

# Practical Selection of Antiemetics

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**An understanding of the pathophysiology of nausea and the mechanisms of antiemetics can help family physicians improve the cost-effectiveness and efficacy of therapy. Nausea and vomiting are mediated primarily by visceral stimulation through dopamine and serotonin, by vestibular and central nervous system causes through histamine and acetylcholine, and by chemoreceptor trigger zone stimulation through dopamine and serotonin. Treatment is directed at these pathways. Antihistamines and anticholinergic agents are most effective in patients with nausea resulting from vestibular and central nervous system causes. Dopamine antagonists block dopamine in the intestines and chemoreceptor trigger zone; indications for these agents are similar to those for serotonin antagonists. Serotonin antagonists block serotonin in the intestines and chemoreceptor trigger zone, and are most effective for treating gastrointestinal irritation and postoperative nausea and vomiting. Complementary and alternative therapies, such as ginger, acupressure, and vitamin B6, have variable effectiveness in the treatment of pregnancy-induced nausea. (Am Fam Physician 2004;69:1169-74,1176. Copyright© 2004 American Academy of Family Physicians.)**

 A patient information handout on nausea and vomiting, written by the authors of this article, is provided on page 1176.

*This article is one in a series coordinated by Allen F. Shaughnessy, Pharm.D., director of medical education for the Pinnacle Health System, Harrisburg, Pa.*

**N**ausea and vomiting are common complications of multiple conditions, procedures, and therapies, and adversely affect quality of life in millions of patients each year. Pregnancy-induced nausea alone has been estimated to cause 8.5 million lost working days annually.<sup>1</sup> Postoperative nausea and vomiting have been shown to increase hospitalization costs by \$415 per patient.<sup>2</sup> In many instances, therapy for nausea and vomiting is directed at specific, well-studied mechanisms that have been shown to cause nausea.

## Mechanism of Action

Treatment of nausea and vomiting ideally involves-correcting the underlying cause. When the exact cause is not known or cannot be corrected, symptoms still can be treated.

Three primary pathophysiologic pathways are involved in the stimulation of the physi-

ologic vomiting center in the medulla that directly mediates nausea and vomiting.<sup>3</sup> This center can be stimulated by vestibular fibers, afferent visceral fibers, and input from the chemoreceptor trigger zone in the base of the fourth ventricle<sup>4</sup> (Figure 1). The neurotransmitters histamine, acetylcholine, serotonin, and dopamine frequently are implicated in these pathways and are the targets of most therapeutic modalities.

## Antiemetics

Table 1 lists the primary classes of antiemetics, as well as specific agents in each class. Table 2 lists major adverse effects associated with each class.

### ANTI-HISTAMINES AND ANTICHOLINERGICS

Antihistamines inhibit the action of histamine at the H<sub>1</sub> receptor, and anticholinergic agents inhibit the action of acetylcholine at the muscarinic receptor. Both drug classes limit stimulation of the vomiting center from the vestibular system (which is rich in histamine and acetylcholine) but have minimal effect on afferent visceral stimulation.<sup>5</sup>

Antihistamines such as meclizine (Antivert) are associated with minor side effects involving the central nervous system, such as confu-

*See page 1028 for definitions of strength-of-recommendation*

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sion, sedation, dizziness, tinnitus, insomnia, incoordination, fatigue, and tremors.<sup>5,6</sup> Scopolamine (Transderm Scop) is a primary antimuscarinic agent with prominent central nervous system activity. Both antihistamines and anticholinergics can have anticholinergic side effects, including dry mouth, urinary retention, blurred vision, and exacerbation of narrow-angle glaucoma. In general, however, these drugs have few severe adverse effects.

Antihistamine and anticholinergic drugs are relatively inexpensive. Antihistamines cost less than 50 cents per dose, and a scopolamine patch, which provides three days of therapy, costs approximately \$5.<sup>7</sup>

#### DOPAMINE ANTAGONISTS

Dopamine antagonists minimize the effect of dopamine at the D<sub>2</sub> receptor in the chemoreceptor trigger zone, thereby limiting emetic input to the medullary vomiting center. Although dopamine antagonists are inexpensive and have diffuse efficacy, they have an extensive side effect profile that includes sedation, orthostatic hypotension, and extrapyramidal symptoms such as tardive dyskinesia.<sup>6,8</sup> Consequently, serotonin antago-

nists have replaced dopamine antagonists for many indications.

