hyperprolactinemia via effects on pituitary regions served by a porous blood-brain barrier.

Refractory motility disorders pose significant challenges. Intestinal pseudoobstruction may respond to the somatostatin analogue octreotide, which induces propagative small-intestinal motor complexes. Acetylcholinesterase inhibitors such as pyridostigmine are also observed to benefit some patients with small-bowel dysmotility. Pyloric injections of botulinum toxin are reported in uncontrolled studies to reduce gastroparesis symptoms, but small controlled trials observe benefits no greater than sham treatments. Surgical pyloroplasty has improved symptoms in case series. Placing a feeding jejunostomy reduces hospitalizations and improves overall health in some patients with drug-refractory gastroparesis. Postvagotomy gastroparesis may improve with near-total gastric resection; similar operations are now being tried for other gastroparesis etiologies. Implanted gastric electrical stimulators may reduce symptoms, enhance nutrition, improve quality of life, and decrease health care expenditures in medication-refractory gastroparesis, but small controlled trials do not report convincing benefits.

SAFETY CONSIDERATIONS

Safety concerns about selected antiemetics have been emphasized. Centrally acting antidopaminergics, especially metoclopramide, can cause irreversible movement disorders such as tardive dyskinesia, particularly in older patients. This complication should be carefully explained and documented in the medical record. Some agents with antiemetic properties including domperidone, erythromycin, tricyclics, and 5-HT_3 antagonists can induce dangerous cardiac rhythm disturbances, especially in those with QTc interval prolongation on electrocardiography (ECG). Surveillance ECG testing has been advocated for some of these agents.

SELECTED CLINICAL SETTINGS

Some cancer chemotherapies are intensely emetogenic (Chap. 103e). Combining a 5-HT_3 antagonist, an NK_1 antagonist, and a glucocorticoid provides significant control of both acute and delayed vomiting after highly emetogenic chemotherapy. Unlike other drugs in the same class, the 5-HT_3 antagonist palonosetron exhibits efficacy at preventing delayed chemotherapy-induced vomiting. Benzodiazepines such as lorazepam can reduce anticipatory nausea and vomiting. Miscellaneous therapies with benefit in chemotherapy-induced emesis include cannabinoids, olanzapine, and alternative therapies like ginger. Most antiemetic regimens produce greater reductions in vomiting than in nausea.

Clinicians should exercise caution in managing pregnant patients with nausea. Studies of the teratogenic effects of antiemetic agents provide conflicting results. Few controlled trials have been performed in nausea of pregnancy. Antihistamines such as meclizine and doxylamine, antidopaminergics such as prochlorperazine, and antiserotonergics such as ondansetron demonstrate limited efficacy. Some obstetricians offer alternative therapies such as pyridoxine, acupressure, or ginger.

Managing cyclic vomiting syndrome is a challenge. Prophylaxis with tricyclic antidepressants, cyproheptadine, or β-adrenoceptor antagonists can reduce the severity and frequency of attacks. Intravenous 5-HT_3 antagonists combined with the sedating effects of a benzodiazepine like lorazepam are a mainstay of treatment of acute flares. Small studies report benefits with antimigraine agents, including the 5-HT_1 agonist sumatriptan, as well as selected anticonvulsants such as zonisamide and levetiracetam.

INDIGESTION

MECHANISMS

The most common causes of indigestion are gastroesophageal reflux and functional dyspepsia. Other cases are a consequence of organic illness.

Gastroesophageal Reflux Gastroesophageal reflux results from many physiologic defects. Reduced lower esophageal sphincter (LES) tone contributes to reflux in scleroderma and pregnancy and may be a factor in some patients without systemic illness. Others exhibit frequent transient LES relaxations (TLESRs) that cause bathing of the esophagus by acid or nonacidic fluid. Overeating and aerophagia override the barrier function of the LES, whereas reductions in esophageal body motility or salivary secretion prolong fluid exposure. Increased intragastric pressure promotes gastroesophageal reflux in obesity. The role of hiatal hernias is controversial—most reflux patients have hiatal hernias, but most with hiatal hernias do not have excess heartburn.

Gastric Motor Dysfunction Disturbed gastric motility may contribute to gastroesophageal reflux in up to one-third of cases. Delayed gastric emptying is also found in ~30% of functional dyspeptics. Conversely, some dyspeptics exhibit rapid gastric emptying. The relation of these defects to symptom induction is uncertain; studies show poor correlation between symptom severity and degrees of motor dysfunction. Impaired gastric fundus relaxation after eating (i.e., accommodation) may underlie selected dyspeptic symptoms like bloating, nausea, and early satiety in ~40% of patients.

Visceral Afferent Hypersensitivity Disturbed gastric sensation is another pathogenic factor in functional dyspepsia. Visceral hypersensitivity was first reported in IBS with demonstration of heightened perception of rectal balloon inflation without changes in compliance. Similarly, ~35% of dyspeptic patients note discomfort with fundic distention to lower pressures than healthy controls. Others with dyspepsia exhibit hypersensitivity to chemical stimulation with capsaicin or with acid or lipid exposure in the duodenum. Some individuals with functional heartburn without increased acid or nonacid reflux are believed to have heightened perception of normal esophageal pH and volume.

Other Factors *Helicobacter pylori* has a clear etiologic role in peptic ulcer disease, but ulcers cause a minority of dyspepsia cases. *H. pylori* is a minor factor in the genesis of functional dyspepsia. Functional dyspepsia is associated with chronic fatigue, produces reduced physical and mental well-being, and is exacerbated by stress. Anxiety, depression, and somatization may have contributing roles in some cases. Functional MRI studies show increased activation of several brain regions, emphasizing contributions from central nervous system factors. Analgesics cause dyspepsia, whereas nitrates, calcium channel blockers, theophylline, and progesterone promote gastroesophageal reflux. Other stimuli that induce reflux include ethanol, tobacco, and caffeine via LES relaxation. Genetic factors may promote development of reflux and dyspepsia.

DIFFERENTIAL DIAGNOSIS

Gastroesophageal Reflux Disease Gastroesophageal reflux disease (GERD) is prevalent. Heartburn is reported once monthly by 40% of Americans and daily by 7–10%. Most cases of heartburn occur because of excess acid reflux, but reflux of nonacidic fluid produces similar symptoms. Alkaline reflux esophagitis produces GERD-like symptoms most often in patients who have had surgery for peptic ulcer disease. Ten percent of patients with heartburn exhibit normal esophageal acid exposure and no increase in nonacidic reflux (functional heartburn).

Functional Dyspepsia Nearly 25% of the populace has dyspepsia at least six times yearly, but only 10–20% present to clinicians. Functional dyspepsia, the cause of symptoms in >60% of dyspeptic patients, is defined as ≥3 months of bothersome postprandial fullness, early satiety, or epigastric pain or burning with symptom onset at least 6 months before diagnosis in the absence of organic cause. Functional dyspepsia is subdivided into postprandial distress syndrome, characterized by meal-induced fullness, early satiety, and discomfort, and epigastric pain syndrome, which presents with epigastric burning pain unrelated to meals. Most cases follow a benign course, but some with *H. pylori* infection or on nonsteroidal anti-inflammatory drugs