Kenneth L. Koch
William L. Hasler *Editors*

Nausea and Vomiting

Diagnosis and Treatment

Springer

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This book is dedicated to my wife Elizabeth who has supported my work day in and day out for many years and for my patients with chronic nausea and vomiting who have encouraged me to continue to try to help them.

Kenneth L. Koch, MD

I dedicate this book to my wife Michelle, also an academic gastroenterologist, who supports and challenges me to be a better doctor, investigator, husband, and father to our three children.

William L. Hasler, MD

Foreword

It is particularly appropriate to begin a book devoted to the diagnosis and treatment of nausea and vomiting with a "Foreword" as the word derives for the fore (bow or prow) part of ship which is possibly the worst place to be for the induction of seasickness.

Although nausea and vomiting are very common symptoms of diverse disorders, they tend to be relatively neglected in contrast to pain; vomiting may be dramatic and demand immediate attention, but nausea is often insidious in onset with little external manifestation in contrast to acute onset abdominal or chest pain. In contrast to pain, nausea and vomiting may be also be considered to be of lesser clinical significance and the impact on patient quality of life may be underestimated. The clinical significance of nausea and vomiting associated with cancer chemotherapy (CINV), anaesthesia and surgery (post-operative nausea and vomiting, PONV) and pregnancy (first trimester and *hyperemesis gravidarum*) are well recognised and have had entire books dedicated to them so are omitted from this volume. The focus of this book is the relatively neglected (but often common) clinical conditions where nausea and vomiting are prominent symptoms.

This book has a primarily clinical diagnostic and treatment focus that is reflected by the editors who are both eminent researchers in nausea and vomiting. The range of health care professions represented by the authors emphasised the multi-system nature of nausea and vomiting and the multi-profession approach to diagnosis and treatment. Health care professionals and patients are the primary audience with this book aiming to be of practical help. The wealth of illustrations and particularly the diagrams illustrating normal and disordered gastric emptying are particularly helpful in understanding what is happening in the abdomen when a patient reports nausea.

Despite the clinical focus, this book should be consulted by those more interested in basic mechanisms as the detailed descriptions of a wide range of clinical problems challenge researchers to provide credible mechanistic explanations; for example, the question of "where is nausea perceived" is fundamental to understanding the significance of nausea as a symptom reported by patients, but convincing mechanistic explanations for the diversity of reporting are lacking. The question of whether there is more than one type of nausea also requires resolution, and this book provides insights into this recurrent pivotal question, but consideration of this question also reveals that techniques for the objective measurement of nausea that do not rely on

self-reporting are lacking. Understanding the basic mechanisms underlying nausea and vomiting from diverse clinical causes is critical to identifying novel therapeutic approaches.

The topics covered by the 15 chapters provide a wide-ranging view of the causes of nausea and vomiting that have a significant impact on patient quality of life and for which fully effective treatment is not always available. The chapters cover the expected digestive tract disorders associated with nausea and vomiting but also review the less commonly considered endocrine, central nervous system and autonomic nervous system disorders. The inclusion of a chapter on pharmacological causes of nausea and vomiting is notable as outside the effects of chemotherapy and anaesthesia therapeutic agents are often overlooked and yet can affect patient compliance for a range of disorders. Understanding why some treatments, but not others, induce nausea is a challenging question with implications for the development of novel pharmacological therapies where there is an unmet need in many areas. The inclusion of a chapter focusing on the paediatric patient draws attention to a relatively neglected group and to the syndrome of cyclical vomiting. The chapter on the psychophysiology of nausea and vomiting provides a reminder of inter-individual differences which need to be taken into account when considering patients' reports of their symptoms in relation to objective clinical measures and in understanding why treatment efficacy may differ between patients with apparently similar presentations.

Anti-emetics were classically based on antagonism of histamine$_1$, muscarinic and dopamine$_2$ receptor antagonism and more recently 5-hydroxytryptamine$_3$ and neurokinin$_1$ receptor antagonists which are particularly effective for CINV and PONV. However, for several of the disorders covered in this book, pharmacological interventions are not very effective. The inclusion of chapters on nutritional management, complementary and alternative medicine and gastric electrical stimulation and acustimulation draws attention to other approaches to treatment on nausea and vomiting which may have broader applications. Even with pharmacological therapies, treatment of nausea remains more challenging than treatment of vomiting and this reflects our relative lack of understanding of the neuropharmacology of nausea as opposed to vomiting.

This book makes an important contribution to understanding some of the more neglected clinical causes of nausea and vomiting and provides a wealth of information and insights that will assist health professionals in diagnosis and treatment of these symptoms which impact patient quality of life and cause concern to their carers.

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Preface

How many nauseas are there? One of the editors was interviewing a patient who was referred for consultation for chronic unexplained nausea with occasional vomiting. Her extensive workup to that point had failed to reveal a cause of nausea. She seemed to be a normal 17-year-old who was in the office with her mother. At an early point in the interview, I said, "Tell me about your nausea." To this question she replied, "Which one?" At the time, I was rather taken aback and so I asked, "How many nauseas do you have?" To my question she replied, "Seven."

As you read the chapters in this book, we hope you will come to appreciate that indeed there are probably at least seven kinds of nausea and certainly, in fact, many, many more mechanisms of pathways to nausea. Nausea is a ubiquitous symptom that even healthy individuals experience in some form or another. But nausea is usually evoked for the safety of the individual and is limited in duration. For example, nausea is elicited in many healthy people in an environment of motion where visual, vestibular, and proprioceptive neurosensory pathways are either overwhelmed or are fooled by the illusion of motion, all of which evokes nausea that ranges from mild to severe and may include vomiting. In these stressful environments of motion, nausea is a symptom that causes the subject to be still, lie down, and seek a motionless environment. Unfortunately, this can be very difficult on a cruise ship in turbulent seas!

Nausea also has a protective function during every individual's ongoing search for nourishment. Even in societies with relatively safe food and packaging processes, there are many dangers in regard to ingesting contaminated foods. If the contaminated food passes visual, olfactory, and gustatory surveillance and is ingested, then there is still the gastrointestinal tract to provide another level of protection by eliciting nausea and then vomiting to expel ingested poisons or toxins. Most human beings have experienced this type of protective nausea and vomiting.

Finally, nausea serves an alarm function alerting us to diseases and disorders in almost every organ system of the body. Nausea as a signal of impeding or ongoing organ dysfunction or disease is probably more common than pain. Every physician or allied health provider has taken care of patients with acute or chronic nausea and vomiting for which the patient seeks treatment and hopefully a specific diagnosis. But to the health care provider, a patient's report of nausea can be an extremely nonspecific symptom. To decipher a specific mechanism of the nausea and a specific diagnosis and treatment can

be difficult, and health care providers can become frustrated when first-line medications fail to control nausea or vomiting.

In *Nausea and Vomiting: Mechanisms and Treatments*, a unique and hopefully helpful approach to these symptoms is provided for health care providers, patients, and others interested in these common symptoms. First, the physiology of nausea and the physiology of vomiting are separated into their own chapters to highlight the differences in this symptom (nausea) and this sign (vomiting) and perhaps stimulate thinking of the two differently. In many conditions if nausea could be controlled or prevented, then perhaps vomiting could be eliminated altogether where nausea (and vomiting) serves no protective function but only adds to suffering.

Secondly, clinical features of nausea and vomiting are reviewed in separate organ-based chapters. For example, nausea related to esophageal diseases and disorders is separated from nausea related to small bowel or gastric disorders or other organs in the gastrointestinal system. Central nervous system and autonomic nervous system diseases and disorders are also associated or cause nausea and vomiting, and these are reviewed in other chapters. In at least some respects, nausea is localizable in the body as shown by preliminary studies using a nausea locator diagram. Nausea and vomiting represent brain-gut and gut-brain interactions needs more study within the large neuroscience umbrella. There is much to learn in regard to the multiple pathways to multiple nauseas. Because the problem of nausea and vomiting is so extensive, we chose to limit the review to some extent and did not address chemotherapy-induced nausea and vomiting, postoperative nausea and vomiting, and the nausea and vomiting of motion sickness.

Treatments for nausea and vomiting remain problematic. For the most part, drug treatments are very nonspecific. Even receptor-specific drugs such as the $5HT_3$ receptor antagonist do not help all patients. Furthermore, some very successful therapies for vomiting have limited benefits to reduce nausea. A comprehensive approach to treatments for nausea, especially chronic nausea, is presented and ranges from nutritional support to drugs to devices and complementary medicines. By carefully interviewing the patient in terms of various qualities of nausea and vomiting, it is hoped a specific pathophysiologic mechanism can be identified which then leads to more specific treatment of the nausea and vomiting that is based on pathophysiological mechanisms.

The editors thank each of the experts who contributed to this book. We hope that the information in these chapters stimulates each reader to appreciate the pathophysiological mechanisms that underlie different pathways to nausea and vomiting. When these pathways can be identified, nausea can be treated better now, today, and much better in the future as more physiological research in nausea and vomiting is carried out and more pathophysiological-based therapies are developed. The suffering associated with chronic unexplained or explained nausea and vomiting is often profound. We hope efforts to understand nausea and vomiting and to develop better treatments will be stimulated by this book.

Sincerely,
Kenneth L. Koch, MD
William L. Hasler, MD

Contents

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Dr. Kenneth Koch is a Professor of Internal Medicine and Head, Section on Gastroenterology at Wake Forest School of Medicine. He completed his undergraduate and medical school degrees at the University of Iowa, Internal Medicine training at Milton S. Hershey Medical Center of Pennsylvania State University, and fellowship in gastroenterology at the University of Florida. Dr. Koch's clinical and research interests include the pathophysiology of nausea and vomiting, gastroparesis, gastric dysrhythmias, and functional dyspepsia. He has authored numerous original works, chapters, and other contributions to the GI literature. Dr. Koch was selected as one of the "Best Doctors in America."

Dr. William Hasler is a Professor in the Division of Gastroenterology in the Department of Internal Medicine at the University of Michigan Health System. He completed his undergraduate degree at the Massachusetts Institute of Technology, his medical school training at the University of Pennsylvania, and his internal medicine residency and gastroenterology fellowship at the University of Michigan. Dr. Hasler's clinical practice focuses on care of gastrointestinal dysmotility including gastroparesis, cyclic vomiting, intestinal pseudoobstruction, and chronic unexplained nausea and vomiting. His research interests center on the pathophysiology of nausea and vomiting and gut transit and sensory abnormalities. Dr. Hasler has authored numerous original works on these areas.

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Physiology of Nausea

1

Kenneth L. Koch

Introduction

Nausea is commonly defined as an unpleasant and noxious feeling in the pit of the stomach that precedes vomiting, but in a recent book on the subject, over 33 different definitions of nausea were listed by physicians and scientists [1]. Patients also have difficulty describing their nausea [1]. Thus, nausea is a peculiar sensation and symptom that is difficult to put into words and to simply define. Interestingly, nausea is perceived in different locations. Patients with chronic nausea and vomiting who were seen in a gastroenterology clinic were asked to indicate on a figure where on their bodies they felt their nausea was located. Table 1.1 shows that 35 % of these patients located their nausea in the epigastrium and substernal area, 12 % in the substernal area only, 31 % in the epigastrium only, 16 % in the periumbilical area, 4 % in the lower abdomen, and only 1 % in their head [2]. These patient-reported locations of nausea suggest that not only the stomach but also the esophagus, small bowel, and colon may be the organs that are relevant to generating the symptom of nausea. Thus, nausea is a noxious, sickening feeling that often precedes vomiting and is commonly located in the abdomen but also in the chest or other areas of the body. Other important attributes of nausea include fatigue, depression, and anxiety characterized as gastrointestinal, somatic, and emotional elements and comprising a nausea profile [3].

Why do we experience nausea? From a homeostasis viewpoint, nausea is a warning signal of (a) danger in the external environment often related to food or motion, and (b) damage or dysfunction in an area or areas of the internal milieu related to digestive tract organs and other organ systems. For example, nausea protects the organism from ingesting potentially harmful foods. The external cues that stimulate nausea include the sight of food that evokes disgust, the smell of foods that evoke disgust, and the taste of bitter foods that evoke disgust. These disgusting, visual, olfactory, and taste stimuli result in or are associated with nausea and protect the individual from ingesting foods that may in fact contain poisons or toxins.

Various movements of the body or the illusions of movement are external stimuli during which otherwise healthy individuals may develop nausea. During movement or during the illusion of movement, visual, vestibular, and proprioceptive sensory organs are stimulated (and/or mismatched) and result in nausea that ranges from mild to severe in susceptible individuals [4].

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Table 1.1 The nausea locator: a vague visceral sensation is given a topographical representation by the patient

Location of nausea	Percentage of patients
Epigastrium only	31
Epigastrium + substernal	35
Periumbilical	16
Substernal only	12
Lower abdomen	4
Head	1

Racial and gender differences contribute to susceptibility to motion sickness. For example, subjects of Asian ancestry are much more susceptible to the illusion of motion than Caucasians or African Americans [5, 6].

In regards to the internal milieu, ingested foods can elicit nausea and vomiting once they have entered the esophagus, stomach, duodenum, and small intestine. If vagal afferent nerves in the mucosa of these organs are activated by noxious foods or food-related toxins, then nausea and vomiting are elicited to expel the ingested harmful agents. Toxins that are absorbed through the gastrointestinal tract mucosa and enter the blood stream may be sensed in the area postrema and an additional level of defense, the central nervous system, is activated to stimulate nausea and vomiting [7].

Diseases of various organs of the digestive tract commonly result in nausea. Inflammation or obstruction in virtually every gastrointestinal (GI) organ, ranging from esophagitis to gastritis to small bowel bacterial overgrowth to constipation, can stimulate some degree of nausea. Most GI diseases that present with nausea also present with some degree of abdominal discomfort or pain. The noxiousness of nausea is very different from the noxiousness of visceral or somatic pain. Somatic pain is localized, the cause more obvious and treatments more available compared with visceral pain, which is usually difficult to localize to specific organs in the digestive tract and may be difficult to diagnose and treat. Nausea has similarities to pain. Nausea comes in waves or is constant and unremitting and can occur during day or night. But nausea often disappears, at least temporarily, after vomiting. Nausea alone can overwhelm one's ability to think, to work, and to function, sapping energy and often forcing the individual to lie down, curl up, and strive to avoid moving and vomiting. In many patients, nausea may be difficult or impossible to reduce or to eradicate with drugs, devices, or complementary medicine approaches, all of which results in the irremediable suffering of nausea.

The physiology and pathophysiology of nausea are poorly understood, in part, because there are many different pathways to nausea. Treatment of nausea tends to be generic, and the specific mechanism driving the nausea is often unknown. Thus, current medications are often ineffective. The author recalls interviewing a patient with unexplained nausea and asking the patient to describe their nausea. The patient responded, "Which one?" to which the author replied, "How many do you have?" The patient thought for about one second and said, "Seven." The author was incredulous at the time, but clearly and certainly, individual patients can indeed suffer from several different types of nausea.

In this chapter, studies of the pathophysiology of nausea will be reviewed with an emphasis on associations of nausea and gastric neuromuscular dysfunction. Dysfunction in other GI organs can also cause nausea and an organ-based review of the peripheral and central mechanisms of nausea is a major purpose of this book. There are many mechanisms driving nausea. Ultimately, however, the stomach is the organ which is involved in any form of nausea that culminates in vomiting, whether the nausea was evoked by motion or food or disease.

The Physiology of Nausea: From Motion to Emotion

Nausea and Motion

The nausea of motion sickness occurs naturally in otherwise healthy people. In susceptible individuals, nausea is evoked during motion experienced in cars, trains, planes, ships, and microgravity. In addition, the illusion of motion experienced watching big screen or 3-D mov-

ies or in a laboratory-based rotating optokinetic drum can induce nausea, sweating and headache, and epigastric discomfort associated with motion sickness [4]. These motion or illusion of motion-induced symptoms are evoked acutely, but mimic in many ways the chronic nausea experienced by patients with GI diseases as discussed in later chapters.

The physiology of nausea, especially nausea related to motion sickness, can be studied in the controlled conditions of a laboratory. Nausea is reliably induced with a rotating, optokinetic drum (Fig. 1.1). The inner surface of the drum is painted with black and white stripes. The rotation of the drum at approximately ten revolutions per minute evokes the sensation of self-motion in one to two minutes. The illusion of motion is associated with the neurosensory mismatch of visual, vestibular, and proprioceptive afferent nerve inputs to the brain. This neurosensory mismatch creates stress for the organism in that there is conflict between the sensation of movement from visual stimuli and no actual movement from proprioception and vestibular sensory inputs to the brain. This is a critical computational problem for any organism. In susceptible subjects, the "stress" of the neurosensory mismatch during the illusion of body motion results in cold sweating, pallor, epigastric discomfort, and nausea [8]. When nausea escalates to an unacceptable intensity, the drum is stopped at the subject's request. After the drum rotation is stopped, visual, vestibular, and proprioceptive stimuli are congruent, homeostasis is reestablished, and nausea disappears.

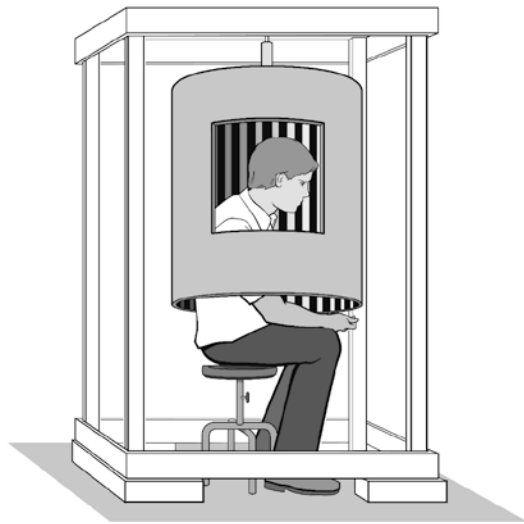

Fig. 1.1 Rotation of an optokinetic drum with black and white stripes on the inner surface evokes the illusion of self-motion and the nausea of motion sickness in susceptible subjects

During onset of nausea, the normal three cycles per minute (cpm) gastric myoelectrical activity (GMA) shifts to gastric dysrhythmias such as tachygastrias [4]. Tachygastrias are abnormal gastric electrical events ranging from 3.5 to 10 cpm [9]. Changes in GMA were studied in healthy subjects during optokinetic drum rotation. Subjects were positioned within the optokinetic drum. At baseline, the subjects had no nausea and normal 3 cpm GMA was recorded. In subjects who became nauseated during drum rotation, the normal GMA abruptly shifted to tachygastria (Fig. 1.2). During this time, parasympathetic tone decreased and sympathetic tone increased as shown by changes in heart rate variability and skin conductance measures [10, 11]. Nausea was reported by the subjects approximately one minute after the gastric dysrhythmias developed suggesting that the gastric dysrhythmia needed to be established for some duration of time before the change in gastric rhythm status was appreciated consciously as an unpleasant nausea sensation. Over the next ten minutes of drum rotation, nausea frequently increased in intensity and gastric dysrhythmias continued until the drum was stopped. During drum rotation, those subjects who became nauseated also had significantly increased plasma vasopressin, cortisol, and epinephrine compared with subjects who reported no nausea during drum rotation [12, 13]. Asian subjects had particularly intense nausea symptoms, more frequent vomiting episodes, and higher levels of vasopressin compared with African American and Caucasian subjects, indicating racial and genetic differences in susceptibility to nausea in these conditions [13]. Subjects who did not develop nausea during illusory self-motion remained in the 3 cpm GMA pattern (Fig. 1.2) and neurohormonal measures were similar to baseline. Thus, in this laboratory model of nausea, the

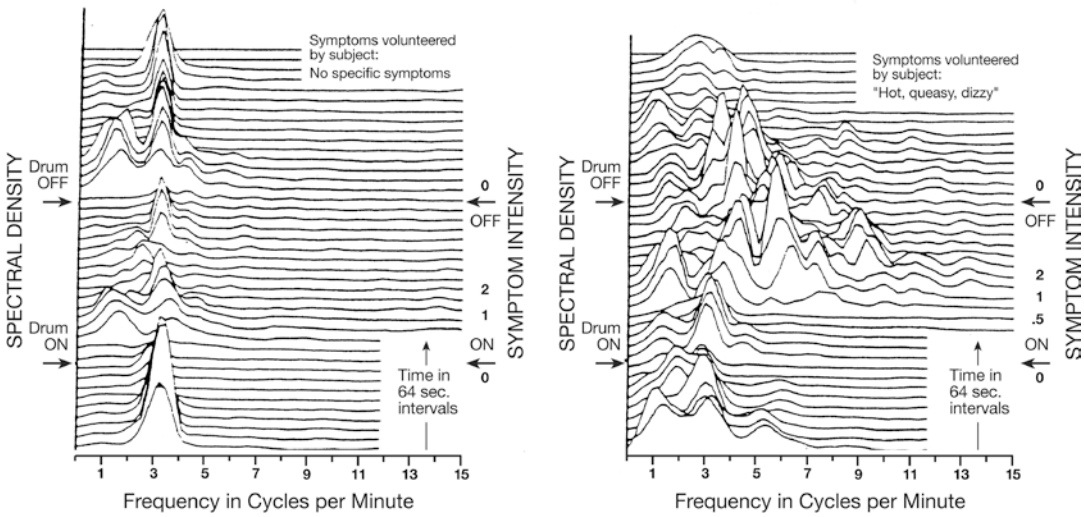

Fig. 1.2 Running spectral analyses of gastric myoelectrical activity (GMA) recorded before and after rotation of the optokinetic drum (Drum On). The left figure shows the running spectral analysis (RSA) of the GMA recorded from a subject who *did not* develop nausea during drum rotation. The *X*-axis is the frequency of the GMA, the *Y*-axis represents time, and the *Z*-axis shows the power of the frequencies. This subject remained in the normal 3 cpm GMA as shown by the peaks in the normal 3 cpm range and did not develop nausea. The right figure shows the RSA of GMA from a healthy subject who developed nausea during Drum On. GMA shifts from normal 3 cpm peaks to multiple peaks in the 3.5–9 cpm tachygastria range during drum rotation (Drum On) in the subject who became "queasy"

illusion of motion resulted in an acute neuroendocrine stress response and an acute peripheral gastric response—tachygastria.

The increase in epinephrine and cortisol indicated adrenal sympathetic nervous system activation and a stress response. The increase and subsequent decrease in vasopressin correlated with the increasing nausea during drum rotation and then the decreasing nausea symptoms after the drum was stopped. Increased vasopressin levels also occurred during nausea induced by morphine sulfate infusions [14]. Infusion of vasopressin also stimulates canine tachygastrias and results in delayed gastric emptying [15]. Thus, release of various neurotransmitters and hormones, such as vasopressin and epinephrine in addition to gastric dysrhythmias, have a role in the physiology of nausea.

Figure 1.3 illustrates central and peripheral neuro-gastric interactions during the induction of nausea based on studies of the nausea of motion sickness. There are several contributing central nervous system (CNS), hormonal, and GMA events involved in the nausea induced by motion. The nausea induced by motion represents stimulation of visual, vestibular, and proprioception sensory pathways that elicit sympathetic nervous system stress responses, but this is not the classic "fight or flight" sympathetic response that energizes subjects to spirited action. Rather, the stress response associated with nausea is accompanied by fatigue, efforts to avoid vomiting, and a strong desire to lie down and be still, the ultimate behavioral effects of nausea.

The stomach is a key peripheral organ in the physiology of nausea elicited during motion sickness. GMA normally ranges from 2.5 to 3.5 cpm in healthy subjects [16, 17]. When the interstitial cells of Cajal (ICCs), the gastric pacemaker cells, are present in normal numbers in the corpus and antrum of the stomach then the normal 3 cpm GMA is recorded by cutaneous and serosal myoelectrical recordings [16, 17]. Gastric enteric nerves, smooth muscle, parasympathetic and sympathetic inputs, and hormonal fluxes can temporarily affect ICC function and thus the rhythmicity of GMA. If activity in one or more neuro-hormonal elements is disturbed,

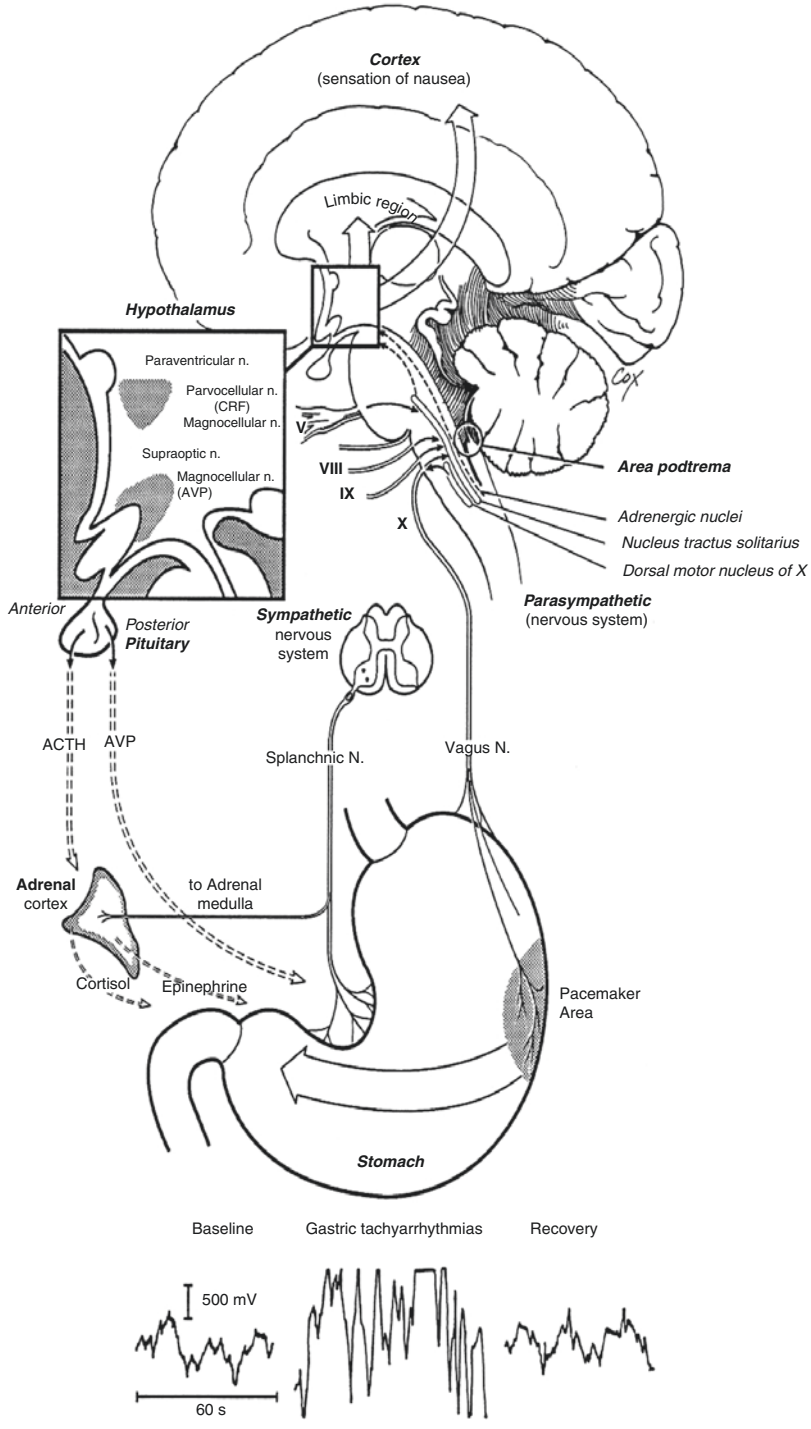

Fig. 1.3 Peripheral and central pathways activated during the shift from normal 3 cpm gastric myoelectrical activity (GMA) to tachygastria and CNS interactions during the nausea of motion sickness are shown. Tachygastria-related changes in vagal afferent activity are transmitted through the nucleus tractus solitarius to higher centers of the brain, ultimately reaching the cortex where nausea is recognized and reported by the subject. During motion sickness, increased levels of vasopressin are released from the posterior pituitary and increased epinephrine is released from the adrenal glands while the sympathetic nervous symptom tone increases, indicating a stress response. As homeostasis is reestablished after the drum is stopped, GMA returns to the normal 3 cpm pattern as shown in the electrogastrogram rhythm strips and nausea disappears

as during the development of in the nausea of motion sickness nausea, then a shift from normal 3 cpm GMA to gastric dysrhythmias occurs and nausea symptoms are experienced. The acute tachygastrias during the nausea of motion sickness develops in the setting of increased sympathetic activity and vagal withdrawal [10, 11]. The presence of the gastric dysrhythmias is necessary, but may not be sufficient to evoke nausea. Other factors such as the increase in epinephrine and vasopressin may also be needed for the full expression of nausea and related symptoms like cold sweating, dry mouth, etc. The presence of nausea is also associated with loss of gastric smooth muscle tone [18]. The change in gastric rhythm and tone affects vagal afferent activity and other sensory neurons within the wall of the gastric corpus and antrum [19]. These changes in GMA and tone during nausea are sensed by vagal afferent activity and transmitted to the nucleus tractus solitarius and higher brain centers. Ultimately, these peripheral inputs from the stomach reach the cortex and nausea is perceived and reported.

Nausea evoked during drum rotation usually proceeds from mild to severe over the course of time (15-min rotation limit), presumably due to an escalation of the stimulation or the neurohormonal responses described above [12, 13]. The pathophysiology of the escalation of nausea intensity is complex because countermeasures are continually evoked to attempt to regain homeostasis even as nausea intensity increases. Napadow et al. described areas in the brain using functional magnetic resonance imaging (fMRI) that are activated during illusory self-motion while patients described increasing severity of nausea [20]. During the transition from mild to moderate to severe nausea, more brain regions, including insular, anterior cingulate, orbitofrontal, somatosensory, and prefrontal cortices were activated. During strong nausea, the linkage of anterior insula and midcingulate was sustained. Activation of these diverse regions reflects the extensive physiological responses in blood pressure and respiratory changes and shifts in GMA that are intimately associated with nausea and the accompanying symptoms features. The exact sequence of the countermeasures in the autonomic nervous and endocrine systems in response to activation of these CNS areas have not been fully elucidated.

The progression from the state of feeling comfortable (and no nausea) to experiencing mild to severe nausea during the illusion of motion in a drum or in an fMRI device represents important laboratory-induced nausea conditions that have implications for understanding chronic nausea. Patients often have low intensity, intermittent nausea that then flares into severe acute episodes that are similar to the acute and severe nausea elicited by illusory self-motion. Therapeutic approaches to prevent or counteract the physiological responses that mediate acute nausea may be helpful for patients with chronic nausea syndromes. More laboratory-based studies of the physiology of nausea are needed to further understand these relationships.

Nausea and Emotion/Disgust

Emotional states such as disgust are often associated with nausea and can also be induced in the laboratory. Disgust is associated with effects on GMA. Healthy subjects viewed neutral to highly arousing pictures used to elicit disgust while GMA was recorded. Analyses showed the percentage of bradygastria (1.0–2.5 cpm) predicted the disgust ratings evoked in the highly arousing picture condition [21]. The onset of bradygastria was considered a prodromal sign for vomiting during disgust, although the presence of nausea was not reported in these studies. In another study, video clips were used to induce ingestive disgust in healthy subjects who underwent electrogastrogram and electrocardiogram recordings and fMRI studies [22]. Groups who reported high and low disgust were identified and separated for analysis. Results showed that disgust ratings were dependent on tachygastria activity and that the brain areas activated during disgust were the posterior and anterior insula, basal ganglia, thalamus, and bilateral somatosensory and somatomotor cortices. The presence of tachygastria was related to significant activation of

mid-anterior insula on the right and the cingulate cortex [23]. The conclusion was that the peripheral physiological changes in the stomach, the tachygastrias, directly contributed to the activation CNS areas (insular cortex) and the emotional responses of ingestive disgust. Thus, the visual stimulation of disgusting foods disrupted the GMA and evoked nausea and disgust. Was peripheral tachygastria the key? It would have been interesting to ask these subjects where they "felt" or where they "located" their nausea in these experiments. As listed in Table 1.1, would they have chosen "Head" or "Epigastrium" or some other location?

Sham feeding stimulates the cephalic vagal phase of digestion during which gastric acid secretion increases and the amplitude of 3 cpm GMA increases, although the chewed food does not actually enter the stomach, because it is spit out [24]. Sham feeding elicited by chewing and spitting out a warm hotdog increased the amplitude of normal 3 cpm GMA in healthy subjects; but during sham feeding using a cold, white, tofu dog, some subjects reported this was a disgusting experience. The GMA shifted from normal 3 cpm pattern to bradygastria in those subjects who reported disgust [25]. In another set of experiments in healthy subjects, n-propylthiouracil strips were placed on the tongue to produce an intense bitter taste. The intense bitter taste also evoked nausea and gastric dysrhythmias [26]. Thus, special sensory organs responding to motion stimuli, disgusting visual stimuli, or noxious taste stimuli can lead to nausea and disruption of normal GMA and the development of bradygastrias and tachygastrias. These motion and emotion studies show the relationship between the acute onset of nausea and the acute onset of gastric dysrhythmias.

Despite exhaustive testing with standard diagnostic procedures such as radiographic studies and endoscopy and gastric emptying studies, many patients have unexplained and chronic nausea. Some of these patients have gastric dysrhythmias and abnormalities of gastric relaxation or tone. Chronic neuromuscular dysfunction of the stomach or of non-gastric GI organs may result in chronic gastric dysrhythmias and chronic nausea syndromes. The pathophysiology of unexplained nausea in these patients is discussed below.

The Pathophysiology of Nausea and Gastric Neuromuscular Dysfunction

In this section, the pathophysiology of chronic nausea related to gastric neuromuscular diseases and disorders will be reviewed. The pathophysiology of nausea originating in the stomach includes gastric mucosal inflammation due to acid or *H. pylori*. Vagal afferent sensory nerves convey the information of mucosal injury and inflammation to the NTS and higher centers where ultimately the nausea sensations are appreciated. This mechanism of nausea related to mucosal diseases is very common and easily diagnosed and treated. The majority of patients with unexplained nausea and vomiting, however, have normal gastric mucosa at endoscopic examination [27]. Thus, neuromuscular abnormalities of the stomach may be the mechanisms of nausea in many of these patients.

The pathophysiology of nausea originating in the stomach includes gastric dysrhythmias and abnormalities of gastric wall tension and stretch which may produce vagal afferent nerve activation that evokes nausea [28]. Gastric dysrhythmias ranging from bradygastrias to tachygastrias are associated with loss of the interstitial cells of Cajal (ICCs) [17, 29]. The ICCs mediate the 3 cpm gastric slow waves and also may serve as stretch/tension receptors [30]. The loss of ICCs is associated with longstanding diabetes mellitus, but in most cases the underlying mechanisms of ICC damage or loss are unknown [31]. The loss of ICCs is associated with the presence of gastric dysrhythmias [17, 31, 32].

Ingestion of meals usually increases nausea in patients with functional dyspepsia, gastroparesis, and gastroparesis-like syndrome [33, 34]. Symptoms may begin within minutes after ingestion of the meal. These patients frequently cannot finish regular-sized meals because nausea, early satiety, and fullness, in addition to nausea, are evoked by very small meal volumes.

Thus, the initial stimulation of the symptoms of postprandial nausea and stomach fullness occurs during distention of the fundus, corpus, and antrum by the ingested volume of liquid or solid food. These early postprandial symptoms occur in those patients who have normal gastric emptying or gastroparesis [35, 36]. Delayed emptying of food (gastroparesis) is a neuromuscular abnormality of the stomach, but the rate of delay does not correlate with nausea [34]. Relaxation of the fundus, corpus, and antrum in response to ingested volume loads is diminished if nitric oxide nerves are damaged or depleted. The intramuscular arrays are stretch receptors and are in close contact with the ICCs and smooth muscle cells. Thus, if gastric muscular walls do not relax and stretch in response to increased wall tension, then these abnormalities in muscular relaxation (in addition to the onset of gastric dysrhythmias) may also contribute to the postprandial symptoms of early satiety and nausea.

During the gastric accommodation of the ingested volume of food, healthy subjects have a sensation of comfortable fullness in the epigastrium [28]. Patients with gastroparesis, on the other hand, report early satiety and nausea after ingesting a nutrient drink in much smaller volumes compared with healthy subjects. Patients with gastroparesis have severe depletion of the ICCs (<2-3 ICCs/hpf), which are associated with bradygastrias and tachygastrias [17, 29, 31, 37]. Patients with functional dyspepsia and gastroparesis-like syndrome have moderate depletion of ICCs (3–4 ICCs/hpf) and normal gastric emptying [32]. Patients with functional dyspepsia (dysmotility-like) also have gastric dysrhythmias and report nausea after ingesting small volumes of water compared with healthy subjects [16]. When ICCs are depleted, the networks of intramuscular arrays and enteric neurons no longer have the full system of interconnections that normally control GMA and gastric tone. In addition to gastric dysrhythmias, depletion of ICCs may lead to poor wall relaxation and increased wall tension during the ingestion of liquid caloric or non-caloric test meals and result, not only in low ingested volumes, but also increased symptoms of nausea and fullness and discomfort. In addition, M1 macrophage-related inflammation in the circular muscle layer in patients with gastroparesis [38] is associated with loss of ICCs, all of which contributes to dysrhythmias and a less compliant stomach. Poor gastric accommodation and gastric dysrhythmias are targets for further research relating nausea and neuromuscular dysfunction during stomach accommodation to a meal.

Provocative test meals to stimulate stomach neuromuscular activities to accommodate, mix, and empty the meal often elicit nausea symptoms within minutes [16, 35, 36]. Gastric neuromuscular dysfunction in patients with or without gastroparesis may present as (a) "spastic" response when there is poor gastric capacity (increased wall tension and decreased stretch in the gastric wall) and (b) "flaccid" response when there is greater than normal gastric capacity (abnormally relaxed stomach). It is interesting that ICC depletion was associated with decreased neuronal nitric oxide in patients with type 2 diabetes, thus linking ICCs with gastric rhythm and tone [39]. Postprandial changes in GMA and accommodation after ingestion of test meals may be relevant to the physiology of nausea, since the rate of gastric emptying does not correlate with nausea symptoms [16, 34, 36]. Figure 1.4 shows a model of the interactions among gastric ICCs, enteric neurons, and smooth muscle that maintain normal 3 cpm GMA and relevance to nausea. When these key gastric elements are perturbed, the shift from normal 3 cpm GMA to gastric dysrhythmias occurs. Neural and hormonal inputs from other GI tract organs and CNS stimuli may also affect GMA.

