AGA Technical Review on Nausea and Vomiting

This literature review and the recommendations therein were prepared for the American Gastroenterological Association (AGA) Clinical Practice and Practice Economics Committee. The paper was approved by the committee on March 4, 2000, and by the AGA governing board on May 21, 2000.

Nausea and vomiting are common and distressing symptoms with a number of underlying causes. They are somewhat unique among gastrointestinal symptoms in that on the one hand they may represent a basic, physiologic homeostatic response to an ingested exogenous toxin; on the other hand, they may indicate a disease process of the gastrointestinal tract, adjacent organs, or central nervous system (CNS). Given the number and variety of diagnostic possibilities, it would appear that the clinical approach to the patient with nausea and vomiting may prove daunting. In practice, however, an appreciation of the principal causes of nausea and vomiting in various clinical contexts, combined with careful attention to the patient's history and physical examination and some relatively simple investigations, should lead to a clear diagnosis of the cause of the patient's symptoms in most cases. With the recognition of the primary cause, whether it be an acute enteric infection, pregnancy, or an exogenous toxin, most instances of acute nausea and vomiting can be readily resolved. Chronic nausea and vomiting, usually defined as the persistence of these symptoms for more than 1 month, often present a greater clinical challenge, in some instances because of failure to isolate the basic cause and in others because of inability to satisfactorily suppress symptoms.

In this review, when dealing with the evaluation and management of nausea and vomiting, we differentiate between patients with relatively acute presentations, and those, albeit less common, instances of chronic, unexplained symptoms. Nausea and vomiting are also among the symptoms included in the definition of dyspepsia; because the evaluation and management of dyspepsia have been dealt with in detail in another review in this series, they are not explored in any detail in this review, which limits its discussion to the symptoms of nausea and vomiting per se. The literature on which this review was based was selected, using MEDLINE, as follows: all references from 1965 to the present that included nausea and vomiting in the title, were in English, and dealt with human subjects (n = 1073); all references from 1996 to the present that included the terms nausea, vomiting, and therapy anywhere (n = 1262); and references derived from review articles, book chapters, etc., that dealt with nausea and vomiting in general or with specific diagnostic or therapeutic issues.

Definitions

Before reviewing the evaluation and management of nausea and vomiting, it is important to be clear on their definitions, the definition of related symptoms, and, in particular, their differentiation from a number of other symptoms prone to cause confusion (Table 1). Nausea is entirely subjective and is commonly described as the sensation (or sensations) that immediately precede vomiting. Patients state that they feel as if they are about to vomit, or use such terms as “sick to the stomach” or “queasy.” Vomiting, in contrast, is a highly specific physical event that results in the rapid, forceful evacuation of gastric contents in retrograde fashion from the stomach up to and out of the mouth. In vomiting, nausea is followed by retching (repetitive active contraction of the abdominal musculature). These contractions generate the pressure gradient that leads to evacuation, the most clearly recognized component of vomiting. Retching may occur in isolation without discharge of gastric contents from the mouth. It is important to emphasize that vomiting is a complex physiologic process, described in detail below, that includes both involuntary and voluntary components. Although usually preceded by nausea, vomiting may occur in the absence of nausea in some settings. Vomiting must be distinguished from regurgitation, which is passive by definition and describes the retrograde flow of esophageal contents into the mouth. Acid regurgitation, for example, is a cardinal symptom of gastroesophageal reflux. Rumination, a phenomenon that may easily be confused with vomiting, is defined as the effortless regurgitation of recently ingested food into the mouth, followed by rechewing and reswallowing or

Abbreviations used in this paper: CNS, central nervous system; EGG, electrogastrography; 5-HIAA, 5-hydroxyindole acetic acid; HT3, 5-hydroxytryptamine3; PCNV, postchemotherapy nausea and vomiting; PONV, postoperative nausea and vomiting; SBFT, small bowel follow-through.

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spitting out. This is a passive phenomenon. It is not preceded by nausea and does not include the various physical phenomena associated with vomiting. As recently emphasized by O’Brien et al., rumination typically begins within minutes of a meal, is usually repetitive, and is rarely associated with retching, but it may be accompanied by weight loss and bulimia. Although originally described among mentally retarded children and those with psychiatric illnesses, it has become clear that rumination can occur in adults and in the absence of either of these entities.

**Dyspepsia** is most commonly defined as chronic or recurrent pain or discomfort centered in the upper abdomen. Although other symptoms such as nausea, vomiting, early satiety, and fullness may be associated with dyspepsia, they are not central to its definition.

### Table 1. Some Definitions of Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>Vomiting</td>
<td>Forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature</td>
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<tr>
<td>Nausea</td>
<td>The unpleasant sensation of the imminent need to vomit, usually referred to the throat or epigastrium; a sensation that may or may not ultimately lead to the act of vomiting</td>
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<tr>
<td>Regurgitation</td>
<td>The act by which food is brought back into the mouth without the abdominal and diaphragmatic muscular activity that characterizes vomiting</td>
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<td>Anorexia</td>
<td>Loss of desire to eat, that is, a true loss of appetite</td>
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<td>Sitophobia</td>
<td>Fear of eating because of subsequent or associated discomfort</td>
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<td>Early satiety</td>
<td>The feeling of being full after eating an unusually small quantity of food</td>
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<tr>
<td>Retching</td>
<td>Spasmodic respiratory movements against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents, referred to as “dry heaves”</td>
</tr>
<tr>
<td>Rumination</td>
<td>Chewing and swallowing of regurgitated food that has come back into the mouth through a voluntary increase in abdominal pressure within minutes of eating or during eating</td>
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</table>

### Differential Diagnosis of Nausea and Vomiting

The differential diagnosis of nausea and vomiting is extensive and includes a broad range of pathologic and physiologic conditions affecting the gastrointestinal tract, the peritoneal cavity, and the CNS as well as endocrine and metabolic functions (Table 2). Table 3 summarizes the anatomic locations, receptors involved, and specific therapeutic approaches for a variety of emetic stimuli.

### Medications and Toxic Etiologies

Adverse medication reactions are among the most common causes of nausea and vomiting. In general, nausea in response to a drug is likely to present early in the course of its use. Thus, medications usually cause acute rather than chronic nausea and vomiting. Drug classes that induce nausea are varied and may have disparate sites of action. Medications that evoke vomiting by an action on the area postrema include dopaminergic agonists (such as L-dopa, bromocriptine), nicotine (including nicotine patches), digoxin, and opiate analgesics. Nausea, for example, affects 40%–70% of cancer patients receiving narcotics for pain control. Other agents, such as nonsteroidal anti-inflammatory drugs and erythromycin, activate peripheral afferent pathways, most likely vagal, which then stimulate the brainstem nuclei that coordinate the act of vomiting. Other medications that may cause nausea and vomiting include cardiac antiarrhythmics, antihypertensives, diuretics, oral hypoglycemics, oral contraceptives, and gastrointestinal medications such as sulfasalazine.

