Chronic Idiopathic Nausea
Katja Kovacic, MD; and Gisela Chelimsky, MD

Abstract
Chronic nausea is a prevalent but poorly described symptom in adolescents. It often co-occurs with other functional gastrointestinal disorders (FGIDs) but may also present in isolation. A multitude of triggers and complex neural pathways underlie the sensation of nausea. These include gastrointestinal and blood-borne insults, dysmotility, vestibular or central nervous system pathways, an aberrant autonomic nervous system, and psychosocial factors. Although clinical algorithms are lacking, diagnosis is typically made on the basis of a thorough clinical history and without extensive testing. Treatment is mainly empiric and may be directed at comorbid symptoms such as migraine, delayed gastric emptying, orthostatic intolerance, and visceral hypersensitivity. Chronic idiopathic nausea is an increasingly prevalent symptom that needs careful clinical assessment and individualized treatment plans.

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C hildhood chronic idiopathic nausea is a poorly defined entity. Nausea is typically defined as a subjective, unpleasant sensation that often precedes vomiting but may occur in isolation and on a chronic basis. This wave-like, aversive feeling is usually referred to in the stomach, but some individuals perceive it in the back of the throat or head.\textsuperscript{1} The non-specific nature of this complaint plays part in the difficulties measuring and defining nausea. Various triggers such as toxins, drugs, inflammation, infection, mucosal injury, hormones, visceral pain, and motion, as well as memories, anxiety, and emotions, may induce nausea. Nausea inhibits further food intake in the setting of toxin ingestion, medical pathology, or physical stress. Nausea may serve as a forewarning to protect an individual from a toxin or other type of bodily insult and has a role in learned aversions to offending substances.\textsuperscript{2} Given the many triggers and causes of nausea, surprisingly little is known about the physiological mechanisms underlying the perception of nausea. When no clear cause is found, chronic nausea is often termed “functional nausea.”

**PREVALENCE**

Many children and adolescents experience refractory nausea of unclear etiology, and the nauseous teenager is a common referral reason to general pediatricians and pediatric subspecialists. Twenty-three percent (range 13% to 41%) of healthy adolescents suffer from weekly nausea based on a large, school-based study of abdominal pain and related gastrointestinal (GI) complaints. Interestingly, nausea was more common in females than in males.\textsuperscript{3} In a study on pain-associated, functional gastrointestinal disorders (FGIDs), chronic nausea was a frequent secondary complaint, occurring at least twice weekly in 53% and daily in 28% of children.\textsuperscript{4} Data from our institution indicate that chronic nausea is common both as a primary complaint and in conjunction with other FGIDs. Predominantly adolescent females with primary chronic nausea also have features of migraines, cyclic vomiting syndrome (CVS), and postural tachycardia syndrome (POTS). In this descriptive study, nearly half of the chronic nausea cohort received a clinical diagnosis of “functional nausea,” despite the lack of such an established classification.\textsuperscript{5} Even with a high prevalence of nausea in children, chronic idiopathic nausea (CIN) is a disorder still classified only by the adult Rome III criteria.

**ROME CLASSIFICATION**

Adult Rome III criteria define CIN as bothersome nausea occurring several times per week, typically not associated with vomiting, and without any identifiable organic cause.\textsuperscript{6} In the adult 2006 Rome III criteria, CIN was classified under the category of functional nausea and vomiting disorders, along with functional vomiting and CVS (Table 1).\textsuperscript{7} In the past, adult Rome II criteria categorized nausea as a symptom of dyspepsia. The pediatric Rome III criteria do not recognize CIN as a separate category even though children may suffer from chronic nausea that becomes their primary complaint. Since descriptive studies and clinical algorithms are lacking, patients often undergo extensive testing to elucidate an organic cause of the nausea. When no cause is identified, treatment is mainly empiric and often targeted to other co-morbid symptoms such as abdominal pain, dyspepsia, or even constipation. Chronic idiopathic nausea is thus both a diagnostic and therapeutic challenge for medical providers.