Another pathophysiologic pathway to nausea is related to the pyloric sphincter which normally regulates flow of chyme from the antrum to the duodenum [28]. If the pyloric sphincter is stenosed, then the normal 3 cpm gastric peristaltic waves in the normal corpus-antrum are still generated, but they fail to empty the stomach and gastroparesis develops secondary to pyloric outlet obstruction occurs [40]. In these patients, the GMA is a normal or high-amplitude 3 cpm signal [40]. In other patients, however, the pyloric

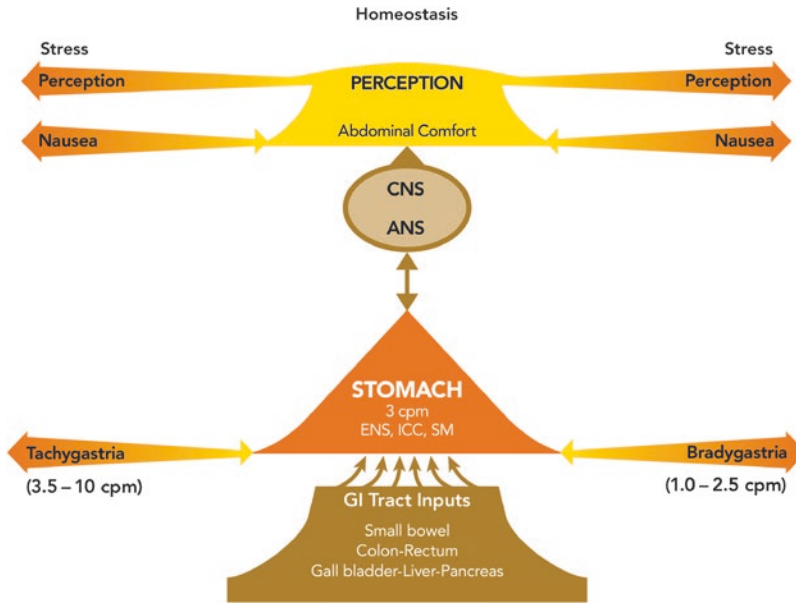

Fig. 1.4 The physiology of nausea includes multiple gut-brain and brain-gut pathways. During the state of comfort (no nausea), the central nervous system (CNS) and autonomic nervous symptom (ANS) and the gastrointestinal organs are in homeostatic balance. The gastric myoelectrical activity (GMA) is in the normal 3 cpm range because ICC, enteric nerve, and smooth muscle are functioning normally. Diseases and disorders of the GI tract organs that elicit nausea ultimately disrupt normal stomach neuromuscular activity through changes in ICC function, enteric nervous system changes, and neural-hormonal fluxes. GMA shifts to tachygastrias and bradygastrias and the symptom of nausea is recognized by the subject. The shifts to nausea and gastric dysrhythmias may be acute and temporary or chronic and fixed. GMA returns to the normal range, for example, during the recovery from the acute nausea of motion sickness. In disease states, however, the gastric dysrhythmias may become chronic abnormalities if ICCs are depleted

sphincter muscle may spasm or the sphincteric contractions are not synchronized with antral peristaltic waves during the postprandial period [41, 42]. The neuromuscular dysfunction of the pyloric sphincter results in postprandial nausea and abdominal discomfort/pain and functional gastric outlet obstruction, a form of obstructive gastroparesis [43]. These patients with neuromuscular dysfunction of the pylorus also have normal 3 cpm GMA because the corpus-antrum is normal and the primary defect is located at the pyloric sphincter. The postprandial nausea and fullness symptoms in these patients may be due to distension of the antrum, while the pylorospasm produces right quadrant abdominal pain. In some patients the upper abdominal pain may be confused with gallbladder pain. Patients with pylorospasm may have diminished neurons, ICCs, or IMAs in the sphincter, all of which interfere with relaxation of the sphincter and coordination with the terminal antral peristaltic waves, a condition called dyschalasia [41]. In this subtype of gastroparesis, balloon dilation or injection of botulinum toxin A into the pylorus or pyloroplasty improves GI symptoms and pyloroplasty normalizes the gastric emptying rate [43, 44]. In contrast to patients with gastric dysrhythmias and gastroparesis, the pathophysiology of nausea is related to pylorospasm or dyschalasia in these patients with gastroparesis and normal 3 cpm GMA.

Another mechanism or pathophysiology of nausea involves the esophagus. Although 31 % of patients with chronic unexplained nausea and vomiting located their nausea in the epigastrium, another 30 % of patients located their nausea in the epigastrium *and* the substernal chest region and 12 % located their nausea *only* in the substernal area, all of which suggests the esophagus is involved in the origins of nausea (Table 1.1).

Nausea is an atypical symptom of gastroesophageal reflux (GERD), a pathophysiological mechanism of nausea that is frequently overlooked because these patients often have little or no heartburn [45, 46]. The relationship between the onset of nausea and concomitant acid reflux into the esophagus is proven by 24-h pH study results. Esophageal vagal afferent neurons in these patients are apparently sensitive to even normal amounts of acid into the esophageal lumen, but the sensation evoked is nausea not heartburn. Thus, the physiology of nausea in some patients relates to esophageal acid reflux and the specific treatment is proton pump inhibitors or sucralfate therapy (as discussed in Chap. 3).

Patients who suffer from nausea have the difficult task of describing their specific nausea or nauseas to their physicians. To the physician, the symptom of nausea may sound very non-specific and not helpful in terms of the specific underlying pathophysiology of the nausea. As described above, however, at least four different pathophysiologies of nausea can be considered: (a) atypical symptoms of gastroesophageal reflux, (b) gastroparesis with gastric dysrhythmias, (c) gastroparesis but with normal 3 cpm GMA (obstructive gastroparesis subtype), and (d) gastric dysrhythmias but normal gastric emptying. If more common causes of nausea like peptic ulcer disease, gallbladder disease, and irritable bowel syndrome are treated or excluded, then one of these four specific mechanisms may be driving the symptoms of nausea. Esophageal and gastric causes of nausea are reviewed in Chap. 3.

If the cause of nausea is established with objective tests based on the pathophysiologies described above, then therapy can be more personalized and rational as suggested below: (a) acid suppression with proton pump inhibitors if pH studies show correlation of reflux events and nausea; (b) eradicating gastric dysrhythmias with prokinetic agents and relaxing the fundus with nitrates if gastric dysrhythmias and poor accommodation are documented, respectively; and (c) pyloric therapies such as balloon dilation or botulinum toxin A injections for patients with gastroparesis and 3 cpm GMA (obstructive gastroparesis). Treatments for gastric dysrhythmias and accommodation defects remain very limited, but these are objective gastric measures for future drug, diet, and device studies.

Gastric dysrhythmias are also associated with dysfunction of enteric neurons that affect ICC activity. If the neurotransmitter/receptor dysfunction is corrected, then ICCs may function again to produce the normal 3 cpm GMA. For example, domperidone, a dopamine$_2$ antagonist, was used to treat symptoms associated with diabetic gastroparesis. Symptoms improved during treatment and gastric dysrhythmias were corrected and 3 cpm GMA was restored [47]. Therefore, in these cases the ICCs were apparently not depleted, but were dysfunctional due to dopamine$_2$ receptor abnormalities. When treatment with the dopamine$_2$ antagonist domperidone was given, then the 3 cpm GMA was restored. Much more investigation of the mechanisms of ICC dysfunction, the presence and eradication of gastric dysrhythmias, and concomitant effects on nausea during drug therapies are needed.

On the other hand, if ICCs are irrevocably depleted, then drug therapies or gastric stimulator therapies directed toward restoring gastric rhythm or emptying may be ineffective. Rational patient selection for any drug or device therapy is critical for success. To this point, for example, the presence of some degree of normal 3 cpm GMA and less tachygastria predicted better symptom outcomes with gastric electrical stimulation [37]. However, if a patient with gastroparesis has normal or high-amplitude 3 cpm GMA, then normal ICC numbers are present and pyloric dysfunction and pyloric therapies should be considered [43, 44]. A novel treatment approach is to regenerate the pyloric sphincter for implantation or regenerate the ICCs or neurons and replace them by injection into the corpus, antrum, or pylorus as needed [48].

To summarize, the pathophysiology of nausea relates, in part, to gastric dysrhythmias and to abnormalities of gastric wall accommodation/relaxation and/or pyloric sphincter dysfunction.

These pathophysiologic abnormalities may be due to dysfunction or depletion of ICCs resulting in gastric dysrhythmias and dysfunction in gastric relaxation/accommodation and gastroparesis in response ingested meals. Thus, while the patient describes nausea which may seem to be quite non-specific, one of several gastric pathophysiological abnormalities may be specifically driving the symptom.

The Pathophysiology of Nausea and Small Bowel and Colonic Dysfunction

The physiology of nausea also involves neuromuscular dysfunction of the small intestine and the colon. Recent studies showed that 40% of patients with gastroparesis *also* have transit abnormalities of the small intestine and/or colon. Symptoms *associated* with gastroparesis may actually originate in the small bowel or colon, not the stomach [49]. Prolonged small intestinal transit time due to disordered neuromuscular function may result in small bowel bacterial overgrowth (SBBO). Some patients with SBBO present with nausea as a chief symptom and locate their nausea in the periumbilical area [2]. Similarly, pain from the small bowel diseases is referred to the periumbilical region. SBBO with abnormal small bowel distention may also affect normal 3 cpm GMA and result in gastric dysrhythmias. Thus, gastric dysrhythmias and/or relaxation abnormalities of the stomach may occur secondary to small bowel dysmotility. Antibiotic treatment is directed toward bacterial overgrowth to reduce nausea and, if present, symptoms of bloating and diarrhea.

Dysmotility of the colon resulting in constipation and colon distention or spasm and the irritable bowel syndrome (IBS) stimulates colonic afferent nerve activity. Patients with IBS and functional dyspepsia have gastric dysrhythmias [50]. For nausea related to colonic neuromuscular dysfunction, the goal should be to restore normal bowel function. If improvement in bowel function is accomplished, then the nausea related to colon dysfunction should be reduced.

Thus, small bowel or colon neuromuscular dysfunction represents underappreciated physiologies of nausea in some patients. Non-gastric diseases and disorders associated with nausea are reviewed in Chap. 4. Recognizing that esophageal, gastric, small bowel, and colon neuromuscular dysfunctions may mediate nausea symptoms provides the pathophysiological rationale for ordering appropriate diagnostic tests beyond endoscopy, such as esophageal manometry, 24-h esophageal pH, 4-h solid-phase gastric emptying, electrogastrogram with water load test, breath test for bacterial overgrowth, and wireless capsule motility tests. Positive tests are reviewed in relationship with symptoms and treatments can then be designed in a more precise, individualized approach for each patient based on objective test results.

Conclusions

In summary, nausea is an extremely common symptom that everyone has experienced at least temporarily at some time. Nausea protects the individual from potentially harmful external dangers particularly related to food and warns of dysfunction or damage in internal organs. Figure 1.4 shows an overview of the interconnections among CNS, stomach, and other GI tract organs that are involved in the physiology and pathophysiology of nausea. Central nervous system stimuli like the illusion of motion evoke nausea, gastric dysrhythmias, and ultimately vomiting. However, nausea also reflects diseases and dysfunction in different GI organs that develop neuromuscular abnormalities such as gastric dysrhythmias or poor gastric accommodation, disorders of the ICCs and enteric neurons within the wall of the stomach. Dysfunction and variable loss of ICCs and enteric nerves results in gastric dysrhythmias. Gastric dysrhythmias affect afferent neural signals from the stomach that reach the cortex and consciousness and are at least one peripheral mechanism of nausea [51]. Further investigations of these brain-

gut and gut-brain interactions are needed to better understand the pathophysiology(ies) of nausea in order to develop new, specific, and better therapies for nausea.

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The Physiology of Vomiting

2

Charles C. Horn

Introduction

The concept of a "reflex arc" dates to nearly four hundred years ago to the writings of the French Philosopher René Descartes [1]. This concept of reflex activation was further established in neurophysiological studies by the English physiologist Charles Sherrington who conducted extensive experiments on spinal cord reflex circuits. In his famous 1906 book, "*The integrative action of the nervous system,*" Sherrington describes a reflex:

> There is the coordination which a reflex action introduces when it makes an effector organ responsive to excitement of a receptor, all other parts of the organism being supposed indifferent to and indifferent for that reaction. In this grade of coordination the reflex is taken apart, as if separable from other reflex actions. This is the "simple reflex". A simple reflex is probably a purely abstract conception, because all parts of the nervous system are connected together and no parts of it is probably ever capable of reaction without affecting and being affected by various other parts, and it is a system certainly never absolutely at rest. But the simple reflex is a convenient, if not a probable fiction (p. 7, [2]).

By this definition, emesis is clearly a reflex, which is a complex set of actions of the inspiratory and expiratory muscles to produce the function of vomiting (expulsion of gastric contents). This chapter is focused on an overview of the physiological processes that determine the emetic reflex. Other responses associated with emesis, including sweating, salivation, and cardiovascular changes [3], will not be discussed in this chapter because they are not required for the production of emesis. The reader is also referred to the excellent succinct review by C.J. Davis on the history of emesis research [4] for a discussion of early work that led to current understanding of the emetic reflex.

What Is Vomiting (Emesis)?

To discuss the physiology of vomiting, we need to define the response separately from other actions, which can appear similar. In this context, emesis is a survival response associated with food intake. Foraging and consumption of food are key survival behaviors, fraught with danger; specifically, feeding can lead to the exposure of internal organs to food-related toxins, including viruses and bacteria [5]. An important physiology problem is to determine which foods are safe for consumption. The United States' Centers for Disease Control and Prevention (CDC) estimates that each year roughly 1 in 6 Americans (or 48 million people) get sick, 128,000 are hospitalized, and 3,000 die of foodborne diseases [6]." Microbial sources of these illnesses include preserved food (fish, meat, fruits, vegetables) contaminated with *Clostridium botulinum*, poultry

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and eggs with *Salmonella*, and mushrooms containing mycotoxins [5]. Spoiled foods can often be identified using smell and taste cues, for example, a rancid odor or sour taste, but olfactory and gustatory signals are not always adequate for detecting toxic foods. Vomiting is a mechanism for voiding the upper gastrointestinal (GI) tract of an unhealthy meal; however, if ingested food goes beyond approximately the middle of the small intestine, the contents might not be returned in the retrograde direction and expelled during the emetic reflex [7]. In contrast to emesis, diarrhea plays the role of removing toxins from the lower intestines. It is important to note that emesis is not completely efficient, with some studies reporting only approximately 50 % recovery of gastric contents following emesis in humans [8, 9]. Finally, emesis, an active coordinated process, is functionally different from passive regurgitation or single gagging responses. As we will see in the next sections, emesis involves a pattern of motor outputs that produce rhythmic contractions of the respiratory muscles to produce a sequence of retches and vomits.

Which Stimuli and Sensory Pathways Activate the Emetic Reflex?

There are four sensory pathways that trigger vomiting [3, 10]. These four inputs project to the nucleus tractus solitarius (NTS) in the caudal hindbrain (see Fig. 2.1): (1) GI vagal afferent fibers; (2) area postrema; (3) vestibular input; and (4) forebrain. Local toxins in the lumen or vascular system of the

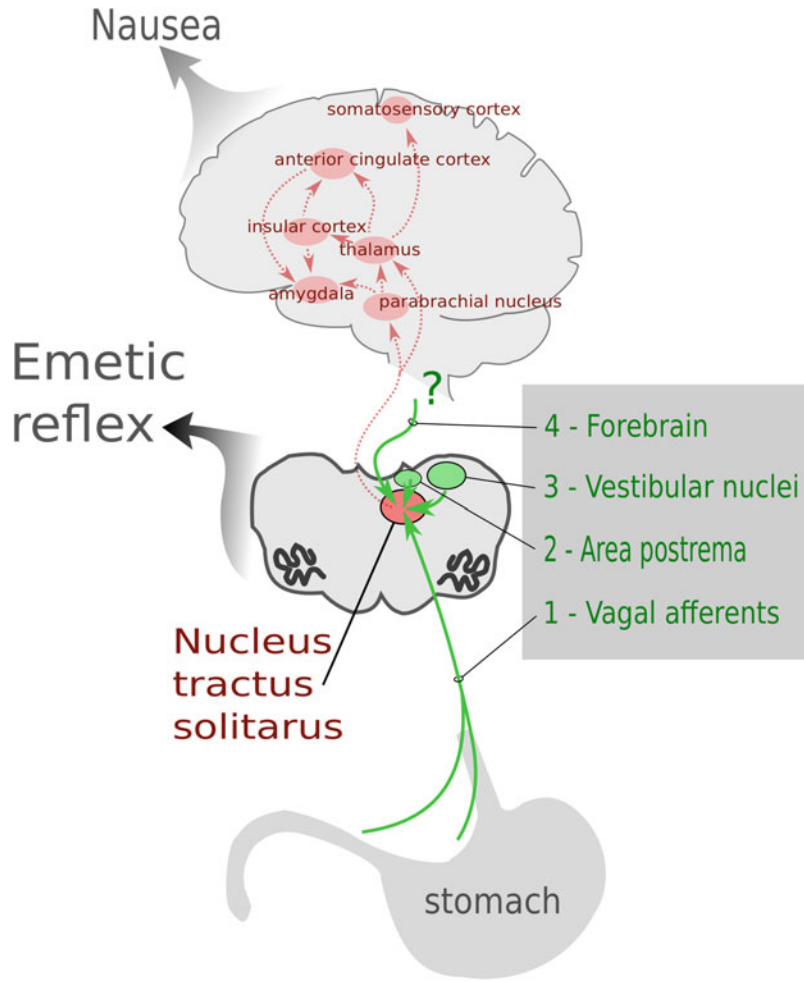

Fig. 2.1 Four afferent pathways that trigger the emetic reflex (*green*). These pathways converge on the nucleus tractus solitarius (NTS) in the lower hindbrain. The neural circuitry of the caudal hindbrain is sufficient to produce emesis [32–34]; potential forebrain pathways for nausea are shown for comparison to emetic pathways (based on Napadow et al. [96])

GI tract can stimulate the release of paracrine factors (e.g., serotonin from enteroendocrine cells), which activate vagal afferent fibers of the stomach and duodenum [11, 12]. Vagal afferents contain receptors for serotonin (5-HT3) receptor subtype and other neuro-signaling agents [13]. The area postrema probably plays a dual role: (1) with activation by toxins that enter the blood stream (the area postrema is a circumventricular organ with a reduced blood–brain barrier [14]) and (2) by direct input from the vagal afferent system [15]. Vestibular nuclei receive motion-related sensory input from the vestibule in the inner ear to stimulate motion sickness [16, 17]. Vomiting can also be produced by activation of one or more descending pathways from the forebrain [18]; the anatomical loci of these descending pathways are unknown (see the "?" mark in Fig. 2.1). Studies show that activation of the temporal lobe, which contains the amygdala, and the insular cortex by epileptic seizures can produce ictal vomiting [19]. These forebrain areas potentially participate in psychogenic-related vomiting [20]. For example, anticipatory vomiting can occur as a learned response to cytotoxic cancer chemotherapy when patients experience multiple cycles of treatment [21].

Consistent with the idea of convergence of emetic inputs, emetic treatments, including gastric irritants, provocative motion, and circulating toxins, produce activation of the NTS, as measured by c-Fos protein immunohistochemistry [22–27]. Immunohistochemistry for c-Fos is used by neuroscientists to anatomically localize neuronal activation in histological sections of brain tissue [28, 29]. Nonetheless, it must be recognized that most (if not all) physiological stress stimuli produce c-Fos expression in the NTS [30, 31]; therefore, the use of the c-Fos technique is limited in specificity. Other limitations of the c-Fos approach include a lack of temporal resolution (activation occurs as an aggregated response over tens of minutes) and not all cells show c-Fos expression when stimulated.

Where Is the Location of the Emetic Central Pattern Generator?

Often the locus of neurons that generate emesis is called the "vomiting center," but we lack information on the precise location and phenotypes of these cells. On the other hand, it is clear that the caudal hindbrain contains this critical emetic circuitry; an isolated hindbrain, surgically transected from the forebrain, can produce fictive emetic episodes (an emetic pattern of neural and muscle responses) when stimulated in animal physiology experiments [32–34]. The neurons that produce emesis, the "final common pathway," are likely distributed among many other types of hindbrain neurons; indeed, the caudal hindbrain contains a highly overlapping network of functional visceral organ control systems (e.g., respiration, cardiovascular control, etc.) [35]. In contrast to a "vomiting center," the emetic neural network can be conceptualized as a central pattern generator (CPG). A CPG is a network of neural connections that produces rhythmic motor patterns. The initiating signal for the emetic CPG is likely from the NTS because this site integrates input from the four sensory inputs that produce emesis (see Fig. 2.1).

Components of the emetic CPG, which are downstream from the NTS, are controversial. Yates and colleagues have provided a succinct recent review [36] and the following is a summary of these components. A necessary requirement for retching and vomiting is patterned motor output to the abdominal and diaphragm muscles, which produces the internal pressure changes essential for emesis. To increase abdominal cavity pressure, it seems reasonable that inspiratory-related neurons in the rostral ventral respiratory group (rVRG) [37] play a key role in vomiting; surprisingly, rVRG neurons are inhibited during emesis [38, 39]. Retrograde neuroanatomical tracing from the diaphragm and abdominal muscles, using transneuronal transport of viruses, has revealed a region in the medial medullary reticular formation (MRF) that provides polysynaptic input to these muscles [40–45]. Indeed, individual MRF neurons supply input to both abdominal and diaphragm muscle groups [41]; and, lesions of the MRF abolish emesis [46]. Furthermore, neurons in the caudal ventral respiratory group (cVRG) are synchronously active with emesis; potentially both cVRG and MRF neurons supply input to the spinal pathways that produce emesis [36]. The intermediate link between these two areas and the NTS is sug-

gested to be the lateral tegmental field (LTF), which receives input from the NTS [36].

What Are the Mechanics of Vomiting?

Motor outputs controlling the mechanics of a successful emetic episode are associated with three temporal phases (see Fig. 2.2). In Phase 1 – the prodrome, efferent vagal neurons, presumably from the dorsal motor nucleus (DMN), initiate a "giant retrograde contraction" that starts in the mid-intestine and functions to return luminal contents to the gastric compartment, which relaxes proximally [7, 47]. In Phase 2 – retching, spinal efferents produce abdominal, crural diaphragm (a medial muscle close to the esophagus), and costal diaphragm (lateral muscle) contractions that cause pressure increases in the abdominal cavity to position the gastric luminal contents under the distal esophagus for the next phase, expulsion or vomiting [48]. Finally, in Phase 3 – vomiting, similar in some aspects to Phase 2, spinal efferents produce abdominal and diaphragmatic muscle contractions but the crural diaphragm is not activated (see Fig. 2.2); consequently, gastric contents freely flow up and out the esophagus (expulsion) [49].

Which Drug Therapies Control Emesis?

This section summarizes current antiemetic therapies; for an in-depth analysis, the reader is referred to Chap. 9 in this book and several extensive reviews [50–53]. Antiemetic drug targets are listed in Table 2.1, along with effects on known emetic sensory pathways (see Fig. 2.1); only established, and

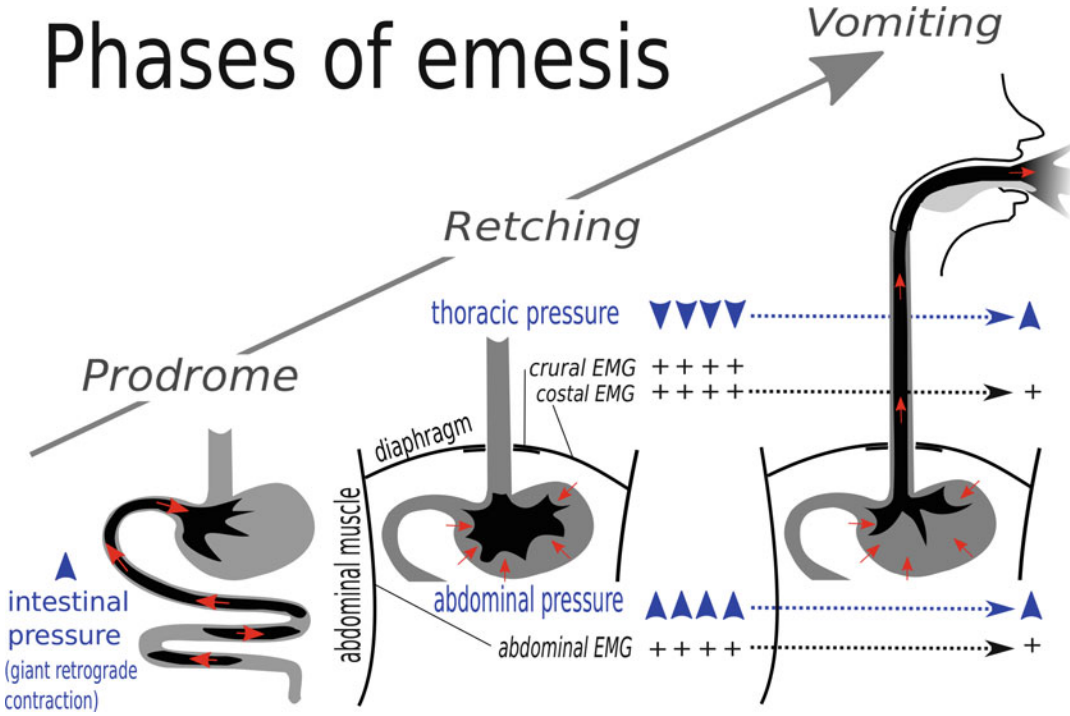

Fig. 2.2 The three phases of emesis, with movement of gastrointestinal contents (*red arrows*): (1) prodromal responses, a giant retrograde contraction from the middle of the small intestine; (2) retching; and (3) vomiting, expulsion of gastric contents. *Up and down blue arrows* indicate pressure changes caused by muscular contractions of the diaphragm and abdomen. Plus signs (*black*) signify electromyographic (EMG) responses from the crural and costal diaphragm and abdominal muscles (see reviews [61, 97])

pathway-specific, emetic stimuli are included: (1) intragastric copper sulfate ($CuSO_4$, a gastric irritant) or cisplatin (intravenous or intraperitoneal injection; an acute response) activates GI vagal afferents [54–56]; (2) systemic injections of nicotine or apomorphine stimulate the area postrema [57, 58], and exposure to provocative motion acts on the vestibular system to produce emesis [59].

Current, clinically available, antiemetics target histamine type 1 (H_1), muscarinic (M), neurokinin 1 (NK_1), and serotonin type 3 (5-HT_3) receptors [50–53]. NK_1 receptor antagonists provide inhibitory control of emesis produced by a wide range of emetic stimuli, i.e., broad-spectrum antiemetic control; this supports the idea of convergence of vagal, area postrema, vestibular, and psychogenic sensory pathways to activate a final common pathway for emesis [60, 61]. In general, H_1 and M receptor antagonists are less effective for controlling emesis in comparison to NK_1 receptor antagonists. H_1 and M antagonists have inhibitory effects on motion sickness and postoperative vomiting [16, 52], possibly due to direct effects on the vestibular nuclei or area postrema. In contrast, 5-HT_3 receptor antagonists are not effective for inhibiting motion sickness [62, 63] but are routinely used to inhibit chemotherapy-induced and postoperative vomiting [64]. The location of 5-HT_3 receptors responsible for antiemesis is unclear because these receptors are located on vagal afferent fibers in the GI tract and their terminal inputs in the NTS [65].

Table 2.1 Antiemetic drugs

	Target	Examples of stimulus effects
Receptor antagonists	H_1	Motion [99]
	$M_{(3/5?)}$	Motion [99, 100]
	5-HT_3	Cisplatin [56, 101]
	NK_1	$CuSO_4$ [102, 103]
		Cisplatin [103–105]
		Nicotine [106]
		Apomorphine [107]
		Morphine [102]
		Motion [105, 108]
Receptor agonists	CB_1	Cisplatin [54, 55]
		Nicotine [109]
		Apomorphine [110]
		Morphine [111]
		Motion [112]
	5-HT_{1A}	CuSO4 [114]
		Cisplatin [114]
		Nicotine [114]
		Motion [113]

H_1 histamine 1, *$M_{(3/5)}$* muscarinic receptors (3/5), *5-$HT_{3–5}$* hydroxytrytamine$_3$, *NK_1* neurokinin$_1$ receptor, *CB_1* cannabinoid$_1$, *5-HT_{1A} 5* hydroxytrytamine$_{1a}$, *$CuSO_4$* copper sulfate

The need to control emesis produced by cytotoxic cancer chemotherapy has resulted in significant research efforts, ultimately leading to large clinical trials [66]. The fruits of this work led to the development of 5-HT_3 and NK_1 receptor antagonists (e.g., Zofran and Emend, respectively, and many similar agents). The physiology of chemotherapy-induced vomiting, particularly with the use of cisplatin and cyclophosphamide agents, has traditionally been divided into acute (up to 24 h) and delayed (greater than 24 h after injection) responses [67]; evidence indicates 5-HT_3 receptor antagonists are effective for controlling the acute phase, whereas NK_1 receptor antagonists are most effective in the delayed phase, albeit in combination with administration of dexamethasone [67]. To some extent, the successes achieved in the control of chemotherapy-induced vomiting, using 5-HT_3 and NK_1 receptor antagonists, have been applied to postoperative vomiting [52]. Postoperative vomiting is generated by dual activation of emesis with inhalational anesthesia and opioids, presumably at sites in the caudal hindbrain [68].

Why Do Some Animals Lack a Vomiting Reflex Circuit?

The presence of the emetic reflex is widespread among mammals. This response is present in several major lineages (see Fig. 2.3), including carnivora (e.g., cat, dog, ferret [86–91]), primates (e.g., human, monkey [82, 83]), Cetartiodactyla (e.g., pigs [84, 85]), and Eulipotyphla (e.g., shrews [69–71]). The reflex appears to be absent in Rodentia (e.g., laboratory rats and mice) and Lagomorpha (e.g., rabbits and hares) [12]. In Horn

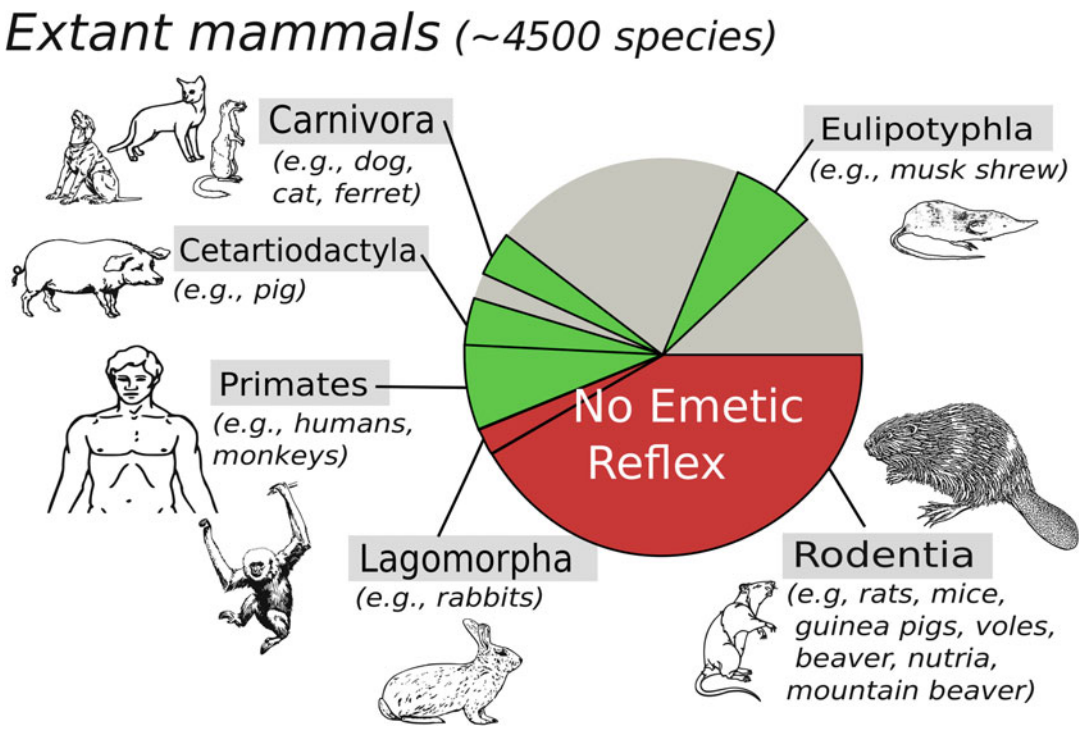

Fig. 2.3 Proportions of extant mammalia that display a vomiting reflex (*green*) compared to those that do not (*red*), based on published relative number of species in each group and emetic testing [34, 98]

et al., we tested representative members of the three main groups of rodents (mouse-related, Ctenohystrica, and squirrel-related) and none were found to have emetic responses to apomorphine, $CuSO_4$, or veratrine (a plant alkaloid) [34]. Using an isolated perfused brainstem preparation, we also showed that laboratory rats and mice lack any coordinated neural efferent activity that would indicate emesis, compared to musk shrew controls [34].

If vomiting is essential for survival, why do rodents lack this reflex? Current theory suggests that other behavioral responses of rodents have replaced emesis, for example, conditioned taste aversion (CTA) and pica (ingestion of clay) (see review [72]). CTA is a classically conditioned response, formed by association of a flavor with visceral sickness, which leads to avoidance of the flavor in the future [73]. In this regard, rodents might only nibble on a small amount of tainted food, not a lethal dose but adequate to produce a CTA. On the other hand, pica is believed to be a way to dilute the effects of a toxin entering the GI tract. Silicate clay (kaolin) can bind toxins [74, 75] and kaolin intake in rats is associated with emetic treatments, including cytotoxic chemotherapy, provocative motion, and apomorphine treatments [76–79]. The pica response can also be inhibited by treatment with antiemetics, such as NK_1 and 5-HT_3 receptor antagonists [80, 81].

Laboratory rats and mice are used for most neuroscience experiments, particularly because of the availability of powerful genetic, physiological, and anatomical techniques; however, an absent emetic reflex in these animals has led to the use of dogs, cats, primates, pigs, and shrews to study the neurobiology of emesis [10].

Conclusion

In summary, the emetic reflex is a "complex" patterned response of several neurological components, essentially engaging the movements of a large part of the torso. We still lack an understanding of why rodents (and lagomorphs) do not

have this response, but an absent neurological circuit in the emetic CPG is suspected since the brainstem of these species appears to have no emetic-related motor output in response to emetic stimulation [34]. The four sensory pathways that trigger the emetic reflex are relatively known; however, there is sparse information on the coding of emetic signals by GI vagal afferents [92]. Furthermore, there is little insight into the nature of descending pathways from the forebrain that participate in cognitive and learned emetic responses. There is also limited information on the detailed components of the emetic CPG; existing data has focused on c-Fos measures, ablation techniques, and single cell electrophysiological recordings. We will need more precise and high-throughput tools, such as optogenetic control of specific cells and multi-electrode technology to determine the details of the CPG. Although research indicates good control of acute chemically-induced vomiting with current antiemetics, for example, chemotherapy and postoperative vomiting, we lack effective therapies for chronic vomiting (and nausea); this is particularly true in cases of gastroparesis, cyclic vomiting syndrome, and hyperemesis gravidarum (an extreme form of pregnancy-related nausea and vomiting) [93–95]. These issues require more research on the physiology of vomiting to develop novel and effective therapies.

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3 Nausea and Vomiting Related to Esophagus and Stomach Diseases

Kenneth L. Koch

Introduction

The aim of this chapter is to review esophageal and gastric diseases and disorders that are the underlying mechanisms for unexplained nausea and vomiting. Nausea and vomiting are usually attributed to stomach disorders. However, nausea can also be due to esophageal diseases. For example, acid reflux events correlated with reports of nausea in patients with unexplained nausea who had normal gastric emptying and normal gastric myoelectrical activity (GMA) [1]. And in a recent study of almost 197 patients with unexplained nausea, 12 % of the subjects located their nausea in the substernal chest area only (Fig. 3.1) [2]. Nausea located or perceived in the substernal area likely originates from the esophagus. Therefore, esophageal disorders described below should not be overlooked in the evaluation of patients who present with unexplained nausea.

Nausea and vomiting are associated with stomach disorders such as gastroparesis, gastric dysrhythmias, and other gastric neuromuscular abnormalities which will be described below. Only 30 % of patients with unexplained nausea, however, located their nausea in the epigastric area only, an area suggesting the stomach as the origin of their nausea (Fig. 3.2) [2]. In addition, another 35 % of these patients located their nausea in the epigastric area *and* in the chest area (Fig. 3.3), suggesting both the stomach and the esophagus were involved in the origins of their nausea.

Esophageal Diseases and Nausea and Vomiting

Clinical Presentation

Patients with esophageal diseases may only report that they are nauseated and deny more typical symptoms of heartburn, dysphagia, or regurgitation. Table 3.1 lists esophageal diseases associated with nausea and vomiting. Even minimal substernal burning should raise suspicions that gastroesophageal reflux disease (GERD) is a possible mechanism for nausea symptoms. In the author's experience, nausea due to GERD is frequently present when the patient awakens in the morning and reflects nocturnal GERD. The nausea may improve temporarily after meals in patients with GERD-related nausea. Patients may report the nausea rises into the substernal chest (with or without burning symptoms) as shown in Fig. 3.1. This history and nausea location should

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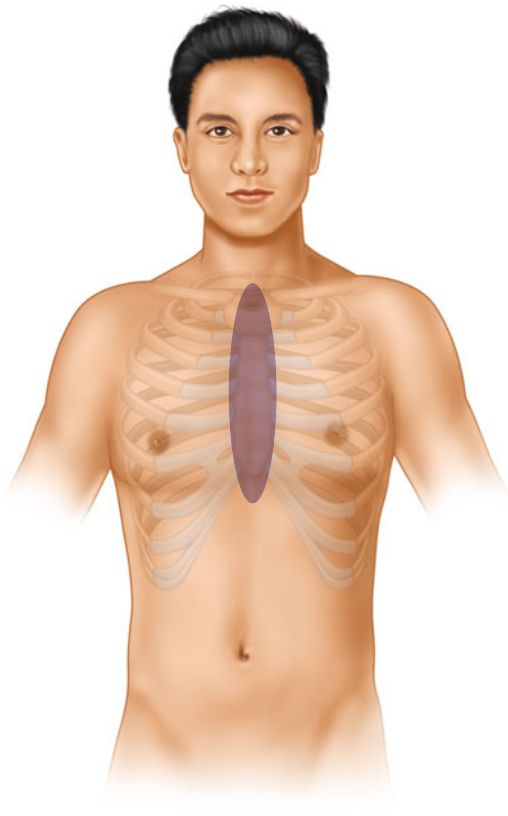

Fig. 3.1 The Nausea Locator is the figure onto which the patient indicates where their nausea is located. The general anatomy is described for the patient: head, neck, collar bones, chest, abdomen, umbilicus, groin, arms, and legs. The patient is given a pen and asked to locate on the figure where their nausea is located. This patient located their recurrent unexplained nausea in the substernal area only

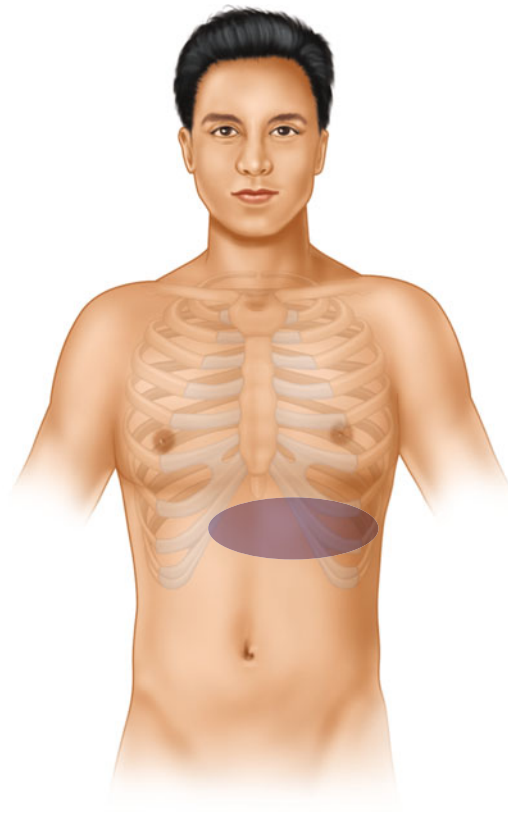

Fig. 3.2 On this Nausea Locator diagram, the patient with unexplained nausea indicated their nausea was located in the epigastric region only

also suggest GERD as a potential mechanism for nausea.