The most extensively studied form of medication-related emesis is that provoked by cancer chemotherapeutic agents. Nausea and vomiting resulting from chemotherapy (postchemotherapy nausea and vomiting; PCNV) are classified as acute (within 24 hours), delayed (≥1 day later), and anticipatory.
### Table 2. Differential Diagnosis of Nausea and Vomiting

<table>
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<th><strong>Medications and toxic etiologies</strong></th>
<th><strong>Disorders of the gut and peritoneum</strong></th>
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<td>Cancer chemotherapy</td>
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<tr>
<td>Severe—cisplatinum, dacarbazine, nitrogen mustard</td>
<td>Gastric outlet obstruction</td>
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<tr>
<td>Moderate—etoposide, methotrexate, cytarabine</td>
<td>Small bowel obstruction</td>
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<td>Mild—fluouracil, vinblastine, tamoxifen</td>
<td>Functional gastrointestinal disorders</td>
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<td>Analgesics</td>
<td>Gastroparesis</td>
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<td>Aspirin</td>
<td>Chronic intestinal pseudo-obstruction</td>
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<td>Auranofin</td>
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<td>Starvation</td>
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Risk factors for acute chemotherapy-induced nausea include lower socioeconomic status, prechemotherapy nausea, female gender, administration of highly emetogenic chemotherapy, and absence of antiemetic therapy. In their analysis, Osoba et al. documented a 20% prevalence of acute PCNV among those with none of those risk factors, compared with 76% in those with 4 or more. The occurrence of acute PCNV in an earlier treatment cycle is a potent predictor of its occurrence in subsequent cycles. Based on a meta-analysis of 4 trials, Pater et al. concluded that treatment factors (i.e., emetogenicity of chemotherapy regime and nature of antiemetic therapy) far outweighed patient or environmental factors in predicting PCNV. Acute vomiting is most likely to occur with cisplatinum, nitrogen mustard, and dacarbazine, all of which produce significant increases in plasma serotonin levels and/or urinary excretion of 5-hydroxyindole acetic acid (5-HIAA), a serotonin metabolite. Animal models show increases in ileal tissue levels of serotonin and increased numbers of serotonin-immunoreactive cells after cisplatinum administration. Cisplatinum-evoked vomiting is reduced by vagotomy, suggesting its mediation by peripheral afferent neural pathways. However, the inability of the peripherally active 5-hydroxytryptamine3 (HT3)-receptor antagonist zatosetron-QUAT to block cisplatinum-induced emesis when given intravenously, coupled with a significant antiemetic effect when given intracerebroventricularly, indicates a central neural component to vomiting evoked by cisplatinum. The acute nausea occurring after use of less emetogenic agents such as cyclophosphamide evokes little or no increase in plasma serotonin or urinary 5-HIAA levels. These findings are consistent with the clinical observations that 5-HT3 antagonists are effective for preventing acute nausea from highly emetogenic agents but are less useful with symptoms produced by less nauseating chemotherapeutic drugs.

In contrast to acute chemotherapy-evoked vomiting, delayed and anticipatory vomiting are mediated by serotonin-independent pathways. Delayed emesis after cisplatinum administration, which may occur in up to 93% of patients, is not associated with urinary 5-HIAA excretion and is not relieved by 5-HT3-receptor antagonists. One investigation has shown increased norepinephrine production during delayed nausea from cisplatinum, suggesting the possibility of other neuroendocrine mediators.

The principal risk factor for delayed PCNV is poor control of acute symptoms, although age and tumor burden may also contribute. In some patients, as many as 24% in one study, symptoms may be prolonged further, lasting longer than 2 weeks. It has been suggested that gastroparesis may contribute to this phenomenon. Anticipatory nausea and vomiting occur in 25%–50% of patients by the fourth course of cancer chemotherapy and are most prevalent among younger patients with underlying anxiety and especially among those who had adverse experiences in their last cycles of chemotherapy.

Radiation therapy for malignancy can produce significant emesis by effects on both the structure and function of the gastrointestinal tract. The incidence of nausea and vomiting is dependent on the location of the region irradiated and is as high as 80% when the upper abdomen is included in the radiation field. Involvement of serotoninergic pathways is indicated by the ability of 5-HT3-receptor antagonists to reduce nausea and vomiting evoked acutely by abdominal radiation therapy.
Other ingested substances may produce prominent nausea and vomiting. Ethanol, when consumed in excess, evokes vomiting by a local action on the gastrointestinal tract and by central actions in the brainstem. Jamaican vomiting sickness occurs after eating unripe akee fruit. Excess intake of vitamin A also may cause nausea, vomiting, and hepatic injury.44

Infectious Causes

Gastrointestinal and systemic infections may produce nausea and vomiting, usually of acute onset. Acute enteric illness resulting in emesis is most prevalent in children younger than 3 years, then decreases in prevalence throughout childhood, only to become more common between ages 20 and 29 years. These illnesses occur at a rate of 1.2 infections per person per year and are most common in the autumn and winter. Viral gastroenteritis may be caused by the Hawaii agent, rotaviruses, reoviruses, and adenoviruses as well as the Snow Mountain and Norwalk agents. Bacterial infections with Staphylococcus aureus, Salmonella, Bacillus cereus, and Clostridium perfringens also produce nausea and vomiting, in many cases via toxins that act on the brainstem. The enterotoxin responsible for the emetic illness resulting from S. aureus has been characterized recently and is distinct from enterotoxins A–E and the toxic shock syndrome toxin 1.35 Nausea in immunocompromised patients may be caused by gastrointestinal infection with cytomegalovirus or herpes simplex.35,36 Nongastrointestinal infections associated with nausea include otitis media, meningitis, and hepatitis.

Disorders of the Gut and Peritoneal Cavity

Obstruction of the stomach or small intestine produces prominent nausea, which may be relieved by vomiting. Gastric outlet obstruction is often intermittent, whereas small intestinal obstruction usually is acute and associated with abdominal pain. Rarely, mesenteric ischemia may present as unexplained nausea and vomiting through the induction of ischemic gastroparesis.37 Other rare causes of protracted nausea and vomiting include retroperitoneal fibrosis38 and mucosal metastases.39

Functional disorders of gastrointestinal motility, such as gastroparesis, chronic intestinal pseudo-obstruction, and the Roux-en-Y syndrome,40 produce nausea because of an inability to clear retained food and secretions. Gastroparesis may occur in relation to systemic diseases such as diabetes mellitus, scleroderma, systemic lupus erythematosus, polymyositis-dermatomyositis, and amyloidosis.41 Delayed solid- or liquid-phase gastric emptying and electrogastrographic abnormalities42 are prevalent in gastroesophageal reflux disease; however, symptoms correlate poorly with scintigraphic abnormalities.35 Gastroparesis may also develop after vagotomy and gastric drainage operations or may be present in the absence of other disease41 (idiopathic gastroparesis44). This condition may be preceded in some patients by prodromal symptoms such as diarrhea, fever, headache, or myalgias suggestive of viral etiology.45,46 Occasionally, there may be more conclusive evidence of a viral etiology.36,47 Nausea in pancreatic adenocarcinoma is associated with the development of gastroparesis; a paraneoplastic mechanism of inhibition of gastric motor function has been proposed.48 The documentation of gastroparesis must not lead the clinician to assume that it is the fundamental cause of a given patient’s symptoms; gastroparesis may be readily confused with gastric outlet obstruction, for example.49

Nausea and vomiting may be prominent symptoms in patients with functional dyspepsia. Delayed gastric emptying has been documented in 30%–82% of patients with functional dyspepsia, regardless of whether ulcer-like, reflux-like, or dysmotility-like symptoms predominate.50 Other abnormalities identified among some with functional dyspepsia include gastric slow wave rhythm disturbances, abnormal partitioning of food within the stomach, impaired relaxation of the gastric fundus, and enhanced perception of gastric distention.50 The relative importance of these phenomena and their role in symptom generation remain to be defined50,51; in some instances, they may be mere epiphenomena or occur secondary to primary central nervous or endocrine disorders.33,50–53 Similarly, differentiation of “idiopathic” gastroparesis from functional dyspepsia, in general, remains arbitrary.