**PATHOPHYSIOLOGY**

The classical brain inputs that induce vomiting, and presumably also nausea, are fairly well-characterized. At least four afferent pathways mediate the inputs for nausea and vomiting. These include the GI tract vagal afferents (chemo- and mechanoreceptors respond to noxious substances and changes in wall tension), systemic blood exposure of drugs and toxins (via area postrema), vestibular inputs by real or apparent motion, and the upper central nervous system (e.g., stress, increased intracranial pressure). Although all these afferent pathways seem to be distinct, they all converge on the nucleus tractus solitarius (NTS) in the brainstem.\textsuperscript{3} The limbic system, including the cingulate cortex, also has inputs to the NTS and in this way, emetogenic signals are thought to influence the autonomic nervous system. The NTS is not a simple brainstem relay nucleus for information. It has plasticity and receives descending modulation inputs from higher brain structures (hypothalamus, limbic, and vestibular system) along with modulation by gut hormones and a variety of afferent inputs.\textsuperscript{1,8} A complex, interconnected neurocircuitry is thus involved in the input signals for vomiting and perhaps nausea. Output neurons from the NTS are activated in sequence, which is best understood as a central pattern generator that coordinates emesis, rather than the concept of a simple “vomiting center.”\textsuperscript{9} The areas involved in emesis are traditionally also associated with nausea. However, although the emetic input signals are relatively well-understood, the neural network involving nausea and the output pathways for nausea and vomiting are still largely unknown.

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In a study on pain-associated, functional gastrointestinal disorders (FGIDs), chronic nausea was a frequent secondary complaint.
Recent functional MRI studies have described the brain circuitry involved in motion-induced nausea, supporting limbic, and subcortical mechanisms. Phasic brain activation during transition to strong nausea was noted in brain regions known to process stress, emotion, and fear conditioning (amygdala, ventral putamen, and dorsal pons/locus ceruleus). A broader network of brain areas showed sustained activation during strong nausea, suggesting that nausea is a multidimensional state involving several brain regions, including limbic and subcortical areas. No activation was found in several cerebellar and medullary (NTS and area postrema) nuclei. These findings may refute the classical thinking of nausea as simply one part of the emetic pathway. However, these data were based on motion-induced nausea and may not translate to other triggers of nausea (ie, drugs, illness, dysmotility, emotions, lightheadedness, etc.). Further studies are needed to elucidate the role of the NTS and to understand if the neural connections are different depending on the origin of the nausea.

Autonomic outflow is an important factor in the perception of nausea, as subjects experiencing nausea display signs of increased sympathetic activity (pulsations, diaphoresis, pupillary dilation, and salivation). Studies on sympathovagal balance in the perception of nausea are somewhat conflicting but indicate a gradual sympathetic activation with increased nausea, gastric tachyarrhythmias, and transient increases in vagal tone before flushes of strong nausea (motion-induced). Autonomic dysfunction is well-described in association with functional GI complaints, including nausea. A descriptive study by Sullivan et al. reported associations between orthostatic intolerance and chronic GI complaints including nausea, with resolution of symptoms upon treatment of orthostasis. This association suggests that nausea in conjunction with symptoms such as lightheadedness, dizziness, fatigue, mental clouding, and headaches (mainly when triggered in the upright position) could be a manifestation of autonomic dysfunction.

Nausea is also one of several symptoms associated with delayed gastric emptying. Gastroparesis is a symptomatic disorder characterized by delayed gastric emptying and several non-specific GI symptoms: nausea, vomiting, early satiety, bloating, and abdominal discomfort. In a larger study of adult patients with gastroparesis, nausea was the most prevalent symptom (92%). A recent pediatric study found that nausea was the only symptom that predicted delayed gastric emptying. Other symptoms classically associated with gastroparesis (vomiting, fullness, bloating, abdominal pain) did not correlate with delayed gastric emptying by 4-hour gastric emptying scintigraphy. Nausea due to functional dyspepsia may be difficult to differentiate from nausea associated with gastroparesis, as symptoms may overlap. Many patients with dyspepsia have both nausea and delayed gastric emptying. However, chronic nausea may not be their primary symptom as other symptoms (ie, early satiety, fullness, epigastric discomfort) often predominate. Although delayed gastric emptying may be a factor in patients with isolated chronic nausea, it is yet unclear if this is a major pathophysiological finding or just another comorbid problem.

Gastric electrical stimulation is used successfully in adults with refractory nausea and vomiting due to gastroparesis. As few therapeutic alternatives exist for medically refractory chronic nausea (+/- vomiting), gastric electrical stimulation is emerging as a new treatment modality in children. Data on symptom improvement for nausea and vomiting are promising, although several studies have not shown a concomitant improvement in gastric emptying. However, there is growing evidence of poor symptom correlation with the rate of gastric emptying. Similarly, some patients improve on prokinetics with lack of objective changes in gastric emptying. Furthermore, the exact mechanisms of high-frequency gastric stimulation are still unclear, but it has potential effects on gastric tone and accommodation, and perhaps central nerve pathways.