Esophageal acid reflux events detected with 24-h pH tests correlated with nausea episodes in patients with chronic unexplained nausea, normal gastric emptying, and GMA and confirmed GERD-related mechanism of nausea [1]. These patients had minimal or no heartburn symptoms. Nausea decreased with aggressive acid suppression and one patient with drug refractory nausea improved after fundoplication. Nausea symptoms poorly correlate with gastroparesis and in some gastroparesis patients, esophageal acid reflux may be the actual mechanism for nausea. Almost 30 % of patients with gastroparesis and gastric dysrhythmias reported nausea episodes that correlated with esophageal acid or non-acid reflux events during 24-h pH monitoring [3].

These esophageal pH studies in patients with or without gastroparesis indicate that the symptom of nausea in some patients is elicited by acid (or non-acid) reflux. In a majority of patients with acid-induced nausea, overall esophageal acid reflux was within the normal range, indicating esophageal mucosal hypersensitivity to the refluxate was the likely underlying mechanism driving symptoms of nausea. Esophageal manometry revealed hypotensive lower esophageal sphincter pressure in a minority of these patients. On the other hand, some patients with predominant nausea and vomiting have severe esophagitis that may be unexpected until documented at endoscopy. In most patients with GERD-related nausea, however, endoscopy is

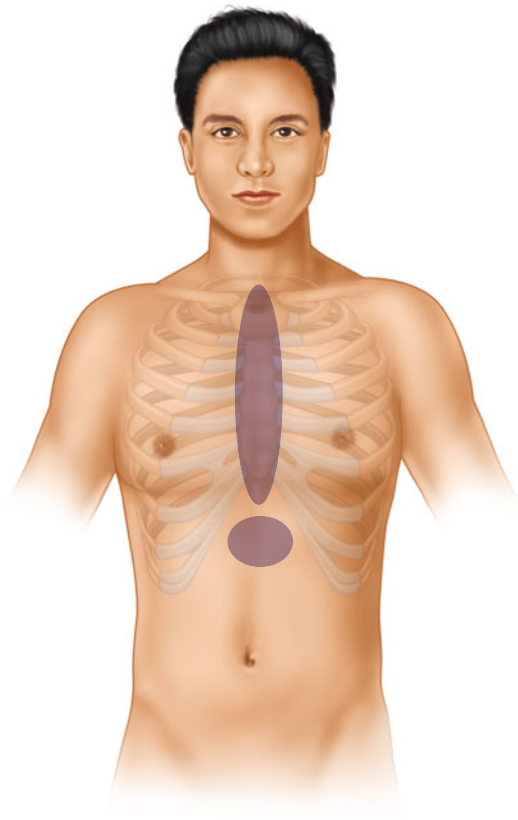

Fig. 3.3 On this Nausea Locator diagram, the patient indicated their nausea was located in the epigastrium and substernal area

Table 3.1 Esophageal diseases and nausea and vomiting

1. Gastroesophageal reflux disease
(a) With esophagitis
(b) Without esophagitis (hypersensitive esophagus)
2. Achalasia
3. Esophageal spasm

completely normal and GERD may not be suspected as the cause of nausea.

Dysphagia also suggests esophageal motility disorders are present in patients with unexplained nausea. GERD-associated defects in esophageal peristalsis and achalasia may result in increased acid contact time of the esophageal mucosa and elicit nausea [4]. Patients with dysphagia due to esophageal spasm may also experience nausea during severe chest discomfort [5].

Regurgitation is oftentimes confused with vomiting by the patient with esophageal motility disorders. If the patient reports vomiting, then the physician should clarify what the patient is actually experiencing. Failure to do so may lead to diagnostic testing of the stomach and small bowel function and esophageal disorders may be overlooked. Regurgitation is the unpleasant reflux of stomach contents, both liquids and solids, into the esophagus. Hypotensive LES pressure is associated with regurgitation, but LES pressure is usually normal in patients with regurgitation. The regurgitated materials may reflux through the esophagus and into the oropharynx, but the patients report they "vomited" the material. However, patients may be spitting out the refluxed material and not actually vomiting. Moreover, after some regurgitation episodes, patients can take swallows that elicit esophageal peristalsis that returns the refluxed material to the stomach. In contrast, during vomiting the gastric contents are forcefully ejected from the stomach through the relaxed LES, esophagus, oropharynx, and mouth with considerable velocity as the abdominal wall muscles contract vigorously [6]. The subject has no control over the vomiting sequence. The physiology of vomiting is described in detail in Chap. 2.

In contrast to regurgitation and vomiting, rumination is the effortless return of gastric contents into the esophagus and mouth [7]. Rumination is not unpleasant for the patient and is not associated with heartburn, pain, nausea, or other symptoms. Gastric content that rises into the oropharynx is usually re-swallowed without difficulty or distress. Rumination occurs in otherwise healthy individuals and should not be confused with vomiting or regurgitation.

Physical Examination

The general physical examination may be entirely normal in patients with nausea from GERD or esophageal motility disorders. Physical findings may include loss of dental enamel in patients with severe GERD. Sclerodermatous changes in the face and digits may be found.

Abdominal tenderness, particularly along the rectus muscles or lower rib margins, may be present due to frequent retching and vomiting.

Diagnostic Evaluation for Esophageal Disorders Causing Nausea and Vomiting

If the history suggests GERD and nausea is located in the substernal area of the chest, then an empiric trial of proton pump inhibitor therapy for 4 weeks is reasonable. This therapeutic trial with a proton pump inhibitor (PPI) twice a day will be diagnostic in that the degree to which nausea is decreased reflects the degree to which acid is the mechanism of the nausea. If PPI therapy markedly reduces the frequency and severity of nausea, then this response is clinical evidence that acid is a key mechanism driving the nausea symptoms.

The diagnostic evaluation should include upper endoscopy for patients with persistent nausea who are already on PPI therapy or who failed an empiric PPI trial. Upper endoscopy will detect macroscopic evidence of esophagitis as well as other causes of nausea, such as gastritis, pyloric stenosis, or duodenitis. In most patients with unexplained nausea and vomiting, the endoscopy findings are normal. The normal endoscopy only indicates no obvious mucosal diseases are present. Eosinophilic esophagitis may present with nausea and vomiting and if suspected on the basis of endoscopy findings, then esophageal biopsies should be obtained [8].

If endoscopy is normal, then more subtle esophageal disorders such as GERD or esophageal motility disorders should be considered. An esophageal manometry and a 24-h pH study are needed to link unexplained nausea and GERD. Acid reflux can be markedly increased or normal in these patients who may or may not have gastroparesis and who have little or no heartburn symptoms [1, 3]. PPI therapies should be stopped seven days before the 24-h pH study in order to increase the chances of esophageal acid reflux to determine if nausea episodes occur during reflux events.

An evaluation of the gastric component of GERD should be considered. Severe difficult-to-control GERD should also raise the possibility of gastroparesis. Gastroparesis occurs in 30–40 % of patients with GERD and is a risk factor for GERD [9]. Obstructive gastroparesis, a subtype of gastroparesis, should also be considered in patients with refractory GERD. Obstructive gastroparesis is due to pyloric dysfunction, either fixed stenosis or neuromuscular dysfunction of the pyloric sphincter termed dyschalasia [10] that results in delayed gastric emptying. The severe delay in gastric emptying secondary to obstructive GP contributes to frequent reflux episodes that are difficult to control with medications and result in severe esophagitis. In these patients the underlying pathophysiological mechanism for GERD includes gastric outlet obstruction. Patients with the obstruction phenotype of gastroparesis have normal or increased amplitude 3 cycles per minute (cpm) GMA as described below.

Treatment of Nausea and Vomiting Related to Esophageal Diseases

If a relationship between nausea and acid reflux is suspected, then an empiric trial with proton pump inhibitor therapy is warranted. If endoscopy reveals obvious esophagitis, then aggressive PPI therapy is usually successful in reducing nausea as the mucosa heals. Candida or eosinophilic esophagitis are treated if those diseases are documented. In cases of severe and refractory esophagitis, gastroparesis from an obstructive abnormality at the pylorus or post bulbar region should be considered. Treatment of gastroparesis is discussed below.

If the endoscopy is normal and the pH study shows a positive relationship between acid reflux events and nausea episodes (e.g., >50 % of reflux events correlated with nausea episodes), then treatment with maximum doses of PPIs is needed. Sucralfate in liquid form (1 g four times per day) may be added for esophageal mucosal barrier therapy. Sucralfate helps decrease nausea in the patient with hypersensitivity to reflux esophageal acid in the author's experience, but placebo-

controlled trials of PPI therapy plus sucralfate for nausea symptoms have not been performed. A histamine$_2$ antagonist drug at bedtime may be used to further suppress acid during the night. These various treatments to control GERD often help the morning nausea frequently reported by patients. Antacids can be used as needed to reduce discrete nausea episodes related to acid reflux. Reduction of nausea by ingestion of antacids also helps convince the patient (and physician) that acid reflux is a mechanism driving their recurrent nausea.

Treatment of documented gastroparesis with diet and drugs may also help reduce esophageal reflux and contribute to decreased nausea. For patients with severe esophagitis and obstructive gastroparesis, pyloric treatments range from endoscopic dilation of the pylorus to botulinum toxin A injection of the pylorus to pyloroplasty [11–13]. Patients with GERD and dyspepsia symptoms reported decreased symptoms and had restoration of normal 3 cpm GMA and improved gastric emptying after radiofrequency ablation procedures for GERD [14]. In a minority of patients with GERD-induced nausea, fundoplication may be considered. A subset of GERD patients also has gastroparesis which limits the fundoplication approach.

Stomach Diseases and Nausea and Vomiting

Patients often report they are "sick to their stomach." Many efforts to understand, diagnose, and treat nausea and vomiting have focused on diseases of the stomach. In a series of 197 patients with unexplained nausea, 31 % indicated they felt their nausea only in the epigastrium, the area of referred sensation for the stomach (Fig. 3.2), and another 35 % of these patients located their nausea in the epigastrium *and* the chest (Fig. 3.3). Thus, two-thirds of patients with unexplained nausea located some or all of their nausea in the epigastrium. Nausea and vomiting are frequently elicited by diseases and disorders in other organs of the GI tract (e.g., chronic cholecystitis or irritable bowel syndrome) and diseases outside the GI tract (e.g., orthostatic intolerance) [15], but the stomach becomes involved in the nausea and vomiting at some point. Therefore, the differential diagnosis of chronic nausea and vomiting is extensive as shown in Table 3.2.

To further assist with a rational approach to finding the cause of unexplained nausea symptoms, an organ-based approach is described in this book. Non-stomach causes of nausea and vomiting are reviewed extensively in other

Table 3.2 Causes of chronic nausea and vomiting

I. Mechanical gastrointestinal tract obstruction (pylorus, common bile duct, small intestine, colon)
II. Mucosal inflammation (esophagus, stomach, duodenum)
III. Peritoneal inflammation (cancer, colitis)
IV. Carcinomas (gastric, ovarian, renal, bronchogenic)
V. Metabolic/endocrine disorders (diabetic mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, uremia)
VI. Medications (anticholinergics, narcotics, L-dopa, progesterone, calcium channel blockers, digitalis, nonsteroidal anti-inflammatory agents, lubiprostone, amylin analogs)
VII. Gastroparesis
Obstructive: pyloric stenosis, pyloric spasm
Ischemic: chronic mesenteric ischemia
Diabetic: Type 1 and 2
Postsurgical: fundoplication, Billroth I, II
Miscellaneous, including pseudo-obstruction
Idiopathic
VIII. Gastric dysrhythmias (tachygastria, bradygastria, mixed dysrhythmias)
IX. Central and autonomic nervous system disorders (tumors, migraine, seizures, stroke, orthostatic intolerance)
X. Psychogenic disorders (anorexia nervosa, bulimia nervosa)

chapters. In this section, however, a clinical approach to the diagnoses and treatment of nausea and vomiting focused on stomach disease is reviewed. The differential diagnosis for unexplained nausea related to and focused on stomach diseases is outlined in Table 3.3.

Clinical Presentation

It is important for the clinician to understand how the patient's nausea comes and goes during a typical day. Clues to the pathophysiologic mechanism(s) driving the nausea can then be discerned. Thus, it is helpful to obtain from the patient a brief chronological description of the onset and offset of nausea and vomiting throughout a "typical bad day." For example, patients who have nausea when they awaken in the morning may have esophageal acid reflux that occurs during the night. Mucosal inflammation of the stomach due to acid/peptic and *H. pylori* diseases is associated with nausea. Burning epigastric discomfort is often minimal but suggests gastritis and duodenitis. Symptoms from these acid-related disorders may be worse in the morning when patients are fasted. If ingesting breakfast relieves the nausea, then gastric acid and a mucosal disorder may be driving the nausea symptoms since food is a buffer, at least temporarily. Rarely, hunger is described as nausea which then decreases with meals. Addison's disease should also be considered if morning nausea is a prominent clinical feature.

Table 3.3 Differential diagnosis of stomach diseases associated with nausea and vomiting

Gastric outlet obstruction
Pyloric stenosis (fixed), post-bulbar stenosis
Pylorospasm, dyschalasia
Mucosal diseases
Gastritis (with or without *H. pylori*)
Duodenitis
Gastric or duodenal ulcers
Carcinomas
Linitis plastica
Gastroparesis
Obstructive:
(a) Fixed pyloric stenosis
(b) Pylorospasm; dyschalasia
Chronic mesenteric ischemic
Diabetic, type 1 and 2
Postsurgical (fundoplication, Billroth I, II)
Miscellaneous, including pseudo-obstruction
Idiopathic
Gastric dysrhythmias and accommodation disorders
Tachygastria, bradygastria, mixed gastric dysrhythmias
Poor/excess gastric accommodation

On the other hand, if ingestion of small quantities of food increases nausea and produces early satiety, excess fullness, or upper abdominal distention, then disorders of gastric accommodation, gastric dysrhythmias, gastroparesis, or pylorospasm-underlying gastric neuromuscular abnormalitie-should be considered. The symptoms typically associated with gastroparesis are early satiety, abdominal discomfort or pain, prolonged fullness, and nausea and vomiting [16]. These symptoms are non-specific, however, and the rate of gastric emptying itself does not correlate with symptoms of nausea and vomiting [16].

These postprandial symptoms plus epigastric or right upper quadrant discomfort or pain may also reflect gallbladder or pancreatic diseases. IBS may also be confused with gastric disorders or gallbladder diseases or even gastroparesis – all of which are associated with nausea. Most patients learn to adjust their dietary choices during the day to avoid foods that they know will worsen nausea or provoke vomiting. The physician should be aware how the patient has altered their diet to decrease postprandial symptoms and whether or not weight loss has occurred.

Patients learn to snack on small volumes of food throughout the day and thereby limit their postprandial nausea and especially vomiting episodes by their dietary choices. Oftentimes patients do not eat lunch if they are at work and are afraid to evoke symptoms by eating. By dinnertime, patients may only ingest small amounts of starches or light meals to limit symptoms. The foods selected by patients with gastroparesis can help to control symptoms and maintain nutrition. Dietary/nutritional recommendations for patients with nausea and vomiting are discussed in Chap.

11. A differential diagnosis can be formulated as the chronology of the patient's nausea, early satiety, and discomfort/pain are understood.

As described above, the location of nausea may also help the physician develop a differential diagnosis and diagnostic test approach. Some patients locate their nausea in the epigastrium *and* in the chest area, suggesting gastric-related and esophagus-related mechanisms of nausea are present (Fig. 3.3). Only 20–30 % of patients with symptoms associated with gastroparesis actually have delayed gastric emptying tests [17, 18]. The majority of symptomatic patients have normal endoscopy and normal gastric emptying and have disorders named with several terms: functional dyspepsia, postprandial distress syndrome, "gastroparesis-like" syndrome, chronic idiopathic nausea, or chronic unexplained nausea and vomiting [17, 19].

The nature of the vomitus also helps in differential diagnosis. Vomitus containing undigested, chewed food suggests gastroparesis. Vomitus containing small amounts of yellow fluid reflects gastric juice. Vomitus containing finely milled particles reflects gastric outlet obstruction. Hematemesis indicates erosion or ulcers reflecting mucosal disease. Recurrent vomiting and retching can lead to Mallory-Weiss tears and hematemesis. Vomiting bilious liquids suggests small bowel obstruction. Uncontrolled, severe vomiting episodes lasting for days but followed by complete recovery may indicate cyclic vomiting syndrome. Projectile vomiting is classically associated with central nervous system (CNS) diseases.

In addition to considering a differential diagnosis of gastric disorders, CNS and autonomic nervous system (ANS) diseases should always be reviewed while obtaining the chronology of the unexplained nausea. Patients who describe nausea upon standing up or getting up from a supine position (in contrast to postprandial exacerbation of nausea) may have orthostatic intolerance and postural orthostatic tachycardia syndrome (POTS). Nausea and vomiting dominates the clinical presentation in some patients with POTS [15], while lightheadedness and syncope are less obvious components of the presentation. Patients with POTS have gastric dysrhythmias and a minority have gastroparesis [15]. POTS needs to be differentiated from orthostatic hypotension due to dehydration. ANS disorders and nausea are reviewed in Chap. 7.

CNS disorders also need to be considered in the evaluation of patients with nausea and vomiting, even those who have an established esophageal or gastric diagnosis. Less than 1% of patients seen in our clinic indicated the location of their nausea was in their head (Fig. 3.4) [2]. These patients had migraine. Patients with migraine headaches can usually differentiate the nausea associated with their headaches and the nausea they perceive in their abdomen. Movement-induced nausea may indicate vestibular diseases, but vertigo should be described by the patient. Nausea and vomiting related to CNS disorders are reviewed in Chap. 8.

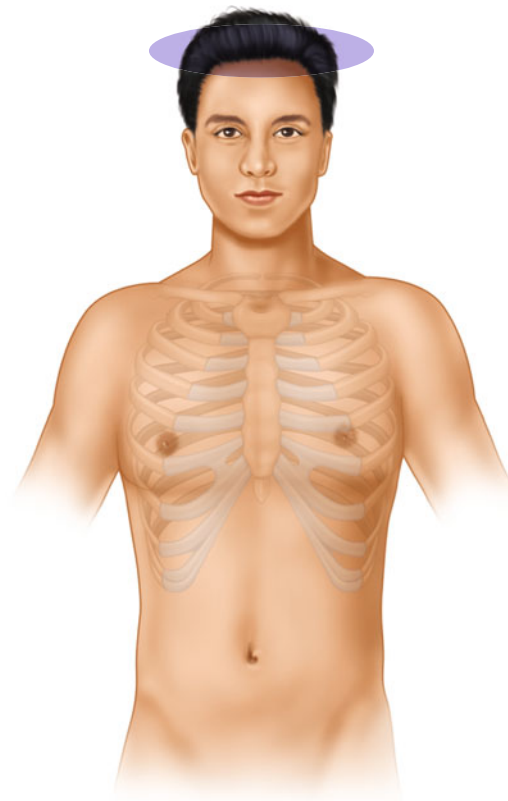

Fig. 3.4 On this Nausea Locator diagram, the patient indicated their nausea was only located in their head

To understand symptoms of postprandial nausea, early satiety, and excess gastric fullness and discomfort, it is important to appreciate normal postprandial gastric neuromuscular function. Therefore, the normal gastric neuromuscular activities in the postprandial period are reviewed below.

Normal Postprandial Gastric Neuromuscular Activity

After ingestion of foods, healthy individuals experience a comfortable fullness in the epigastrium, a pleasurable reward for ingesting foods that will nourish the body. During this pleasant postprandial period, the stomach produces considerable neuromuscular work (Fig. 3.5). Gastric neuromuscular work begins with fundic relaxation which occurs to accommodate the volume of food ingested [6]. Vagal-mediated release of nitric oxide relaxes the fundic smooth muscle.

Solid foods within the fundus are slowly emptied into the corpus and antrum which together are considered the mixing chamber of the stomach. Ingested solid foods are mixed or triturated until the foods are reduced to a nutrient suspension termed chyme which contains one to two millimeter food particles in suspension of gastric juices. As chyme is formed, the work of gastric emptying begins. Gastric emptying is highly regulated such that each peristaltic wave empties 2–4 ml of chyme through the pylorus and into the duodenum.

Three gastric peristaltic contractions normally occur each minute because they are paced by the normal 3 cycles per minute (cpm) gastric slow waves (Fig. 3.6). Gastric slow waves originate from interstitial cells of Cajal (ICC) and propagate from the pacemaker area on the greater curvature of the proximal corpus and migrate aborally toward the pylorus at a rate of 3 cpm. Plateau and action potentials linked to the slow waves form the migrating circular muscle contractions that are the gastric peristaltic waves that triturate and empty gastric contents. The pylorus regulates outflow by contracting or relaxing in coordination with the 3 cpm antral peristaltic waves [6]. This process of emptying a solid meal is slow and gentle. In healthy subjects, a 257 calorie Eggbeaters™ test meal elicits the gastric neuromuscular work of fundic relaxation and antro-pyloric peristalsis to accomplish trituration and emptying of the test meal over a 4-h process to completely empty the meal from the stomach into the duodenum.

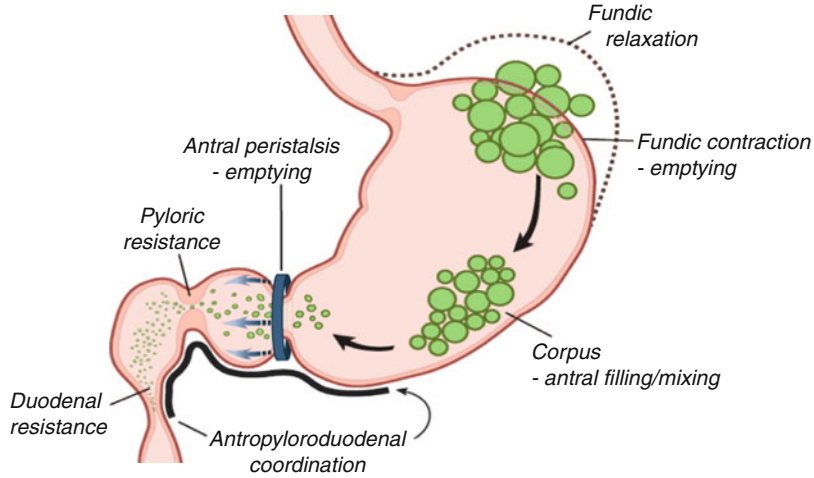

Fig. 3.5 Normal postprandial gastric neuromuscular work is shown. The key gastric neuromuscular activities are fundic relaxation and corpus-antral peristalsis. The fundus relaxes to accommodate the ingested volume of solid food. The recurrent peristaltic waves in the corpus and antrum (**a**) triturate (or mill) the meal, and (**b**) empty the milled food termed chyme in two to four ml aliquots through the open pyloric sphincter into the duodenum (Modified from Ref. [6] See text for details)

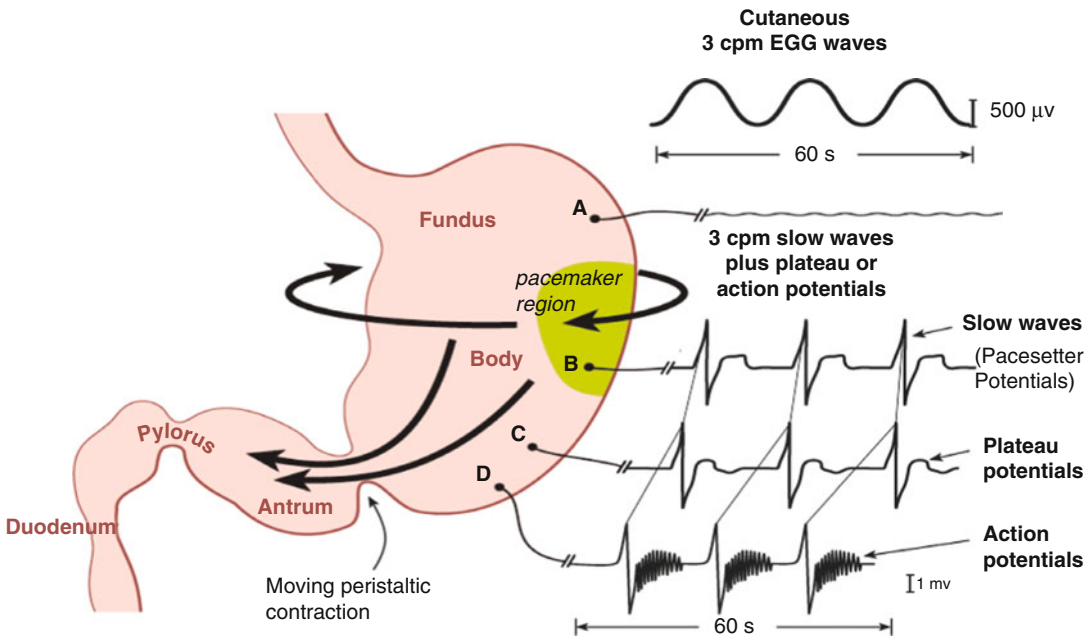

Fig. 3.6 The illustration shows gastric electrical activity recorded from serosal electrodes. Note that electrode *A* channel in the fundus does not have the 3 cpm myoelectric activity that is recorded in the body and antrum (electrodes *B*, *C*, *D*). Slow waves with or without plateau potentials and action potentials originate in the gastric pacemaker region on the greater curvature of the stomach between the fundus and the corpus. In 20 s sweeps, these electrical waves migrate both circumferentially and distally through the corpus and antrum and dissolve at the pylorus. In response to the release of acetylcholine, stretch, or other stimuli, plateau potentials and action potentials are elicited during circular muscle contraction. The linkage of slow waves and plateau and action potentials results in peristaltic contractions which produce trituration and gastric emptying of the ingested food. Also shown are 3 cpm electrogastrogram (EGG) waves recorded with cutaneous electrodes. The 3 cpm waves represent the integrated sum of the gastric myoelectrical activities (GMAs) sweeping from the pacemaker region to the pylorus every 20 s (Modified from Ref. [6])

Gastric Neuromuscular Disorders and Nausea and Vomiting

Every aspect of normal gastric neuromuscular activity elicited by the ingestion of foods can become dysfunctional. Poor fundic accommodation, gastric dysrhythmias, antral hypomotility, and pylorospasm have been described in patients with nausea and vomiting [6]. Figure 3.7 illustrates gastric neuromuscular disorders that include subtle alterations in fundic relaxation, GMA, antral motility, and pyloric function, all of which may be present, but may or may not result in a delay in emptying of a test meal.

Patients with one or all of these gastric neuromuscular disorders have the symptoms *associated* with gastroparesis, such as nausea and vomiting, but over 70 % of patients with these symptoms do not have delayed gastric emptying [6, 19]. These patients have normal upper endoscopy and normal gastric emptying and have gastroparesis-like symptoms after ingestion of food [16]. This collection of symptoms is also termed functional dyspepsia or postprandial distress syndrome [17, 19], and if nausea and vomiting are prominent then the terms chronic unexplained nausea and vomiting (CUNV) or chronic idiopathic nausea (CIN) are used [17]. Approximately 60 % of these patients have subtle neuromuscular disorders of the stomach such as gastric dysrhythmias with or without gastric accommodation defects [20–22].

At the other end of the continuum, the most severe gastric neuromuscular dysfunction results in a delay in gastric emptying in the absence of mechanical obstruction. These patients have

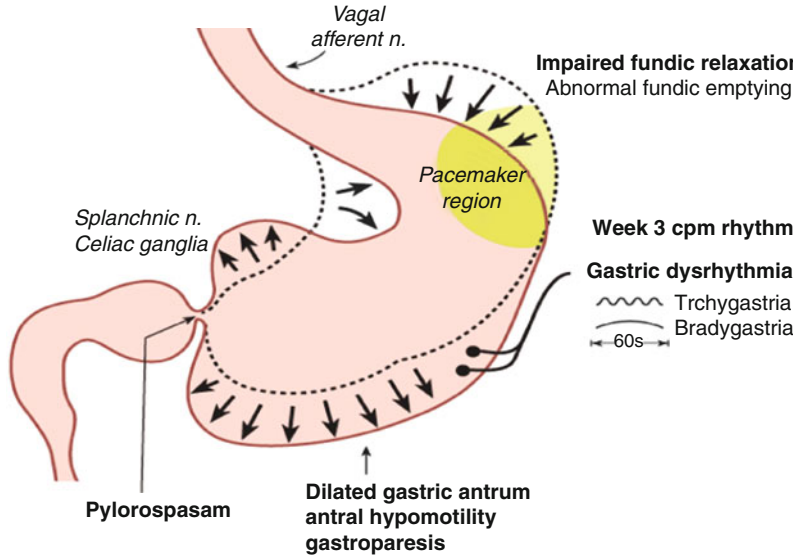

Fig. 3.7 Neuromuscular dysfunction of the stomach includes: (1) impaired fundic relaxation due to lack of nitric oxide release from the vagus nerve, (2) gastric dysrhythmias ranging from tachygastrias to bradygastrias to mixed dysrhythmias due to depletion of the gastric ICCs, (3) dilated gastric antrum and antral hypomotility, and (4) pylorospasm. These neuromuscular dysfunctions may or may not result in gastroparesis (Modified from Ref. [6])

gastroparesis, recurrent nausea and vomiting, and some experience significant weight loss. If gastroparesis is documented by an appropriate solid-phase gastric emptying study, then six categories of gastroparesis should be considered (Table 3.4). The reversible forms of gastroparesis should be ruled out: obstructive and ischemic gastroparesis. The two most common categories of gastroparesis are idiopathic and diabetic gastroparesis [6]. Idiopathic gastroparesis is the largest category; in these patients, gastroparesis is often preceded by viral illness, food poisoning, or exposure to antibiotics or anesthetics. Thirty to forty percent of patients with type 1 or type 2 diabetes develop gastroparesis [23]. These patients often have a history of difficult to control glycemia. Hyperglycemia itself (>220 mg/dl) induces gastric dysrhythmias and decreased antral contractility [24].

An approach to the diagnosis and treatment of patients with normal endoscopy with CUNV, with or without gastroparesis, based on distinct neuromuscular gastric pathophysiologies is reviewed below.

Physical Examination

The physical examination in patients with nausea and vomiting and gastric neuromuscular disorders may be normal. Patients often appear healthy. Surprisingly, over 40 % of patients with gastroparesis are overweight or obese [25]. These patients' physical appearance is unfortunately off-putting to many physicians given that patients are presenting with nausea and vomiting symptoms. The weight gain in these patients is not understood but has been attributed, in part, to the high starch diets that are easier for the stomach to empty compared with healthier foods like fresh fruits and vegetables that often elicit noxious early satiety and nausea symptoms. Decrease in physical activity often accompanies chronic nausea, a symptom which also elicits depression and fatigue, all of which leads to weight gain.

However, a subset of patients with nausea and vomiting and gastroparesis cannot maintain their weight. These patients appear emaciated. Cheilosis and hair loss may be noted. Heart and lung exams are usually normal. The abdomen may be scaphoid or distended and tympanitic. A distended abdomen suggests intestinal pseudo-obstruction, bacterial overgrowth, or constipation, or all of the above. An abdominal bruit may be present and may indicate chronic mesenteric ischemia, a rare but reversible cause of gastroparesis.

Abdominal scars from previous surgical incisions should be palpated for local tenderness. Oftentimes these scars are exquisitely tender and may actually represent the *sourc*e of the patient's abdominal pain and nausea. Carnett's sign should

Table 3.4 Causes of gastroparesis

Diagnosis	Incidence (%)
1. Idiopathic gastroparesis[a]	40
2. Diabetic gastroparesis (type 1 and 2)	30
3. Postsurgical gastroparesis (antrectomy, vagotomy, fundectomy, fundoplication)	20
4. Obstructive gastroparesis (pyloric stenosis versus spasm)[b]	10
5. Ischemic gastroparesis[b]	<1
6. Miscellaneous causes (collagen vascular diseases, muscular dystrophies, Parkinson's, amyloidosis)	<1

[a] Potential causes: Postviral; drug induced; degenerative or inflammatory processes of enteric nerves, interstitial cells of Cajal, smooth muscle

[b] Reversible form of gastroparesis

be elicited [26, 27]. If Carnett's sign is positive, then the abdominal pain is actually due, at least in part, to an abdominal wall syndrome. This abdominal pain may have been attributed to "the stomach" by the patient and physician. For this reason, Carnett's sign is extremely important in the physical examination of patients with unexplained nausea and abdominal pain and is described below in detail.

To test for Carnett's sign, the patient lies in supine position on the examination table and indicates with their hand where the abdominal pain is located. Abdominal wall pain is localized by a single finger to a highly focused point, often at or near an abdominal scar produced at a trocar site from previous laparoscopic cholecystectomy or other abdominal operations. The examining physician gently presses on the tender point until modest discomfort is elicited (e.g., two or three over ten). The patient is then asked to flex their head until the physician feels the rectus muscles contract. At the same time the patient is asked to rate their abdominal pain. Carnett's sign is positive if the abdominal pain immediately *increases* to a higher level (perhaps even to a seven or nine over ten) *and* reproduces the patient's typical abdominal pain, the same pain often attributed to the stomach disorder or gastroparesis. This is a positive Carnett's sign and indicates the source of pain is in the abdominal wall. (Another and more provocative way to increase rectus muscle contraction is to ask the patient to do a straight leg lift.) In many cases, the patient's typical nausea is also elicited as the pain increases during a positive Carnett's test.

If pain does not increase during head flexion, then the scar is not relevant to the pain syndrome. If pain *decreases* during head flexion, then the pain may be due to an intra-abdominal disease or disorder. The splinting of the abdominal wall during head flexion reduces the pressure on the diseased intra-abdominal organ and thus pain is reduced. Treatment of an abdominal wall syndrome should be addressed by pain clinic specialists. Abdominal hernias and other anatomical defects should also be excluded as a cause of pain. See Chap. 5 for a full review of abdominal wall pain and nausea and vomiting.

Laboratory Tests

Routine laboratory tests should be ordered. A CBC is obtained to determine if anemia is present. Liver function tests and a lipase exclude hepatitis and pancreatitis. Vitamin D and B_{12} levels are determined. In the appropriate patients, HbA1c, rheumatoid factor, ANA, and CRP are measured. Tests for TSH and fasting cortisol are important to rule out hypo- or hyperthyroidism and adrenal diseases. A low-fasting cortisol should be followed up with a cosyntropin stimulation test. Referral to endocrinology should be considered. Nausea and vomiting due to endocrine disorders are discussed in Chap. 6.

Standard Diagnostic Tests

Endoscopy is performed to diagnose esophageal, gastric, or duodenal mucosa abnormalities which may underlie the patient's nausea and vomiting. Chronic cholecystitis or gallbladder emptying abnormalities may also cause the same postprandial symptoms associated with gastroparesis. Gallbladder diseases must be excluded as chronic gallbladder symptoms are similar to nausea, abdominal discomfort/pain and vomiting that are caused by gastric, small bowel (small bowel

bacterial overgrowth), and colonic neuromuscular disorders (irritable bowel syndrome). Gallbladder ultrasound and emptying tests are needed to exclude gallbladder disease. A breath test for small bowel bacterial overgrowth should be ordered. Celiac disease and malabsorption should be considered. Symptoms consistent with irritable bowel syndrome should be treated.

In many patients with unexplained nausea and vomiting, the standard diagnostic tests are normal and empiric treatment with acid suppression therapy or prokinetic drugs are not helpful. Gastric neuromuscular disorders should be considered and tests to diagnose these disorders are reviewed below.

Diagnostic Tests of Gastric Neuromuscular Function

If endoscopy and gallbladder and pancreatic tests are normal and constipation or irritable bowel syndrome have been treated as much as possible, then tests of gastric neuromuscular function are needed. These tests establish objective pathophysiological abnormalities and diagnoses related to stomach neuromuscular dysfunction that may explain the patient's symptoms and direct treatments. Tests of gastric emptying and GMA are reviewed below.

Gastric Emptying Tests

Three gastric emptying tests are currently available. The standard test is the 4-h solid phase gastric emptying test using a 255 calorie egg substitute sandwich test meal [28]. The Eggbeaters™ is labeled with technetium sulfur colloid. Normal values for men and women are established. Gastroparesis is defined as greater than 60 % of the meal retained in the stomach at 2 h and greater than 10 % retained at the end of 4 h of gastric neuromuscular work.

The wireless motility capsule is a device which is ingested with a standard nutrient bar that contains approximately 260 calories with similar carbohydrate and protein proportions as the Eggbeaters test meal. The wireless capsule records and transmits intraluminal pH, pressure, and temperature. As the capsule empties from the stomach into the duodenum, the pH increases and the time of gastric transit or emptying is determined [29]. The normal time for gastric emptying of the capsule is less than 5 h. Gastroparesis is diagnosed when gastric emptying is 5 h or longer. Small bowel transit and colonic transit can also be determined using this test.

A breath test for gastric emptying was approved by the FDA in 2015. A muffin containing C^{13}–labeled Spirulina platensis is ingested and breath samples are obtained for 4 h after the meal. C^{13} counts are determined in the breath samples each hour and the gastric emptying curve is established. Normal or abnormal gastric emptying correlates well with the technetium-labeled gastric emptying test [30]. However, patient selection issues for this test are important. If the patient has pancreatic or small bowel mucosal diseases or if liver disease or lung diseases are present, then the absorption, metabolism, and exhalation of the C^{13}, respectively, may be delayed and result in false positive tests for gastroparesis.

Results of the three gastric emptying tests indicate delay in the emptying of the test meal, but the tests *do not define the cause* of the delay in gastric emptying (e.g., gastric outlet obstruction). The causes of gastroparesis should be reviewed in the context of the patient's history, physical exam, and laboratory findings (Table 3.4). Reversible causes of gastroparesis due to pyloric or duodenal obstruction or chronic mesenteric ischemia should be considered.