Abdominal disorders that do not directly involve the lumen of the gastrointestinal tract may also produce nausea and vomiting. Inflammatory conditions, such as pancreatitis, appendicitis, and cholecystitis, may activate afferent neural pathways arising from the peritoneum. Biliary colic, in the absence of inflammation, produces nausea via activation of afferents by distention of the biliary tree. Fulminant hepatic failure results in nausea, presumably caused by retention of as yet undefined emetic toxins and elevation of intracranial pressure.54 Nausea and vomiting have also been reported in association with chemoeembolization of hepatic tumors.55

CNS Causes

Any condition associated with increased intracranial pressure, be it tumor, infarction, hemorrhage, infection, or congenital disorder, may produce emesis, with or without concomitant nausea, via activation of brain stem
structures mediating vomiting. Focal lesions, especially those involving the brain stem and posterior fossa, may also cause and present as gastroparesis. Studies in canine models show that the induction of emesis is maximal at an intracranial pressure of 80 mm Hg. Nausea and vomiting may also be consequences of seizure disorders and are cardinal symptoms of migraine. Rare examples of CNS disorders presenting as nausea and vomiting include brain stem demyelination, neuroenteric cysts of the cerebellorontine angle, and active neurocysticercosis lesions.

Labyrinthine disorders produce nausea and vomiting, often with associated vertigo. Motion sickness is induced by chronic repetitive movements, which stimulate afferent neural pathways that project to the vestibular nuclei and lead to activation of the brain stem nuclei, triggering the somatic and gastrointestinal aspects of emesis. This activation is mediated primarily via histamine H1 and muscarinic cholinergic rather than dopaminergic or serotonergic pathways; therefore, antihistamines and anticholinergics have assumed an important role in therapy. Motion sickness is associated with extensive autonomic activation resulting in pallor, diaphoresis, and salivation. Space sickness, experienced extensively autonomic activation resulting in pallor, diaphoresis, and salivation. Space sickness, experienced in relation to these disorders is largely undefined; it is likely that multiple factors are involved. Activation of the area postrema has been postulated to occur in uremia, diabetic ketoacidosis, and hypercalcemia; a disruption of gastrointestinal motor activity may be more relevant to the pathogenesis of nausea and vomiting related to thyroid and parathyroid disease.

Pregnancy is the most common endocrinologic cause of emesis, which occurs in approximately 70% of women during the first trimester. On average, symptoms begin and end 39 days and 84 days after the last menses, respectively, and peak during the ninth week of gestation. Nausea of pregnancy is more common among women who are primigravid, younger, less educated, overweight, and not employed outside the home. In general, first trimester vomiting is not deleterious to either the fetus or the mother and, in fact, has been reported to be associated with a reduced incidence of both miscarriage and fetal death. It has been suggested that the favorable pregnancy outcome reported with nausea and vomiting may be related to less use of tobacco and alcohol. However, hyperemesis gravidarum, a condition of intractable vomiting that complicates between 1% and 5% of pregnancies, may result in dangerous fluid and electrolyte abnormalities. The cause of nausea of pregnancy is uncertain, but it is likely to be hormonally related. Although symptoms parallel the early increase in β-human chorionic gonadotrophin (β-HCG), the role of this hormone remains to be defined. For example, no reproducible differences in β-HCG release have been identified between those women who become nauseated and those who do not. There is a strong association between prior intolerance to oral contraceptives and subsequent first trimester nausea, suggesting potential roles for estrogen and progesterone. Acute fatty liver of pregnancy can produce severe nausea and vomiting in the third trimester and can be complicated by liver failure, disseminated intravascular coagulation, and fetal and/or maternal death.

**PONV**

The prevalence of nausea and vomiting may complicate 11%–73% of surgical procedures. One study of almost 4000 patients reported rates of 37% and 23% for nausea and vomiting, respectively, in patients undergoing general anesthesia. Variations in reported prevalence are attributable to several factors. Postoperative nausea is more prevalent in women (risk 3 times that of men) and in younger patients (risk 2 times that of older patients). Prevalence is also increased by the use of certain inhalation agents (nitrous oxide, in particular) and by concomitant use of opiate medications; the use of propofol as an intravenous anesthetic agent lowers the risk of PONV. PONV is more likely to occur after general than regional anesthesia, and its prevalence increases in parallel with the duration of surgery and

Endocrinologic and Metabolic Causes

Endocrinologic and metabolic causes of nausea and vomiting include uremia, diabetic ketoacidosis, hyperparathyroidism, hypoparathyroidism, hyperthyroidism, and Addison disease. The pathogenesis of symptoms in relation to these disorders is largely undefined; it is likely that multiple factors are involved. Activation of the area postrema has been postulated to occur in uremia, diabetic ketoacidosis, and hypercalcemia; a disruption of
anesthesia. PONV is especially common after gynecologic and middle ear surgery and also occurs more commonly with abdominal and orthopedic surgery than with laparoscopic or other extra-abdominal operations. PONV is also more likely in those with a history of PONV or motion sickness.

Cyclic Vomiting

Cyclic vomiting, also referred to as “abdominal migraine” or “abdominal epilepsy,” is a rare syndrome, characterized by discrete acute episodes of nausea and vomiting, separated by intervening asymptomatic periods, often associated with migraine headaches, motion sickness, and atopy. The mean age at onset is 5 years, and it demonstrates a female predominance. Affected children typically experience 8 attacks per year, and the mean duration of each attack is 20 hours. An association with mitochondrial DNA mutations has recently been described. In a recent review of 225 children under 18 years of age who presented with the typical features of this syndrome, 121 were ultimately found to have an organic intra-abdominal, neurologic, endocrine, or metabolic cause. Pfau et al. emphasized the importance of the patients’ history in differentiating cyclic vomiting from other causes of chronic vomiting in children; among 106 children with chronic vomiting, only 12% of those with a true cyclic pattern were found to have a gastrointestinal cause for their symptoms, in contrast to 76% of those with a more chronic pattern. Cyclic vomiting has recently been reported among adults and has been postulated to result from disordered pituitary prostaglandin release.

Miscellaneous Conditions

Nausea and vomiting may be prominent symptoms in acute myocardial infarction; although these symptoms were formerly regarded as being particularly common among those with inferior or posterior wall infarction, more recent studies suggest that the presence of nausea and vomiting correlates with infarct size rather than location. Nausea may also occur in congestive heart failure, presumably from passive congestion of the liver and gut, and has been reported after radiofrequency catheter ablation for treatment of cardiac arrhythmias. Prolonged starvation may lead to nausea and vomiting. Nausea and vomiting may also complicate fluorescein angiography.

Functional Nausea and Vomiting

Functional nausea and vomiting is the term used to describe chronic unexplained symptoms. In some situations, these symptoms may be associated with overt psychiatric features, and might therefore be classified as psychogenic; in others with vomiting, such manifestations are either absent or subtle. The relationship of this patient group to those with functional dyspepsia and other related disorders is unclear, although the demonstration of a similar response to low-dose antidepressant therapy suggests a degree of demographic and/or pathophysiologic overlap.