**DIAGNOSIS**

The subjective nature of the perception of nausea and the multitude of triggers and possible etiologies presents a diagnostic challenge. Evaluation often overlaps with investigations performed for recurrent vomiting, and similar to vomiting, chronic nausea can be due to disorders involving multiple systems. These may include the GI tract (inflammatory mucosal disorders, infections, dysmotility), hepatobiliary tract (cholelithiasis, gallbladder dyskinesia, hepatitis), kidneys (uremia, electrolyte disturbances), brain (migraine, dysautonomia, malignancies), and many systemic illnesses (autoimmune disorders, drug-induced, etc.). Retrospective data indicate that extensive diagnostic testing may be unnecessary in an otherwise healthy adolescent with features of migraines, early-morning symptoms, and/or other functional GI symptoms. The yield of endoscopic evaluation (98% normal) and imaging studies is remarkably low and may only result in family distrust with the final diagno-

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**TABLE 1.**

**Adult Rome III 2006 Classification**

<table>
<thead>
<tr>
<th>Adult Rome III Criteria: Nausea and Vomiting Disorders</th>
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<tbody>
<tr>
<td>Chronic Idiopathic Nausea (CIN)</td>
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<td>Cyclic Vomiting Syndromes (CVS)</td>
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**Vomiting Disorders**

Adult Rome III 2006 Criteria:

- Nausea and vomiting due to gastroparesis
- Gastroparesis
- Gastroparesis (vomiting, fullness, bloating, abdominal pain)
- Delayed gastric emptying
- Gastroparesis (vomiting, fullness, bloating, abdominal pain) does not correlate with delayed gastric emptying by 4-hour gastric emptying scintigraphy
- Nausea due to functional dyspepsia may be difficult to differentiate from nausea associated with gastroparesis
- Symptoms may overlap
- Many patients with dyspepsia have both nausea and delayed gastric emptying
- Chronic nausea may not be their primary symptom as other symptoms (early satiety, fullness, epigastric discomfort) often predominate
- Although delayed gastric emptying may be a factor in patients with isolated chronic nausea, it is yet unclear if this is a major pathophysiological finding or just another comorbid problem

**Gastric electrical stimulation**

- Used successfully in adults with refractory nausea and vomiting due to gastroparesis
- As few therapeutic alternatives exist for medically refractory chronic nausea (+/- vomiting)
- Gastric electrical stimulation is emerging as a new treatment modality in children
- Data on symptom improvement for nausea and vomiting are promising, although several studies have not shown a concomitant improvement in gastric emptying
- However, there is growing evidence of poor symptom correlation with the rate of gastric emptying
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sis when no specific etiology is found. When testing does not reveal a medical diagnosis, the disorder is often termed “functional nausea,” which appears to affect mainly adolescent females. A thorough clinical history that includes a detailed review of systems is thus essential to exclude organic pathology. In addition to the characteristics of nausea (intensity, frequency, post-prandial, time of day, triggers), physicians should inquire about associated GI symptoms including but not limited to: abdominal pain and location, stooling pattern, associated vomiting, bloating, early satiety, post-prandial fullness, heartburn, and regurgitation. In our experience, important extra-intestinal symptoms to assess include: presence of migraine headaches, sleep disturbances, anxiety/depression, social stressors, chronic fatigue, musculoskeletal pain, and orthostatic symptoms (lightheadedness, palpitations, etc.) Family history of migraines, FGIDs, orthostatic intolerance, and psychiatric disorders are also important to assess. In the absence of red flags (anemia, blood in stool, weight loss, morning vomiting, neurological signs), and if clinical history supports a functional disorder of chronic nature, a diagnosis of chronic idiopathic nausea can likely be entertained without an extensive medical work-up.

TREATMENT

Although treatment should be directed at the underlying cause, if no etiology is found, there are no published treatment trials on chronic nausea to serve as guidance. Like other functional disorders, chronic nausea is often associated with school disability. The primary goal is to maintain school attendance and physical activity despite symptoms. This often requires an interdisciplinary approach that may include a psychologist to help cope with various social stressors. If stressors are thought to cause or exacerbate symptoms, treatment strategies can include cognitive-behavioral therapy, relaxation techniques, hypnotherapy, and biofeedback.

Medication trials may be warranted to reduce nausea and provide further diagnostic direction. Some of these include trials of acid suppression, antihistamines, 5-HT3 antagonists, ginger, prokinetics, treatment of orthostatic intolerance, and anti-migraine therapies.