Gastric Myoelectrical Activity (GMA) Tests

Electrodes placed on the abdominal skin in the epigastrium are used to record the bioelectric signal termed an electrogastrogram (EGG) [31]. In healthy subjects the normal GMA rhythm is 3 cpm. The amplitude of the 3 cpm GMA increases in response to standard tests such as a water load test (WLT) [22]. The 3 cpm rhythm indicates a normal complement of ICCs, the gastric pacemaker cells, are present in the gastric wall. Healthy subjects who have normal 3 cpm

GMA have >5 ICCs per high power field (hpf) [32, 33]. On the other hand, patients with gastroparesis have a variety of gastric dysrhythmias and <5 ICCs/hpf [33]. Tachygastrias are defined as frequencies from 3.5 to 10 cpm, bradygastria ranges from 1 to 2.5 cpm, whereas the normal frequency range is 2.5–3.5 cpm [31, 33, 34].

Most patients with gastroparesis have depleted ICCs (<5 ICCs/hpf) and have tachygastrias, bradygastrias, and a variety of slow wave conduction defects [32, 33]. In patients with gastroparesis, the ICCs/hpf are in the 1–2 range [32, 33]. Interestingly, patients with CUNV and normal gastric emptying have gastric dysrhythmias and numbers of ICCs that are intermediate (2–3 ICCs/hpf) between patients with gastroparesis and those with normal gastric emptying as [34]; and almost 60 % of patients with dysmotility-like functional dyspepsia (e.g., CUNV) had gastric dysrhythmias – tachygastrias, bradygastrias, and mixed dysrhythmias – after ingestion of a non-caloric WLT [22].

Combining the Results of the Gastric Emptying and EGG Tests: Four Pathophysiological Phenotypes in Patients with Unexplained Nausea and Vomiting

The goal of testing gastric neuromuscular function is to establish diagnoses that will explain symptoms and guide treatments. By combining results of gastric emptying tests (GET) and tests of GMA, four distinct categories are formed that are helpful in determining the cause of unexplained nausea and vomiting. Patients with CUNV often have very similar presentations, but they actually have very different GET and GMA phenotypes from a gastric neuromuscular disorders viewpoint. Figure 3.8 shows a cohort of patients from our clinic with gastroparesis and abnormal or normal GMA. Almost 80 % of the patients with gastroparesis had a gastric dysrhythmia, indicating marked depletion of ICCs (Category 1). An example of tachygastria in such a patient is

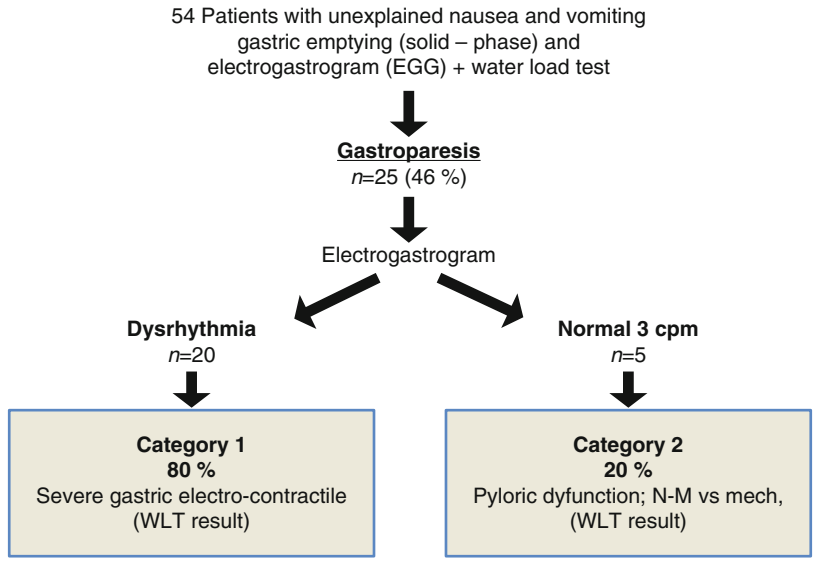

Fig. 3.8 A pathophysiological approach to gastric neuromuscular diseases using two diagnostic modalities: (**a**) solid phase gastric emptying and (**b**) electrogastrogram with water load test. Patients with gastroparesis and gastric dysrhythmias have depleted ICCs (<5 ICCs/hpf) (*Category 1*). In contrast, patients in *Category 2* have gastroparesis and normal 3 cpm myoelectrical activity and thus have normal ICCs (>5 ICCs/hpf) in the corpus-antrum. Pyloric dysfunction such as pylorospasm or pyloric obstruction in *Category 2* patients results in gastric outlet obstruction due to fixed stenosis or pyloric neuromuscular dysfunction. Patients in either category may have gastric accommodation deficits as indicated by the water load test (WLT) result. The WLT volume may be normal (>550 ml) or abnormal (<550 ml), indicating gastric accommodation dysfunction

shown in Fig. 3.9. Therapies for these patients are described below.

On the other hand, 20 % of the patients with gastroparesis had normal 3 cpm GMA (Category 2). In patients with gastroparesis, the normal 3 cpm GMA is a *discordant* finding because normal 3 cpm GMA indicates there is a normal complement of ICCs (>5 ICCs/hpf) in the corpus-antrum, and yet these patients have delayed gastric emptying. Figure. 3.10 shows an example of normal 3 cpm GMA recorded in an electrogastrogram in a diabetic patient with documented gastroparesis. The combination of gastroparesis and *normal* 3 cpm GMA suggests that the key abnormality in these patients is pyloric dysfunction [35]. This combination is an obstructive gastroparesis phenotype and is further discussed below.

The combination of high-amplitude 3 cpm GMA and gastroparesis was described in patients with fixed, mechanical obstruction at the pylorus (e.g., peptic ulcer disease). Treatment was surgical [35]. Thus, one form of obstructive gastroparesis is delayed gastric emptying secondary to a mechanical fixed obstruction at the pylorus. This form of obstructive gastroparesis should not be missed and treatment is pyloric dilation or surgical operation.

In most patients with gastroparesis and normal 3 cpm GMA, the pylorus is normal at endoscopy, suggesting pylorospasm or dyschalasia is the pyloric disorder causing gastroparesis [12]. Postpyloroplasty gastric emptying tests showed normal or even rapid gastric emptying in this subtype of obstructive gastroparesis as shown in Fig. 3.11

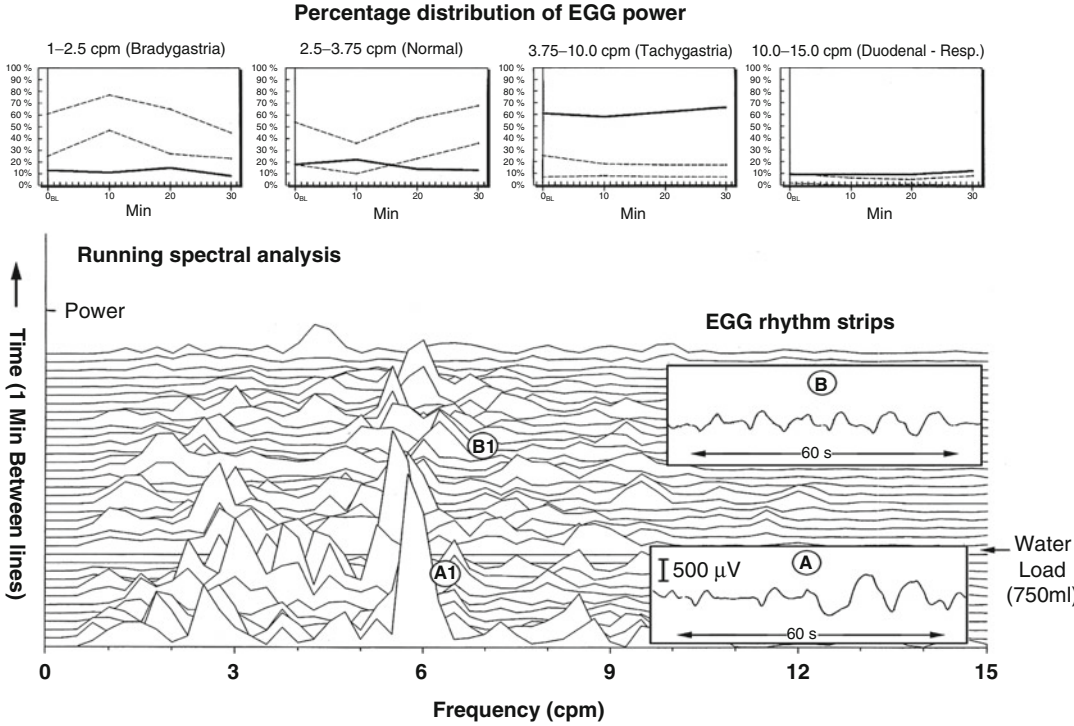

Fig. 3.9 Tachygastria recorded in an electrogastrogram (EGG) after a water load test in a patient with gastroparesis is shown (Category 1). The EGG rhythm strips show a 6 cpm tachygastria before and after a normal water load test volume of 750 ml. The normal volume of water ingested suggests that gastric accommodation or capacity is normal. However, the EGG and running spectral analysis shows that the predominant peaks are in the 6 cpm tachygastria frequency range as shown in *A* and *A1* and *B* and *B1*. The *X*-axis shows frequency in cycles per minute, the *Y*-axis shows time in minutes, and the *Z*-axis shows the power of various frequencies in the EGG signal. There are very few peaks in the normal 3 cpm rhythm, reflecting that ICCs are depleted in the corpus-antrum. Percentage distribution of EGG power diagrams show that the percentage in the tachygastria range is markedly increased and the percentage in the normal 3 cpm range is below normal. This patient has tachygastria and gastroparesis (Category 1)

[13]. The fact that gastric emptying normalized after the pyloric therapy indicates that the pylorus was a key pathophysiological abnormality in this obstructive subtype of gastroparesis.

On the other hand, the majority of patients with CUNV have normal endoscopy *and* normal gastric emptying. As shown in Fig. 3.12, these symptomatic patients with normal gastric emptying are further characterized by the GMA results. Almost 60 % of CUNV patients have gastric dysrhythmias such as tachygastria, bradygastria, or mixed gastric dysrhythmia (Category 3). In these cases the loss of ICCs is severe enough to result in gastric dysrhythmia, but not gastroparesis. Many of these patients also ingested < 550 ml of water during the WLT, indicating poor gastric accommodation or capacity as shown in Fig. 3.13 [22]. Ingestion of water or Ensure™ during the EGG recording is a provocative test to stimulate GMA, but ingestion also immediately evokes nausea and the symptoms associated with gastroparesis [22]. Gastric dysrhythmias and accommodation dysfunction defined during the EGG and water or caloric load tests are mechanisms of nausea and postprandial symptoms to be considered in these patients [18, 20, 22]. Moreover, a pathophysiological basis for these symptomatic patients with gastric dysrhythmias but normal gastric emptying is now appreciated as they have decreased ICCs [34].

Finally, some patients with CUNV have *normal* gastric emptying *and normal* 3 cpm GMA (Category 4). These objective findings indicate that gastric bioelectric rhythm and the neuromuscular work of gastric emptying are normal. However, if a poor WLT volume evokes nausea,

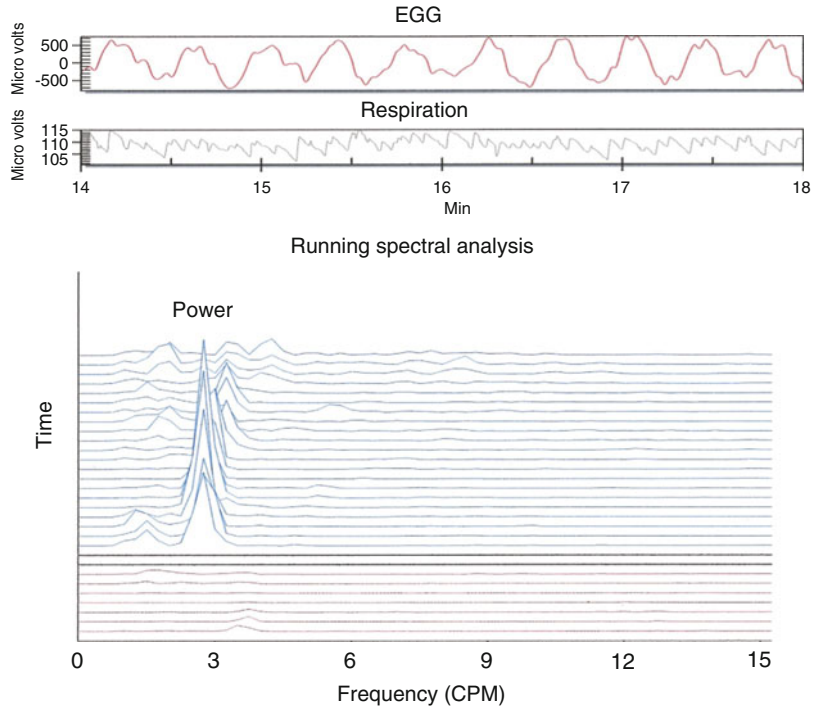

Fig. 3.10 Normal 3 cpm GMA recorded in an electrogastrogram (*EGG*) in response to the water load test in a patient with diabetic gastroparesis is shown. The normal 3 cpm GMA in the EGG rhythm strip indicates normal numbers of ICCs are present in the corpus-antrum. Thus, this patient has gastroparesis and normal 3 cpm GMA (Category 2), suggesting gastric outlet obstruction or pylorospasm is responsible for the delayed emptying. Note the EGG shows regular 3 cpm GMA and the running spectral analysis shows peaks in the 3 cpm range after the water load. The *X*-axis indicates gastric frequency, the *Y*-axis it time, and the *Z*-axis is the power in the various frequencies from 1 to 15 cpm. The two *solid dark lines* in the running spectral analysis indicate the time when the water was ingested

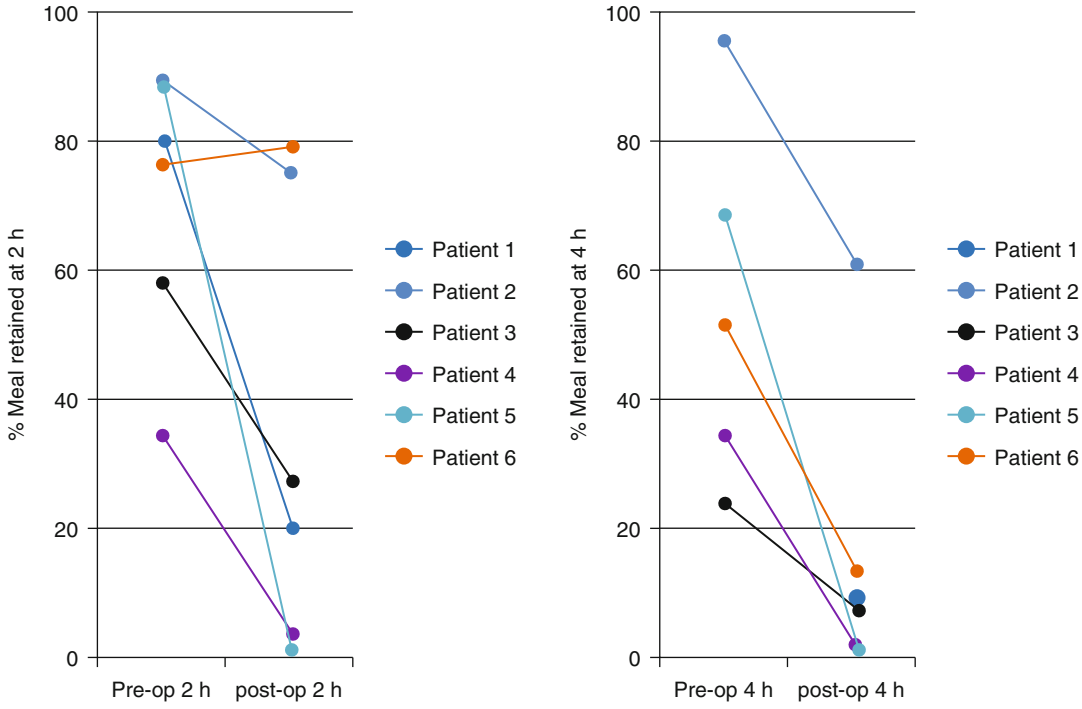

Fig. 3.11 Effect of pyloroplasty on gastric emptying in patients with GP and normal 3 cpm GMA. Pre-pyloroplasty (Pre-Op) and the post-pyloroplasty (Post-Op) emptying tests are shown. Percentages of meal retained at 2 and 4 h are significantly improved after pyloroplasty. Five of the six patients have normal gastric emptying at 4 h. Patient 2 had diabetic gastroparesis and although gastric emptying improved after pyloroplasty, gastric emptying did not normalize

then a gastric accommodation disorder and visceral hypersensitivity may be present in these patients. On the other hand, if the WLT volume is normal and nausea is not evoked, then the nausea and vomiting in these patients likely is related to *non-gastric* disorders/diseases, because endoscopy, GMA, gastric emptying, and gastric accommodation are all normal. Non-gastric diseases like atypical GERD, chronic cholecystitis, small bowel bacterial overgrowth or irritable bowel syndrome should be reviewed. Moreover, causes of nausea and vomiting outside of the digestive system also should be reviewed. Nausea and vomiting from other organ systems such as endocrine or ANS and CNS are described in Chaps. 6, 7, and 8.

In summary, combining results from two testing modalities – gastric emptying and GMA – defines a continuum of gastric neuromuscular disorders (and four pathophysiologic subtypes) in patients with similar unexplained nausea and vomiting syndromes (Fig. 3.14). The fourth group (Category 4) actually identifies normal gastric neuromuscular function and suggests that *non-gastric* or *non-GI* causes of symptoms should be considered in this patient group. These four groups of patients with similar CUNV symptoms have distinct pathophysiological attributes that can guide patient education, therapy, or further diagnostic testing as described below.

Nausea and Vomiting and Stomach Neuromuscular Diseases: A Rational Treatment Approach

The dietary, drug, device, and pyloric therapies for patients with gastroparesis and CUNV are described below in the context of the patients' objective physiological test results of gastric emp-

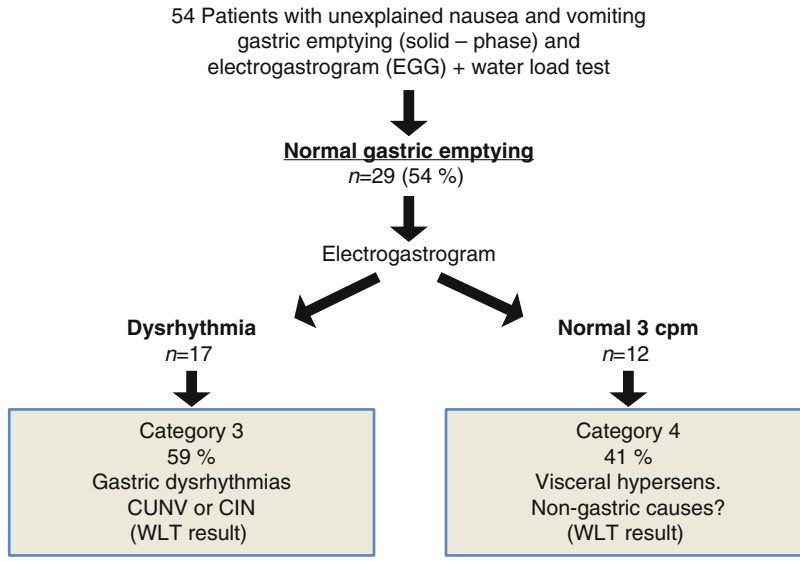

Fig. 3.12 A pathophysiological approach to gastric neuromuscular diseases using two diagnostic modalities: solid phase gastric emptying and electrogastrogram with water load test. The majority (>75 %) of patients with unexplained nausea and vomiting have normal gastric emptying but almost 60 % of these patients have gastric dysrhythmia, an objective finding that may explain their symptoms (*Category 3*). These patients have gastric dysrhythmias and decreased ICCs, but the loss of ICCs is less than in patients with gastroparesis. *Category 4* patients have *normal* gastric emptying *and normal* 3 cpm GMA, indicating stomach neuromuscular function is normal. However, if the WLT is abnormal or normal, then symptoms may be due to poor gastric accommodation or visceral hypersensitivity, respectively. If WLT volume is normal and no nausea is evoked, then it is likely that symptoms are due to *non-gastric* causes. See text for details

tying and GMA: *Category 1*: Gastroparesis and gastric dysrhythmia; *Category 2*: Gastroparesis and normal GMA; *Category 3*: Normal gastric emptying and gastric dysrhythmia; *Category 4*: Normal gastric empting and normal GMA.

Gastroparesis with Gastric Dysrhythmias (Category 1)

Diet for Hydration, Symptom Reduction, and Nutrition

Category 1 patients with gastroparesis, gastric dysrhythmias, and decreased gastric compliance need advice and counseling about their food choices for reducing postprandial symptoms and for maintaining nutrition. Advice and counseling regarding diet is provided for less than 20 % of patients with gastroparesis [25]. Caloric, vitamin, and mineral deficiencies are common. A simple three-step diet for patients with nausea and vomiting with or without gastroparesis is shown in Table 3.5. The food choices in the three-step diet are based on the physiologic principles that nutritious liquids and certain solid foods need minimal trituration and are generally emptied from the stomach easier even in patients with gastroparesis [6].

The liquids recommended in Step 1 contain glucose, salt, and potassium and are ingested to avoid dehydration on days when nausea is severe and vomiting is frequent. The Step 2 liquid foods such as soups and smoothies are nutritious liquids that are easier to triturate and empty than solid foods. In terms of solid nutrients, starches are triturated and emptied faster than proteins (e.g., mash potatoes versus red meats) as outlined in Step 3. Fatty or fried foods normally delay gastric emptying and are poor choices in patients who already have delayed emptying. Diets of small particle foods (like Step 3 choices) decreased symptoms associated

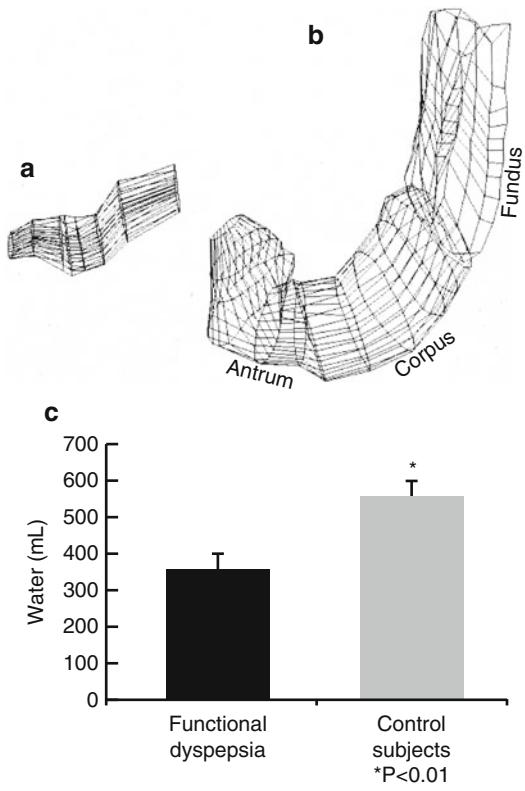

Fig. 3.13 Ultrasound images (3-D) of the stomach during fasting (**a**) and 10 min after a healthy subject ingested a 500 ml soup meal (**b**) are shown. After ingestion of the soup meal not only the fundus but also the corpus and antrum have all accommodated the ingested volume. The figure illustrates postprandial gastric accommodation and capacity in response to a liquid volume. The average volume of water ingested over a 5-min period during the water load test in healthy control subjects and patients with functional dyspepsia (dysmotility-like dyspepsia) is shown in (**c**). Control subjects ingested approximately 550 ml of water and felt completely full, whereas patients with functional dyspepsia (dysmotility type) ingested only 350 ml and felt completely full but also reported nausea. The poor water load volume indicates poor gastric capacity or accommodation

with gastroparesis significantly more than the standard diabetic diet in patients with diabetic gastroparesis [36]. Fibrous foods such as fresh fruits and vegetables are the most difficult to triturate in that they require more neuromuscular work to break down and empty compared with the items in Step 1 and 2. Thus, ingestion of fibrous foods (including foods considered FODMAPs) and fats often increase symptoms that are associated with gastroparesis [37]. Most patients learn these dietary lessons the hard way and then adjust their diets. By choosing appropriate foods with knowledge that gastroparesis means weak stomach contractions and poor stomach accommodation (capacity), patients can reduce symptoms and maintain nutrition. Nutritional management for patients with nausea and vomiting is presented in Chap. 11.

Medications

Few specific medications with discrete gastric neuromuscular receptor targets are available for the treatment of nausea and vomiting related to gastric neuromuscular disorders such as gastroparesis with gastric dysrhythmias (Category 1) or gastric dysrhythmias (Category 1 and 3). Currently available prokinetic agents are limited to metoclopramide and erythromycin (Table 3.6). Erythromycin may help symptoms of early satiety and prolonged fullness. Metoclopramide and domperidone increase gastric emptying, can convert gastric dysrhythmias to normal 3 cpm rhythms [38–40], and decrease nausea. Domperidone is available from the FDA on a compassionate clearance basis. A variety of antinauseants and antiemetic agents are also listed in Table 3.6. There are no therapeutic trials to provide objective results for these drugs in our patients with nausea and vomiting from GI neuromuscular disorders (Category 1 and 3). A comprehensive review of prokinetic, antinauseant, and antiemetic drugs and complimentary therapies for nausea and vomiting are provided in Chaps. 9 and 12, respectively. When symptoms are refractory to multiple drug trials and dietary changes in Category 1 patients, then gastric electrical stimulation may be considered.

Gastric Electrical Stimulation Therapies

Electrical therapies also include acustimulation applied to traditional Chinese acupuncture points. These therapies can be used with medications and diet described above. Gastric electrical stimulation therapies should be considered in Category 1 patients with gastroparesis and gastric dysrhythmias who have nausea and vomiting despite diet advice and multiple medication trials (Table 3.7).

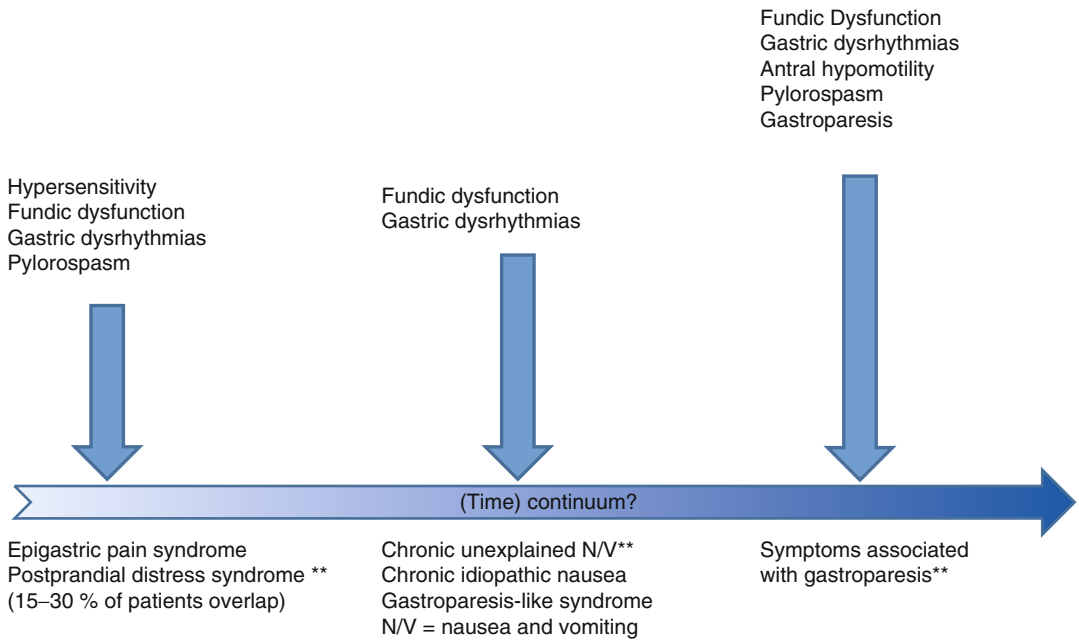

Fig. 3.14 Continuum of gastric neuromuscular disorders. This figure shows a continuum of gastric neuromuscular dysfunction. Subtle changes like visceral hypersensitivity, poor fundic or stomach accommodation, and gastric dysrhythmias may mediate postprandial symptoms in some patients. Clinical diagnostic labels include terms such as dysmotility-like or epigastric pain-like dyspepsia, postprandial distress syndrome, CUNV, CIN – the gastroparesis-like symptoms. At the other end of the continuum is gastroparesis. Patients with gastroparesis have the same symptoms and usually have all of the neuromuscular disorders on the continuum. However, a subset of gastroparesis patients has normal 3 cpm GMA (not gastric dysrhythmias) and is termed obstructive gastroparesis. The spectrum of gastric neuromuscular disorders is mediated by a variable loss of ICCs and enteric neurons in the corpus, antrum, and pylorus (** Early satiety, prolonged fullness, nausea, vomiting, discomfort/pain)

Electrical stimulation is applied directly to the stomach through two electrodes placed on the antrum 10 cm from the pylorus (Enterra™ therapy, Medtronic, Inc., Minneapolis, MN). The basic stimulation parameters produce high frequency, low amplitude input (14 Hz, 330 microsec, 1 s on, 4 s off, 12 cpm, 5 milliamps) and reduce vomiting episodes and often improve nausea. However, double-blind trials in diabetic gastroparesis have not shown significant symptom improvement with active compared with placebo stimulation [41]. For patients with recalcitrant nausea and vomiting, gastric electrical stimulation is an option through a humanitarian device exemption from the FDA. Gastric electrical stimulation is more efficacious in patients with diabetic gastroparesis compared with patients who have idiopathic gastroparesis. Patients with more preserved 3 cpm GMA (and less tachygastria) have better symptom response to GES compared with patients with little or no 3 cpm GMA and more tachygastria [42]. Obstructive gastroparesis should be excluded before embarking on GES since pyloric therapies (botulinum toxin A, balloon dilation, pyloroplasty) are effective and are more relevant to the pathophysiology of gastroparesis. A detailed review of gastric electrical stimulation is presented in Chap. 10.

Enteral and Total Parenteral Nutrition

In Category 1 patients in whom diet, drug, and device therapies have failed to control nausea and vomiting, weight loss and undernutrition are common. If more than 10 % of body weight is lost, these patients need nutritional support in the form of jejunal feedings through a surgically

Table 3.5 Diet for nausea and vomiting in patients with gastric neuromuscular disorders

Diet	Goal	Avoid
Step 1: *Sports drinks and bouillon*		
For severe nausea and vomiting: Small volumes of salty liquids, with some caloric content to avoid volume depletion Chewable multiple vitamin	1000–1500 mL/day in multiple servings (e.g., 12, 120-mL servings over 12–14 h) Patient can sip 30–60 mL at a time to reach approximately 120 mL/h	Citrus drinks of all kinds; highly sweetened drinks
Step 2: *Soups and smoothies*		
If Step 1 is tolerated: Soup with noodles or rice and crackers Smoothies with low fat dairy Peanut butter, cheese, and crackers in small amounts Caramels or other chewy confection Ingest above foods in at least six small-volume meals/day Chewable multiple vitamin	Approximately 1500 calories/day to avoid volume depletion and maintain weight (often more realistic than weight gain)	Creamy, milk-based liquids
Step 3: *Starches*, *chicken*, *fish*		
If Step 2 is tolerated: Noodles, pastas, potatoes (mashed or baked), rice, baked chicken breast, fish (all easily mixed and emptied by the stomach) Ingest solids in at least six small-volume meals/day Multiple vitamin (liquid or dissolvable)	Common foods that patient finds interesting and satisfying and that provoke minimal nausea/vomiting symptoms	Fatty foods that delay gastric emptying; red meats and fresh vegetables that require considerable trituration; pulpy fibrous foods that promote formation of bezoars

Modified from Koch [54]

placed jejunostomy (Table 3.7). Many patients with gastroparesis also have small bowel motility disorders and small bowel bacterial overgrowth, and these possibilities should be investigated and treated [43]. An initial trial of enteral feeding with a naso-duodenal tube is advisable to test overall tolerability. Enteral feeding rates must be started slowly at 10–20 ml per hour. Various formulas may be tried before a tolerable and effective enteral feeding program is established. Details on enteral feeding for patients with gastroparesis are found in Chap. 11.

In a minority of patients, total parenteral nutrition is required because gastric failure is profound, and small bowel failure (e.g., chronic intestinal pseudo-obstruction) is also present. Patients may not have small bowel dilation, but small bowel neuromuscular function may be poor. Thus, enteral feedings are not tolerated, and adequate caloric intake cannot be achieved. In these cases, TPN is the only option, but catheter-related sepsis usually develops at some point during the TPN.

Gastroparesis and Normal 3 cpm GMA: Obstructive Gastroparesis (Category 2)

Combining the two diagnostic modalities for gastric empting and GMA, Category 2 patients have gastroparesis and normal 3 cpm GMA (Figs. 3.8 and 3.10). These findings indicate pyloric stenosis or pyloric neuromuscular dysfunction and represent a distinct phenotype/subtype of gastroparesis – obstructive gastroparesis [12, 35]. In these cases, therapies are directed toward the pylorus. First, it is important to rule out fixed stenosis at the pylorus or post bulbar duodenum at endoscopy to ensure that mechanical causes of gastroparesis are excluded. In these cases, the mechanical obstruction is the key problem and

Table 3.6 Drugs used to treat nausea and vomiting due to gastric neuromuscular disorders

Therapy	Mechanisms and sites of action	Dosage	Adverse effects
Prokinetic therapy			
Macrolides			
Erythromycin	Motilin receptor agonist	125–250 mg four times daily	Nausea, diarrhea abdominal cramps, rash
Substituted benzamides			
Metoclopramide	Dopamine (D_2) receptor antagonist; 5-HT_3-receptor antagonist; 5-HT_4 receptor agonist	5–20 mg before meals and at bedtime	Extrapyramidal symptoms, dystonic reactions, anxiety, depression, hyperprolactinemia, tardive dyskinesia
Domperidone[a]	D_2-receptor antagonist (peripheral)	10–20 mg before meals and at bedtime	Hyperprolactinemia, breast tenderness, galactorrhea
Serotonin agonists			
Cisapride*	5-HT_4 receptor agonist	5–20 mg before meals	Cardiac dysrhythmias, diarrhea, abdominal discomfort
Tegaserod*	Partial 5-HT_4 receptor agonist	2–6 mg three times daily	Diarrhea, abdominal pain
Ghrelin agonist	Ghrelin receptor	TBD	Diarrhea, abdominal pain
Pro-relaxant therapies			
Dicyclomine	Muscarinic antagonist	10–20 mg before meals	Drowsiness, dry mouth
Botulinum toxin A (pyloric therapy)	see Endoscopic Therapies		
Anti-nauseant therapy			
Serotonin antagonists			
Ondansetron	5-HT_3 receptor antagonist	4–8 mg twice daily, either orally or intravenously	Headache, increased liver enzymes
Granisetron	5-HT_3 receptor antagonist	2 mg oral once daily or 3.1 mg transdermal patch	Headache, increased liver enzymes, constipation
Phenothiazines			
Prochlorperazine	Central nervous system (CNS) sites	5–10 mg three times daily	Hypotension, extrapyramidal symptoms
Antihistamines			
Promethazine	CNS, H_1 receptor antagonist	25 mg twice daily	Drowsiness
Dimenhydrinate	H_1 receptor antagonist	50 mg four times daily	Drowsiness
Cyclizine	H_1 receptor antagonist	50 mg four times daily	Drowsiness
Butyrophenones			
Droperidol	Central dopamine receptor antagonist	2.5–5 mg intravenously every 2 h	Sedation, hypotension
Antidepressants			
Amitriptyline	CNS sites	25–100 mg at bedtime	Constipation
Nortriptyline	CNS sites	10–75 mg at bedtime	Constipation

(continued)

Table 3.6 (continued)

Therapy	Mechanisms and sites of action	Dosage	Adverse effects
Mirtazapine	CNS sites	15 mg at bedtime	Weight gain
Benzodiazepines			
Lorazepam	CNS sites	0.5–1 mg four times daily	Drowsiness, lightheadedness
Alprazolam	CNS sites	0.25–0.5 mg three times daily	Drowsiness, lightheadedness
Cannabinoids			
Dronabinol	CNS	5–10 mg two times daily	Sedation

[a] compassionate clearance use
[*] not FDA approved

Table 3.7 Electrical therapies, nutritional support, and endoscopic therapies

Therapy	Mechanisms and sites of action	Dosage	Adverse effects
Electrical therapies			
Acustimulation Acupressure Acupuncture	Spinal/vagal afferents? Endorphins	Variable NA	Local tenderness
Gastric electrical stimulation[a]	Vagal afferents effect?	12 cpm, 330 ms, 5 mÅ	Pocket infections
Nutritional support			
Gastrostomy	Venting paretic stomach	As needed	See Chap. 11
Jejunostomy	Enteral nutritional support	As needed	See Chap. 11
Total parenteral nutrition	Bypass paretic stomach	As needed	Sepsis, thrombosis of central veins See Chap. 11
Endoscopic therapies			
Botulinum toxin injection into the pylorus	Relax pyloric muscle	25–50 units per quadrant	None
Balloon dilation of pylorus	Stretch pyloric muscle	20 mm balloon, 2 min	Post-dilation pain
Radiofrequency ablation at LES	Improve GEPG, improve gastric myoelectrical activity	NA	Transient dysphagia

CNS central nervous system, D_2 dopamine$_2$, *5-HT* 5-hydroxytryptamine, *GEPG* gastroesophageal pressure gradient, H_1 histamine$_1$, *LES* lower esophageal sphincter, *NA* not applicable
[a] investigational device exemption

the neuromuscular apparatus of the corpus and antrum is normal. If fixed pyloric stenosis is found, then balloon dilation or surgical treatment with pyloroplasty, Billroth I, or Billroth II, is required to eradicate the obstruction [35].

In most patients with gastroparesis and normal 3 cpm GMA, the upper endoscopy is normal even though retained food may be seen and the pylorus may appear grossly normal. These patients have a subtype of obstructive gastroparesis related to pylorospasm or dyschalasia. Dyschalasia is pyloric dysfunction wherein the pylorus contracts and does not relax appropriately during distal antral peristaltic waves [10]. If the gastric peristaltic waves are not in synchrony with the pyloric sphincter function, then gastric emptying is delayed. In these patients, the solid-phase gastric emptying test reveals gastroparesis, but the EGG and water load test reveals normal 3 cpm GMA, indicating normal ICC numbers in

the corpus-antrum. Thus, the most relevant pathophysiology in these patients is pyloric dysfunction.