Clinical Approach to Nausea and Vomiting

Given the vast number and diversity of potential causes of nausea and vomiting, a carefully considered and orderly approach to the evaluation and treatment of patients with nausea and vomiting is needed to maintain cost effectiveness and avoid misdiagnosis (see Medical Position Statement). A comprehensive history and physical examination form the framework on which the diagnostic evaluation of these patients is based. A clear understanding of each patient’s symptoms, and precisely what they mean by these symptoms, is crucial (Table 1). The acuteness of the symptomatology should be determined at the initial encounter. The nature of an acute illness can usually be detected on the basis of history and physical examination, supplemented where indicated by plain abdominal radiographs and appropriate blood tests. In this context, several issues need to be addressed. Is there an acute emergency, such as mechanical obstruction, perforation, or peritonitis? Does the patient need to be hospitalized for incapacitating symptoms, dehydration, and/or electrolyte abnormalities? Alternatively, can diagnostic tests, such as barium studies or endoscopy, be performed on an outpatient basis? Furthermore, are there clinical clues that the problem is likely to be self-limited, such as would be expected with viral gastroenteritis? Can a potentially offending medication be identified and discontinued? Should empiric treatment with an antimetic, gastric acid-suppressing, or prokinetic agent be initiated?

The broad categories of clinical conditions that may cause these symptoms should be considered when a patient with chronic nausea and vomiting is evaluated. Symptom characteristics or the nature of associated symptoms often tend to incriminate one of these diagnostic categories. Medication-related toxicity and other iatrogenic causes can usually be identified by history alone. If symptoms suggest obstruction, radiographic studies should first be performed to exclude a mechanical cause. Partial or intermittent obstruction may at times be difficult to detect. Mucosal disorders of the stomach
and/or duodenum, such as peptic ulcer disease, may also cause chronic nausea and vomiting and are most accurately diagnosed by endoscopy. If neither obstruction nor mucosal disease is evident, systemic illness, CNS lesions, and psychologic factors should be considered. Finally, the possibility of an underlying motility disorder such as gastroparesis or small bowel dysmotility should be considered; if detected, an underlying cause should be sought.

On occasion, the cause of nausea and vomiting may remain undiagnosed after a careful initial evaluation. In some, the nature of the underlying disorder may begin to emerge over time and will become evident on subsequent reassessments. In some, persistent symptoms may be psychogenic in origin or attributable to the cyclic vomiting syndrome. Although psychogenic vomiting is best illustrated by such disorders as anorexia nervosa or bulimia, it may also occur in relation to such conditions as panic disorders.

Initial Evaluation

**History.** Attention should be paid in the first instance to a clear definition of the clinical problem and to the differentiation of vomiting from regurgitation and rumination.

**Symptom duration, frequency, and severity.** Because the differential diagnosis of acute nausea and vomiting differs considerably from that of chronic nausea and vomiting, the definition of symptom duration is of paramount importance. Acute onset of nausea and vomiting suggests gastroenteritis, pancreatitis, cholecystitis, or a drug-related side effect. Most commonly, and particularly when nausea and vomiting are associated with diarrhea, headache, and myalgias, the cause is viral gastroenteritis; in this instance, symptoms should resolve spontaneously within 5 days. A more insidious onset of nausea, without vomiting, should raise suspicion of gastroparesis, a medication-related side effect, metabolic disorders, pregnancy, or even gastroesophageal reflux disease. Nausea and vomiting are considered chronic when their duration is longer than 1 month.

**Characteristics of vomiting episodes.** The timing and description of the vomiting should be noted. Vomiting that occurs in the morning before breakfast is typical of that related to pregnancy, uremia, alcohol ingestion, and increased intracranial pressure. Intracranial disorders, especially those that result in increased intracranial pressure, are suggested by “projectile vomiting,” although “ordinary” emesis may also occur. Vomiting, in this circumstance, may not be preceded by nausea. Brainstem tumors frequently present with vomiting (30%–46%) and are usually accompanied by long tract or cranial nerve signs.

The onset of vomiting caused by gastroparesis or gastric outlet obstruction tends to be delayed, usually by more than 1 hour, after meal ingestion. Certain vomiting patterns may suggest specific psychiatric disorders. In anorexia nervosa or bulimia, vomiting typically occurs during or soon after a meal. Continuous vomiting may be associated with a conversion disorder, and habitual postprandial or irregular vomiting is more typical of a major depression. Patients with chronic psychogenic vomiting often report a history of organic or functional illness of the gastrointestinal tract. The original symptoms of “organic” origin are reinforced by the short-term benefits of initial therapy, and the now chronic symptoms represent a learned form of behavior.

Details regarding the quality and quantity of the vomitus may also prove helpful. Regurgitation of undigested food is suggestive of such esophageal disorders as achalasia, esophageal stricture, or Zenker’s diverticulum. Vomiting of partly digested food or chyme several hours after a meal suggests gastric outlet obstruction or gastroparesis, both of which often occur in the absence of significant pain. If the partially digested food is free of bile, gastric outlet obstruction is suggested; in contrast, bilious vomiting is characteristic of small bowel obstruction. A feculent or putrid odor to the vomitus, also a feature of intestinal obstruction, reflects bacterial degradation of stagnant intestinal contents.

**Associated symptoms.** Associated symptoms, such as abdominal pain, fever, diarrhea, vertigo, or a history of a similar contemporaneous illness among family and/or friends may guide the clinician toward the correct diagnosis. A precise description of any associated pain may help to localize the underlying disease process, by suggesting the presence of a biliary or pancreatic disorder, for example. Abdominal pain preceding vomiting usually indicates an organic lesion, such as an obstruction. With small bowel obstruction, pain is typically prominent, severe, and colicky and may temporarily improve after a vomiting episode.

Significant weight loss may indicate a malignant process; however, benign gastric outlet obstruction from ulcer disease may cause weight loss of similar degree by inducing sitophobia.

The presence of CNS symptoms such as headache, vertigo, neck stiffness, and focal neurologic deficits suggests a central cause of nausea and vomiting. The “classic” brain tumor headache—severe, worse in the morning, and associated with nausea and vomiting—occurs in
a minority of patients; very rarely, intractable vomiting is the sole manifestation of a brainstem tumor. A history of intermittent episodes of vomiting, in association with a history of migraine, suggests the cyclic vomiting syndrome.

Although complaints of early satiety and postprandial abdominal fullness/bloating and abdominal pain, in association with nausea and vomiting, may suggest underlying gastroparesis, these symptoms correlate poorly with results of gastric emptying studies. In one recent study, for example, female gender, prominent symptoms of abdominal fullness/distention, and vomiting were the only historical features, among several evaluated, that proved predictive of gastroparesis in a large number of patients with dyspepsia. This finding has led some to question the role of gastroparesis in symptom production in functional dyspepsia.

**Physical Examination**

The physical examination is important for assessment of the consequences of nausea and vomiting and may help in determining the underlying condition. Signs of weight loss and dehydration should be sought. If the patient is not overtly hypotensive when supine, orthostatic vital signs should be obtained; a postural decrease in blood pressure and increase in pulse rate suggest significant dehydration; a decrease in blood pressure without any change in pulse rate suggests the presence of autonomic neuropathy.

The general examination will detect such important signs as jaundice, lymphadenopathy, abdominal masses, and occult blood in stool and may reveal features suggestive of thyrotoxicosis or Addison’s disease.

The abdominal examination is of considerable importance. Emphasis should be placed on detection of distention, visible peristalsis, and abdominal or inguinal hernias. The definition of specific areas of tenderness is important: tenderness in the midepigastrium suggests an ulcer; in the right upper quadrant, cholecystitis or biliary tract disease. Listening over the epigastrium for a suction splash on shaking the abdomen and pelvis or rapidly palpating the epigastrium will help identify gastric outlet obstruction or gastroparesis. Auscultation may demonstrate increased bowel sounds in obstruction or absent bowel sounds in ileus.

