)</p> <p>Promethazine 25 mg (n = 79)</p>	<p>Efficacy: Metoclopramide = Promethazine</p> <p>Safety: Metoclopramide > Promethazine</p> <p>Rate of Vomiting Metoclopramide = Promethazine</p> <p>Reduction in VAS score (10-mm visual analog scale) Metoclopramide = Promethazine</p>	<p>Drowsiness</p> <ul style="list-style-type: none"> • metoclopramide: 58.6% • promethazine: 83.6%; p < 0.001 <p>Dizziness</p> <ul style="list-style-type: none"> • metoclopramide: 34.3% • promethazine: 71.2%; p < 0.001 <p>Dystonia</p> <ul style="list-style-type: none"> • metoclopramide: 5.7% • promethazine: 19.2%; p = 0.02 <p>Treatment-related withdrawal rate</p> <ul style="list-style-type: none"> • metoclopramide: 0 • promethazine: 7 (9.2%); p = 0.014

<p>Braude et al, 2005³⁰</p> <p>Randomized, controlled, double-blind study</p>	<p>97</p>	<p>Adult patients with moderate to severe symptoms of nausea and/or vomiting of any etiology</p>	<p>Droperidol 1.25 mg (n = 22)</p> <p>Metoclopramide 10 mg (n = 25)</p> <p>Prochlorperazine 10 mg (n = 24)</p> <p>Placebo (n = 26)</p>	<p>Droperidol ≥ Metoclopramide = Prochlorperazine > Placebo</p> <p>Reduction in VAS nausea score (100-mm visual analog scale)</p> <ul style="list-style-type: none"> • droperidol: -54.5 • metoclopramide: -40.2 • prochlorperazine: -40.5; <p>p = 0.04</p>	<p>Akathisia droperidol > metoclopramide or prochlorperazine</p>
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