Category 2 patients may also benefit from the gastroparesis diet until successful pyloric therapies are carried out. Patients in Category 2 with 3 cpm GMA and gastroparesis may or may not respond to prokinetic agents since treatment of pyloric dysfunction (pylorospasm or dyschalasia) is the more rational approach. Endoscopic therapy for these patients includes botulinum toxin A (100–200 mg) injection or balloon dilation of the pylorus (Table 3.7). Although botulinum toxin A injection was no better than placebo in decreasing symptoms in previous trials [44], the patients were not selected on the basis of 3 cpm GMA activity which defines the obstructive gastroparesis subtype. In our series almost 80 % of patients with gastroparesis and 3 cpm GMA had symptom improvement with two or more botulinum toxin A or balloon dilation pyloric therapies [12]. These results also suggested that more than one treatment of the pylorus may be needed to improve symptoms in the patients with gastroparesis and 3 cpm GMA.

Pyloric therapies may also include pyloroplasty. In six patients, who had repeated improvement in symptoms and experienced weight gain after botulinum toxin A or balloon dilation, pyloroplasty was performed [13]. In these patients gastric emptying which was severely delayed was normal after pyloroplasty, providing objective evidence that pyloric neuromuscular dysfunction (pylorospasm and/ordy achalasia) was the key pathophysiological mechanisms underlying their gastroparesis (Fig. 3.11). Symptoms improved in five of the six patients. The 3 cpm GMA recorded in these patients supports the notion that the corpus-antrum neuromuscular apparatus was normal and the primary pathophysiological abnormality was pyloric dysfunction. Patients with gastroparesis and poor pyloric compliance also had symptom improvement after pyloric therapies [45]. Surgical pyloroplasty improved symptoms in gastroparesis in one study of patients with idiopathic and diabetic gastroparesis [46]. However, a rational approach for surgical pyloroplasty would be to select the gastroparesis patients with normal 3 cpm GMA who had excellent symptom responses to the less invasive btA injection or balloon dilation of the pylorus.

Normal Gastric Emptying and Gastric Dysrhythmias (Category 3) in Patients with CUNV

By combining the two test modalities, further pathophysiological abnormalities in patients with CUNV are identified. Patients with normal gastric emptying and gastric dysrhythmias (Category 3) have the same symptoms as patients who have gastroparesis [16]. This condition is termed postprandial distress syndrome, gastroparesis-like syndrome, or CUNV or CIN. These patients have decreased ICCs but not as depleted as patients with gastroparesis [34]. Domperidone, metoclopramide, and cisapride converted gastric dysrhythmias to the normal 3 cpm pattern and improved symptoms in these patients with CUNV or dysmotility-like dyspepsia [40, 47]. Thus, gastric dysrhythmias are therapeutic targets for antiarrhythmic drugs to improve the gastric dysrhythmias and decrease symptoms. Patients in Category 3 may benefit from prokinetic agents since metoclopramide, cisapride, and domperidone can reverse gastric dysrhythmias [40]. Drugs such as metoclopramide and domperidone shift the gastric dysrhythmias to normal 3 cpm, suggesting that in these patients the gastric dysrhythmias are related to enteric nerve abnormalities that affect ICC function rather than depletion of ICCs.

Another therapeutic approach for Category 3 patients with nausea and vomiting with normal gastric emptying and gastric dysrhythmias addresses abnormal fundic accommodation (gastric compliance or capacity) [6, 20–22]. Patients in Category 3 may also find the Nausea and Vomiting Diet helpful, especially if gastric accommodation dysfunction is severe. Many patients report both early satiety and nausea. The early satiety in particular is thought to be due to fundic accommodation abnormalities. Poor fundic relaxation also indicates increased fundic tone and increased wall tension. The volume of

water ingested during the EGG with water load test is an indirect measure of gastric capacity and accommodation and thus relaxation of the gastric walls. During the water load test, approximately 550 ml of water is ingested in 5 min by healthy subjects to achieve the sense of "complete fullness" [22]. Almost 60% of the patients with normal gastric emptying had abnormal water load volumes (less than 550 ml ingested), indicating decreased stomach capacity and accommodation [48].

From a dietary standpoint, these patients are advised that their stomachs will only "relax" to accommodate a certain limited number of ounces as defined by the water load test volume. Therefore, liquid or solid meals should be less than these volumes in order to limit symptoms induced by stretch on the gastric wall. Patients with idiopathic gastroparesis consumed an average volume of only 282 ml of Ensure and reported they were completely full. The ingestion of this small volume immediately induced an increase in nausea symptoms, suggesting the stretch on gastric wall are related to this post-meal nausea [49]. No drugs are available to relax specifically the gastric fundus, but trials of calcium channel blockers, nitrates, or buspirone may be considered.

Normal Gastric Emptying and Normal GMA (Category 4) in Patients with CUNV

As shown in Fig. 3.12, some patients with CUNV have normal gastric emptying and normal 3 cpm GMA and WLT volume. These patients probably do not have a gastric cause of their symptoms. Patients in Category 4 usually tolerate the Nausea and Vomiting Diet and are frequently able to ingest regular diets. When these two gastric neuromuscular tests are normal, the physician should consider *non-gastric* and *non-GI* possibilities in the differential diagnosis and then obtain appropriate testing to further investigate other pathophysiologic mechanisms for the symptoms. For example, these patients may have atypical GERD and esophageal manometry and 24-h pH tests are needed to confirm this possibility. Chronic cholecystitis, small bowel bacterial overgrowth, and IBS are other non-gastric diagnoses to consider. The possibility of diseases outside of the GI system like orthostatic hypotension or migraine should be reviewed.

Conclusions and The Future

Diseases and disorders of the esophagus and the stomach are the source of nausea and vomiting in many of our patients. Most of these patients do not have gastroparesis. They have nausea due to other mechanisms that range from atypical GERD to gastric dysrhythmias to poor gastric compliance and capacity. In regards to the stomach, there is a continuum of neuromuscular dysfunction that ranges from abnormal fundic compliance and gastric dysrhythmias to frank gastroparesis. Only a minority of patients with gastroparesis have improved symptoms over 2-year follow up even at expert centers [50]. New diet, drug, and device treatments, based on the pathophysiology of symptoms, are needed now. The pathophysiologic basis of these neuromuscular abnormalities, particularly the variable loss of the gastric pacemaker cells – the ICCs – is increasingly appreciated and correlated with nausea symptoms, gastric dysrhythmias, and severity of gastroparesis. Subtypes of gastroparesis, such as the obstructive phenotype, need to be identified because therapy should be directed at the pylorus. Botulinum toxin A and balloon dilation of the pylorus and pyloroplasty improve symptoms and gastric emptying in this obstructive subtype of gastroparesis, but many more therapies can now be explored including endoscopic pyloromyotomy [51].

Further research on the ICC and enteric neuron abnormalities in the gastric corpus and antrum will guide future therapies. Enteric neuron dysfunction may affect the ICC function and result in gastric dysrhythmias. For example, if ICCs are intact but the enteric neurons are abnormal, then specific receptor agonist/antagonist drugs may be helpful in improving enteric neuron

function *and* restoring normal ICC activity and the normal 3 cpm GMA. Therapies directed at the inflammatory pathways to shift the macrophage phenotype toward the normal M2s and improve ICC numbers are needed [52].

GES devices with more effective and sophisticated stimulation parameters to help with symptoms or with more traditional pacing function to improve gastric emptying are also needed, but even more importantly, patient selection for stimulation therapies needs more precision. For example, patients with gastroparesis and increased normal 3 cpm GMA (outlet obstruction phenotype) would not be helped by GES, but they would be helped by pyloric therapies. On the other hand, if ICCs are dramatically depleted, then patients with gastric dysrhythmias such as tachygastrias and severe gastroparesis may be identified as likely to fail or respond poorly to medical and GES approaches. In these cases, regenerative medicine techniques such as injecting ICCs or selected enteric neurons into the corpus, antrum, or pylorus to improve gastric and pyloric neuromuscular function and symptoms are future possible therapeutic approaches [53].

Exciting diagnostic and therapeutic opportunities now need exploration in order to help our patients with unexplained nausea and vomiting due to esophageal and gastric causes. Further basic, clinical, and translational research will help to objectively define the spectrum of gastric neuromuscular diseases and lead to more rational therapies to relieve the irremediable suffering of nausea and vomiting.

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4 Nausea and Vomiting Related to Non-esophageal and Non-Gastric Diseases of the Gastrointestinal Tract

Allen A. Lee

Introduction

Nausea is the subjective sensation of distress and often associated with the feeling of impending vomiting. Meanwhile, vomiting is the physical act of forcefully expelling gastric contents through the mouth. The etymology of vomit is instructive as it comes from the Latin word vomitorium, which is a passageway located behind a tier of seats in an amphitheater used as an exit. The root of the word, vomere, translates to "spew out." Indeed, the vomitoria at the Roman Coliseum were so efficient that the entire venue of 50,000 people could reportedly empty within 15 min [1]. The modern definition was not used until 1923 when Aldous Huxley incorrectly described the vomitorium as a room where Romans could vomit in order to eat more [2].

Socioeconomic Costs

Nausea and vomiting contribute significantly to socioeconomic costs to patients, employers, and the health care industry. Camilleri *et al.* conducted a national telephone survey in the USA and found that 9.5 % of respondents had symptoms of nausea at least one time per month for the past 3 months with women having more frequent symptoms than men (11.9 % vs. 6.8 %). Vomiting was noted in 2.7 % of all respondents and was associated with the most missed days of work (mean 4.4) [3]. Data taken from the National Health Interview Survey in 1993 show that nausea and vomiting led to over 67 million missed days of work [4]. The socioeconomic costs from nausea and vomiting are enormous and account for medical expenses of $1.25 billion with $21.8 billion in lost productivity [5].

Differential Diagnosis

The differential diagnosis for non-esophageal and gastric causes of nausea and vomiting in the gastrointestinal tract is quite broad (Table 4.1).

Infectious Causes

Acute gastroenteritis is a major cause of diarrheal illness associated with nausea, vomiting, fever, or abdominal pain. Approximately 375 million episodes of acute gastroenteritis occur each year leading to 600,000 hospitalizations and 5,000 deaths [6, 7]. Acute gastroenteritis is most prevalent in children under the age of 5 years with an estimated prevalence of 8 % while prevalence in adults is estimated to be 3–7 % [7–9].

Viruses are the most common causes of acute gastroenteritis. Norovirus is the most common

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Table 4.1 Differential diagnosis of non-esophageal and non-gastric causes of nausea and vomiting in the gastrointestinal tract

Etiology	Main causes
Infectious	Viral gastroenteritis
	Norovirus
	Bacterial gastroenteritis
	Salmonella
	Campylobacter
	E. coli
Mechanical obstruction	Small bowel obstruction
	Adhesions
	Tumors
	Hernias
	Large bowel obstruction
	Malignancy
	Volvulus
	Diverticular disease
Organic gastrointestinal disorders	Inflammatory
	Pancreatitis
	Cholecystitis
	Hepatitis
	Inflammatory bowel disease
	Malignancy
	Pancreatic adenocarcinoma
	Vascular disease
	Mesenteric ischemia
Systemic inflammatory disorder	SLE
	Systemic sclerosis
	Sjögren's syndrome
	Behçet's disease
	Henoch-Schönlein purpura
Motility disorders	Enteric dysmotility
	CIPO
Functional disorders	Irritable bowel syndrome

SLE systemic lupus erythematosus, *CIPO* chronic intestinal pseudo-obstruction

cause of acute gastroenteritis in the USA and accounts for 50% of acute diarrheal outbreaks [10]. Enclosed populations such as on cruise ships, nursing homes, dormitories, and hospitals are particularly susceptible to Norovirus. Rotavirus, norovirus, adenovirus, and astrovirus are common viral causes of gastroenteritis in infants and young children [11, 12].

Bacterial infections are much less common causes of acute gastroenteritis with studies reporting positive stool cultures ranging from 1.5 to 5.6% [13]. However, in severe cases of diarrhea (≥4 unformed stools per day for more than 3 days), stool cultures were positive in 87% of cases [14]. Data from the Centers for Disease Control and Prevention report *Salmonella* were the most commonly identified bacterial pathogen (16.2 cases per 100,000 people) leading to gastroenteritis in the USA in 2012 [15]. *Campylobacter* (14.3 cases), Shiga toxin-producing *E. coli* 0157:H7 strain (1.1 cases), vibrio (0.4 cases), and *Yersinia* (0.3 cases) were also identified as bacterial causes of acute gastroenteritis.

Acute infectious gastroenteritis can be classified into non-inflammatory (typically viral, milder disease) vs. inflammatory (mostly invasive or toxin-producing bacterial, more severe disease). If vomiting is the predominant symptom, viral gastroenteritis or foodborne illness with a preformed toxin should be suspected. Stool samples are generally not necessary but should be obtained in severe cases, fevers (≥38.5 °C), persistent diarrhea (≥14 days duration), or presence of dysentery. High-risk individuals, including elderly or immunocompromised patients, hospitalized patients and/or those receiving antibiotics (testing for *Clostridium difficile*), people employed as food handlers, nursing home residents, or day-care workers should also have stool samples obtained.

Mechanical Obstruction

Mechanical obstruction of the bowel presents when there is interruption in the normal flow of intestinal contents. Bowel obstruction is a substantial cause of morbidity and mortality, accounting for approximately 15% of ER visits for evaluation of abdominal pain [16]. The bowel progressively dilates as intestinal secretions and swallowed air accumulate proximal to the point of mechanical obstruction [17]. If the process of bowel dilatation continues, luminal pressure eventually can compromise vascular perfusion to

the bowel leading to ischemia, necrosis, and perforation. A closed loop obstruction, where a segment of bowel is obstructed proximally and distally, may undergo progressive dilatation rapidly and is at high risk for development of volvulus and subsequent ischemia [18].

Obstruction can occur anywhere along the gastrointestinal tract with the small bowel being the most common location (75 %) for mechanical obstruction [19]. The main risk factor for small bowel obstruction (SBO) is prior abdominal surgery leading to postoperative adhesions, seen in approximately 60% of cases [20]. Lower abdominal surgeries, including appendectomies, colorectal surgery, gynecologic procedures, and hernia repairs are associated with higher risk for the development of adhesive disease [21, 22]. Tumors and complicated hernias are the next most common causes of bowel obstruction in the USA and Europe followed by Crohn's disease, gallstones, volvulus, and intussusception [19, 23].

Clinically, patients can present with acute onset of abdominal pain, nausea, emesis, abdominal distention, and progressive obstipation. Symptoms can vary depending on the extent (partial vs. complete), etiology, and location (proximal vs. distal) of the obstruction. Patients with distal obstruction often present with severe abdominal pain and marked distention as the proximal bowel acts as a reservoir. Meanwhile, patients with more proximal obstruction typically present with more pronounced nausea and emesis with less abdominal distention.

Organic Gastrointestinal Disorders

Acute Pancreatitis

Acute pancreatitis is a common disorder that accounts for over 220,000 hospital admissions annually in the USA. Despite advancement in our understanding of the disease, mortality has not improved over the past few decades and ranges between 10 and 30 % in those with severe disease [24]. Acute pancreatitis results from inappropriate activation of trypsinogen to trypsin, which leads to zymogen activation, pancreatic autodigestion, and ultimately pancreatic inflammation [25]. This inflammatory cascade is not limited to the pancreas and may progress to a systemic inflammatory response syndrome, multi-organ failure, or even death.

The etiology of acute pancreatitis is gallstones in approximately 40 % of cases and is more likely in Caucasian females over the age of 60 [26]. Alcohol accounts for an additional 35 % of cases and is more common in men [24]. There appears to be a complex but dose-dependent risk between alcohol consumption and the development of pancreatitis [27]. Metabolic abnormalities (e.g., hypertriglyceridemia), bile duct obstruction (e.g., tumor, pancreas divisum), post-ERCP pancreatitis, medications (e.g., azathioprine, thiazides, and estrogens), autoimmune, and trauma are less common causes of acute pancreatitis.

Acute pancreatitis is characterized by epigastric pain radiating to the back. Approximately 90 % of patients will also have presence of nausea and vomiting [28]. Serum amylase and lipase levels are more than three times the upper limit of normal. Abdominal imaging with computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound may demonstrate inflammatory changes around the pancreas. Acute pancreatitis is a clinical diagnosis with characteristic symptoms in the setting of elevated pancreatic enzymes and/or abnormal radiographic imaging.

Mesenteric Ischemia

Mesenteric ischemia is a collection of diverse conditions resulting in impaired blood flow to the gut. Mesenteric ischemia can be classified into acute and chronic forms. It can be further subdivided into arterial, venous, and non-occlusive forms.

Acute Mesenteric Ischemia

Acute mesenteric ischemia (AMI) is a rare but life-threatening condition. AMI accounts for less than 1 per 1,000 hospital admissions but mortality

can range between 30 and 90 % depending on the etiology [29, 30]. Because of its relative infrequency, AMI may be missed leading to delayed diagnosis and potentially worse outcomes. One study from Sweden suggested that mortality may exceed 90 % and AMI was only considered in the differential diagnosis in 33 % of cases [30].

The etiology of AMI can be divided into occlusive and non-occlusive causes. Occlusive causes account for the vast majority of cases (85 %) with embolization to the mesenteric arterial circulation (40–50 %) accounting for the majority of cases. Atrial fibrillation, prior myocardial infarction with subsequent impaired wall motion, and structural heart disease with right-to-left shunts are common risk factors. Because of the acute occlusion from embolic sources, collateral circulation is limited and symptoms typically progress rapidly. The superior mesenteric artery (SMA) is more commonly involved than the celiac axis or inferior mesenteric artery because of the less acute angle of takeoff from the aorta [31]. The embolus typically obstructs distal to the jejunal and middle colic SMA branches and most often affects the mid jejunum [32].

Thrombotic causes account for approximately 25 % of cases and is typically seen in patients with underlying atherosclerotic disease. Thrombotic AMI is generally more insidious in presentation as there is often collateral flow around pre-existing atherosclerotic disease. Up to 50–75 % of patients have prior symptoms of post-prandial abdominal pain and weight loss, which suggests underlying chronic mesenteric ischemia [33]. Rupture of an unstable plaque, often at the origin of the SMA, leads to AMI. Thrombotic AMI has the highest mortality, perhaps a consequence of the proximal obstruction leading to involvement of a larger segment of bowel [29].

Mesenteric venous thrombosis (MVT) accounts for less than 5 % of all AMI cases [29]. Hypercoagulable state (including factor V Leiden, prothrombin 20210 mutation) is the predominant risk factor but other predisposing factors include malignancy, portal hypertension, and intra-abdominal inflammatory processes (e.g., diverticulitis, pancreatitis, inflammatory bowel disease). MVT carries the most favorable prognosis compared to other forms of AMI with an overall mortality of 44 % on a large, systematic review [29]. However, more recent studies suggest mortality rates may actually be 10–20 % possibly due to better diagnostic studies and prompt initiation of treatment [34–36].

Non-occlusive causes are responsible for approximately 20–30 % of AMI but incidence is declining due to improved care of critically ill patients as well as use of systemic vasodilators in heart failure [37]. Despite the decline in incidence, mortality from non-occlusive mesenteric ischemia (NOMI) is extremely high likely due to the co-morbid conditions associated with this population. Risk factors for NOMI are conditions associated with low flow state, including severe cardiovascular disease, sepsis, or drugs that reduce intestinal perfusion [38].

Clinically, patients with AMI typically present with severe periumbilical abdominal pain that is out of proportion to the physical exam. Nausea and vomiting are common associated symptoms. Embolic causes of AMI typically have acute onset of abdominal pain while thrombotic causes of AMI will often have a long history of intestinal angina prior to acute worsening of pain. Personal history of thromboembolic disease or family history of clotting disorders should alert one to the possibility of MVT while suspicion for NOMI should be high in history of low-flow states, such as severe cardiomyopathy.

In contrast to the severity of abdominal pain, the exam is typically benign and unimpressive. Leukocytosis with white blood cell count greater than 15,000/mL and elevated lactate are seen in 90 % of cases [39, 40]. Lactate levels may also correlate with severity of injury, extent of injury, and even patient outcomes [39, 41]. Diagnosis is typically made by radiographic studies with the gold standard being angiography. More recently, CT angiography has supplanted angiography as a noninvasive means for diagnosing AMI. MR angiography can also be considered, but the long acquisition times associated with MRI limit its utility in the diagnosis of AMI.

Chronic Mesenteric Ischemia

Chronic mesenteric ischemia (CMI) is a relatively uncommon disease mainly due to the significant collateral vascular network in the gut. CMI is defined by the presence of typical symptoms in the setting of high-grade narrowing or occlusion of at least two major visceral arteries (celiac axis, superior mesenteric artery, or inferior mesenteric artery). Atherosclerotic narrowing at the origin of the celiac or superior mesenteric artery is the cause of CMI in the vast majority of cases [42]. Less common causes of CMI include median arcuate ligament syndrome (compression of the celiac artery from the median arcuate ligament of the diaphragm), fibromuscular dysplasia, vasculitis (e.g., polyarteritis nodosum, Takayasu arteritis), and aortic dissection [38].

Clinically, patients typically present with the classic triad of post-prandial abdominal pain, sitophobia (fear of eating), and weight loss. Patients describe a dull, crampy epigastric abdominal pain that starts shortly after a meal and lasts 1–2 h which is also described as "intestinal angina." One study suggests that symptoms occur because of hypoperfusion of the small intestine as blood is shunted to the stomach [43]. Nausea, vomiting, diarrhea, and early satiation may be seen in one-third of patients.

There is a marked female predominance (3:1) in CMI and most patients are typically over the age of 60. Tobacco use is common with smoking being reported by 57 % of patients in one report [44]. Atherosclerotic disease in other vascular beds is also common with approximately 50 % of patients exhibiting coronary artery disease, cerebrovascular disease, or peripheral vascular disease.

Imaging demonstrating high-grade stenosis or occlusion of at least two major mesenteric vessels in the context of typical symptoms confirms the diagnosis of CMI. CT angiography is often used as the initial test given its non-invasive approach as well as sensitivity and specificity exceeding 90 %. Duplex ultrasonography of the mesenteric vessels can also be considered. Sensitivity is approximately 90 % for high-grade stenosis (>50 % occlusion) of the superior mesenteric or celiac arteries [45–47]. Furthermore, a negative duplex ultrasonography can essentially rule out CMI given the high negative predictive value of duplex ultrasonography [48].

Systemic Autoimmune Diseases

Systemic Lupus Erythematosus (SLE)

Systemic autoimmune diseases can present with a variety of gastrointestinal manifestations including nausea and vomiting. Systemic lupus erythematosus (SLE) can affect any part of the gastrointestinal tract from the mouth to the rectum. GI symptoms from SLE are common and may occur in more than 50 % of patients [49]. Oral ulcers are the most common GI manifestation of SLE, but one series reports prevalence of nausea and vomiting in 50 % of patients [50].

Onset of symptoms such as abdominal pain, nausea, and vomiting may herald more severe, potentially life-threatening disease activity including lupus mesenteric vasculitis (LMV). Prevalence of LMV is reported to be anywhere from 0.2% to 6.4 % in Western countries [49]. LMV is a small vessel vasculitis that can involve both small arteries and venules. Deposition of immune complexes, C3 complement, and fibrinogen may be seen histologically [51]. Abdominal pain, nausea, and vomiting are frequent symptoms seen in LMV and are almost always seen in the context of active disease elsewhere. Vasculitis can progress to ischemia and infarction with sequelae including gastrointestinal bleeding, stricture formation, and perforation. Pneumatosis cystoides intestinalis (PCI) may rarely be present. Contrary to other conditions where PCI is a benign condition, PCI is associated with necrotizing enterocolitis in LMV and can occasionally lead to perforation [52].

Scleroderma

Progressive systemic sclerosis (scleroderma) is a connective tissue disorder characterized by proliferative vascular lesions with subsequent fibrosis

of organs and multiple organ systems. The GI tract is the most commonly involved non-cutaneous organ in 90% with nearly all patients (98.9%) displaying GI symptoms [53]. Abdominal distention was the most common symptom (87.8%), followed by heartburn (68.9%), diarrhea (67.8%), abdominal pain (68.9%), nausea (61.1%), and vomiting (60.9%).

Scleroderma may affect the entire GI tract from mouth to anus and is believed to occur as a consequence of initial vascular damage, subsequent tissue ischemia, leading to collagen deposition and fibrosis in the GI vasculature and smooth muscle [54]. Involvement of the small bowel is the second most common organ in the gastrointestinal tract behind the esophagus. Small bowel dysmotility may be seen in 40–88% of scleroderma patients with antroduodenal manometry showing evidence of reduced activity and hypomotility in the fasting state [55, 56]. This may manifest with symptoms of nausea, early satiety, anorexia, and malabsorption with one study suggesting that nausea and vomiting may be seen in 57% of patients [57]. Small intestinal dysmotility is associated with increased morbidity and may lead to life-threatening conditions including pseudo-obstruction as well as small intestinal bacterial overgrowth.

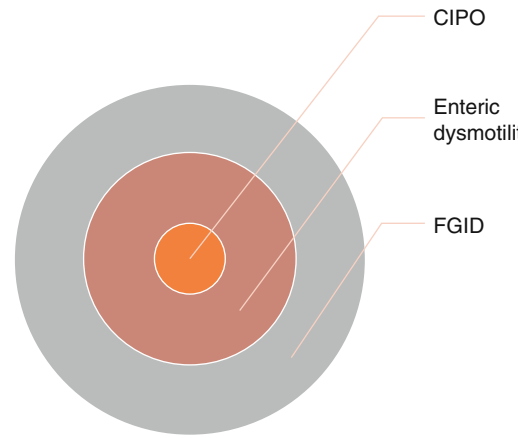

Fig. 4.1 The relative prevalence and relationship between functional gastrointestinal disorders (FGIDs), enteric dysmotility, and CIPO. FGIDs are defined by specific symptom criteria while enteric dysmotility is defined by manometric abnormalities. CIPO is defined by manometric abnormalities in the presence of radiologic evidence of dilated bowel. *FGID* functional gastrointestinal disorders, *CIPO* chronic intestinal pseudo-obstruction

Motility Disorders

Gastrointestinal motor activity is controlled by the enteric nervous system (ENS). The ENS sends signals to smooth muscle in the gut which then generates pressure changes responsible for propulsive motility. Alterations in either the ENS or smooth muscle involved in this process may lead to gut dysmotility. There is a continuum of chronic GI symptoms including abdominal pain, nausea, vomiting, distention, and constipation which ranges from functional GI disorders (diagnosed using symptom-based criteria such as the Rome criteria) [58], to enteric dysmotility (abnormal antroduodenal manometry in the absence of visceral dilatation) [59] and chronic intestinal pseudo-obstruction (CIPO) (manometric abnormalities in addition to radiologic criteria) [60] (Fig. 4.1). Mild abnormalities in gut motility may be seen in functional GI disorders, such as irritable bowel syndrome or chronic idiopathic constipation, while more severe dysmotility may be seen in rare but potentially life-threatening diseases, such as CIPO.

Enteric Neuropathy

The enteric nervous system (ENS) is comprised of a vast network of neurons distributed throughout the entire GI tract as well as the biliary tract and pancreas. The ENS is a collection of ~500 million neurons that is unique in its ability to control most gut functions including regulating secretion and absorption, vascular tone, and motility largely independent of the central nervous system (CNS) [61]. Enteric neuropathies, or disruption of normal ENS function, may lead to GI disorders and symptomatology. Enteric neuropathy can be classified as primary (idiopathic) vs. secondary (part of a systemic disease). Enteric neuropathy can also be classified histopathologically as inflammatory or degenerative in nature.

Inflammatory Neuropathies

Inflammatory neuropathies are characterized by a dense lymphoplasmacytic infiltrate involving the myenteric or submucosal plexuses as well as the axonal processes of the ENS (Fig. 4.2). Involvement of the myenteric plexus, or myenteric ganglionitis, is more common and often secondary to other disease processes.

Paraneoplastic Syndromes

Paraneoplastic syndromes may lead to an inflammatory neuropathy with subsequent involvement of the stomach (gastroparesis), small bowel (intestinal pseudo-obstruction), and colon (constipation, colonic inertia, or megacolon). The most common malignancy associated with paraneoplastic enteric neuropathy is small cell lung cancer [62] but other malignancies including bronchial carcinoid [63], thymoma [64], neuroblastoma [65], and ovarian cancer [66] have also been reported. Antineuronal antibodies directed against the RNA-binding protein family Hu (ANNA-1 or anti-Hu) are the most common autoantibody expressed [67, 68]. Anti-voltage-gated Ca^{2+} channel (P/Q- and N-type) antibodies are most often detected in Lambert-Eaton myasthenic syndromes related to small cell lung cancer [69]. After anti-Hu, antibodies targeting the N-type Ca^{2+} channels are the most common autoantibodies in paraneoplastic enteropathies. Antibodies directed against the Purkinje cell protein Yo (anti-Yo, anti-Purkinje cell cytoplasmic) as well as anti-ganglionic type acetylcholine receptors may also be observed (Table 4.2) [70].

Systemic Inflammatory Disease

Systemic inflammatory diseases commonly have associated gastrointestinal manifestations. Inflammatory infiltrates of plasma cells, lymphocytes, and mast cells involving both the myenteric and submucosal plexus have been well described in Crohn's disease and may predict early post-operative recurrence of disease [71]. The finding of enteric ganglionitis in other conditions is unclear. Low-grade lymphocytic myenteric ganglionitis in the proximal jejunum was described in 9 of 10 patients with severe irritable bowel syndrome (IBS) [72]. These authors proposed that an inflammatory enteric neuropathy might contribute to sensorimotor abnormalities seen in IBS. Interestingly, enteric neuropathy classically shows a dense lymphocytic infiltrate associated with neuronal degeneration and loss, severe impairment in gut motility, and occasionally associated with bowel dilatation [70, 73]. However, there were relatively few lymphocytes (1.9–7.1 per ganglion) seen in IBS patients. This raises the possibility that the degree of inflammatory infiltrate in the myenteric plexus may predict the severity of neuromuscular dysfunction with milder cases exhibiting symptoms

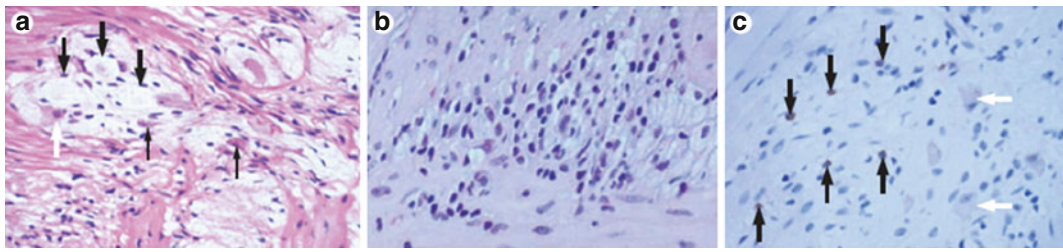

Fig. 4.2 Representative histopathology illustrating degenerative and inflammatory enteric neuropathies. (**a**) Degenerative neuropathy. A myenteric ganglion is shown with numerous degenerate neurons with different features including normal neurons (depicted by *white arrows*), shrunken, apoptotic neurons (*thin black arrows*), and frank degeneration (*thick black arrows*). Samples were stained using hematoxylin and eosin (original magnification ×180). (**b**) Inflammatory neuropathy. The myenteric ganglion contains numerous small inflammatory cells (original magnification ×320). (**c**) Periganglionic and intraganglionic T cells demonstrated by CD3 immunostaining (*black arrows*). Residual myenteric neurons are depicted by *white arrows* (original magnification ×320) (Reprinted with permission from Knowles [61])

Table 4.2 Anti-neuronal antibodies in inflammatory neuropathy

Anti-neuronal autoantibodies	Molecular target	Associated paraneoplastic syndrome	Associated malignancy	GI motor disorder
ANNA-1 (Anti-Hu)	HuD, HuC, HuR, Hel-N1	Opsoclonus myoclonus; ataxia	SCLC	Gastroparesis, CIPO, megacolon
Anti-VGCC	Voltage-gated Ca^{2+} channels, including P/Q and N-type channels	Lambert-Eaton syndrome	SCLC	CIPO
Anti-ganglionic acetylcholine receptors	Nicotinic receptors	Dysautonomia	Thymoma, SCLC	Gastroparesis, CIPO, constipation
Anti-Yo	Cdr2	Paraneoplastic cerebellar degeneration	Gynecologic tumors (e.g., ovary)	CIPO

Adapted with permission from De Giorgio [70]

SCLC small cell lung cancer, *VGCC* voltage gated calcium channel, *CIPO* chronic intestinal pseudo-obstruction

typical of functional GI disorders while severe cases may present with intestinal failure, pseudo-obstruction, and/or bowel dilatation.

Degenerative Neuropathies

Diabetes Mellitus

Diabetes mellitus can affect the entire gastrointestinal tract. As such, symptoms of abdominal pain, nausea, postprandial fullness, diarrhea, and constipation are more common in diabetics than healthy controls. Diarrhea or constipation (15.6 %) was the most prevalent symptom while nausea and vomiting were seen in 5.2 % and 1.7 %, respectively [74].

Animal models of diabetes mellitus show a decrease in the number of enteric neurons throughout the gastrointestinal tract [75–77]. Studies in humans have also demonstrated neuronal loss related to diabetes mellitus. Full thickness gastric biopsy samples in diabetic gastroparesis patients have exhibited loss of neurons, particularly nitrergic neurons as shown by decreased expression of nNOS compared with matched controls [78].

Studies also consistently report loss of interstitial cells of Cajal (ICC) in diabetic gastroenteropathy as well [79]. ICC are mesenchymal cells that are critically important for normal gastrointestinal motility. They act as pacemaker cells and lead to a generation of slow wave transmission in the GI tract. They also modulate neurotransmission between motor neurons of the enteric nervous system, efferent input from the autonomic nervous system, and smooth muscle cells in the GI tract [80]. Loss of ICC as a result of diabetes mellitus may lead to impaired pacemaker activity, altered neurotransmission, and dysmotility in the GI tract.

Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by neuronal inclusions called Lewy bodies and Lewy neurites, whose main components are aggregated and phosphorylated α-synuclein. Hypersalivation, dysphagia, nausea, constipation, and defecatory dysfunction are more common in PD than in matched controls [81]. Nausea is a common complaint experienced by patients with PD with some reports suggesting prevalence of up to 24 %, including 16 % of subjects not receiving any treatment [82].

Although PD is a CNS disorder typically affecting the substantia nigra, alterations of the ENS and gastrointestinal dysfunction may also be present. Using full-thickness biopsy samples from deceased subjects, α-synuclein pathology was reported in the distal esophagus with highest frequency followed

by stomach, small bowel, colon, and rectum [83]. Another study utilizing mucosal biopsies taken during routine colonoscopy found Lewy neurites in the submucosal plexus in 21 of 29 PD patients compared to none in 10 age-matched controls [84]. Interestingly, the amount of Lewy neurites in the ENS correlated with constipation symptoms suggesting a pathogenic role in PD.

Myopathic Disorders

Gut smooth muscle is composed of circular smooth muscle and outer longitudinal muscle, which comprises the muscularis propria. Disorders of enteric smooth muscle may also lead to abnormal motor function and gut dysmotility.

Amyloid

Amyloidosis is characterized by extracellular deposition of proteinaceous fibrils with a β-sheet fibrillar structure and distinctive properties after staining with Congo Red dye [85]. There are two major types of amyloid. Primary amyloidosis (AL) results from deposition of immunoglobulin light chains or their fragments, which are produced by aberrant clones of B cells. AL secondary to multiple myeloma is the most common type of amyloidosis in the USA. Secondary amyloidosis (AA) results from accumulation of an acute phase reactant, serum Amyloid A, which is produced in response to inflammation [86]. AA is typically seen in the setting of underlying rheumatoid arthritis, inflammatory bowel disease, or familial Mediterranean fever.

The kidneys and the heart are the most common site of involvement. The gastrointestinal tract is less commonly involved but the small bowel is the most commonly affected organ in the GI tract, with 31 % of patients being affected at autopsy [87]. Symptoms occur from infiltration of amyloid into any gut layer or deposition into the ENS. Amyloid deposition into the small bowel may cause abnormalities in motility, malabsorption, ulcers, or bleeding [88].

Chronic intestinal pseudo-obstruction from amyloid is a rare but well-described complication in both AL and AA amyloidosis. This may occur either from deposition of amyloid into smooth muscle (myopathy) or involvement of the enteric nervous system (neuropathy). One study of 16 patients with amyloidosis and CIPO suggested that AL patients are more predisposed to myopathic causes of CIPO, while patients with AA amyloidosis are more likely to have enteric neuropathy [89].

Scleroderma

As mentioned previously, systemic sclerosis (SSc) commonly affects the gastrointestinal tract with the small bowel being the second most common site of involvement in the alimentary tract. Sjogren proposed a progression of GI involvement from scleroderma that initially involves vascular damage leading to neural dysfunction. Patients are often asymptomatic until smooth muscle atrophy occurs. Muscle fibrosis heralds the final stage in scleroderma and restoration of function may not be possible given muscle function may be lost [90].

Intestinal dysmotility is common with an estimated prevalence of 40–88 %[56]. Small bowel hypomotility is associated with high morbidity and mortality and can lead to complications including small intestinal bacterial overgrowth, malabsorption, and pneumatosis cystoides intestinalis. CIPO is a rare but serious complication from SSc with one series suggesting a prevalence of 8 % in SSc patients [91].

Antroduodenal manometry may demonstrate abnormalities in phase III of MMC including interrupted propagation, decreased frequency with low amplitude, or complete absence of phase III activity. In the fasting state, there may be uncoordinated or minimal motor activity while a decreased motility index may be seen in the fed state [54]. Some studies suggest that antroduodenal manometry may help select appropriate patients for therapy with octreotide, as patients with advanced SSC may be less responsive [56, 92].

Chronic Intestinal Pseudo-Obstruction (CIPO)

CIPO is a rare disease characterized by impairment in gut propulsive motility, which resembles mechanical obstruction in the absence of any obstructive process. Dudley *et al*. first described CIPO in 1958 when exploratory surgery failed to reveal an etiology for symptoms in 13 patients thought to have a mechanical cause of bowel obstruction [93]. The etiology of CIPO is idiopathic in the majority of cases. Secondary causes of CIPO are numerous and are similar to secondary causes of enteric dysmotility (Table 4.3).

CIPO is characterized by recurrent symptoms mimicking obstruction. The most common symptoms of CIPO include abdominal pain (80%), nausea and vomiting (75%), constipation (40%), and diarrhea (20%). The clinical picture is typically dominated by episodes of pseudo-obstruction but patients often have chronic symptoms as well. Nausea, vomiting, and weight loss are common symptoms when dysfunction primarily affects the proximal GI tract while abdominal pain, abdominal distention, and constipation can occur if the dysfunction primarily affects the lower GI tract. Patients are predisposed to development of small intestinal bacterial overgrowth (SIBO) leading to symptoms of diarrhea, steatorrhea, and further malnutrition.