The extremities should be examined for changes suggesting scleroderma or peripheral neuropathy. Fingernails should be inspected for findings suggestive of self-induced vomiting. On inspection of the teeth, the discovery of loss of dental enamel may indicate either recurrent vomiting, as in bulimia, or the consequences of gastroesophageal reflux disease.

Neurologic examination unfortunately is often omitted in the evaluation of these patients. Crucial information may be readily obtained even by the nonneurologist if a number of simple maneuvers are performed: assessment of orthostatic hemodynamic changes, examination of the cranial nerves (including checking for nystagmus), fundoscopic examination, and observation of the patient’s gait. Cranial nerve abnormalities and/or long tract signs suggest a central cause of the patient’s symptoms.

Psychiatric causes, such as depression and anxiety, may also be recognized by the attentive physician during performance of the history and physical examination.

**Blood Tests**

The selection of laboratory studies and diagnostic tests should be directed primarily by the outcome of the history and physical examination. The goals of such tests are (1) to assist in identifying the underlying cause and (2) to evaluate for consequences of vomiting. Basic laboratory testing includes a complete blood count and erythrocyte sedimentation rate together with electrolyte and standard chemistry profiles. In women, a pregnancy test is usually obtained, not only to define whether pregnancy might be the cause of symptoms, but also as a prerequisite to performing any radiologic studies. Further laboratory tests may include screening for abnormal thyroid function by estimating the serum level of thyrotropin-stimulating hormone. Serum drug levels may indicate toxicity among patients who are taking digoxin, theophylline, or salicylates. Severe and sustained vomiting, resulting in loss of water and electrolytes, may lead to dehydration and a hypokalemic metabolic alkalosis, caused in part by the loss of hydrochloric acid—containing gastric secretions. These laboratory tests may also provide the first clues to detection of other systemic disorders; for example, suspicion of Addison’s disease will be aroused by the detection of hyponatremia. Further evaluation for metabolic disorders is indicated when screening results prove abnormal or when the patient history is compatible.

**Diagnostic Evaluation**

The diagnostic evaluation should be directed first and foremost by the patient’s history. As testing proceeds, symptomatic treatment may be initiated on an empiric basis. Some would go so far as to recommend a therapeutic trial as the initial approach in those without “alarm” symptoms. However, no controlled trials have confirmed the cost effectiveness of such an approach among patients whose primary presentation is nausea and vomiting. The relative costs, benefits, and risks of available diagnostic tests
are compared in Table 4. The approach to the diagnosis of mucosal or obstructive disease of the upper gastrointestinal tract is not reviewed in detail here; remarks are confined to a few specific comments. If the clinical presentation is in any way suggestive of mechanical obstruction, upright and supine abdominal radiographs should be obtained; they can be normal or show only nonspecific changes in 22% of patients with varying degrees of partial small bowel obstruction. Although mucosal abnormalities (such as ulcers) or a proximal mechanical obstruction may be detected by either endoscopic or contrast radiologic studies, standard esophagogastroduodenoscopy is both more sensitive and more specific for detection of mucosal lesions. Double-contrast barium techniques have increased the sensitivity of radiologic studies; standard esophagogastroduodenoscopy is both more sensitive and more specific for detection of mucosal lesions. Double-contrast barium techniques have increased the sensitivity of radiologic studies; the error rate, compared with endoscopy, is substantially lower than for single-contrast studies. Radiologic studies in general are more readily available, are less expensive, and are not associated with such rare sedation- and endoscopy-related complications as respiratory depression, perforation, and hemorrhage. Two radiographic techniques are available to visualize the small intestine: the small bowel follow-through (SBFT) examination and the enteroclysis (or small bowel enema). The SBFT is accurate in the presence of high-grade obstruction and usually provides an adequate assessment of the terminal ileum but may fail to detect low-grade obstruction and smaller mucosal lesions. This has led some to advocate the enteroclysis study, which necessitates the placement of a nasoduodenal or oroduodenal tube directly into the small bowel; to achieve this, sedation using a benzodiazepine may occasionally be required. Compared with SBFT, enteroclysis is more accurate in detecting small mucosal lesions and mild to intermediate grades of small bowel obstruction and small bowel cancers. However, small bowel tumors can be difficult to detect even with advanced radiologic studies. Recent studies suggest that computed tomographic scanning, performed after administration of oral and intravenous contrast, may be the technique of choice for the detection and localization of intestinal obstruction. This modality has the additional advantage, in the context of the patient with unexplained nausea and vomiting, of identifying abdominal masses, as well as pancreatic, hepatobiliary, or retroperitoneal pathology.

### Tests of Gastric Motor Function

The most commonly used screening test of gastric motor function, relevant to this patient population, is the assessment of gastric emptying rate, usually performed using a meal labeled with a γ-emitting radionuclide.
Antroduodenal manometry and electrogastrography are performed only in a few tertiary referral centers.

**Gastric emptying.** Radioisotopic tests of gastric emptying offer a relatively easy, accurate, and noninvasive means to assess gastric motor function. The patient ingests a radiolabeled meal, and its retention in or disappearance from the stomach is then monitored over time by serial images obtained using a γ camera placed over the upper abdomen. The radiation exposure from a standard solid-phase scintigraphic study of gastric emptying is approximately twice that incurred with an abdominal x-ray. Solid-phase meals are more sensitive than liquid-phase meals in detecting gastroparesis because normal emptying of liquids is often preserved until gastroparesis is advanced. Breath tests and ultrasonography are being examined as alternatives to scintigraphy.

The diagnosis of gastroparesis is typically based on the combination of compatible symptoms, delayed gastric emptying on scintigraphy, and the absence of obstruction and mucosal disease on endoscopic and/or radiologic evaluation of the upper gastrointestinal tract. An abnormal gastric emptying test result suggests but does not prove that symptoms are caused by gastroparesis; furthermore, emptying studies do not determine the cause of the gastroparesis.

**Electrogastrography.** Cutaneous electrogastrography (EGG) is performed by placing electrocardiography-type electrodes on the abdominal skin over the surface markings of the antrum and recording the frequency (normally approximately 3 cycles per minute) and regularity of gastric myoelectrical activity in the fasting state and for 60–120 minutes after a test meal. Dysrhythmias are classified as rapid (tachygastria, >4 cycles/min) and slow (bradygastria, <2 cycles/min). The amplitude of the signal provides a summation of gastric myoelectrical activity and correlates indirectly with gastric contractility. A reduction in or absence of the expected postprandial increase in the EGG amplitude, or power, has been shown to correlate with delayed gastric emptying and antral hypomotility. Gastric dysrhythmias (both bradygastria and tachygastria) have been observed in patients with idiopathic gastroparesis, diabetic gastroparesis, nausea of pregnancy, and motion sickness. In addition, gastric dysrhythmias have been recorded on occasion in those with unexplained nausea and vomiting in the absence of altered gastric emptying. Although correlations between gastric emptying and EGG results are far from perfect, it seems reasonable to state, based on limited available data, that abnormal EGG results, especially in the postprandial period, usually predict delayed gastric emptying. Although some have suggested that gastric dysrhythmias may correlate better with symptoms than gastric emptying rate, the place of this technique in the evaluation of these patients has not been defined.