Forty-four percent of children with chronic idiopathic nausea had good response to amitriptyline.

Low-dose tricyclic antidepressants (TCAs) with anti-migraine properties (amitriptyline, doxepin) have been used to treat functional GI disorders for many years. Based on the plausible relationship between migraines and functional GI disorders such as CVS, and the association between chronic nausea and migraines, anti-migraine therapy may be an effective treatment option. Based on retrospective data, 44% of children with chronic idiopathic nausea had good response (at least 50% improvement) to amitriptyline at a mean dose of 50 mg nightly. Although the pharmacologic mechanisms are unclear, amitriptyline acts as a serotonin agonist and affects both norepinephrine and serotonin-mediated nerve pathways, in addition to having strong anticholinergic effects. Amitriptyline appears to have visceral analgesic properties and may influence several of the pathways involved in regulation of the emetic reflex. In our clinical experience, TCAs (amitriptyline 0.5 mg/kg to 1 mg/kg nightly) have moderate efficacy in chronic nausea, but the mechanisms are unclear. TCAs may improve abdominal pain, migraines, sleep disturbances, and anxiety and perhaps decrease the perception of nausea. As amitriptyline is potentially associated with increased QT segment, and since QT prolongation is present in many healthy children, many centers perform electrocardiogram prior to initiation, while increasing the dose and upon reaching the final dose of the TCA.

Similarly, cyproheptadine is an agent with established efficacy for anti-migraine prophylaxis and the treatment of functional GI disorders. Likewise, cyproheptadine has multiple pharmacologic properties, including antihistamine and antiserotonin effects. It is unclear which mechanism influences upper GI symptoms, but its effectiveness in treating children with dyspepsia and antinomism on 5-HT2A and/or 5-HT2B receptors in the gastric fundus may improve gastric accommodation and reduce the hypersensitivity to distention noted in some children with functional abdominal pain. Cyproheptadine also exerts appetite-stimulating effects, which may help alleviate nausea.

If delayed gastric emptying is a factor contributing to the nausea, a trial of prokinetics such as low-dose erythromycin (3 mg/kg to 5 mg/kg orally four times daily) may be beneficial. Prokinetic agents may improve the contractility of stomach antrum and correct gastric dysrhythmias. Some prokinetic agents (metoclopramide, domperidone) also have antiemetic properties, but side effects (tardive dyskinesia with metoclopramide, cardiac arrhythmias, and hyperprolactinemia with domperidone) and availability limit their usefulness. Erythromycin (mainly the intravenous form) may cause QT prolongation. Drug interactions with erythromycin must be carefully considered, especially with medications that inhibit CYP3A4, which may potentiate side effects. If delayed gastric emptying is suspected, dietary interventions with low fat and fiber intake can be tried, as these retard gastric emptying. Liquid calories in the form of supple-
mental nutrient drinks are likely better tolerated, as liquid emptying is often preserved in patients with delayed gastric emptying of solids.16

Alternative medications have some proven benefit in a variety of functional GI disorders. Several studies have found ginger effective for nausea of diverse causes such as motion sickness, morning sickness of pregnancy, and postoperative nausea. A systematic review of six randomized, controlled trials of ginger found that 1 g daily reduced nausea compared to placebo in the majority of cases.42 Proposed actions of ginger include improved GI motility,43 5-HT3 antagonism, and possible CNS effects.42 STW 5 is a combination herbal remedy with proven benefits in functional dyspepsia and irritable bowel syndrome. Although, with high placebo effects, multiple clinical trials (two in children) have shown significant efficacy for upper GI symptoms. Some of these have shown comparable efficacy to standard prokinetics. Adverse effects are uncommon (0.04%) and mainly include increased gastrointestinal complaints, hypersensitivity, skin rash, alopecia, and hypertension. No serious adverse effects have been reported. However, although used in Europe, this drug is not yet approved for use in the United States.44

If identified, treatment of orthostatic dysfunction may alleviate chronic nausea. In our experience, simple measures such as increased hydration, life-style changes with adequate sleep, regular exercise, and a low-dose mineralocorticoid (fludrocortisone) may benefit some patients.

Treatment of chronic idiopathic nausea is often difficult and needs to be carefully individualized. However, a thorough history that addresses comorbid symptoms and attempts to pin-point possible mechanisms involved may be sufficient to find successful treatment and improve quality of life.17

REFERENCES


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