Diagnosis of CIPO is mainly based on clinical evidence as well as exclusion of obstruction on imaging studies and/or endoscopy. Radiographic evidence of dilated bowel loops with air-fluid levels is an important diagnostic clue in this disorder. Antroduodenal manometry (ADM), while not specific, may be helpful in establishing the diagnosis of CIPO [60]. One study of 42 patients with CIPO demonstrated all subjects had manometric abnormalities including non-propagated bursts of phasic pressure activity (duration > 2 min, amplitude > 20 mmHg, frequency > 10 waves/min) during fasting and/or fed state, uncoordinated fasting pressure activity that is sustained (duration > 30 min), and inability to convert fasting into fed pattern after ingestion of a meal [60]. ADM may also help to differentiate whether dysmotility is myogenic or neuropathic in etiology. Myopathic disorders are characterized by coordinated but abnormally low-amplitude (<20 mmHg) contractions. Neuropathic disorders from enteric neuropathy typically show normal amplitude but uncoordinated contractions. Neuropathy from autonomic disorders characteristically shows an impaired fed response or post-prandial antral hypomotility [94].

Histopathology may be helpful in establishing the correct diagnosis but is rarely obtained given the rare nature of the disease as well as requirements for special handling and processing of tissue. Historically, the role of full thickness biopsy has been controversial, as surgery often would lead to worsening symptoms. Interest in full thickness biopsies has been renewed with the advent of minimally invasive techniques, such as laparoscopic surgery. Histopathology may reveal three major patterns

Table 4.3 Secondary causes of enteric dysmotility and CIPO

Sites affected in enteric dysmotility/ CIPO	Primary causes
Autonomic nervous system	Stroke
	Encephalitis
	Multiple system atrophy
	Diabetes mellitus
Enteric nervous system	Paraneoplastic
	Viral infections
	Diabetes mellitus
	Neurofibromatosis type I
Enteric smooth muscle	Myotonic Dystrophy
	Systemic scleroderma
Mixed enteric neuro-myopathy	Scleroderma
	Dermatomyositis
	Amyloid
	Ehlers-Danlos
Mixed enteric neuro-myopathy	Hypothyroidism
	Hypoparathyroidism
	Pheochromocytoma
Mixed enteric neuro-myopathy	Radiation enteritis
	Chemotherapy
	Medications (clonidine, phenothiazines, antidepressants, antiparkinsonians, anthraquinones)

Adapted from Stanghellini [114]

including neuropathy, mesenchymopathy, and myopathy indicating whether the predominant abnormality is located in the ENS, ICC, or smooth muscle, respectively [70, 95]. Enteric neuropathy is the most common diagnosis in enteric dysmotility (60–70 % based on published series) whereas myopathy is more common in CIPO as well as in the pediatric population [59, 96, 97].

Functional Causes

Irritable bowel syndrome (IBS) is defined by Rome III criteria as recurrent abdominal pain or discomfort at least 3 days per month in the previous 3 months with two or more of the following: improvement with defecation; onset associated with a change in frequency of stool; and/or onset associated with a change in form (appearance) of the stool [58]. It affects up to 10–15 % of the population in the USA and is the most common reason for referral to gastroenterology [98, 99]. There is a high prevalence of nausea and vomiting in IBS patients with 24–73 % of patients reporting nausea and vomiting in 7–27 % [100–102]. There appears to be significant gender differences as well with one study suggesting that females with IBS have a much higher prevalence of nausea than their male counterparts (49 % vs. 18.2 %) [103].

The pathophysiology of IBS is incompletely understood but classically thought to be multifactorial with physiological abnormalities as well as psychosocial factors playing a role [104]. Evidence of altered gut motility may be seen with slow colonic transit noted in approximately 25 % of patients with constipation-predominant IBS whereas 15–45 % of diarrheal-predominant IBS patients have accelerated colonic transit and high amplitude propagated contractions [105–107]. Visceral hypersensitivity measured by rectal barostat is the most frequently described abnormality in IBS [108]. Altered serotonergic (5-HT) signaling has been postulated as a factor in IBS with increased circulating levels of 5-HT demonstrated in diarrheal-predominant IBS and decreased 5-HT levels in constipation-predominant IBS [109]. The importance of 5-HT in IBS is highlighted by the use of selective serotonergic agonists and antagonists in the treatment of different IBS phenotypes [110]. Alterations of the gut microbiome is also proposed to be an important factor in the pathophysiology of IBS with studies suggesting that IBS patients show an abundance of firmicutes and/or decrease in bacteroidetes bacteria [111]. In addition, current evidence suggests that patients with IBS may have increased gut permeability leading to mucosal inflammation, immune activation, and visceral hypersensitivity [112, 113].

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Nausea and Vomiting Associated with Abdominal Wall Pain

5

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Introduction

Pain is a complex and multidimensional process which involves physical, emotional, and perceptual integration. It has the prime objective of protecting against tissue damage. In chronic painful states, neuroplastic changes maintain persistent perception and responsiveness to noxious stimuli, or exaggerated responses to normally non-noxious stimuli. Such changes can occur in primary afferent terminals (peripheral sensitization) but also in the spinal cord and in the brain (central sensitization) in both neurons and glia. Nausea and vomiting related to chronic pain are mainly associated with headaches and other sites or as side effects of medications and other interventions used to manage pain. While nausea and vomiting from visceral sources of abdominal pain are largely recognized, nausea associated with chronic abdominal wall pain frequently is missed as an associated symptom.

Chronic abdominal wall pain (CAWP) is defined as pain of more than 1-month duration which is localized with fixed, point tenderness usually in an area less than 2.5 cm in diameter and which is commonly exacerbated by abdominal wall muscle tension [1]. Patients with CAWP may be mistakenly treated as if they are suffering from visceral pain and vice versa. It is estimated that 10–30 % of patients with chronic abdominal pain have CAWP [2]. The peak incidence of CAWP is between the ages of 30 and 50 years and women are more likely to be affected than men [3–7].

The intercostal nerves run a tortuous course through the upper abdominal wall muscles. After turning at a 90° angle, the nerves pass from the posterior sheaths of the abdominal wall through fibrous openings and then branch while passing through the anterior sheaths. The "abdominal cutaneous nerve entrapment syndrome" (ACNES) was proposed to result from ischemia of these nerves as they pass through the abdominal wall muscles. Pain may additionally result from changes in intra- or extra-abdominal pressure on nerve endings or from tension due to scarring [3, 6]. Invariably, nausea associated from such pains may be protracted and difficult to distinguish from the nausea caused by an underlying dysmotility disorder, medication use, or other causes. However, the hallmark of nausea associated with ACNES is its exacerbation with intense pain and the concurrent anxiety. Commonly, these patients undergo repeated clinical examinations and expensive invasive investigations directed to visceral sources, which produce extensive utilization of health resources

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and significant delays in diagnosis and treatments [1, 2].

Sources of CAWP include chronic myofascial pain, pain referred from abdominal or thoracic viscera by viscero-somatic or viscero-cutaneous convergence in the spinal cord with somatic sites, thoracic radicular lesions, radiculitis, and peritoneal/abdominal wall lesions leading to nerve injury [1, 3]. Surgery itself may cause iatrogenic direct damage to cutaneous nerves or promote cutaneous nerve entrapment by scar tissue formation or surgical sutures leading to ACNES [3–6]. ACNES can be caused by direct surgical trauma and promoted by unusual anatomic variants of cutaneous nerve branches [3–6]. Peripheral nerve entrapment can occur at various anatomic locations. The most common site of abdominal wall nerve entrapment is the lateral border of the rectus muscle [3].

Diagnosis and Treatment

The first step in evaluating a patient with suspicion of CAWP as the cause of nausea is to rule out intra-abdominal pathology. Performance of an accurate medical history, exhaustive medical examination, endoscopic screening options, proper diagnostic imaging, and laboratory tests aid in excluding other conditions causing abdominal pain. CAWP is best diagnosed based on a detailed history and a careful physical examination. Tenderness usually is well localized with point tenderness on palpation. Conversely, visceral pain is usually poorly localized on abdominal compression [8, 9]. Carnett's test is the key part of the physical examination for diagnosing abdominal wall pain [8]. To perform this test, the patient is positioned prone with slightly flexed knees and hips to decrease abdominal wall tension. The painful area is initially palpated when the patient is relaxed and then palpated again after he/she is asked to tighten the abdominal muscles by straining or lifting the head and shoulders off the bed. A positive Carnett's test is defined when pain on palpation increases during these maneuvers. In contrast, reductions in pain during abdominal wall tensing suggest a visceral source of pain.

A positive response to trigger point injections or nerve blocks may confirm the diagnosis of CAWP and is considered one of most cost-effective procedures in gastroenterology [3–9]. Limitations to this approach are the high placebo response rate to such injections, especially in long-term chronic pain patients [10], and false positive Carnett's sign testing with visceral abdominal conditions which have associated peritoneal involvement [11]. Trigger points are frequently present in patients with CAWP and Carnett's sign positivity. Symptoms vary from localized tenderness on light palpation to forceful guarding of the painful area of the abdomen.

The *injection of an abdominal wall trigger point* using local anesthetic, sometimes combined with corticosteroids or clonidine, is relatively easy to perform. The goals of trigger point injection are to relax the abdominal musculature and decrease localized inflammation to break the cycle of chronic pain. Marked improvement or resolution of pain following injection supports the diagnosis of CAWP as the cause of chronic pain. Contraindications to trigger point injection include systemic or local infection and allergies to local anesthetics or adjuvants in the injection mixture.

Caution should be used in patients on anticoagulants. After sterile skin preparation with isopropyl alcohol or chlorhexidine, a 25–27 gauge 1.5 in. needle is introduced into the trigger point perpendicular to the abdominal wall. Care must be taken not to penetrate too deeply into the peritoneal cavity. Not uncommonly, the patient may report a transient increase in pain as the trigger point is penetrated. Fanning of the needle with multiple 1–3 mL local injections can be performed to thoroughly anesthetize the trigger point. Ultrasound can be employed to direct proper needle insertion and anesthetic injection to minimize the risk of inadvertent intraperitoneal penetration. No evidence exists that any local anesthetic is superior to another. Short acting agents (lidocaine or tri-chloroprocaine) may produce pain resolution within 5–10 min. However, most clinicians employ longer acting

agents like ropivacaine or bupivacaine with additional additives such as methylprednisolone, triamcinolone, or clonidine for long-term pain control. Repeated injections may be needed to sustain pain relief over time. Rare complications include intraperitoneal needle puncture, subcutaneous or intramuscular hematoma, needle breakage, infection, vasovagal syncope, intravascular injection, local anesthetic toxicity, and scarring. Lipodystrophy (loss of subcutaneous abdominal wall fat) may result when the steroids are injected into the epidural adipose tissue rather than the abdominal muscles and presents as a visible abdominal wall depression (see Fig. 5.1).

Differential retrograde epidural block has been advocated as a diagnostic tool to distinguish visceral and non-visceral sources of pain and, by extension, the associated nausea and vomiting. To this date, a few reports with small patient cohorts have argued in the favor of retrograde differential epidural block as a predictor of future chronic abdominal pain treatment response [12–15]. This technique involves placing an epidural catheter with subsequent injection of saline (placebo) twice followed by incremental doses of local anesthetic. The diagnostic value of this procedure relies on the differential sensitivity of different nerve fibers of varying size and myelination. Sympathetic fibers and visceral afferent nerves (C fibers) are relatively more sensitive to local anesthetic blockade compared to large sensory or motor fibers (A δ fibers) by a tenfold margin [15]. It must be recognized that the retrograde differential nerve block has not been validated. Drawbacks of this method include difficulties in isolating subgroups of nerve fibers in the desired size range using a single local anesthetic, the long time interval needed to complete the procedure (frequently 2–3 h), and the neuro-axial placement of the catheter [3, 15].

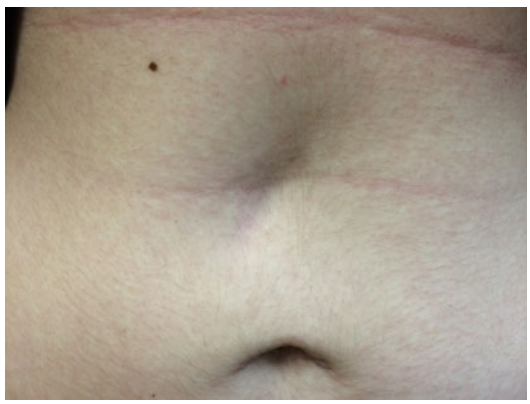

Fig. 5.1 Lipodystrophy following abdominal wall trigger point injection of steroids. This infrequent complication of trigger point injection is the direct result of steroid injection to subcutaneous abdominal wall adipose tissue

Transversus abdominis plane (TAP) block is a newer diagnostic and therapeutic block that may help differentiate somatosensory pain from that of visceral origin [16]. The TAP block was first described back in 2001, detailing injection of local anesthetic into the transversus abdominal plane situated between the internal oblique and transversus abdominis muscles [17, 18]. The TAP block delivers the analgesia to the entire anterolateral abdominal wall between the costal margin and inguinal ligament [19]. More recent introduction of ultrasound guidance for TAP blockade allows precise installation of local anesthetics around the anterior branches of the thoracolumbar ventral rami blocking most of the somatic nerves of the anterior abdominal wall [20]. Using a posterior approach, ultrasound visualizes the three muscular layers of the lateral abdominal wall in order from superficial to deep including the external oblique, internal oblique, and transverse abdominis muscles (Fig. 5.2). The value of a single TAP block in distinguishing a source of abdominal pain originating from the abdominal wall is still debatable, but initial data are encouraging [16–20]. When it comes to treatment of CAWP using TAP block, a single guided anesthetic injection or even a continuous infusion can be used [17].

Lumbar paravertebral block is another type of somatic blockade delivering local anesthetic to the potential space between the vertebral body medially, the psoas major muscle anterolaterally, and the transverse processes and intertransverse ligaments posteriorly. This method permits delivery of the local anesthetic to segmental nerve roots to facilitate proper diagnosis of pain originating from specific lumbar nerves. Upper lumbar nerves may be blocked without resultant

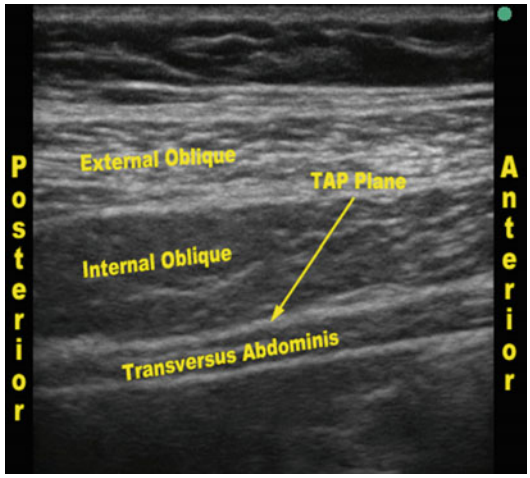

Fig. 5.2 Three muscular layers as frequently imaged during TAP block (Taken with permission from Crews and Henshaw [21])

impaired motor function, however obturator or femoral nerve blockade at the L2 level or lower may produce weakness. The procedure also may elicit sympathetic blockade from epidural spread. Segmental block may assist in localizing the origin of lower abdominal and groin pain to specific lumbar nerve roots. This may be beneficial for the diagnosis and treatment of disc herniation, spinal and foraminal stenosis, and chronic abdominal pain from nerve entrapment after inguinal herniorrhaphy.

Other advanced therapies to treat CAWP and (perhaps) its associated nausea include peripheral nerve blockade, neurolysis, cryoablation, alcohol or phenol injection, radiofrequency ablation, or surgical neurectomy [22–24] (Fig. 5.3). All these modalities have been used to treat abdominal wall pain, nerve entrapment syndromes (ilioinguinal, iliohypogastric, genitofemoral nerves), neuropathic pains, and neuralgia from direct abdominal wall injuries or surgeries [25]. It is important to note that ilioinguinal, iliohypogastric, or genitofemoral neuralgia is difficult to distinguish from true ACNES in the lower abdomen [2]. All peripheral nerve blocks can be used for diagnostic, therapeutic, or even preoperative analgesia. Traditionally, such blocks were conducted using an electrical stimulator or paresthesia guidance. More recently, ultrasound-guided techniques have provided real-time, precise delivery of the block [26]. The approach to abdominal wall pain is summarized in Fig. 5.3. The abdominal wall is innervated by the spinal nerves exiting at T7-T12. Irritation of a nerve root due to disc herniation or degeneration typically produces neurogenic pain in a radicular pattern and presents as unexplained abdominal pain. Similarly, patients with long-standing diabetes mellitus can infrequently experience abdominal neuropathic pain originating from the thoracic nerves [27]. Thoracic nerves (T7-12) are also commonly affected by shingles and herpes simplex producing neuropathic abdominal pain that may be accompanied by nausea and vomiting [28]. Thoracic disc herniation causes myelopathy, sensory deficits, and thoracic radicular pain, but on occasion can present as nausea, vomiting, and abdominal pain [29, 30]. Epidural injection of corticosteroids can be an initial therapeutic step, if surgery is not indicated based on the lack of motor deficits. Thoracic epidural anesthetic and analgesic techniques provide visceral and somatosensory analgesia as well as sympathectomy which promotes intestinal motility and increases visceral blood perfusion [31–34]. When required, a temporary epidural catheter can be placed in the mid thoracic dermatomal regions to deliver local anesthetics and opioids to provide rescue analgesia.

Pediatric chronic abdominal pain syndromes frequently present with associated nausea and vomiting. Peripheral nerve blockade has become an important therapeutic approach in children to control pain and facilitate responses to physical therapy [35]. Ultrasound-guided techniques provide safer approaches to anesthesia delivery with improved success rates [36, 37]. TAP and ilioinguinal/iliohypogastric nerve blocks are commonly used in children suffering from CAWP; the *rectus sheath block* is used frequently in children with periumbilical abdominal wall pain and also for single incision laparoscopic surgery and umbilical hernia repairs [37–39]. Under ultrasound guidance, local anesthetic is injected in the potential space between the rectus abdominis muscle and its posterior sheath.

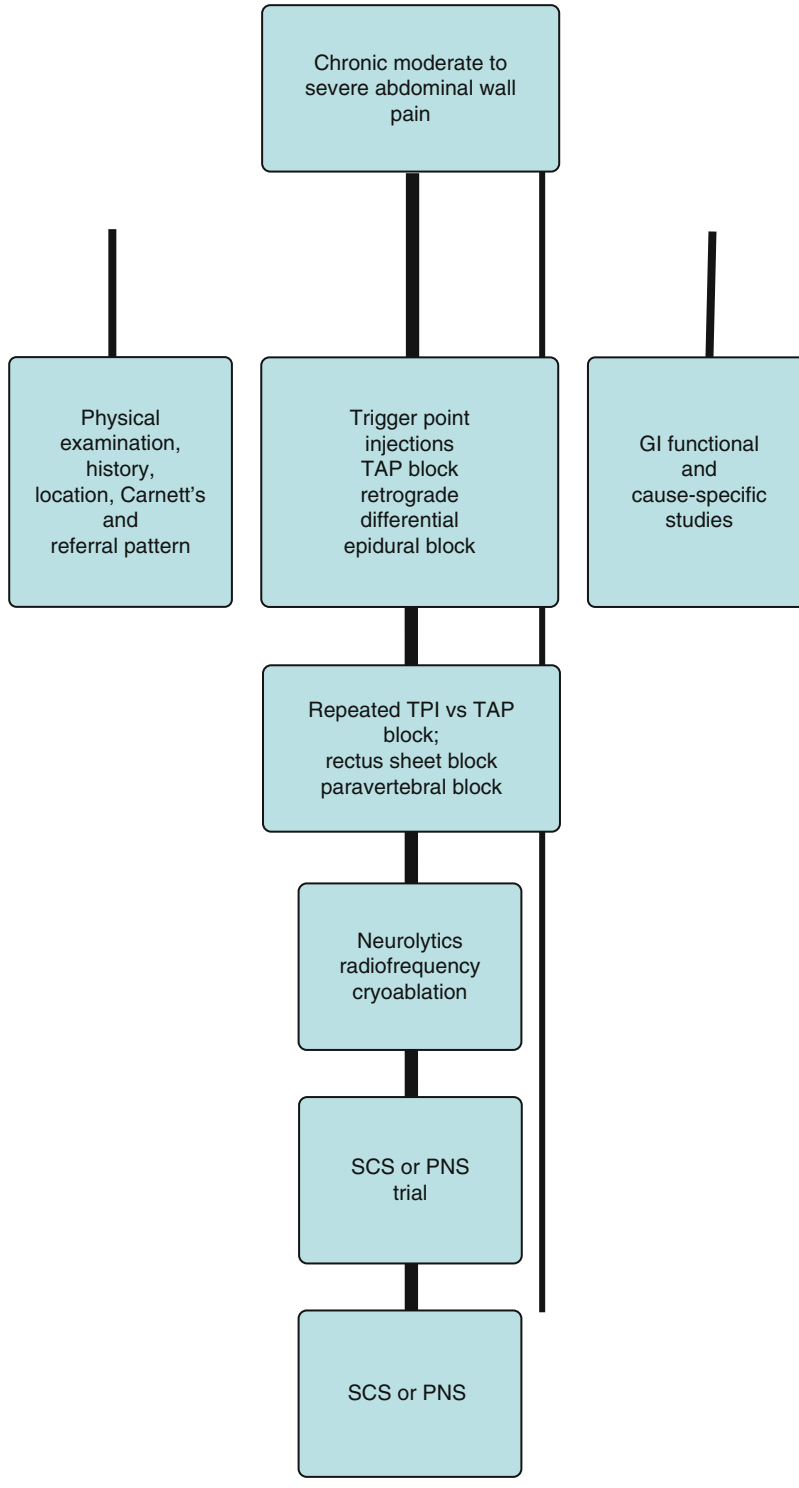

Fig. 5.3 Proposed algorithm for treatment of abdominal wall pain and nausea associated with abdominal wall pain. Note that this algorithm employs several areas of detailed concurrent evaluation by different specialists. Steps proposed are not generated from detailed evidence-based literature, but rather case reports, series, and larger retrospective and prospective studies (*TPI* trigger point injection, *TAP* transverse abdominal plane, *SCS* spinal cord stimulation, *PNS* peripheral nerve stimulation)

Chronic opiate use is a common cause of nausea and vomiting among patients with CAWP, with an incidence of 10–50 % [40]. Affected patients commonly also report associated bloating, abdominal distension, and constipation. Some use the term narcotic bowel syndrome to describe the centrally mediated dysfunction in opioid receptor activity which presents with severe abdominal pain accompanied by distension, nausea, and vomiting [41]. Treatment includes a program of opioid weaning, complemented with treatment membrane stabilizers and neuromodulatory antidepressants to decrease pain and limit depression, anxiety, and withdrawal symptoms [41].

Peripheral nerve stimulation (PNS) is an emerging subcategory of neuromodulation and has been used to treat severe CAWP. Indications for PNS include neuralgias and neuropathic damage of the genitofemoral, ilioinguinal, and iliohypogastric nerves [42]. In the past, surgical electrode implantation was required for PNS. However, newer ultrasound guided percutaneous protocols have been developed for lead placement to avoid operative intervention. PNS with subcutaneous or peripheral field stimulation may be combined with spinal cord stimulation (SCS) for improved long-term analgesia for CAWP [42].

Spinal cord stimulation is mainly intended for cases of refractory neuropathic, chronic truncal pain. Traditional low-frequency SCS also has demonstrated safety and efficacy in treating chronic abdominal pain [31, 32, 43]. Advantages of this therapy include its minimally invasive nature, superior patient control of stimulation, reduced opioid intake, and, consequently, fewer side effects. Despite its frequent use in chronic abdominal pain syndromes, there is little high quality evidence in the clinical literature to support such therapy in these patients. SCS may relieve chronic abdominal pain by several possible mechanisms [33]. Suppression of lumbosacral spinal neuron responses to the noxious colorectal stimuli by SCS is produced by placing the electrical lead either near the lumbar or cervical dorsal columns. Antidromic activation of primary afferent fibers within the dorsal column at high intensities, spinal gating mechanisms, and suppression of sympathetic tone also might play roles in controlling chronic abdominal pain from both visceral and somatic sites [33, 34].

In conclusion, a recent surge of various minimally invasive therapies for control of chronic abdominal wall pain has provided the basis for better control of the nausea associated with severe abdominal wall pain. An accurate algorithm for managing CAWP has not yet been generated, mainly as a consequence of the lack of high quality, prospective studies in this area.

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Nauseа, Vomiting, and Hormonal Disorders

6

Jorge Calles-Escandón
and Hugo Rivadeneyra Pasten

Introduction

Patients with established (and treated) endocrine and metabolic diseases can suffer from gastrointestinal diseases that cause nausea and vomiting just like any other patient who does not have any hormonal or metabolic derangement (Table 6.1). It is beyond the scope of this chapter to detail the workup for all the etiologies of nausea and vomiting that are related to hormonal and/or metabolic changes. We will not discuss the approach to the differential diagnosis of nausea and vomiting. We will initially discuss the current approach to establish diagnosis of some selected hormonal diseases which are associated with nausea and vomiting and which may pose a challenge in the differential diagnosis of these symptoms. We will review the current state of the knowledge as it relates to diabetes and gastroparesis (GP), a leading cause of nausea and vomiting in these patients. Finally, we will present in detail the management of the glycemia in patients with diabetes and gastroparesis, a formidable challenge for clinicians and patients as well.

Adrenal Insufficiency (AI)

AI is a life-threatening disorder that can result from primary adrenal failure or secondary adrenal disease due to impairment of the pituitary gland. It is the clinical manifestation of deficient production or action of glucocorticoids, with or without deficiency in mineralocorticoids and adrenal androgens [1]. The cardinal clinical symptoms of AI – as first described by Thomas Addison in 1855 – include weakness, fatigue, anorexia, abdominal pain, nausea, weight loss, orthostatic hypotension, and salt craving; characteristic hyperpigmentation of the skin occurs with primary adrenal failure. AI was invariably fatal until 1949, when cortisone was first synthetized and glucocorticoid replacement treatment became available.

AI may be primary when the adrenal is directly affected, which can occur via several mechanisms (immunity, infections, ischemia, congenital metabolic diseases such as adrenal

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Table 6.1 Common hormonal and metabolic alterations associated with nausea and vomiting

	Possible mechanism	Diagnosis
Diabetes type 1 and 2	Glucose toxicity, neuropathy (interstitial cells of Cajal)	Hyperglycemia, elevated HbA1c
Hyperthyroidism	Not defined	Low TSH, High T4
Hypothyroidism	Slow gastric emptying	High TSH, low T4
Adrenal insufficiency	Not defined	ACTH stimulation test
Pregnancy	Progesterone, placental hormones	High levels of HCG
Alterations in calcium and sodium concentrations	Not determined	Serum levels
Hyperprolactinemia	Not determined	High prolactin level, pituitary adenoma
Hyperparathyroidism	Effects of calcium on CNS, slow nerve conduction? Delayed gastric emptying?	High Calcium, normal/high PTH level
Neuroendocrine tumors	↑Acid output → gastritis ↑VIP → diarrhea, dehydration ↑Glucagon → ↓gastric emptying	Elevated gastrin levels High VIP levels High glucagon levels

TSH thyroid stimulating hormone, *ACTH* adrenocorticotrophin hormone, *CNS* central nervous system, *VIP* vasoactive intestinal polypeptide, *HCG* human chorionic gonadotrophin, *PTH* parathyroid hormone, *HbA1c* hemoglobin A1c

leukodystrophy, etc.) or secondary when the pituitary gland has lost its capacity to secrete ACTH.

Secondary AI has become the most frequent etiology of AI due to the widespread use of exogenous corticosteroids in the therapy of many disease states (COPD, asthma, lupus, etc.). Chronic use of corticosteroids (using any route, PO, IV, nasal instillation, inhalation) leads to suppression of ACTH release. The lack of ACTH stimulation on the adrenal glands leads not only into suppression of cortisol secretion but also a decrease in actual glandular tissue. Thus the clinical spectrum of AI has changed since the original description by Addison and hence physicians need to raise their suspicion for AI in patients with nausea/vomiting with or without body weight and think of AI as a possible etiology for these symptoms. Some alerts are raised by the history: (a) Patients who have been (or are) treated chronically with corticosteroids, (b) thin individuals with a history of fatigue and chronic nausea/vomiting and/or abdominal pain, and (c) hyperkalemia and/or hyponatremia specially if patient has low blood pressure [1]. Regardless of the cause of AI, the outcome is a decrease in secretion of cortisol (primary and secondary) and mineralocorticoids (primary only) and therefore the diagnostic approach is aimed at demonstrating low levels of cortisol and decreased responsiveness of the adrenal gland to ACTH.

As a screening test for AI, a blood sample for cortisol and ACTH at around 8:00 am is recommended. This timing often poses a challenge for many ambulatory patients, and also for inpatients. Consequently, we recommend a full ACTH stimulation test, which is considered the current "gold standard" rather than a random cortisol level. The test can be performed in hospital settings and in ambulatory patients, is easy to do, and can be completed in 1 h. A basal sample is taken for measurement of ACTH and cortisol. After a dose of 250 mcg of ACTH 1–24 (Consyntropin) is given, blood samples for cortisol are taken 30 and 60 min later. The interpretation of results from the ACTH stimulation test is presented in Table 6.2.

Thyroid Disease

Both hyper- and hypothyroidism are associated with nausea and vomiting; however, this is not the usual clinical manifestation that brings

Table 6.2 Cortisol and ACTH in adrenal insufficiency (AI)

	Basal	30′ post ACTH	60′ post ACTH
Cortisol (mcg/dl)	Normal 10–20		
	Suggestive 5–10	Normal ≥ 17[a]	Normal ≥ 17[a]
	Strong suggestion <5	AI ≤ 17[b]	AI ≤ 17[b]
ACTH (pg/mL)	Normal 5–46 Primary AI >46 Secondary AI < 20	----------	----------

AI Adrenal Insufficiency, *ACTH* Adrenocorticotrophin hormone
[a]At least one of the two samples
[b]Both samples need to be low for diagnosis of adrenal insufficiency

patients to the hospital. The mechanisms of nausea and vomiting in hyper- and hypothyroidism have not delineated. Hyperthyroidism is associated with increased number of bowel movements and in some cases diarrhea. Excess thyroid hormone increases the cellular response to catecholamines and this could decrease the intestinal transit time by increasing peristalsis [2]. We did not find data on the effects of thyroid hormone excess on gastric neuromuscular function, but thyroid hormone excess may cause tachygastria, which is associated with nausea and vomiting. Hypothyroidism is associated with decreased gastrointestinal transit time and classically the clinical presentation is constipation. In very advanced cases of hypothyroidism, nausea may be a prominent symptom associated with delayed gastric emptying [3–5]. Diagnostic tests for thyroid function are relatively simple. We recommend ordering levels of TSH and free thyroxine if there is suspicion for hyper- or hypothyroidism in patients with chronic nausea and vomiting. Furthermore, gastric emptying tests should not be ordered until thyroid function has been proven normal or normal thyroid levels have been achieved with treatment in patients with known hypo- or hyperthyroidism.

Diabetes

Gastroparesis [6] has received much attention recently due to the severity of nausea and vomiting, effects on glucose control, and scarcity of effective treatments [7, 8]. When gastroparesis (GP) afflicts patients with type 1 (T1DM) or type 2 diabetes mellitus (T2DM), the consequences are particularly severe and usually poorly responsive to treatments [9]. Symptoms associated with GP such as early satiety, prolonged fullness, nausea, and vomiting of undigested food do not only reduce the quality of life but also impede good control of blood glucose levels which may lead to frequent visits to the emergency room and multiple hospitalizations [10–12]. In patients with diabetes complicated by GP, ingested food is not emptied in a predictable time period; thus, the anticipated nutrient absorption is unpredictable. Consequently, in those patients treated with insulin, the selected dose and timing of insulin therapy to control postprandial glucose may be inappropriate. In many patients with GP and diabetes, the erratic postprandial glucose levels result in swings from hypoglycemia to severe hyperglycemia. A vicious cycle exists in diabetes complicated with GP since hyperglycemia itself elicits gastric dysrhythmias and slows gastric emptying in normal and diabetic individuals [13–16].

Epidemiology

The estimates of prevalence of GP in DM vary widely. Although in tertiary centers, up to 40 % of patients with T1DM are reported to have GP [17], surveys in Olmsted County, Minnesota indicated a prevalence of 5 % in T1DM and 1 % in T2DM [18]. Our own data from an analysis of more than 40 million medical records is much

closer to the Olmsted County estimate supporting a prevalence of GP in diabetes of less than 5% [19]. Thus, GP in diabetes is not so common but it has a large negative impact on the lifestyle of patients and intensively increases the use of hospital resources by these patients. Although good control of glycemia prevents or delays many of the chronic complications of T1DM [20–22], the effect of good glucose control on the onset or progression of GP in DM is unknown. Compared with T2DM, T1DM patients with GP are younger, thinner, and tend to have more severe delays in gastric emptying [9]. Mortality is increased in patients with diabetes when they develop GP and is usually related to cardiovascular events.

Normal Postprandial Gastric Neuromuscular Activity (Fig. 6.1)

The normal stomach performs a series of complex neuromuscular activities in response to the ingestion of solid foods [23]. First, the fundus relaxes to accommodate the volume of ingested food (Fig. 6.1). Normal fundic relaxation requires an intact vagus nerve and is mediated by enteric neurons containing nitric oxide. The relaxation of the fundus allows food to be accommodated without excess stretch on the fundic walls. Secondly, the corpus and antrum produce recurrent peristaltic waves that mix or triturate the ingested solids into fine particles termed chyme.

Thirdly, emptying of chyme into the duodenum begins when the ingested solid foods are sufficiently triturated. The peristaltic waves empty aliquots of chyme through the pylorus into the duodenum (Fig. 6.1). The emptying of food from the stomach is altered by the nature of the constituents (carbohydrate, protein, and fat) and the fiber and indigestible components. Finally, normal postprandial neuromuscular activity is associated with a sense of comfortable fullness. In contrast, patients with diabetes and GP have the ingestion of food elicits early, satiety, nausea, and epigastric discomfort or pain [24].

Pathophysiology of Diabetic Gastroparesis

Full-thickness biopsies of the gastric corpus from patients with T1DM, T2DM, and GP indicate the disease is primarily a disease of gastric enteric neurons and interstitial cells of Cajal (ICC). Interestingly, these neurons are surrounded by an immune infiltrate composed primarily of type 2 macrophages, suggesting a role for the immune system [25–29]. The pathophysiological alterations in stomach function in GP include abnormal fundic relaxation results from loss of nitric

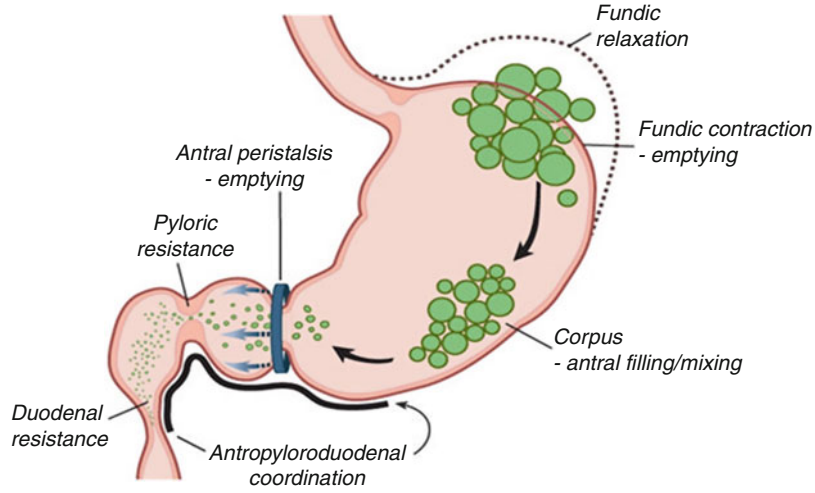

Fig. 6.1 Normal postprandial gastric neuromuscular work: emptying a solid meal (Modified from [40])

oxide release from the vagus nerve. Dysfunction of the ICCs which are also stretch receptors may also have a role in poor fundic relaxation (Fig. 6.2). The depletion of ICCs and presence of abnormal enteric neurons are the mechanisms of gastric neuromuscular dysfunction associated with the presence of gastric dysrhythmias and loss of the normal 3 cpm myoelectrical rhythm. The pyloric sphincter also regulates gastric emptying. Relaxation of the pyloric sphincter to allow antroduodenal flow is mediated by nitric oxide released from enteric neurons. In a subset of patients with diabetic GP and normal 3 cpm gastric myoelectrical activity, pylorospasm (failure of pyloric relaxation in coordination with antral peristaltic waves) results in GP.

Clinical Presentation

Symptoms associated with diabetic GP are early satiety, prolonged fullness, bloating, nausea, vomiting, abdominal discomfort, and pain. These are nonspecific symptoms. Approximately 20 % of patients develop these symptoms acutely. Nausea is the most bothersome and predominant symptom in patients with diabetes with GP. Vomitus frequently contains previously ingested chewed food. Prolonged stomach fullness and vague epigastric discomfort are common. Symptoms are similar in patients with T1DM and T2DM, although T2DM patients tend to have more fullness and bloating. In a minority of patients (20 %) with GP, abdominal pain is the predominant symptom [20]. The symptoms of GP range from periods of quiescence to periods of severe nausea and vomiting; the intensity of the latter frequently results in emergency room visits and hospitalization. Patients with uncontrolled nausea and vomiting may develop dehydration, hypovolemia, acidosis, and full-blown diabetic ketoacidosis (DKA).

Tests for Gastroparesis

GP is confirmed by nuclear medicine gastric scintigraphy. A standardized solid meal (Egg Beaters®) is ingested and then followed by 1-min duration scintigrams at each hour for a total of 4 h [30]. An upper endoscopy should be completed to rule out esophagitis, peptic ulcer disease, or mechanical obstruction. The gastric emptying test meal is usually not tolerated while the patient is ill and in hospital. This test is more reliably and consistently completed when the patient is a stable outpatient. An emerging technology is the Wireless Capsule Motility Test

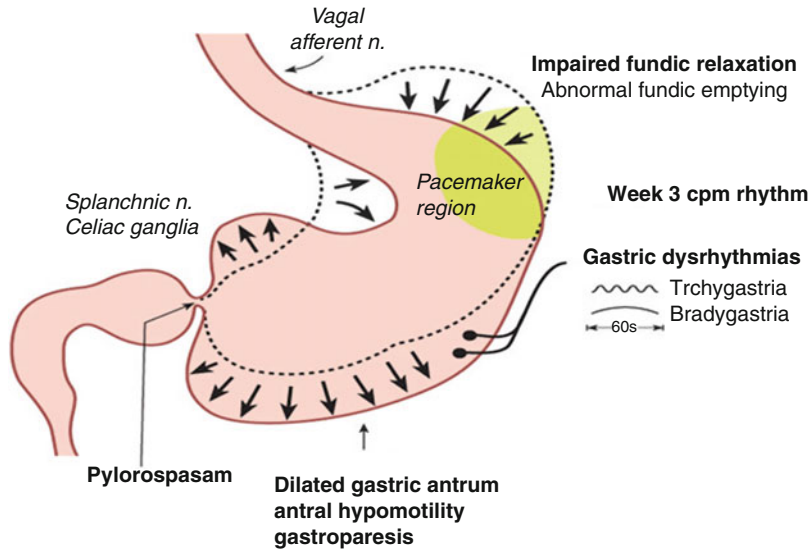

Fig. 6.2 Gastric neuromuscular disorders in diabetic gastropathy (Modified from [40])

which measures intraluminal pH, pressure, and temperature. The capsule is swallowed during ingestion of a nutrient bar; no further food intake is allowed for 5 h. A sudden change from a low pH (acid) to a neutral or alkaline pH indicates exit of the capsule from stomach into duodenum. If the capsule does not empty from the stomach into the duodenum in 5 h, then delayed gastric emptying is confirmed.