**Antroduodenal manometry.** Antroduodenal manometry involves the direct recording of intraluminal pressure changes (an indirect measurement of contractile activity) through perfusion ports or solid-state transducers incorporated in a catheter positioned under fluoroscopic guidance in the distal stomach and duodenum. Recordings may last from 5 hours (stationary study) to 24 hours (ambulatory study), are performed both in the fasting state and after meals, and may be analyzed either by direct visual inspection or using a computer. In the fasting state, the presence of the migrating motor complex and its site of initiation, direction of propagation, frequency, and duration are assessed. After the meal, conversion to the fed state is identified, and the duration of the fed pattern is calculated. Postprandial antral hypomotility is a common finding among those with unexplained nausea and vomiting and delayed gastric emptying, and manometry has also been reported as useful in identifying those with primary or diffuse motor disorders. However, the interpretation of antroduodenal manometric recordings requires substantial experience and a recognition of the considerable range of normal variation. The specificity of many reportedly abnormal patterns has rarely been confirmed by correlation with histologic studies.

It is only fair to mention that few data are available to guide the clinician in the appropriate performance of manometry in patients with unexplained nausea and vomiting; in one study, 42% had abnormal results, yet the manometric findings resulted in significant changes in therapy in only 13%. What then is the role of manometry in the assessment of unexplained nausea and vomiting? If tests of gastric function reveal delayed emptying or abnormal myoelectrical activity, there is little added value in performing antroduodenal manometry, unless an awareness of small bowel dysfunction will alter treatment. When the gastric emptying or EGG results are normal or equivocal and severe symptoms persist despite empiric therapeutic trials, antroduodenal manometry may be indicated. Occasionally, findings consistent with chronic intestinal pseudo-obstruction may be revealed or features consistent with mechanical obstruction identified in patients in whom they had not
been detected radiographically. Others have emphasized the value of a normal result: by demonstration of normal motor function in the antrum and the duodenum, any lingering questions regarding dysmotility can be resolved and the diagnostic evaluation redirected elsewhere.

Abdominal Imaging

In addition to the aforementioned role of computed tomography scanning, ultrasonography may also provide valuable information if gallbladder, pancreatic, or hepatobiliary pathology is suspected.

Evaluation for Central Disorders

Although much feared, it is rare for an adult patient with vomiting related to an intracranial mass not to have either neurologic symptoms, most commonly headache, or neurologic signs, such as cranial nerve findings, long tract signs, or papilledema. Because objective neurologic findings may occasionally be absent in patients with intracranial lesions, an imaging study should be considered in those with severe, unexplained chronic nausea and vomiting; magnetic resonance imaging, by virtue of superior visualization of the posterior fossa, is now considered the study of choice in this situation.

Evaluation for Psychogenic Causes

In patients with chronic unexplained nausea and vomiting, psychologic assessment may be of benefit. Once common organic causes and gastrointestinal dysmotility have been excluded, psychogenic vomiting should enter the differential diagnosis. A definitive diagnosis of psychogenic vomiting may be especially difficult to make but may be aided by recourse to a number of instruments designed to detect significant psychologic contributions to functional symptoms. On the Minnesota Multiphasic Personality Inventory and other instruments, elevated scores for hypochondriasis, depression, and hysteria have been demonstrated among patients with nausea of presumed psychogenic origin.

Management of Nausea and Vomiting

General principles

Treatment of the patient with nausea and vomiting must address a number of important issues. These include (1) correction of any fluid, electrolyte, or nutritional deficiencies that may have resulted from vomiting itself or the food aversion that may accompany these symptoms; (2) identification and elimination of the underlying cause of the symptoms where possible; and (3) suppression or elimination of the symptoms themselves if the primary cause cannot be identified easily and promptly eliminated.

In the patient with either acute or chronic vomiting, dehydration and malnutrition may be caused by cessation of oral intake of fluid, electrolytes, and nutrients and by direct loss of fluid and electrolytes in the vomitus. In a normal individual, the salivary glands and the stomach each secrete 1–2 L of fluid per day—these secretions contain sodium, hydrochloric acid, and potassium; if vomiting is protracted, dehydration, hypokalemia, and metabolic alkalosis will result. Hypokalemia will be exacerbated by the exchange of sodium for potassium in the renal tubule in an attempt to conserve sodium losses. Contraction of extracellular fluid, bicarbonate losses, and shifts of hydrogen into the cells as a further consequence of potassium deficiency also contribute to alkalosis. Therefore, a primary goal of treatment of the patient with protracted vomiting is careful assessment of fluid and electrolyte status followed by appropriate replacement. Fluid replacement should be based on the administration of normal saline solutions with appropriate potassium supplementation. If it becomes clinically necessary to place a nasogastric tube to relieve gastric distention, for example, the output from the nasogastric tube should be measured on a regular basis and appropriate replacement performed. In some circumstances, such as in the patient with nausea and vomiting related to gastroparesis, dietary measures may be of considerable importance; strategies may include consumption of frequent small meals, reduction of the fat content of meals, avoidance of indigestible or partially digestible material (to prevent bezoar formation), and elimination of carbonated beverages to reduce gastric distention. If necessary, the diet may be further modified by use of a blender or, in more extreme circumstances, by provision of all calories in the form of liquid formulas.

Pharmacologic Approaches

A major limitation of the available literature on pharmacologic treatment of nausea and vomiting is the striking paucity of controlled trials of therapies for the most common causes of these symptoms. This may relate in part to the fact that nausea and vomiting in many of these circumstances are short-lived and resolve spontaneously. Most clinical trials have been performed in circumstances associated with a high risk of nausea and vomiting—surgery, intensive chemotherapy, and radiation therapy. Although these may provide useful information on the relative efficacy of various agents, it may not be appropriate to extrapolate results to other clinical
situations. One important theme that emerges from the literature is the difference in therapeutic response between nausea and vomiting; the former is often more resistant to pharmacologic interventions, both prophylactic and therapeutic. This may relate to the differences in the physiology of these symptoms.

Two broad categories of agents are used: antiemetics and prokinetics. Antiemetics act primarily within the CNS to suppress nausea and prevent vomiting (Table 5). The principal classes of drugs that have been used for symptomatic treatment of nausea and vomiting are phenothiazines, antihistamines, anticholinergics, dopamine antagonists, and serotonin antagonists. Other classes of compounds that have been shown to have antiemetic properties are butyrophenones, cannabinoids, other substituted benzamides, steroids, and benzodiazepines.

**Antiemetic Agents**

Although a variety of anticholinergic agents have been shown to have antiemetic effects, their clinical utility has been limited by relatively modest efficacy and poor tolerance because of the frequency of other anticholinergic side effects. Currently, the only anticholinergic agent that enjoys any degree of use is scopolamine, administered as a transdermal patch. It is used primarily for prophylaxis and treatment of motion sickness; more selective antimuscarinic agents, such as zamifenacine (an M₁-, M₅-receptor antagonist), appear equally effective. 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.

**Antihistamine drugs** with histamine H₁-receptor antagonistic properties have central antiemetic effects. Agents such as meclizine and diphenhydramine are available both over the counter and by prescription for symptomatic therapy of nausea and vomiting. Disorders such as motion sickness, vertigo, and migraine, in which nausea and vomiting are of labyrinthine origin, are managed primarily by histamine H₁- and cholinergic muscarinic M₁-receptor antagonists. In clinical studies, dimenhydrinate, dramamine, cyclizine, cinnarizine, marezine, scopolamine, and meclizine, among others, have shown efficacy in the prevention and treatment of motion sickness. These agents induce variable degrees of drowsiness.