Rare reactions to dopamine antagonists include neuroleptic malignant syndrome and blood dyscrasias. Because droperidol (Inapsine) has been associated with QT prolongation, 12-lead electrocardiography is recommended before treatment is initiated. Droperidol carries a “black-box” warning about the risk of sudden cardiac death; consequently, some pharmacies no longer stock the drug. However, various experts<sup>9,10</sup> argue that the warning about droperidol is based on case reports, and that randomized controlled trials (RCTs) have found droperidol to be safe and cost-effective when given in antiemetic dosages.

Dopamine antagonists are relatively inexpensive, typically costing approximately \$1 per dose. Rectal and parenteral doses cost three to five times more than oral doses.<sup>7</sup>

#### SEROTONIN ANTAGONISTS

Selective serotonin antagonists inhibit the action of serotonin at the 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptor in the small bowel, vagus nerve, and chemoreceptor trigger zone. This action subsequently decreases afferent visceral and chemoreceptor trigger zone stimulation of the medullary vomiting center. Because of their diffuse blockade of serotonin, these agents have become the primary treatment for a variety of causes of nausea.

In general, the serotonin antagonists have been shown to be safe, with minimal significant side effects. Headache, diarrhea, and fatigue (the most common side effects) occur independently of dosage and route of administration.<sup>11,12</sup> Hypersensitivity reactions to these agents occur rarely but have been associated with complications ranging from urticaria to bronchospasm and anaphylaxis. Transient elevation of liver enzyme levels occurs in a small number of patients treated with serotonin antagonists.

In clinical trials, serotonin antagonists have caused self-limited, asymptomatic QT prolon-

### Etiology of Nausea and Vomiting

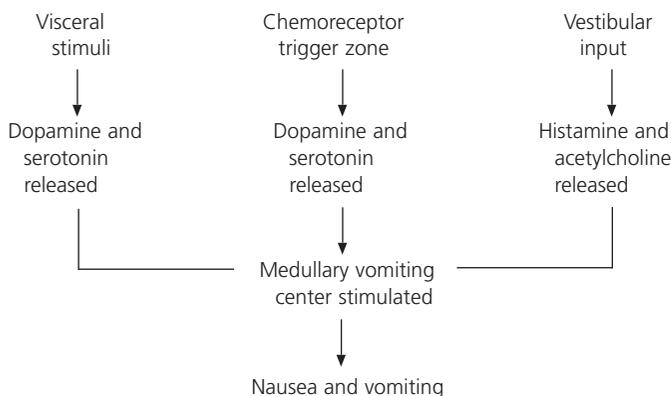


FIGURE 1. Physiologic mechanisms that result in nausea and vomiting.

TABLE 1

**Antiemetic Agents****Antihistamines**

Bucizine (Bucladin-S)  
 Cyclizine (Marezine)  
 Dimenhydrinate (Dramamine)  
 Diphenhydramine (Benadryl)  
 Meclizine (Antivert)

**Anticholinergic agent**

Scopolamine (Transderm Scop)

**Dopamine antagonists**

Chlorpromazine (Thorazine)  
 Droperidol (Inapsine)  
 Metoclopramide (Reglan)  
 Prochlorperazine (Compazine)  
 Promethazine (Phenergan)

**Serotonin antagonists**

Dolasetron (Anzemet)  
 Granisetron (Kytril)  
 Ondansetron (Zofran)

**Other agents**

Dexamethasone  
 Methylprednisolone (Medrol)  
 Trimethobenzamide (Tigan)

gation and QRS widening.<sup>13</sup> Therefore, these agents should be used with caution in patients with underlying QT prolongation.