Treatment of the Patient with Diabetes and Gastroparesis

Patients with DM and GP may develop these following medical emergencies:

1. Acute exacerbations of GP symptoms (nausea, vomiting, pain) leading to dehydration, hypovolemia, and rarely into vascular collapse
2. Hyperglycemic crisis, usually ketoacidosis, the symptoms of which resemble closely those of acute exacerbation of GP
3. Severe hypoglycemia
4. Combinations of all of the above

The best treatment approaches for the in-hospital management of patients with diabetes and GP with severe medical emergencies has not been defined. The recommendations that follow derive from the experience of the authors of this chapter and from the protocol developed for the GLUMIT study, which was mainly an outpatient program [31].

Acute Management of Exacerbation of Symptoms Associated with Gastroparesis

The initial treatment must focus on restoration of volume status, correction of electrolyte imbalances, and stabilization of glucose with intravenous (IV) insulin drip (in the presence of hyperglycemia or DKA) and/or dextrose infusion (in the presence of hypoglycemia). Drug and device treatment approaches for nausea are presented in other chapters of this book and we will not review them in this chapter. After stabilization with IV fluids (if needed), patients are transitioned to oral intake using a three-step-diet approach as outlined in Table 6.3 and discussed in depth in Chap. 11.

One of the keys in the American Diabetes Association's recommended medical nutrition therapy for patients with diabetes is an increase in consumption of food items such as salads, fresh raw fruits, and fresh raw vegetables [32]. These foods, however, are some of the most difficult foods for the gastroparetic stomach to triturate and empty. Therefore, nutritious liquids, such as soups or smoothies that require much less gastric neuromuscular work to empty, are advised for patients with GP. Solid foods such as potatoes and pasta require less trituration and are emptied with less gastric neuromuscular work compared with red meats and fibrous foods. Highly fibrous foods, such as fresh oranges, celery, prunes, leeks, and sunflower-seed shells may contribute to the formation of bezoars. Carbohydrate may be limited for the patient with diabetes, but often, it is the soft, starchy carbohydrate foods that are most well tolerated by patients with GP. In addition, meals should be of low fat content since both fat and fiber tend to delay gastric emptying.

These nutrition changes require reeducation of the patient with diabetes and GP and their physicians. Consultation by a registered dietitian nutritionist (RD or RDN) who is knowledgeable in GP is invaluable. The goal is good nutrition and minimal postprandial symptoms while selecting appropriate foods for the severity of GP. (See Chap. 11 for nutritional management of patients with nausea and vomiting.)

Glucose Control in the Patient with Diabetes and Gastroparesis

Glucose control in the patient with diabetic GP can be extremely difficult in the outpatient and inpatient environments. This difficulty is dic-

Table 6.3 Diet for nausea and vomiting in patients with diabetic gastroparesis

Diet	Goal	Avoid
Step 1: sports drinks and bouillon		
For severe nausea and vomiting: Small volumes of salty liquids, with some caloric content to avoid volume depletion Chewable multiple vitamin each day	1000–1500 mL/day in multiple servings (e.g., 12, 120-mL servings over 12–14 h) Patient can sip 30–60 mL at a time to reach approximately 120 mL/h	Citrus drinks of all kinds; highly sweetened drinks
Step 2: soups and smoothies		
If Step 1 is tolerated: Soup with noodles or rice and crackers Smoothies with low fat dairy Peanut butter, cheese, and crackers in small amounts Caramels or other chewy confections Ingest above foods in at least six small-volume meals/day Chewable multiple vitamin each day	Approximately 1500 cal/day to avoid volume depletion and maintain weight (often more realistic than weight gain)	Creamy, milk-based liquids
Step 3: starches, chicken, fish		
If Step 2 is tolerated: Noodles, pastas, potatoes (mashed or baked), rice, baked chicken breast, and fish (all easily mixed and emptied by the stomach) Ingest solids in at least six small-volume meals/day Chewable multiple vitamin each day	Common foods that patient finds interesting and satisfying and that provoke minimal nausea/vomiting symptoms	Fatty foods that delay gastric emptying; red meats and fresh vegetables that require considerable trituration; pulpy fibrous foods that promote formation of bezoars

Modified from [40]

tated to some extent by the relationship between fluxuating glycemia and variable gastric emptying rates [15]. Hyperglycemia itself results in gastric dysrhythmias and slows gastric emptying. GP imposes unpredictable swings in glucose excursions due to unappreciated swings in gastric emptying rates and delivery of calories into the duodenum.

The rate of gastric emptying of ingested nutrients is influenced by the severity of GP; on a day-to-day basis, gastric emptying rates in response to various foods are not predictable. Diet choices are also compromised by nausea and vomiting. Vomiting reduces absorption of anticipated calories. Liquid nutrients and solid foods may be retained in the paretic stomach much longer than expected by the patient or by the treating physician. Thus, both postprandial hypoglycemia and/or hyperglycemia are distinctive features of patients with diabetes and GP due to the mismatch of insulin dosing and the slow and frequently erratic entry of nutrients into the duodenum and jejunum (Fig. 6.3).

Pharmacological Glucose Management

Patients with T1DM require insulin replacement as do most (if not all) of the patients with T2DM and GP. We do not recommend use of oral agents or noninsulin injectable medications (pramlintide, GLP-analogues) for management of glycemia in patients with T2DM and GP. First, due to GP, oral medications may not empty from the stomach for hours, resulting in erratic pharmacokinetics and pharmacodynamics [33]. The sulfonylureas are associated with protracted hypoglycemia in these patients. The GLP-1 incretin mimetics slow stomach peristalsis and are associated with nausea and vomiting themselves and hence are not recommended [34, 35]. While DPP4-inhibitors do not

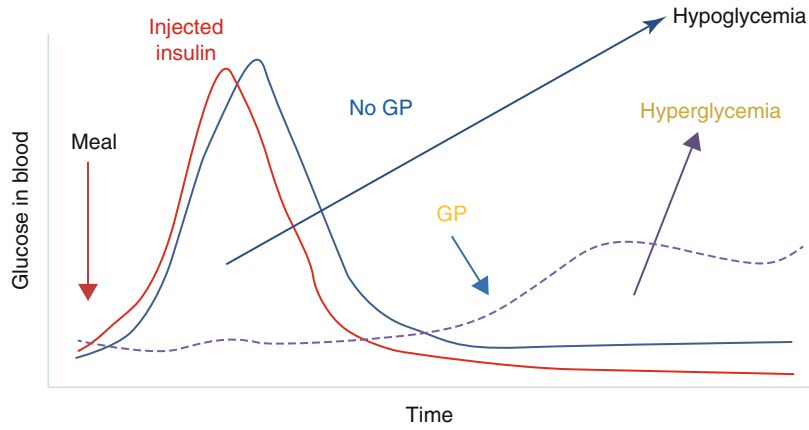

Fig. 6.3 Delayed glucose excusion after meal and injected insulin lends to hypoglycemia in patients with gastroparesis. Higher glucose exclusions occur hours after meal ingestion in gastroparesis patients

have much effect on slowing gastric emptying [35, 36], their efficacy depends upon good insulin reserve, and most patients with T2DM and GP have longer duration of diabetes and likely have severely decreased capacity to secrete insulin. Besides the latter, no clinical trials have been published on the possible safety or efficacy of the use of these agents in patients with GP. The use of the PPAR-agonists in diabetes (without GP) is controversial while other agents (SGLT2 inhibitors) have not been tested in these patients or may cause diarrhea and abdominal distension (i.e., disaccharidase inhibitors) aggravating gastrointestinal symptoms. Thus, at this stage and until new data emerges we favor the use of insulin in the patient with T2DM and GP.

The current paradigm of insulin administration in type 1 and insulin-using type 2 diabetes is based on the basal-bolus model which is often easier to achieve with use of insulin pumps rather than multiple insulin injections of rapid and long-acting insulins [37]. A basic assumption of the meal bolus is that gastric emptying of the ingested meal is completed within 4 h and intestinal absorption of nutrients is completed within 4–6 h. The administration of mealtime insulin is "timed" to match anticipated nutrient absorption. This is problematic for patients with GP because the onset and duration of the small intestinal absorption phase is critically dependent on the rate of gastric emptying. Besides the slow emptying of the stomach, the day-to-day variability in gastric emptying of common foods is unknown.

Insulin Administration for the Patient with Gastroparesis

Whenever possible, we recommend use of continuous insulin infusion (insulin pump) for managing glycemia in patients with diabetes and GP. A published study [38] and our own data support this modality of insulin administration [31]. If insurance coverage and costs present an insurmountable obstacle, then multiple daily injections are the next best option. We do not favor the use of premixed insulin preparations. Monitoring of glycemia for insulin adjustment is preferably established with a system based on finger stick testing augmented with continuous glucose monitoring (CGMS).

Basal Insulin Administration

The estimated initial dose of basal insulin can be calculated using a formula of 0.3 units/kg/day for a T2DM patient and 0.15 units/kg/day for someone with T1DM. In the inpatient setting, for the patient receiving an intravenous (IV) drip of insulin, the basal dose can be estimated from the hourly rate of infusion, extrapolated to 24 h and reduced by 25 %, provided that the infusion has lasted for more than 12 h and has been stable in

the last 4–6 h of administration (less than 10 % variance in the hourly rate). For patients with diabetic GP, we recommend an overlap of at least 4 h (we prefer 6–8 h) between initiation of the basal insulin and cessation of the IV drip. Our preferred basal insulin is insulin glargine. If the patient routinely uses an insulin pump, we restart the pump.

Traditional adjustment of the basal insulin is based on the blood glucose level measured before breakfast, which assumes postabsorptive state (some 11–14 h after last meal). In patients with diabetic GP, however, the postabsorptive state is not so easy to define since gastric emptying may be delayed all day and an unknown amount of food (accumulated breakfast, lunch, and/or dinner from the previous day) is emptied during the night. Thus, the prebreakfast glycemia may not reflect real basal glycemia but ongoing postprandial glycemic excursions.

There are several approaches to attempt to better estimate the postabsorptive glycemia in these patients. First, the patient may skip breakfast for 2–3 days in a row and measure capillary glycemia every 1–2 h after waking up until lunch time to determine if glycemia remains stable or falls slightly, reflecting the postabsorptive state. Second, the patient may skip dinner and measure capillary glycemia frequently through the night. Third, a better approach is to use CGMS to detect trends. Patients and physicians need to examine in detail overnight trends. An overnight surge of glucose starting near or at midnight may suggest very late gastric emptying from the last supper or even from combined supper and lunch, as opposed to a steady and gradual increase which may indicate a need to adjust the basal insulin. The identification of these trends is demanding, but it is very useful to avoid hypoglycemia and severe hyperglycemia.

Bolus Insulin Administration for Meals

The challenges in determining meal bolus are much more complex than for the basal insulin. Instead of discrete postprandial "peaks" of increase and decrease of glycemia, most of the patients with diabetes and GP in whom we examined profiles of glycemia using CGMS display almost constant hyperglycemia interrupted by unpredictable dips into the normal or low glucose ranges [39]. This persistent hyperglycemia is probably the result of efforts of patients and doctors to avoid hypoglycemia in a setting in which tools to deliver insulin for these patients have not been tested in robust clinical trials. In spite of the above caveats, some general recommendations can be made regarding the insulin meal bolus for patients with GP to minimize risk of hypoglycemia and attempt to minimize hyperglycemia. If using injections, we suggest the following alternatives:

- Use regular insulin (rather than rapid-acting insulin analogues) in some patients because it has longer duration effect
- Administer insulin after the meal (not before)
- Give dose-fractionated insulin in two to three "mini shots" spaced within 4–6 h after meal ingestion

If using pumps, we suggest:

- Start meal bolus approximately 15–30 min after meal ingestion
- Use the dual-wave bolus delivery feature and program a small initial first wave (i.e., 10–20 %) and program the second wave to last for 4–6 h

Monitoring Blood Glucose for Meal Boluses

We recommend that whenever feasible CGMS be used. The patterns of the 24-h readings of pre- and postprandial glycemia in the individual patient should be carefully examined. We recently finished GLUMIT, a trial that tested the safety and efficacy of using CSII and CGMS in 45 patients with GP and diabetes. In this study, we used some of the abovementioned principles and found that this approach reduced HbA1c by 1.1 % and was associated with a reduction in the time that patients spent in the hypoglycemic and

hyperglycemic range. Patients also reported improvement in gastric symptoms [31].

Summary and Conclusions

Nausea and vomiting are very common manifestations of numerous gastrointestinal and non-gastrointestinal diseases. Thyroid dysfunction affects gastric emptying and can cause nausea and vomiting as well as diarrhea and/or constipation. Adrenal insufficiency is a cause of chronic nausea and vomiting easily diagnosed by stimulated levels of cortisol. The most common endocrine cause of chronic nausea and vomiting is type 1 and type 2 diabetes due to gastroparesis , neuropathy, and Cajalopathy. The insightful and careful management of diet therapy and insulin therapy based upon detailed assessment of postprandial glucose excursions in patients with diabetic gastroparesis are critical areas on which to focus. Continuous glucose monitoring with insulin pump therapy, progress toward the artificial pancreas, and teams of dedicated gastroenterologists, diabetologists, and dieticians are needed to improve glycemia, nausea, and vomiting in patients with diabetic gastroparesis.

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Nausea and Vomiting Related to Autonomic Nervous System Disorders

7

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Abbreviations

5-HT	5 Hydroxy tryptamine
Ach	Acetylcholine
AFT	Autonomic function testing
ANS	Autonomic nervous system
CAN	Cardiovascular autonomic system
CCK	Cholecystokinin
CINV	Chemotherapy-induced nausea and vomiting
CNS	Central nervous system
CRF	Corticotropin-releasing factor
CTZ	Chemoreceptor trigger zone
CVS	Cyclical vomiting syndrome
DAN	Diabetic autonomic neuropathy
DMV	Dorsal motor nucleus
ENS	Enteric nervous system
GABA	γ-Aminobutyric acid
GI	Gastrointestinal
HPA	Hypothalamic-pituitary-adrenal
HRV	Heart rate variability
HUT	Head-up tilt
ICC	Interstitial cells of Cajal
IGP	Intragastric pressure
LES	Lower esophageal sphincter
NE	Norepinephrine
NK	Neurokinin
NMH	Neurally mediated hypotension
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NTS	Nucleus tractus solitarius
OI	Orthostatic intolerance
PNS	Peripheral nervous system
POTS	Postural orthostatic tachycardia syndrome
QSART	Quantitative sudomotor axon reflex test
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TSS	Total symptom score
TST	Thermoregulatory sweat test
VIP	Vasoactive intestinal polypeptide

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Introduction

The functions of the gastrointestinal (GI) tract are independent of voluntary control with exception of the initiation of swallowing and control of the external anal sphincter. Autonomic GI functions are controlled by the intrinsic enteric nervous system (ENS) and the extrinsic neural systems (sympathetic and parasympathetic nervous systems) via the autonomic nervous system (ANS). Thus, it is not surprising that disorders of the autonomic nervous system can manifest in a wide variety of GI symptoms. ANS disorders that

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affect the GI tract primarily affect the neuromuscular functions rather than sensory or secretory functions [1].

Orthostatic intolerance (OI) including postural orthostatic tachycardia syndrome (POTS) is one of the most common autonomic disorders; it has a wide variety of GI manifestations ranging from nausea and vomiting to abdominal pain and constipation [2–4]. Treatment of the underlying orthostatic intolerance was found to resolve the GI symptoms [5]. Chronic intestinal pseudo-obstruction is associated with nausea and vomiting and shows many associated features suggestive of autonomic neuropathy [1]. Patients with gastroparesis exhibit features of autonomic neuropathy. Human studies have shown increased sympathetic activity in nausea and vomiting caused by vestibular stimulation [6, 7]. Chemotherapy-induced nausea and vomiting (CINV) was associated with abnormalities on autonomic testing [8]. In a study of 8 children with functional abdominal pain, abnormalities in autonomic function testing (orthostatic intolerance and abnormal sweat test) were noted in at least 75% of patients [9]. Conversely, patients with dysautonomia of various etiologies have associated nausea and vomiting. Most of the antiemetic agents, especially the newer ones like 5-HT_3 antagonists and NK_1 antagonists, may act in part via autonomic pathways. Disorders of the ANS can be associated with GI manifestations of nausea and vomiting. Some examples of these include orthostatic intolerance, POTS, cyclical vomiting syndrome (CVS), gastroparesis, migraines, and familial dysautonomia.

Overview of the ANS

The ANS is a part of the peripheral nervous system (PNS) and controls involuntary body functions. The ANS innervates all the organs in the body; it regulates respiration, the cardiovascular system including vasomotor activity, thermal regulation, abdominal and pelvic organs, glands, skin, iris of the eyes, and some reflexes. The primary function of the ANS is to maintain internal homeostasis in response to changes in the environment. ANS function is mediated via centrally integrated responses as well as local and regional reflexes initiated via the organ or the environment. Afferent neurons receive the information, relay it to coordinating centers in the central nervous system (CNS) where appropriate signals are generated, and then send it to the effector organs via efferent neurons.

The autonomic nervous system itself is divided into the sympathetic (thoracolumbar) and parasympathetic (craniosacral) limbs. While the sympathetic and parasympathetic limbs have opposing effects, these two limbs work together in coordination to maintain optimal functional status of the body in response to different stresses and demands at different times. The enteric nervous system (ENS) has also been included as the third limb of the ANS by some authorities [10–12].

Autonomic efferent fibers exit the CNS at different locations: parasympathetic fibers exit from cranial and sacral regions starting at the level of cranial nerves while sympathetic fibers exit from thoracolumbar region ending near the 2nd lumbar spinal cord segment. Intervening regions of the CNS give rise to somatic nerves. The efferent ANS is a two-neuron visceral motor system. The cell bodies of these presynaptic efferent neurons arise either in the brain stem or in the spinal cord gray matter (CNS) and the axons that arise from the CNS (preganglionic fibers) end at autonomic ganglia which are located at three areas: sympathetic trunk, preaortic ganglia, and near the walls of organs that are innervated. The first two are mostly sympathetic while the last one is parasympathetic, also called the intramural ganglia. Second order neurons (postsynaptic neurons) have their cell bodies in these ganglia and their axons end at the target organs.

Afferent autonomic neurons have their cell bodies in the cranial and dorsal root ganglia. Their peripheral fibers originate in the walls of the viscera and the axons travel alongside somatic afferent nerves through cranial nerves or dorsal spinal roots into the CNS. In the case of the vagal visceral afferent fibers, the cell bodies are in the superior and inferior vagal ganglia. Their central processes end in the vagal nucleus or nucleus tractus solitarius (NTS) of the medulla [13].

At each synaptic site, autonomic neurons secrete different transmitters to serve different functions. All preganglionic and parasympathetic postganglionic neurons secrete acetylcholine (Ach). Most postganglionic sympathetic neurons use norepinephrine (NE) with the exception of those supplying the adrenal medulla and sweat glands where ACh is secreted.

Certain autonomic signals are coordinated at the autonomic ganglia without reaching the central coordinating areas, in addition to organ-to-organ communication. Examples of entero-enteric reflexes include slowing of gastric emptying in response to acid in the proximal small bowel [14] and stimulation of pancreatic secretion when nutrients enter the small intestine [15]. The afferent neurons that convey the signals to the ganglia involved in these reflexes are called intestinofugal neurons; these neurons are unusual in the sense that their cell bodies are located in the gut wall and the axons terminate in the ganglia [15].

Brief Review of the Autonomic Pathways of Nausea and Vomiting

Nausea and vomiting may occur together or independent of each other and this may be due to differing pathophysiologic mechanisms. Newer antiemetic agents like the 5-HT_3 and NK_1 receptor antagonists while being very effective for vomiting still are unsatisfactory for the management of nausea [16–19].

The mechanism of vomiting involves a central emetic center. Rather than being a distinct anatomical area, this center is more of a functional zone or a signal generating area in the medulla and comprises the reticular formation, NTS, dorsal motor nucleus of the vagus (DMV) and ventrolateral medulla [20–22]. This center receives input from various areas of the body, including vagal afferents from the gastrointestinal tract, stimuli from the vestibular and visual areas, psychogenic stimuli from the cerebral cortex and chemoreceptor trigger zone (CTZ) [21]. The CTZ is located in the area postrema, is functionally outside of the blood brain barrier (BBB), and is activated by various endogenous and exogenous chemicals including medications. Efferent fibers from the emetic center travel via mainly the vagus nerve but also via cranial nerves V, VII, IX, and X [23]. (See Chap. 2 for review of the pathophysiology of vomiting).

Mechanism of Nausea and Vomiting of GI Tract Etiology

Chemoreceptors and mechanoreceptors in the GI tract can sense various chemical (e.g., acids, irritants, toxins) and mechanical (distension) stimuli. Detection of these various stimuli is the function of the enterochromaffin cells (ECC), which in turn release mediators that stimulate the vagus nerve [24]. Afferent vagal fibers take this signal to the emesis center. A variety of chemical mediators are involved including 5-hydroxytryptamine (serotonin, 5-HT) acting on the 5-HT_3 receptor, substance P acting on the NK_1 receptor, and cholecystokinin (CCK). Various other mediators are involved in enhancing or attenuating the effects of these mediators. For example in the case of 5-HT release, acetylcholine (muscarinic M3 receptors), norepinephrine (β receptors), histamine (H_2 receptors), and 5-HT itself increase 5-HT release, whereas γ-aminobutyric acid (GABA) B receptors, vasoactive intestinal polypeptide (VIP), and somatostatin inhibit 5-HT release [25]. Antagonists to these various chemical mediators form the basis of antiemetic medications.

The site of action of these antiemetic medications is either central or peripheral or both. 5-HT receptors exist at the vagus nerve endings as well as in the brainstem areas including NTS, DMV, and area postrema [26]. Neurokinin (NK) receptors have also been found in the CNS vagal neurocircuits as well as in the vagal afferents [26–28].

Pathophysiology of Nausea

Historically, nausea and vomiting have been thought to be a continuum of the same pathophysiologic mechanism caused by similar

stimuli and involving the same neural circuits but of varying intensity and/or duration. A temporal association exists between the stimulus and subsequent nausea via a constant level of stimulation and the intensity of nausea increases in parallel to the duration of stimulus [29]. The neural pathways involved in the pathogenesis of nausea have not been clearly defined; the hypothalamus and inferior cerebral cortical gyrus may be involved [30].

Experimental methods of studying nausea include gastric distention using a barostat [31]. Distension of the distal stomach induced nausea and gastric dysrhythmia and these effects were not blocked by granisetron (a 5-HT_3 antagonist) or atropine. Distal gastric distension also induced bloating and pain and these symptoms were also not alleviated by 5-HT_3 blockers.

A variety of physiological changes accompany nausea [32]. These include features of sympathetic activation (tachycardia, sweating, and vasoconstriction) as well as an increase in plasma levels of vasopressin, and gastric dysrhythmias. There is a correlation between the onset of nausea and rise in plasma vasopressin level [29]. In human studies, exogenous administration of vasopressin produced nausea and gastric tachyarrhythmia [33]. (See Chapter. 1 for review of the pathophysiology of nausea).

Role of the Vagus Nerve in Pathogenesis of Nausea and Vomiting

The vagus nerve plays a critical role in the pathogenesis of nausea and vomiting. Vagal afferents carry stimuli in the viscera to the CNS. The importance of the vagus nerve is illustrated in studies of vagotomy or vagal nerve stimulation. Wang and Borison showed that vagotomy abolished nausea and vomiting caused by intragastric administration of copper sulfate [34]. Electrical stimulation of the vagus nerve has been shown to elicit a vomiting response [35]. In ferret models, gastric or duodenal mucosal stimulation caused activity in the vagal afferents [36]. The afferent signals travel in the vagus nerve in the C type fibers.

Studies have shown increased c-fos activity in the reticular formation, nucleus tractus solitaries, dorsal motor nucleus of the vagus, and ventrolateral medulla during vomiting, highlighting the importance of these areas in the emetic response [22, 37, 38]. Area postrema ablation studies have shown that administration of emetogenic substances can cause abolishment or attenuation of vomiting [39].

Multiple autonomic reflexes accompany the vomiting response. These include excessive salivation, tachycardia, breath holding, sweating, and the motor activities of the upper GI tract including lower esophageal sphincter (LES) relaxation, retrograde peristalsis, and contraction of the abdominal muscles. The NTS plays a critical role in the coordination of these reflexes [40]. All the structures that have communication with the NTS also play important roles in regulation of the medullary reflexes involved in nausea and vomiting [22, 41]. Activation of the vagal afferents by emetogenic stimuli activates regions in the NTS that control the sensory aspects of swallowing and cardiovascular and respiratory functions [21, 22, 38]. Neurons of the NTS communicate with the adjacent DMV from where preganglionic parasympathetic neurons arise, which transmit the integrated response back to the GI tract [41]. DMV neurons are also under complex control by innervation from the NTS itself, as well as by numerous neurotransmitters (e.g., opioid peptides [42, 43], Serotonin [44], tachykinins [45, 46], and dopamine [47, 48]).

Postganglionic neurons are of two types—excitatory and inhibitory. Excitatory neurons are cholinergic and cause muscle contraction. Inhibitory neurons that cause muscle relaxation are nonadrenergic and noncholinergic and release either VIP or nitric oxide (NO). During the actual act of vomiting, vagal efferent signals cause retropulsive activity in the intestine, gastric contraction, and relaxation of the lower esophageal sphincter (LES) and pyloric sphincters [49–51].

It has been shown that receptors to 5-HT exist in the brainstem areas including NTS, DMV, and area postrema. This, along with the observation that centrally applied 5-HT_3 receptor antagonists block CINV, suggests that the action of 5-HT

may not be limited to peripheral sites [26, 38, 52, 53]. In addition, 5-HT released from ECC may also activate neurons in the ENS to modulate GI motility [27, 54, 55]. Neurokinin receptors have also been found in the CNS vagal neurocircuits as well as in the vagal afferents [28, 56, 57].

Gastric dysrhythmias associated with nausea and vomiting are mediated by vagal efferents. Vagotomy and vagal inhibition by anesthetics block these arrhythmias [49, 50]. During motion-induced models of emesis, atropine was found to abolish the gastric arrhythmias associated with emesis [33].

Role of Sympathetic Nervous System in Nausea and Vomiting

Very little is known about the role of sympathetic limb of ANS in nausea and vomiting; studies and literature related to this subject are limited. Nausea and vomiting reflex is predominantly controlled by the vagal limb of ANS, so most of the studies on nausea and vomiting are focused on the vagus nerve. Since parasympathetic and sympathetic systems have opposite but complementary functions, it can only be assumed that while parasympathetic arm is actively participating in the process, the sympathetic is exerting a complementary balancing effect. Nevertheless, studies have shown changes in sympathetic function in diseases that are associated with nausea and vomiting. Adult cyclic vomiting syndrome (CVS) is associated with an increase in sympathetic activity and vagal inhibition leading to alteration in gut motility [58, 59]. Schaub et al. have shown that nausea is associated with increased sympathetic and decreased parasympathetic tone [60]. Animal studies support the previous findings that there is increased sympathetic activity just before retching [61]. Other human studies have concluded that instead of direct effect on the gut, vestibular stimulation increases sympathetic outflow to the skin, producing cutaneous expression of motion sickness [6]. Some researchers hypothesize that sympathetic activity can be a defensive reaction against nausea and vomiting [7]. Additionally, Uchino et al. also explain similar results from their animal study claiming that the increased sympathetic activity suppresses the emetic response evoked by motion sickness.

In a study of patients with anorexia nervosa, Abell et al. found impaired sympathetic autonomic function in anorexic patients with statistically significant lower resting diastolic blood pressure (BP) and skin conductance and impaired response to the cold pressure test compared to the control group [62]. Abell et al. also found a statistically significant correlation between the sympathetic adrenergic measure of vasoconstriction to cold stress and the slope of solid gastric emptying in diabetic patients presenting with symptoms of gastroparesis [63].

Orthostatic Intolerance and POTS

Orthostatic intolerance (OI) refers to a variety of symptoms as a result of intolerance to an upright posture. These symptoms include loss of consciousness or lesser cognitive deficits like dizziness, vertigo, difficulty in concentration or memory loss, as well as headaches, fatigue, changes in blood pressure, tachycardia, and GI symptoms like nausea and abdominal pain [64]. OI includes conditions like orthostatic hypotension including neurally mediated hypotension and syncope (NMH) as well as postural orthostatic tachycardia syndrome (POTS) and is estimated to affect some 500,000 patients in the US [65]. Up to one-third of patients with POTS may develop neurally mediated syncope [66]. Neurally mediated syncope is the result of impaired cerebral perfusion due to sudden change in autonomic nervous system activity [67]. Vaso-vagal, situational (e.g., cough, swallowing, micturition) or carotid sinus syncope are examples of neurally mediated syncope. Syncope in these conditions is preceded by symptoms such as pallor, diaphoresis, nausea, abdominal discomfort, yawning, sighing, and hyperventilation.

According to the consensus statement on the definition of these disorders, POTS is defined by a sustained heart rate increase equal to or more than 30 beats/min within 10 min of standing or

head-up tilt in the absence of orthostatic hypotension. The standing heart rate for all subjects is often ≥ 120 beats/min [67]. This definition does not apply to patients with a lower resting heart rate and the rise in pulse rate needs to be at least 40 beats per minute (BPM) in children.

The manifestations of POTS result from decreased cerebral perfusion and increased sympathetic activation [67]. Patients with OI and POTS can exhibit a variety of GI symptoms: in a series of adults with POTS, a considerable number of patients presented with GI symptoms of nausea (39 %), bloating (24 %), diarrhea (18 %), constipation (15 %), and abdominal pain (15 %) [2–4, 68].

In the pediatric literature, there have been case reports and case series of patients presenting with abdominal pain thought to be of functional origin; further testing revealed they had autonomic dysfunction. Treatment of the underlying OI led to resolution of the abdominal pain [9, 69, 70]. One pediatric study (age range 9–17 years) looked at 24 patients whose main GI symptoms were abdominal pain (71 %), nausea (56 %), and vomiting (50 %). When specifically asked, these patients also described other OI symptoms like lightheadedness and dizziness. Upon autonomic testing, 4/24 (17 %) were found to have POTS, 12/24 (50 %) had NMH and 8/24 (33 %) had both POTS and NMH. Follow-up was available for 18 of these patients and 14/18 (78 %) had complete symptom resolution with treatment of the OI [5].

The pathogenesis of POTS is not clearly understood and likely represents a clinical endpoint or syndrome. POTS has been classified into different subtypes including hypovolemic, neuropathic and hyperadrenergic [71, 72]. The pathophysiology of POTS can be better understood based on the different subtypes.

Neuropathic POTS

[72, 73] is characterized by peripheral sympathetic denervation in the lower limbs as demonstrated by abnormal sudomotor tests. There is also impaired norepinephrine (NE) release in the lower limb in response to upright posture [73]. In one retrospective study, more than half of the patients had evidence of peripheral sudomotor denervation [68]. The underlying pathophysiologic disturbance in these patients is believed to be impaired peripheral vasoconstriction causing pooling of venous blood [74].

Hyperadrenergic POTS

The plasma NE level in the upright posture is 600 pg/mL or more in 30–60 % of patients with POTS suggestive of increased central sympathetic drive. These patients also have evidence of sympathetic stimulation like elevated blood pressure, tachycardia, and sweating [68, 75, 76].

In certain cases, genetic mutations have been identified to explain the etiology of POTS. In a 2000 study, the gene responsible for POTS was identified in one family. This gene codes for a NE transporter, and deficiency in this gene product allows for excessive NE levels [77]. POTS occurs more commonly in patients with connective tissue disorders like Ehlers–Danlos syndrome (EDS) [78, 79].

Mast cell activation

Some patients with POTS have mast cell activation and flushing with their orthostatic tachycardia [80]. GI symptoms may be an associated symptom. Diagnosis is most often made with an elevated histamine in a 4-h urine sample [81].

Autoimmune mediated autonomic neuropathy

An autoimmune basis for POTS is suggested based on the fact that an antecedent viral infection and antibodies to ganglionic ACh receptors are seen in some POTS patients. In a large retrospective study of 152 patients, an antecedent viral infection was seen in 90 % and antibodies to ganglionic ACh receptors in 14.6 % of patients [68].

Hypovolemic POTS

A relative hypovolemia has been proposed as a possible pathophysiologic mechanism of POTS. Reduced plasma, red cell, and total blood volumes have been found in many POTS patients [3, 82, 83]. A study found reduced daily urinary sodium excretion (100 mEq/L Na/24 h) in 28.9 % of POTS patients [68]. Yet another study found

low plasma renin activity in hypovolemic POTS patients; it has been suggested this may be due to renal autonomic denervation [84].

Cyclic Vomiting Syndrome (CVS)

CVS is a clinical syndrome of recurrent episodes of nausea and vomiting separated by symptom-free periods. First described in 1882 by Samuel Gee in a series of 9 pediatric patients and initially thought to be a childhood disorder, it is now known to affect patients in all age groups. There appear to be similarities and differences in pediatric versus adult onset of the disease [85, 86]. A number of other symptoms, chief among them abdominal pain, may accompany the episodes and the disorder is known to be associated with other disorders as discussed below.

The Rome III criteria for the diagnosis of CVS require certain features be fulfilled for the preceding 3 months, with symptom onset at least 6 months before diagnosis. The criteria are as follows:

(i) Stereotypical episodes of nausea and vomiting
(ii) Three or more discreet episodes in the preceding year; and
(iii) Absence of symptoms between attacks [87].

In both adults and children, the episodes of nausea and vomiting last from hours to days and are accompanied by abdominal pain. Episodes are triggered by physical or mental stress as well as certain foods. Migraine headaches are associated with both adult and pediatric CVS.

In children the incidence of CVS has been reported to be approximately 3 per 100,000 children per year [88] with a prevalence of 0.04–2 % [59, 89]. The disorder is diagnosed at a median age of 7.42 years (range 1.8–15) [88]. Factors triggering the episodes include physical or mental stress like infections, anxiety, or panic attacks. Anxiety-provoking situations for children may include exams or social events. Vomiting attacks are accompanied by pallor (87 %), lethargy (91 %), anorexia (74 %), nausea (72 %), and abdominal pain (80 %) [90]. In the natural history of the disease, as the patients grow, they may "grow out" of the episode, start having migraines instead of vomiting episodes, or may continue having CVS [91].

CVS in adults was reported by Abell in 1988 in a series of 8 patients. Since then the disorder has been increasingly recognized in adults; currently in the medical literature, adult studies predominate over pediatric [85]. The essential features of adult CVS are the same as pediatric CVS—episodes of nausea and vomiting interspersed with symptom-free periods, similar exacerbating factors and association with abdominal pain, which can be severe, in 58–71 % of patients [86, 92]. A cyclic vomiting-like syndrome has also been associated with chronic cannabis abuse and this is also referred to as cannabinoid hyperemesis syndrome [93]. Other variants of CVS include some diabetic patients without gastroparesis who experience episodic vomiting with symptom-free intervals as in CVS [94]. Another group of diabetic gastroparesis patients may have cyclic episodes of vomiting and meet the criteria for both conditions. Some patients may have recurrent morning nausea with limited vomiting which resolve later in the day [85]. Associated conditions seen in adults with CVS include migraine headaches, psychiatric disease, gastroesophageal reflux disease, irritable bowel syndrome, gallbladder disease, and insulin-dependent diabetes mellitus [85].

Pathogenesis of CVS

The pathogenesis and pathophysiology of CVS remain to be elucidated. The role dysregulated central neural pathways and neuroendocrine mediators involved in the afferent and efferent brain–gut pathways of nausea and vomiting may be part of the pathophysiology of CVS [85]. In one model of pathogenesis, it is thought that in individuals who are susceptible to developing the condition due to certain factors (e.g., family history of migraines, autonomic and GI dysfunction, and mitochondrial dysfunction) triggering factors (physical and mental stress), initiate the vomiting cascade. Why this leads to repeated bouts of emesis lasting hours to days is unknown [85].

Role of the Hypothalamic-Pituitary-Adrenal (HPA) Axis in CVS Pathogenesis

The stress response involves the endocrine, nervous, and immune systems to maintain homeostasis when faced with stressors. This response involves important centers located in the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland which is commonly referred to as the hypothalamic-pituitary-adrenal (HPA) axis [95].

Corticotropin-releasing factor (CRF) is the principal regulator of the HPA axis and is involved in the synthesis and release of cortisol from adrenal cortex. The CRF also appears to have important roles outside of the HPA axis including regulation of the ANS, learning and memory, feeding, and reproduction-related behaviors [96–100]. The peptides in the CRF family include CRF and urocortin (Ucn) 1, 2, and 3 [95] and CRF receptors are of two main subtypes, namely, CRFR1 and CRFR2 [101]. CRFR2 is present in peripheral organs including heart, skeletal muscle, skin, and the gastrointestinal tract [101–103].

During periods of stress, CRF peptides, via their action on CRF receptors, inhibit gastric activity and accelerate colonic peristalsis and defecation [104]. The gastrointestinal motor response to CRF also seems to involve pathways independent of the HPA axis and mediated by modulation of the autonomic nervous system [105, 106].

CRFR1 receptors are present on intestinal mast cells [107]. There is evidence that intestinal mucosal mast cells are involved in communication between the gastrointestinal tract and the central nervous system [108]. Activation of mast cells by CRF may cause release of 5-HT, nerve growth factor, proteases, and proinflammatory cytokines. Thus, CRF may indirectly be involved in activating the emetic response by activating mast cells and indirectly stimulating vagal afferents [107–109].

Role of the Autonomic Nervous System in CVS Pathogenesis

Nausea and vomiting are accompanied by signs and symptoms of autonomic activation even when they occur in the absence of a clinical syndrome like CVS. For example, pallor, tachycardia, and sweating indicate sympathetic arousal, and salivation and relaxation of the gastric fundus are due to vagal activity. Furthermore, the retro peristaltic activity of the upper GI tract is part of the actual act of emesis.