**Phenothiazine compounds** have long been recognized as possessing significant antiemetic properties. Their actions appear to be mediated primarily through a central antidopaminergic mechanism in the area postrema. Commonly used agents in this class include prochlorperazine, promethazine, chlorpromazine, thiethylperazine, and perphenazine. These compounds are variably available in tablet or capsule form, as suspensions, as suppositories, and for injectable use and are commonly used for more severe episodes of nausea and vomiting, including those related to vertigo, motion sickness, and migraine. Of this group, prochlorperazine is perhaps one of the most widely used agents for the treatment of moderate to severe nausea and vomiting and has demonstrated efficacy in PONV and PCNV. Its availability in formulations suitable for oral, rectal, and parenteral use provides considerable flexibility, particularly for the patient who is unable to tolerate orally administered compounds. Side effects of these compounds are relatively frequent and include sedation, orthostatic hypotension, and extrapyramidal symptoms, including dystonia and tardive dyskinesia. Rarely, other phenothiazine-type idiosyncratic reactions, such as the neuroleptic malignant syndrome, blood dyscrasias, and cholestatic jaundice, have also been reported.

### Table 5. Antiemetic Agents

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*Available in transdermal form.*
The butyrophenones, haloperidol and droperidol, also probably act via a central antidopaminergic effect.\textsuperscript{179} Droperidol, in particular, has been shown to be useful in the treatment of anticipatory and acute chemotherapy-related nausea and vomiting, and also in the therapy of PONV. Side effects include sedation, agitation, and restlessness.

Serotonin (5-HT) antagonists have recently been added to the list of clinically effective antiemetic agents.\textsuperscript{180} A particular advance has been the development of a number of relatively specific 5-HT\textsubscript{3} antagonists, including ondansetron, granisetron, tropisetron, and dolasetron. They may well operate at both central and peripheral locations. Given that the highest density of 5-HT\textsubscript{3} receptors is in the area postrema, it is thought that the primary site of action of these compounds is on the chemoreceptor trigger zone.\textsuperscript{181} They are well tolerated, and side effects such as gastrointestinal upset and headache appear to be relatively uncommon.

Domperidone\textsuperscript{182} and metoclopramide\textsuperscript{183} are substituted benzamides that act primarily as dopamine antagonists and appear to have both central and peripheral actions. They also appear to have some direct and indirect cholinergic effects. Both agents are distinctive in that they exert both antiemetic and prokinetic effects. They are differentiated by the fact that domperidone penetrates the blood–brain barrier poorly, so although it has effects on the chemoreceptor trigger zone, which is on the blood side of the barrier, it does not enter the CNS to any significant extent and is therefore free of the centrally mediated extrapyramidal side effects that are relatively common with metoclopramide. Both have been shown to be moderately effective in the treatment of nausea and vomiting and have been used in a variety of clinical contexts. Domperidone is not yet available for use in the United States, but metoclopramide is available for oral and parenteral use—an advantage in the patient with severe episodes of central vomiting.\textsuperscript{59,60,65} Both have been shown to exert prokinetic effects on the esophagus, stomach, and upper small intestine and thus have been used in the treatment of gastroesophageal reflux and gastroparesis in particular. Because of their dual action as prokinetics and antiemetics, they may be particularly useful in the patient with nausea and vomiting related to gastroparesis such as diabetic gastropathy. Because of the relative rarity of extrapyramidal effects with domperidone, it has also proved useful in the therapy of nausea and vomiting related to dopaminergic agents used in the treatment of Parkinson’s disease.\textsuperscript{184} In the treatment of acute chemotherapy-related nausea and vomiting, metoclopramide has been found to be inferior to ondansetron; however, there is some suggestion that domperidone may be superior to serotonin antagonists for delayed PCNV.

A major limiting factor in the use of metoclopramide is the relative frequency of significant adverse effects. Adverse effects appear to be particularly common in young children and the elderly and include fatigue and such extrapyramidal phenomena as dystonia, dyskinesia, akathisia, opisthotonos, and oculogyric crises. Metoclopramide also induces hyperprolactinemia, which may result in gynecomastia and galactorrhea. The overall incidence of adverse effects with metoclopramide is 10%–20%. The overall frequency of side effects with domperidone appears to be in the region of 5%–10%; extrapyramidal effects are distinctly uncommon, but hyperprolactinemia-related effects and headaches do occur. Other agents classified as substituted benzamides that also have antiemetic effects are benzoquinamide, trimethobenzamide, and alizapride. These have been used in the treatment of moderate to severe nausea and vomiting in a variety of clinical contexts.

Anecdotal reports led to the investigation of cannabinoids in the treatment of nausea and vomiting. These agents appear to act centrally in the region of the medulla oblongata. Of this class of compounds, 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.\textsuperscript{178} Side effects include sedation, hypotension, ataxia, dizziness, and euphoria.

A variety of other agents have been used for the treatment of severe chemotherapy-related nausea and vomiting in particular. Corticosteroids, especially dexamethasone, have been used primarily in combination with other agents such as metoclopramide and ondansetron in the treatment of chemotherapy-related nausea and vomiting, acting perhaps by reducing prostaglandin formation. Benzodiazepines such as lorazepam and diazepam have also been shown to be effective as adjunctive agents in the treatment of cytotoxic chemotherapy-related nausea and vomiting.

The latest class of compounds to show efficacy as antiemetics are the neurokinin-1 antagonists, which in preliminary studies have shown impressive efficacy in both acute and delayed PCNV.\textsuperscript{185}

**Prokinetic Agents**

Prokinetic agents are used primarily in gastroesophageal reflux disease, gastroparesis, and other putative dysmotility syndromes. A number of common
themes emerge from a review of the pharmacology of motility. Given the ubiquity of many of these receptors in various neuronal systems, it is not surprising that the usefulness of several prokinetic agents has been limited by CNS and cardiovascular side effects. With many agents, tolerance has been a problem, and long-term efficacy often proves elusive.

Cholinergic agonists also act as prokinetics; several studies have demonstrated some efficacy for metoclopramide in gastroesophageal reflux disease and gastroparesis. Domperidone has demonstrated efficacy in gas-somach and clebopride may also potentiate acetylcholine release. Cisapride, a substitute benzamide, has been the focus of several experimental and clinical studies. Its mode of action involves the facilitation of acetylcholine release from myenteric neurons through a 5-HT4 receptor-mediated effect. Among oral prokinetic agents (metoclopra-mide, domperidone, erythromycin, and cisapride), cisapride appears to have the most diffuse gastrointestinal effects. It also appeared to benefit from an apparently low incidence of adverse effects; neurologic and hormonal abnormalities are distinctly unusual, and mild diarrhea and abdominal cramping are the only problems consistently associated with its use. Recently, however, concern was raised after reports of a proarrhythmic effect of cisapride, usually occurring in the context of cotherapy with other agents that impair cisapride metabolism or prolong the Q–T interval. This concern led to withdrawal of cisapride in the United States and elsewhere and to extensive warnings and requirement of pretherapy electrocardiograms in many other countries. With regard to the development of tolerance on long-term therapy, the status of cisapride remains somewhat uncertain, although studies to date suggest that this may be less of a problem than with metoclopramide and domperidone. Some studies have certainly shown continuing efficacy for up to 1 year in gastroparesis. Several studies have demonstrated benefits with cisapride in gastroparesis and pseudo-obstruction. In both short- and long-term studies, the Mayo clinic group demonstrated improvements in gastric emptying and motility in patients with gastroparesis and chronic intestinal pseudo-obstruction. However, the relationship between objective improvements in emptying and symptom relief was somewhat inconsistent. Recently, Camilleri et al. suggested that aspects of autonomic function may influence the response to cisapride.