The 5-HT<sub>3</sub> antagonists are the newest and most expensive antiemetics. The three primary agents—ondansetron (Zofran), dolasetron (Anzemet), and granisetron (Kytril)—have similar efficacy. Costs for these agents in the treatment of patients with postoperative nausea range from approximately \$17 to \$195 per dose.<sup>7</sup>

**Clinical Situations****NAUSEA INDUCED BY VESTIBULAR OR CENTRAL NERVOUS SYSTEM CAUSES**

Antiemetics frequently are used to treat nausea induced by vestibular or central nervous system causes. Unlike other forms of nausea, which tend to be mediated by dopamine and serotonin, vestibular system–induced nausea is mediated primarily by histamine and acetylcholine (Table 3). Consequently, the American Gastroenterological Association (AGA) recommends the use of antihistamines and anticholinergics in the treatment of nausea secondary to vertigo and motion sickness.<sup>14</sup>

Migraine headaches frequently are associated with nausea. Although the mechanism is

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not well understood, antiemetics are useful in the treatment of nausea, and of the headache itself. Because of the efficacy of dopamine antagonists in treating migraine headaches, dopamine is thought to be a primary mediator. A small RCT<sup>15</sup> involving 29 patients found that intramuscular droperidol and meperidine (Demerol) provided equal pain relief.

Evidence-based guidelines<sup>16</sup> developed by a committee from the American Academy of Family Physicians, the American Academy of Neurology, and other organizations support the use of intravenous metoclopramide (Reglan) and intravenous, intramuscular, and rectal prochlorperazine (Compazine) as single-agent therapies in patients with acute migraine headaches and nausea. The committee concluded that oral antiemetics and 5-HT<sub>3</sub> antagonists are appropriate for adjunctive treatment of migraine-associated nausea.

**PREGNANCY-INDUCED NAUSEA**

Between 70 and 85 percent of women have nausea during pregnancy, and an estimated 0.5 percent develop hyperemesis gravidarum.<sup>17</sup> The pathogenesis of nausea in pregnancy is

TABLE 2

**Major Adverse Effects of Antiemetic Agents**

<i>Antiemetic class</i>	<i>Adverse effects</i>
Antihistamines and anticholinergics	Sedation, urinary retention, blurred vision, exacerbation of narrow-angle glaucoma
Dopamine antagonists	Sedation, extrapyramidal effects, QT prolongation, severe hypotension; rarely, seizures, agranulocytosis, neuroleptic malignant syndrome, blood dyscrasias
Serotonin antagonists	QT prolongation, QRS widening; rarely, hypersensitivity reactions

**TABLE 3**  
**Selection of Antiemetics by Clinical Situation**

<i>Situation</i>	<i>Associated neurotransmitters</i>	<i>Recommended antiemetic</i>
Migraine headache	Dopamine (probably a primary mediator)	For headache and nausea: metoclopramide (Reglan) or prochlorperazine (Compazine) For nausea: oral antiemetics, metoclopramide, prochlorperazine, serotonin antagonists
Vestibular nausea	Histamine, acetylcholine	Antihistamines and anticholinergics (equally effective)
Pregnancy-induced nausea	Unknown	For nausea: ginger, vitamin B <sub>6</sub> . For hyperemesis gravidarum: promethazine (Phenergan, first-line agent); serotonin antagonists and corticosteroids (second-line agents)
Gastroenteritis	Dopamine, serotonin	First-line agents: dopamine antagonists Second-line agents: serotonin antagonists Use in children is controversial.
Postoperative nausea and vomiting	Dopamine, serotonin	Prevention: serotonin antagonists, droperidol (Inapsine), dexamethasone Treatment: dopamine antagonists, serotonin antagonists, dexamethasone

not completely understood but is thought to be multifactorial. Several antiemetic drug classes have been shown to be effective treatments.

A recent Cochrane review found that antiemetics generally are effective in treating pregnancy-induced nausea, but that little information exists about fetal outcomes.<sup>17</sup> Consequently, many physicians avoid using antiemetics until patients have dehydration, weight loss, or electrolyte abnormalities. When these criteria are met, treatment with promethazine (Phenergan) usually is initiated.

One small RCT<sup>18</sup> in patients hospitalized

because of hyperemesis gravidarum found that promethazine is as effective as ondansetron and is more cost-effective. Another small study<sup>19</sup> showed that oral methylprednisolone (Medrol) is superior to promethazine in the treatment of hyperemesis gravidarum and can replace or augment other agents in refractory cases.

Complementary and alternative therapies have become popular in the treatment of pregnancy-induced nausea. Pyridoxine (vitamin B<sub>6</sub>) has been shown to be safe and effective in dosages of 50 to 200 mg per day.<sup>17,20</sup> One RCT<sup>21</sup> found that oral ginger (1 g per day) is more effective than placebo in controlling nausea and vomiting in early pregnancy; use of ginger generally is thought to be safe.<sup>20</sup> Current evidence on the efficacy of acupressure and acupuncture in treating pregnancy-induced nausea is inconclusive.<sup>17</sup>

#### **INTESTINAL IRRITATION**

Intestinal irritation is a frequent cause of nausea. Agents such as Norwalk virus, rotavirus, and Salmonella species cause 1.2 intestinal infections per person per year.<sup>14</sup> Medications such as aspirin and ferrous sulfate can cause nausea through visceral stimulation. Because visceral fibers are mediated primarily by serotonin, 5-HT<sub>3</sub> antagonists are effective in the treatment of these disorders.<sup>14</sup>

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<i>Key clinical recommendation</i>	<i>Strength of recommendation</i>	<i>References</i>
Pyridoxine (vitamin B6) is effective and generally thought to be safe in treatment of patients with pregnancy-induced nausea.	A	17, 20
Promethazine (Phenergan) is similar in efficacy to ondansetron (Zofran), and oral methylprednisolone (Medrol) is more effective than promethazine in the treatment of patients with hyperemesis gravidarum.	B	18, 19
Oral ginger probably is effective and is thought to be safe in treatment of patients with pregnancy-induced nausea.	B	20, 21
Intravenous metoclopramide (Reglan) and intravenous, intramuscular, or rectal prochlorperazine (Compazine) are recommended for treatment of patients with nausea and acute migraine.	Metoclopramide, B; prochlorperazine, C	16
Antihistamines and anticholinergics are recommended for treatment of patients with nausea secondary to vertigo or motion sickness.	C	14
Serotonin antagonists are recommended for treatment of patients with intestinal irritation resulting in postoperative nausea and vomiting.	C	14

Anecdotal reports also indicate significant success for treatment with dopamine antagonists, which may be more cost-effective first-line agents than serotonin antagonists.

Treatment of nausea in children with gastroenteritis remains controversial. In a 1996 position statement,<sup>22</sup> the American Academy of Pediatrics recommended that the use of antiemetics be avoided in children because of potential side effects and questionable benefit. However, many family physicians now use 5-HT<sub>3</sub> antagonists in dehydrated children. RCTs have shown that oral and intravenous ondansetron therapy is safe in children and reduces hospital admission rates.<sup>23,24</sup>

#### POSTOPERATIVE NAUSEA AND VOMITING

Nausea affects an estimated 30 percent of patients within 24 hours after surgery.<sup>25</sup> The nausea is mediated primarily by two pathophysiologic pathways. First, intestinal irritation and postoperative stasis stimulate the vomiting center via visceral fibers rich in serotonin. Second, general anesthetics directly activate the chemoreceptor trigger zone which, in turn, stimulates the vomiting center via dopamine and serotonin.

Traditionally, dopamine antagonists such as droperidol and promethazine have been used to treat patients with postoperative nausea and vomiting. Metoclopramide, another dopamine antagonist with prokinetic activity, commonly is used in patients with nausea caused by intes-

tinal stasis. In general, low-dosage droperidol therapy is safe and effective for preventing postoperative nausea and vomiting, and is more cost-effective than treatment with 5-HT<sub>3</sub> antagonists.<sup>10,26</sup> However, serotonin antagonists also minimize postoperative nausea, and the AGA recommends using them as first-line agents for preventing and treating postoperative nausea and vomiting.<sup>14</sup>

Dexamethasone has been shown to be a useful adjunct to serotonin antagonists in the prevention and treatment of postoperative nausea and vomiting.<sup>27</sup>

A reasonable approach to preventing and treating postoperative nausea and vomiting begins with the identification of risk factors, which include female sex, history of postoperative nausea and vomiting, nonsmoking status, perioperative opioid use, general anesthesia, and abdominal, gynecologic, or ear, nose, and throat procedures.

If a patient is at low risk for postoperative nausea and vomiting, prophylaxis is not required, and serotonin antagonists can be used as rescue medications after surgery. In the moderate-risk patient, droperidol should be used for prophylaxis and serotonin antagonists for rescue medications if breakthrough nausea occurs. In a patient at high risk for nausea and vomiting after surgery, droperidol and dexamethasone should be used for prophylaxis, and serotonin antagonists should be given to treat breakthrough nausea.<sup>28</sup>

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