Although it has been recognized for some time that erythromycin, a macrolide, is associated with significant gastrointestinal effects, the possibility that these are related to the stimulation of motility was not recognized until recently. It is now clear that erythromycin exerts a dose-dependent stimulatory effect on foregut motility and inhibits isolated pyloric pressure waves and pyloric tone. These direct effects on contractile activity translate into acceleration of gastric emptying, abolition of the lag phase of solid emptying, emptying of nondigestible solids, and the induction of “dumping.” Although several studies have consistently demonstrated the efficacy of intravenous erythromycin, the efficacy of oral administration is more controversial. Thus, not all studies have demonstrated long-term benefits in such conditions as gastroparesis, postvagotomy gastric stasis, the roux syndrome, and intestinal pseudo-obstruction. In a recent comprehensive interview, Camilleri concluded that erythromycin was most useful in acute situations and recommended a regimen that began with intravenous erythromycin (3 mg/kg every 8 hours) and continued with oral administration (250 mg 3 times a day) for 5–7 days. Current research seeks to develop a macrolide, devoid of antibiotic activity, that has more predictable efficacy when administered by mouth and is associated with a lower incidence of adverse effects than erythromycin.

Specific Clinical Situations

Intractable Nausea and Vomiting Related to Gastroparesis

Surgical treatment of gastroparesis and motility disorders has proven disappointing in general, and the temptation to proceed to bypass procedures should be particularly resisted. Results of resection in patients with diabetic gastroparesis have also been disappointing. However, for patients with postoperative gastroparesis in whom medical management has failed, resection may be considered. If resection is performed, a subtotal gastrectomy, rather than less extensive resections, appears to give the best results.
Endoscopic placement of a percutaneous endoscopic gastrostomy (PEG) may provide the patient who has prominent distention with relief when symptoms are distressing. Recently, two pilot studies have suggested that gastric pacing may dramatically relieve symptoms among patients with intractable nausea and vomiting related to gastroparesis.207,208

**PONV**

In PONV, the focus has been on prevention rather than therapy; of 75 randomized trials and 4 meta-analyses reviewed, only 8 trials and 1 meta-analysis addressed the management of established nausea and vomiting. Furthermore, few attempts have been made to address the overall efficacy of a prophylactic strategy. In their assessment, Tramer et al.209 suggest that although prophylaxis with ondansetron (one of the more effective agents in comparative trials) was slightly more effective than treatment of PONV when it developed, it was less cost-effective and associated with more adverse effects. From trials of prophylaxis, certain themes emerge. Nausea is more difficult to prevent than vomiting, and the omission of nitrous oxide210 and inclusion of propofol in induction and maintenance of anesthesia211,212 will reduce the prevalence of PONV. Of the multitude of pharmacologic agents tested, the 5-HT₃ antagonists and droperidol have proven most effective in comparisons both with placebo and with other agents in large randomized trials.213–224 Comparisons between various 5-HT₃ antagonists or between members of this class of compounds and droperidol have generally found similar efficacies for all.213,216,218,222–224 Tramer et al.225 performed an important meta-analysis of 53 trials involving 7177 patients who had received 24 different ondansetron regimens and 5712 control subjects. These subjects were at high risk for PONV, as indicated by average early and late incidences of PONV of 40% and 60%, respectively, among those who received no therapy or placebo. They concluded that with an optimal regimen (8 mg intravenously, 16 mg orally), the best number needed to treat to prevent PONV in a high-risk group was between 5 and 6. Major adverse effects were headache and abnormal liver enzyme levels.225 5-HT₃ antagonists are also effective in the treatment of established PONV; intravenous doses of ondansetron ranging from 1 to 8 mg have a response rate that is, on average, 25% higher than that of placebo.226 Other studies show similar efficacy for granisetron227 and tropisetron.228

**Chemotherapy- and Radiation-Related Nausea and Vomiting**

For the prevention of acute PCNV, the combination of a 5-HT₃ antagonist and dexamethasone is now the preferred option.229–236 In a meta-analysis, addition of dexamethasone to a 5-HT₃ antagonist increased the complete control rate from 39%–79% to 58%–92%.230 The various 5-HT₃ antagonists appear to be of similar efficacy and have a comparable incidence of side effects.231,233,235,237 Doses used in this context are considerably higher than in other circumstances.231,235,237,238 Cocktails containing high-dose metoclopramide (2 mg/kg intravenously), dexamethasone, antihistamines, and benzodiazepines have also been shown to be effective in prevention and treatment of PCNV but have largely been replaced by regimens that incorporate a 5-HT₃ antagonist. 5-HT₃ antagonists, either alone or in combination with corticosteroids, appear to be less effective in the prevention and treatment of delayed PCNV.23,233,239–245 For this situation, a combination of dexamethasone and metoclopramide is recommended;246 however, even this regime still has a failure rate of approximately 40%. There is some evidence of efficacy for benzodiazepines and substituted benzamides.242,246 Most exciting, in this context, is the recent report of the efficacy of a neurokinin-1–receptor antagonist in the prevention of PCNV. The addition of this oral agent to a combination of granisetron (10 μg/kg) and dexamethasone (20 mg) not only increased the complete control rate for acute emesis from 67% to 93% but demonstrated a complete control rate of 80% for delayed vomiting—a rate not achieved previously by other regimens.247 Few studies have addressed the prevention and treatment of anticipatory PCNV; available evidence suggests that in the prevention and control of acute and delayed PCNV, benzodiazepines and relaxation therapy may have some efficacy.247,248

5-HT₃ antagonists have also been shown to be more effective than either placebo or other agents such as chlorpromazine, dexamethasone, and prochlorperazine in the prevention of radiotherapy-induced nausea and vomiting,249–252 as well as in the treatment of nausea and vomiting that is unrelated to chemotherapy and radiation therapy in cancer patients.253

**Morning Sickness and Hyperemesis Gravidarum**

Prevention and treatment of morning sickness and hyperemesis gravidarum are complicated by a gen-
eral reluctance to use pharmacologic agents in pregnant patients. Debendox, formerly a widely used preparation for the treatment of these symptoms, was withdrawn because of possible teratogenic effects, and the development of therapeutic agents in this area was significantly compromised by the unfortunate consequences of the use of thalidomide in Europe. Conventionally, antiemetics are not prescribed before 12 weeks' gestation. Because of its relative safety, pyridoxine has been advocated, although evidence of its antiemetic efficacy is lacking. For more severe symptoms and for hyperemesis, hospitalization, fluid and electrolyte replacement, thiamine supplementation, and administration of antiemetics including antihistamines, such as meclizine, and phe-nothiazines, such as promethazine, may be used. Alternative therapies such as acupressure have also been effective. For more severe cases of hyperemesis gravidarum, parenteral prochlorperazine, chlorpromazine, and metoclopramide have been used. Only 4 randomized trials of any therapy for hyperemesis gravidarum have been conducted. Although adrenocorticotropin proved no better than placebo, a recent trial suggested that oral methylprednisolone was superior to promethazine. Although the failure rate was similar with both therapies, those who received the steroid therapy had a shorter duration of vomiting and were far less likely to experience an early relapse. Other studies have suggested efficacy for ginger but no advantage for ondansetron over promethazine. For those with hyperemesis gravidarum that is resistant to those interventions, total parenteral or enteral nutrition may be necessary.

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