The involvement of the ANS in CVS has been explored in multiple studies. A study of 21 patients with CVS, 40 patients with migraines, and 36 healthy controls explored the association of CVS and migraines with other disorders thought to have autonomic abnormalities as their pathogenic basis—orthostatic intolerance, reflex syncope, interstitial cystitis, Raynaud's syndrome, chronic regional pain syndrome (CRPS), irritable bowel syndrome, functional dyspepsia, functional abdominal pain, fibromyalgia, and chronic fatigue syndrome [110]. Adult CVS was significantly associated with orthostatic intolerance and fibromyalgia as compared to controls.

Abnormalities in rate of gastric emptying have been noted in CVS patients. One study looked at the prevalence of rapid gastric emptying in 545 patients referred to a tertiary academic motility center for a variety of symptoms ranging from nausea and vomiting to abdominal pain and diarrhea. Rapid gastric emptying (less than 50 % retention at 1 h) was noted in 48 of these patients. Thirty-five percent of these patients were diagnosed with CVS [111]. Fifty-nine to seventy-seven percent of adult CVS patients were found to have rapid gastric emptying in the interepisodic period [112, 113]. However, during the symptomatic period, in those patients who could tolerate a gastric emptying test, delayed gastric emptying was noted in some patients [113]. Abnormalities in ANS function have been suggested as accounting for these observed disturbances in gastric emptying [85].

Multiple studies have directly assessed autonomic function in CVS patients. Initial studies looked at pediatric patients and found evidence of autonomic dysfunction. A study by To et al. in 14 pediatric CVS patients found enhanced sympathetic and reduced parasympathetic vagal modulation of the heart [114]. Chelimsky and

Chelimsky found CVS in children to be associated with primarily sympathetic dysfunction, affecting mainly the vasomotor and sudomotor systems and they postulated a vagally modulated sympathetic effect as the best mechanistic model to account for all current physiologic data on cyclic vomiting and gastroparesis [115]. Subsequent adult studies have shown similar findings. Twenty-one adult patients with CVS underwent autonomic testing in a study by Hejazi [58]. Autonomic abnormalities, both sympathetic and parasympathetic, were noted in 9 (43 %) of these 21 patients with a predominance of sympathetic disturbances. ANS abnormalities were seen only in the adult onset CVS patients. The authors suggested that adult CVS may represent a manifestation of dysautonomia as opposed to pediatric onset CVS where other factors (migraines and mitochondrial DNA abnormalities) may be more important. Venkatesan et al. performed autonomic testing in 20 adult CVS patients and 20 controls [116]. Ninety percent of adult CVS patients had abnormalities on the tests of sympathetic function, either OI or abnormal sudomotor tests; however, parasympathetic function was preserved in all CVS patients.

Gastroparesis

Following ingestion of a meal a series of gastric neuromuscular events occur [117]. The gastric fundus undergoes receptive relaxation. At this phase there is a decrease in intragastric pressure (IGP) followed by gradual increase until the satiety point is reached [118, 119]. Receptive fundic relaxation is mediated by vagal reflexes [120]. The food is then further broken down and mixed with gastric secretions by trituration which is mediated by contractions of the gastric body and antrum. The impulse for these contractile waves is generated in the interstitial cells of Cajal (ICC) which function as gastric pacemakers. The pacemaker signals arise at the proximal gastric body along the greater curvature and propagate distally. The triturated food is then emptied into the duodenum at a controlled rate of 3 pumps per minute, which is the same rate as the gastric peristaltic contractions [117]. The pylorus acts as a gatekeeper, regulating the size and amount of gastric contents that are allowed through [121].

The sequence of these events is coordinated by interactions between gastric smooth muscle, the enteric nervous system, ICCs, and the autonomic nervous system [122]. Disorders of these structures may result in gastric motor dysfunction [123–125], which may lead to delayed gastric emptying (gastroparesis), rapid gastric emptying (dumping syndrome), or other motor dysfunctions such as impaired fundic relaxation causing functional dyspepsia.

Vagal afferents from the stomach are stimulated by mechanical and chemical stimuli and efferent vagal fibers control gastric GI motor and secretory functions [126]. Gastric accommodation is mediated by a vago-vagal reflex [120]. Vagotomy, or electrical vagal stimulation performed to inhibit vagal function in humans, had modulatory effects on food consumption, inducing early satiety and weight loss [127]. Studies using the recently developed endoscopic functional luminal imaging probe (EndoFLIP), to measure pyloric resistance have shown correlation between pyloric diameter and compliance with gastroparesis symptoms [128, 129].

Gastroparesis is a disorder of gastric function due to delayed gastric emptying in the absence of mechanical obstruction [130]. Symptoms include early satiety, nausea, vomiting, and bloating with a predominance of nausea and vomiting [131]. Upper abdominal discomfort is present in 46–89 % of patients [131, 132], likely due to visceral hypersensitivity to gastric distension [133]. While not the predominant symptom, when present it is not alleviated by treatment of the underlying motility disorder [132].

Gastroparesis has been reported to affect up to 5 million individuals in the United States [134] with a predominance of female patients. In a study of 343 patients with functional dyspepsia, delayed gastric emptying was seen in 33.5 % of patients [135]. In a population-based study in Olmstead County, the prevalence of definite gastroparesis per 100,000 population was 37.8 in women and 9.6 in men [136].

The three main etiologies of gastroparesis are diabetes, idiopathic, and postsurgical. In a study of 146 patients, the etiologies were idiopathic in 36 %, diabetes in 29 %, postsurgical in 13 %, and other causes in 22 % [131].

Diabetic Gastroparesis

Gastroparesis is one of the complications of diabetes and occurs in both type 1 diabetes (T1DM) and type 2 diabetes (T2DM), though the prevalence is less in T2DM. In Olmstead County, the proportion of diabetics developing gastroparesis over 10 years was 5 % for T1DM and 1 % for T2DM. In tertiary centers, the prevalence was much higher: 40 % for T1DM and 10–30 % for T2DM [136–138].

The rate of progression of gastroparesis seems to be slower for T2DM compared to T1DM. It is unclear whether good glycemic control can prevent or slow the progression of gastroparesis [139, 140]. The occurrence of gastroparesis in diabetics not only induces GI symptoms, but poses serious problems for diabetes management. Erratic nutrient and medication absorption lead to problems with glycemic control. The first sign of development of gastroparesis may be problems with blood glucose control even in the absence of GI symptoms [140].

Pathophysiology of Gastroparesis

Diabetes can lead to rapid gastric emptying in the early stages and later to the development of delayed gastric emptying [138, 141, 142]. Diabetes-related vagal neuropathy can lead to impaired fundic relaxation causing dyspepsia [143, 144]. A variety of changes have been noted in the vagus nerve, enteric nervous system, and ICC. Vagal nerve damage has been observed both in the enteric nervous plexus and outside of the GI tract [145, 146] along with loss of nerves in the motor vagal neurons and the sensory sympathetic ganglia [147–149], and depletion of ICCs [150, 151] as well as enteric nervous system neurons [152]. In streptozocin-induced diabetes in rats, there were alterations in the presence and/or expression of neurotransmitter enzymes like neuronal nitric oxide synthase (nNOS) in vagal visceral afferents [153].

Depending on the stage of the disease, the prevalence of diabetic cardiovascular autonomic neuropathy varies from 7.7 % for recent onset T1DM to 90 % in potential pancreas transplant recipients [154, 155]. Twenty percent of randomly selected asymptomatic diabetics had abnormal cardiovascular autonomic function [124]. Diabetic autonomic neuropathy (DAN) affects the vagus nerve, and due to the widespread vagal innervation of almost all organs, it can manifest in a variety of symptoms such as resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, brittle diabetes, and hypoglycemic autonomic failure [124].

It is important to note that DAN not only poses symptomatic problems but portends an increased risk of mortality. Among diabetic patients with asymptomatic autonomic neuropathy, 5-year mortality rates of 27 % were noted compared with an 8 % mortality rate with normal autonomic function tests [156]. Mortality rates of 53 % versus 15 % over the 5-year period were found in diabetic patients with and without abnormal autonomic function tests. Deaths were due to renal failure, and sudden death and presence of gastric symptoms in patients with abnormal autonomic function tests carried a particularly poor prognosis [157]. Thus, diabetic gastroparetics may benefit from formal autonomic testing.

Three tests, R-R variation, Valsalva maneuver, and postural blood pressure testing, have been recommended for longitudinal testing of the cardiovascular autonomic system (CAN) [158]. Reduced heart rate variability (HRV) is the earliest indicator of CAN [124] and is associated with increased risk of coronary heart disease and death [124, 159]. HRV is the change in the time intervals between adjacent heartbeats and is reflective of the functioning of the ANS [160]. HRV indices provide a noninvasive assessment of cardiovascular control mechanisms. Commercial devices are available to provide automated measurement of HRV.

Autonomic Function Testing (AFT)

Clinical tests have been developed that assess the functional integrity of different aspects of the autonomic function system. Standard tests of autonomic functions include sudomotor (sympathetic cholinergic), cardiovagal (parasympathetic), and sympathetic adrenergic system function.

Sudomotor function tests These tests assess the integrity of the sweat-inducing pathways which involve sympathetic cholinergic pathways and comprise the quantitative sudomotor axon reflex test (QSART) as well as the thermoregulatory sweat test (TST) [161].

Quantitative sudomotor axon reflex test (*QSART*) evaluates the functional integrity of the postganglionic sympathetic sudomotor axon and is performed by acetylcholine iontophoresis into the skin. A capsule with a hygrometer is placed over the skin on the test site and the amount of sweat under the capsule is measured at various times. Sweating response is recorded at one site in the upper extremity and three sites in the lower (forearm, proximal leg, distal leg, and foot) and the results are compared with established normal values. QSART test assesses peripheral small fiber neuropathy.

Thermoregulatory sweat test (*TST*). TST is performed by increasing the ambient temperature and warming the body to induce sweating. Since the entire sweating pathway is involved in this test, it assesses the function of thermoregulatory sympathetic pathways from central structures (hypothalamus) to the sweat gland. A powder that changes color in the presence of sweating is applied to the body and the color change and symmetry of this is analyzed [162].

Tests of Cardiovagal Function

The HRV to respiration test is a measure of cardiac parasympathetic function. Typically the patient is made to breathe at 6 breaths per minute and the HRV is recorded. Normally there is an increase in heart rate with inspiration and decrease with expiration. Diminished HRV indicates parasympathetic dysfunction. Measures that are used include amplitude of the beat to beat variation as well as standard deviation of the R–R interval, the mean square successive difference, the expiratory-inspiratory ratio (E:I ratio), and the mean circular resultant [163, 164].

The Valsalva maneuver evaluates sympathetic, vagal, and baroreceptor function; the efferent baroreflex arc consists of sympathetic and parasympathetic pathways [163]. The patient exhales against resistance for a fixed time and the blood pressure and heart rate are recorded. Various indices of vagal cholinergic function can be calculated including the Valsalva ratio, which is the most important. The Valsalva ratio is the ratio of the shortest R-R interval (during the tachycardia period) to the longest R-R interval (during the bradycardia period). A value of 1.1 or less was defined as an abnormal response with 1.21 or greater as normal [165].

Tests of adrenergic function include blood pressure (BP) and heart rate responses to the Valsalva maneuver, head-up tilt (HUT) study, plasma norepinephrine, and meta-iodobenzylguanidine (MIBG) cardiac uptake. Information about the adrenergic components of the baroreflex can be obtained during the Valsalva maneuver [166].

HUT assesses blood pressure and heart rate response to an upright position and is useful primarily for the detection of orthostatic intolerance. Normally the HR shows an increase of 5–20 BPM and BP remains relatively constant [161].

Some simple tests of autonomic function can be done in the clinic and include pressor stimuli test, postural adjustment tests, and photoplethysmography.

Pressor stimuli tests include sustained handgrip, cold pressor test, and cortical arousal test. In the sustained handgrip test, isometric exercise is performed by squeezing on a dynamometer or a partially inflated sphygmomanometer cuff maintaining at least 30% maximum handgrip for at least 3 min. In the cold pressor test, a hand is immersed in ice slush, usually just below 4 °C, for up to 2 min. These tests raise blood pressure by activation of peripheral receptors, stimulating sympathetic efferent pathways. There is also a cerebral component to these tests. Cortical arousal test is performed by stressors such as sudden noise, mental arithmetic, or more complex

tasks. These stimuli normally elevate blood pressure and heart rate; in patients with central or efferent sympathetic lesions, the response to these stimuli is impaired or absent. The cold pressor test can also be evaluated by photoplethysmography [164, 167].

Postural tests [168] are completed by assessing the change in blood pressure or heart rate upon assuming an upright position after having been supine for a period of time. In the postural change in blood pressure, the blood pressure is measured with the patient supine for at 10–20 min and then after standing up after 1, 2, and 5 min. The blood pressure should not drop more than 20 mmHg systolic or 10 mmHg diastolic. In the postural change in heart rate, the test is completed in the same manner, measuring the pulse rate. There is an initial increase in heart rate that is maximal at approximately the fifteenth beat after standing, with a subsequent decrease from the initial tachycardia. The R-R interval at beats 15 and 30 after standing can be measured to give the 30/15 ratio. Values less than 1.03 indicate autonomic neuropathy [169].

Digital Blood Flow

This is done by measuring the blood flow to a finger by conventional plethysmography or photoplethysmography. A sudden inspiratory gasp causes reflex digital vasoconstriction as a spinal reflex, and this is easily measured plethysmographically. The response is impaired or absent in patients with a lesion of the cord or sympathetic efferent pathway.

Photoplethysmography

When light of a suitable wavelength is directed into the nail bed of a finger, the hemoglobin in the underlying nail bed capillaries absorbs, reflects, and scatters the rays. Photoplethysmography works by measuring the proportion of these effects. The relative proportion of these effects is dependent upon the amount of hemoglobin present in the nail bed capillaries. During systole, the arterial diameter increases and more blood and hemoglobin in the capillaries alters the absorption, reflection, and scattering of the light. This can be captured to create a waveform, the photoplethysmograph, which may be used for a variety of analyses including capillary pulse amplitude and HRV [170].

The TM-Oxi system assesses cardiac sympathetic and parasympathetic ANS function using an automatic oscillometric blood pressure device and a pulse oximeter. The SudoPath system uses stainless steel electrodes placed under the soles of the feet, where there is a high density of sweat glands, to measure skin conductance, which is dependent on sweating. Sudomotor function is indicative of SNS function. The ANSAR ANX-3.0 autonomic monitoring system is a noninvasive real-time digital autonomic monitoring system. This system uses United States Food and Drug Administration certified software that computes sympathetic and parasympathetic activity using spectral analysis of respiratory activity along with spectral analysis of HRV [171].

Multiple studies have utilized autonomic function testing for disorders manifesting nausea and vomiting. A study by Al-Shekhlee et al. involving POTS patients found that POTS includes subgroups with and without autonomic neuropathy. In the subset with autonomic neuropathy, decreased sweat output on the QSART was the most frequent abnormal finding [172]. In a study by Hejazi et al. [58] involving adult patients with CVS, autonomic testing demonstrated autonomic dysfunction in 43 % patients.

ANS Dysfunction and GI Motility Disorders

Studies have found a significant prevalence of autonomic disturbances in patients presenting with various symptoms of functional GI disorders as outlined above [9, 173]. In a study by Aslam et al. [167], abnormalities in serum catecholamine levels and autonomic function were seen in patients with diabetic gastroparesis and liver cirrhosis, with a system that utilized photophethysmography to determine adrenergic function.

One study looked at changes in systemic autonomic tests and heart rate variability before and after gastric neuromodulation in patients with nausea and vomiting. Systemic autonomic testing alone was performed in 39 patients, and systemic autonomic systemic testing and heart rate variability changes were recorded in a second group of 35 patients. After gastric neuromodulation,

changes in autonomic testing, including an increase in cholinergic function and decrease in sympathetic function, were noted. It was proposed that gastric neuromodulation may work via modulation of the ANS [174].

Oubre et al. evaluated the utility of AFT and patient outcomes for patients presenting with GI motility disorders. Eighteen patients were studied and 9 received AFT testing and result-guided therapy and the other 9 received symptom-based medical therapy without AFT. In the AFT group total symptom score (TSS) improved 35% (versus 0% in the non-AFT group) and symptom improvement was 65% (versus 0% in the non-AFT arm) assessed over a long-term period of 24–42 months [175]. Daboul et al. studied a similar group of 34 randomly selected patients presenting with symptoms of GI motility disorders. AFT revealed various abnormalities in 32/34 (94%) patients. Based on AFT results, individualized therapeutic recommendations (e.g., drugs, devices, and/or behavior) were given for each patient. At follow-up obtained at a mean of 5.4±0.5 (range 1–12) months, the TSS for these patients decreased from 10.3±0.8 at baseline to 7.5±0.8 ($p<0.001$). The authors concluded AFT may provide useful information that impacts clinical care [176].

Conclusion

In conclusion, a variety of conditions that present with nausea and vomiting have underlying autonomic abnormalities. These include conditions such as orthostatic intolerance, POTS, cyclic vomiting syndrome, gastroparesis, as well as chronic unexplained nausea and vomiting and gastroparesis-like syndrome, anorexia nervosa, and vestibular stimulation. POTS patients have abnormal sudomotor tests, increased plasma NE in upright position, and antibodies to ganglionic ACh receptors. Autonomic denervation has been implicated in POTS. CVS is associated with disturbance in ANS function primarily in the sympathetic measures. Diabetic gastroparesis is associated primarily with vagal neuropathy, although there may be a sympathetic abnormality in some patients.

Treatment directed at the underlying autonomic disorder such as orthostatic intolerance and POTS alleviates nausea and vomiting. Currently used pharmacological treatments work at least partially by their action on the ANS. Tricyclic antidepressants are thought to act centrally to modulate the vomiting process in CVS [85]. β-blockers have direct action on the adrenergic pathway and anticonvulsant agents like levetiracetram have neuromodulatory actions. Gastric electrical stimulation is a very effective therapy for diabetic gastroparesis and its mechanism of action is attributed, at least in part, to modulation of the ANS. Formal autonomic testing or simpler office-based tests can be used to diagnose ANS dysfunction. Treatment of ANS dysfunction may help nausea and vomiting in patients with GI motility disorders, disorders traditionally thought to be functional, but may in fact be due to a variety of ANS abnormalities.

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8 Nausea and Vomiting Related to the Central Nervous System Diseases

Braden Kuo and Prashant Singh

Introduction

Nausea and vomiting are common symptoms of various central nervous system diseases [1, 2]. They are seldom the only manifestation of primary central nervous system process and are generally accompanied with other symptoms/signs such as headache in migraine, focal neurologic symptoms in stroke, and seizures in primary brain tumor or brain metastasis. The prevalence and severity of nausea and vomiting vary based on underlying disease process and individual's dynamic threshold (described below). These symptoms have global impact on patients and result in significant health as well as economic burdens [3]. With this in mind, the aim of this chapter is to discuss the central causes of nausea and vomiting and briefly highlight our current understanding of the central pathways of nausea and vomiting.

Pathophysiology

The underlying mechanisms involved in nausea are complex and encompass psychological states, the central nervous system, autonomic nervous system, inputs from gastrointestinal tract, and the endocrine system.

The concept of dynamic threshold was introduced to understand the pathophysiology underlying nausea [4]. It is proposed that each individual has a threshold for nausea that changes minute by minute. At any given moment, the threshold depends on the interaction of certain inherent factors of the individual with the more changeable psychological states of anxiety, anticipation, expectation, and adaptation [4]. This dynamic interaction likely explains the inter- and intraindividual variability that is typically encountered in the face of a nauseogenic stimulus [4].

Stimuli which give rise to nausea and vomiting originate from four pathways—cerebellar and vestibular, cerebral cortex and limbic system, area postrema, and gastrointestinal tract via vagus nerve [5, 6]. In this chapter, we would focus on the central pathways of nausea.

Central Pathway of Nausea and Vomiting

Our knowledge about the central mechanism underlying nausea is very limited [7, 8]. The autonomic nervous system mediates several prodromal signs that are not uniquely related to nausea and vomiting such as sweating, salivation, etc. Autonomic nervous system is intimately connected to the central pathways of nausea and vomiting [5, 6, 9]. Chemosensitive receptors

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detect the presence of emetic agents in the blood and this information is relayed via the area postrema to the nucleus tractus solitarius (NTS) [10]. Abdominal vagal afferents which detect gastric tone and contents also project to the NTS [10]. In addition, neural pathways from vestibular system also project to NTS. Neurons from the NTS then project to a central pattern generator, which coordinates the various actions involved in the act of emesis in addition to directly projecting to neurons in the ventral medulla and hypothalamus, from which higher brain areas can be reached [10]. However, the final common pathway of emesis and the exact location of central pattern generator have not been defined well [5].

Many studies have suggested that cerebral cortex is also involved in pathways of nausea [8, 11]. Recent investigations using functional magnetic resonance imaging techniques in healthy adults have shown that medial prefrontal cortex and pregenual anterior cingulate cortex, areas of the brain involved in higher cognitive function and emotion, are positively correlated with increase in heart rate during nausea, suggesting the importance of cognitive and emotional centers in modulating the parasympathetic to sympathetic shift associated with nausea [8, 12]. Studies have shown that certain brain regions such as insula are involved in sympathetic as well as parasympathetic modulation during both phasic as well as sustained autonomic response during nausea. There is also some evidence suggesting divergent central control for sympathetic and parasympathetic response to nausea [9]. Activity in default mode network and visual motion areas have been shown to have negative correlation with parasympathetic outflow at peak nausea [9]. In contrast, lateral prefrontal cortical activity has been shown to negatively correlate with sympathetic outflow during recovery, soon after cessation of nauseogenic stimulation [9].

Napadow et al. studied humans predisposed to motion sickness and suggested that nauseogenic stimulus causes activation of amygdala, putamen, and locus coeruleus which translates into fear conditioning and emotional triggering. This ultimately leads to the sensation of strong nausea [8]. This is followed by continued, sustained activation in cortical areas such as insula, anterior cingulated cortex, nucleus accumbens, orbitofrontal, somatosensory, and prefrontal cortex. These areas are involved in the interoceptive, limbic, somatosensory, and cognitive network which alerts the suffering individual of the changes in interoceptive signaling, so that appropriate autonomic and motor responses are initiated in a timely manner [8]. Many of these areas involved in nausea circuit, specifically anterior cingulate cortex, insular cortex, nucleus accumbens, and amygdala, are known to be involved in processing of acute as well as chronic painful stimulus [13, 14]. It is plausible that brain perceives peripheral noxious stimulus through similar pathways, which in some cases lead to chronic pain and in others to chronic nausea. Understanding the central mechanisms of nausea and vomiting will be important for the development of therapies.

Central Causes of Nausea and Vomiting

As suggested above, nausea and vomiting could be generated via both central as well as peripheral stimuli. The most common central causes of nausea and vomiting are listed in Table 8.1. Chronic headaches such as migraine are generally associated with nausea and vomiting. In addition, any condition that increases intracranial pressure (e.g., mass, infarction, infection) can result in vomiting with or without nausea. Many of these causes have additional neurologic signs such as cranial nerve dysfunction, focal neurologic deficits, or seizures. Conditions that affect the vestibular system such as labrynthitis and Ménière's disease could also cause these symptoms in association with other symptoms such as vertigo. Demyelinating disease affecting area postrema is uncommon but important central cause of nausea and vomiting. Similarly, certain seizure disorders such as temporal lobe seizures could also lead to vomiting as an ictal manifestation. In the next section of this chapter, we would be discussing some of these causes in more detail.

Table 8.1 Central causes of nausea and vomiting

Increased intracranial pressure
Stroke
Hemorrhagic
Ischemic
Intracranial mass
Primary brain tumor
Brain metastases
Infection
Meningitis
Encephalitis
Brain abscess
Anatomical causes
Hydrocephalus
Pseudotumor cerebri
Idiopathic intracranial hypertension
Secondary causes
Migraine
Seizure disorder
Demyelinating disorder
Neuromyelitis optica
Multiple sclerosis
Vestibular causes
Labrynthitis
Meniere's disease
Motion sickness
Postoperative nausea and vomiting
Chemotherapy-induced nausea

Migraine

Nausea and vomiting are one of the cardinal symptoms of migraine. In a clinic-based study from Canada, nausea was present in over 90 % of the patients visiting headache specialists [15]. In a population-based study of about 6500 individuals with episodic migraine, half reported nausea more than half the times and another 29 % reported less than half the times they experienced nausea with headaches [16]. Nausea also appears to be more common in females compared with males [16]. Nausea in patients with migraine seems to have a global impact as it is associated with more headache symptoms, occupational disability, medical leaves, and self-reported financial burden [3, 16]. In addition, nausea symptoms are potential barrier to effective migraine treatment. In 2010, National Headache Foundation Survey, 4 in 10 patients with migraine endorses delaying or avoiding their oral medication because of migraine-associated nausea and vomiting [16]. Thus, nausea and vomiting independently contribute to migraine-related disability and represents more severe subset of patients with migraine. Patients with episodic migraine and frequent headache-related nausea have a twofold risk of developing into patients with chronic migraine [17].

Using a PET-based study, Maniyar et al. have shown nausea in migraine is associated with activation in rostral dorsal medullary areas such as nucleus tractus solitarius (NTS), dorsal motor nucleus of the vagus nerve and nucleus ambiguus along with periaqueductal gray matter which are all known to be involved in nausea pathway [18]. The study showed that migraine in nausea is not related to pain and trigeminal activation [18, 19].

Treatment of migraine itself can relieve nausea and vomiting in several cases. In addition, trying to avoid individual triggers for nausea and vomiting in some patients may also be recommended. Oral medications are less effective once the migraine event has started because of decrease in gastrointestinal motility and subsequent drug bioavailability [20]. In addition, oral triptans contribute to the development of nausea among migraine patients who are nausea-free before treatment [20]. In patients with nausea, oral drugs may be effective. Nevertheless, if the patients are vomiting, the treatment should be administered parenterally, intranasally, or rectally to guarantee their absorption. When needed, the treatment with tripatans and/or analgesics can be combined with antiemetics such as chlorpromazine, metoclopramide, domperidone, or promethazine [21]. Drugs such as metoclopramide are also prokinetic and thus could also improve migraine-associated gastric stasis [21]. In randomized controlled trials, intravenous chlorpromazine (1 mg/Kg) and droperidol (2.75 mg, 5.5 mg, and 8.25 mg) have all been shown superior to placebo in providing headache relief at the end of 1–2 h in patients with acute attacks of migraine [22–24]. Similar results have been shown for other antiemetics such as metocloperamide which has been shown to superior to placebo in reducing

headache pain and requiring rescue drugs in treatment of acute migraine attack [25].

Parkinson's Disease

About 25 % of the patients with Parkinson's disease have nausea or vomiting with half of them complaining of severe symptoms [26]. In Parkinson's disease, the stimulus for nausea and vomiting could be central or peripheral in origin. Studies have consistently reported delayed gastric emptying in 55–100 % of patients with Parkinson's disease [27–30]. There is some evidence that it might be more impaired in patients with familial Parkinson's disease than sporadic Parkinson's disease [28]. While most of the studies did not find a correlation between disease severity and gastric emptying time, one study did [27, 29, 31, 32]. However, the inability of patients with very severe disease to undergo scintigraphy may have limited this evaluation [30]. Gastric emptying rate has not been shown to correlate with duration of Parkinson's disease or gastrointestinal symptoms [30]. Delayed gastric emptying has therapeutic implications as it has been shown to have effect on drug delivery and possibly response fluctuations [30, 33–35]. Majority of patients with Parkinson's disease have high frequency fasting gastric dysrhythmias on electrogastrography, a finding that has been shown to be associated with nausea and vomiting [36–38]. The delayed gastric emptying and gastric dysrhythmias in patients with Parkinson's disease is likely because of involvement of both enteric as well as central nervous system. Lewy body deposition has been described not only in myenteric and submucosal plexus of stomach but also central structures of autonomic nervous system including dorsal motor nucleus of vagus and could be contributing to these findings [30].

In addition to delayed gastric emptying and gastric dysrhythmias in patients with Parkinson's disease, nausea could also result from pharmacological treatment of Parkinson's disease [39]. Nausea is a very common side effect of dopaminergic therapy which generally occurs immediately after initiating therapy [39]. Nausea occurs in about 15–35 % of the patients starting dopaminergic treatment [39, 40]. Nausea occurs because of agonistic effect of these drugs on dopamine receptors in the gut as well as area postrema. Dopa decarboxylase inhibitors such as carbidopa prevent peripheral conversion of levodopa to dopamine and could improve levodopa-induced nausea and vomiting [41]. Carbidopa is, however, ineffective in mitigating the nausea induced by dopamine agonists. Domperidone, a peripheral D2 receptor antagonist that does not cross blood brain barrier (BBB), has been shown to reduce nausea from dopaminergic medications [42, 43]. In a randomized controlled trial of 182 patients with Parkinson's disease, trimethobenzamide has been shown to reduce nausea or vomiting during the first 8 weeks of apomorphine therapy without worsening Parkinsonism features [44]. Other antiemetics such as metocloperamide, promethazine, and prochlorperazine can worsen the Parkinson's disease and thus should be avoided [30].

Stroke

Vomiting has been reported in up to 15 % of all stroke patients [45]. It is more often seen in hemorrhagic stroke patients than patients with ischemic stroke with up to 24 % of patients with intracerebral hemorrhage complaining of vomiting as compared to 9 % of patients with ischemic stroke [45, 46]. The frequency of stroke is even higher (up to 1.5 times) in patients with subarachnoid hemorrhage as compared to intracerebral hemorrhage [45]. In a study combining results of 19 prospective studies, presence of vomiting at the time of presentation increased the probability of having hemorrhagic stroke by threefold [46]. In addition, patients with vomiting at the time of presentation of stroke (ischemic or hemorrhagic) have been shown to have fivefold increased risk of death when compared to those who did not [45]. Cases of cyclic vomiting syndrome after a stroke have also been reported [47].

As the vertebral, basilar, and posterior cerebral arteries supply blood to brainstem, nausea and vomiting are also one of the fairly common

symptoms of posterior circulation stroke. At a tertiary care center, 27 % of about 400 consecutive patients with posterior circulation transient ischemic attack/stroke complained of nausea and vomiting [48]. In these cases, diplopia, dysarthria, dysphagia, vertigo, drowsiness, and various other features such as cranial nerve deficits usually coexist at the presentation of nausea and vomiting and aid in diagnosis [49].

Although nausea and vomiting occur commonly in patients with hemorrhagic or ischemic stroke, their pathophysiology is not very well understood. Cerebral edema after stroke leading to increased intracranial pressure and meningeal stimulation could be contributing to the symptoms of nausea and vomiting in these patients [50, 51].

Demyelinating Diseases

Neuromyelitis optica (NMO) is a central nervous system demyelinating autoimmune disorder characterized by relapsing attacks that are characterized by involvement of optic nerves, spinal cord, and periventricular brain regions. Medullary involvement of NMO is characterized by intractable nausea, vomiting, and hiccups which often precede NMO relapses but can also occur as isolated clinical manifestation of the disease [52, 53]. Intractable nausea and vomiting are present in 16–43 % of the patients with NMO [52–54]. Intractable nausea and vomiting are the initial presenting in about 13 % patients with NMO [55]. In such cases, nausea and vomiting are often evaluated by gastroenterologists and neurological evaluation is delayed or not pursued [53, 56].

NMO is likely an organ-specific autoimmune disorder mediated by IgG antibodies targeting water channel aquaporin (AQP-4) of central nervous system [54, 57]. These autoantibodies penetrate the CNS through endothelial transcytosis or at area of relative blood brain barrier (BBB) permeability or injury and bind to aquaporin channels on the surface of astrocytes [58]. Area postrema is a key structure involved in the central pathway of vomiting and consists of loose tissue containing glia and neurons, has a thin ependymal cover, and is penetrated by convoluted capillaries that lack tight epithelial junctions forming relatively permeable BBB [59, 60]. In addition, it is one of the most vascularized brain regions. There is also slowing of blood in this region due to specialized pericapillary pool of interstitial fluid [56, 60]. Furthermore, AQP-4 water channels are present in abundance in area postrema region. All these factors collectively make area postrema the preferential target of AQP-4 IgG antibodies in NMO [56]. Histopathological studies have demonstrated selective AQP-4 loss in area postrema accompanied by tissue rarefaction, inflammation, variable complement deposition, and nonlytic alteration in astrocytes [56]. The involvement of area postrema has also been confirmed on MRI in patients with NMO presenting with intractable nausea and vomiting [53]. Studies have shown 16-fold increased risk of having nausea, vomiting in NMO patients with involvement of area postrema as compared to those who did not, emphasizing involvement of area postrema as the basis of intractable nausea and vomiting in this debilitating disease [56].

Early detection of IgG AQP-4 antibodies is the key to diagnosis and could allow the patients to receive immunosuppressive therapies, at times, before the onset of optic neuritis or transverse myelitis [55]. MRI of brain could also aid in the diagnosis by showing involvement of periventricular structures.

The first-line treatment of acute attack is intravenous corticosteroids for five consecutive days [58]. Plasmapheresis is the second-line treatment if intravenous corticosteroid fail. Intravenous immunoglobulins have also been investigated and have shown some efficacy. Several immunosuppressive therapies including azathioprine, mycophenolate moefitil, rituximab, mitoxantrone, and methotrexate have been used successfully for maintenance therapy for attack prevention [58]. Most of the patients with intractable vomiting require inpatient hospitalization for hydration and intravenous antiemetic therapy.

Nausea and vomiting are very uncommon in other demyelinating diseases such as multiple sclerosis. However, case reports of nausea and

vomiting as primary presenting manifestation of multiple sclerosis has been reported [61, 62].

Brain Metastasis

Nausea and vomiting in patients with cancer are generally due to chemotherapy and radiation. In addition to these, there are gastrointestinal (bowel obstruction, peritoneal carcinomatosis, severe constipation), metabolic (hypercalcemia), and psychiatric (anxiety related) causes of nausea and vomiting [63]. In patients with advanced oncological disease, nausea and vomiting could also be related to central nervous system especially brain metastasis [63]. Brain metastasis occurs in 9–17 % of cancer patients with lung, breast and melanoma being the commonest causes [64]. In addition to increasing intracranial pressure by mass effect, brain and leptomeningeal metastasis can also raise intracranial pressure by causing obstructive hydrocephalus and hemorrhage in metastases. Furthermore, direct effect on structures involved in nausea/vomiting pathways leading to vomiting without causing raised intracranial pressure or hydrocephalus has also been reported [65]. The treatment is often directed to brain metastasis in the form of surgery and/or whole brain radiation, stereotactic radiosurgery alone or in combination [66]. There is some evidence that targeted and immune therapies are useful in melanoma and renal cancers with brain metastases [67, 68]. Symptomatic patients with brain metastases also benefit from dexamethasone 4–8 mg/day in divided doses [66]. Higher doses along with emergent surgery should be considered in patients with hydrocephalus and impending brain herniation [67].

Seizure

Vomiting is rarely the main manifestation of epileptic episode [69]. In a study of 900 adults and children with epilepsy, Panayiotopoulos et al. reported that only 24 patients had vomiting during ictal episode [70]. In the study, all 24 patients were prepubertal children with a similar clinical pattern of nocturnal partial seizures. International League Against Epilepsy has recently identified a form of early onset benign childhood epilepsy, Panayiotopoulos syndrome, characterized by tonic eye deviation and ictal vomiting [71–73]. These seizures are often accompanied by autonomic symptoms such as pupillary changes, pallor/flushing, alterations in heart rate, breathing irregularities and temperature instability [74]. In a study by Kivity et al., less than 50 % of the patients with Panayiotopoulos syndrome had ictal vomiting and those with ictal vomiting had significantly higher frequency of prolonged vomiting than those who did not [72]. In addition, ictal vomiting has also been described in adults with complex partial seizures of temporal lobe origin [75]. In cases of temporal lobe seizures, it was thought to be localizing to right or nondominant lobe temporal lobe seizures [76, 77]. However, several cases of ictal vomiting from dominant temporal lobe seizures have also been reported [69, 78, 79].

Studies have shown that mesial and anterior temporal lobe structures had most active interictal epileptiform discharges and ictal vomiting was associated with spread of electroencephalographic seizure pattern to more lateral and superior regions of temporal lobe [77]. Sometimes, interictal electroencephalogram can be normal in these patients and an ictal electroencephalogram might be needed for diagnosis [69]. One study showed that although the seizure onset zone was localized in the temporomesial structures, but the occurrence of ictal vomiting correlated in time with a discharge affecting exclusively the anterior part of both insular lobes [79]. These findings may point to activation of insular or limbic circuits whose descending influence on vomiting center or chemoreceptor trigger zone would initiate the vomiting reflex [77, 79].

In children with Panayiotopoulos syndrome, a large proportion of patients are not routinely treated with antiepileptic drugs. Low seizure frequency and severity, parental and child preference, and nocturnal seizure predominance were shown to be the most important factors influencing a policy of no treatment [74]. The evidence

base for treatment choice for this syndrome is acknowledged to be poor, with some studies suggesting that carbamazepine and sodium valproate are "possibly" effective, and levetiracetam, oxcarbamazepine, gabapentin, and sulthiame "potentially" effective as initial monotherapy [74]. In adult patients with temporal lobe seizures, various antieplieptic are used alone or in combination [69]. Some cases are difficult to control with antiepileptics alone and might require surgical intervention [75].

Pseudotumor Cerebri

Pseudotumor cerebri refers to symptomatic intracranial hypertension in patients without intracranial mass lesion, ventriculomegaly, or underlying central nervous system infection or malignancy [80]. Idiopathic intracranial hypertension (IIH) is the primary form of pseudotumor cerebri that most commonly occurs in obese adolescent or adult females but can occur in males also. Secondary pseudotumor cerebri may be clinically indistinguishable from IIH, but results from an identified medical conditions (polycystic ovarian syndrome, Addison disease), medication toxicity (Vitamin A and derivatives, antibiotics especially tetracyclines, hormones), venous abnormality (cerebral venous sinus thrombosis, superior vena cava syndrome, etc.), or decreased absorption of CSF due to damage to the arachnoid granulations (postbacterial meningitis or subarachnoid hemorrhage) leading to elevated intracranial pressure [80].

Headache is the most common symptom of pseudotumor cerebri occurring in up to 90% of the patients with visual loss due to papilledema being the most feared complication [81, 82]. However, dizziness, tinnitus, nausea, and vomiting are also associated with IIH and can be incapacitating for some patients. The pathophysiology of these symptoms are not clearly understood but are thought to be due to compressive neuropathy of vestibule-cochlear nerve from intracranial pressure [83].

Diagnosis of pseudotumor cerebri is based on papilledema, normal neurological examination (except cranial nerve findings), neuroimaging consistent with the diagnosis, elevated lumbar puncture opening pressures, and normal CSF composition [80]. Its treatment includes weight loss in obese patients and acetazolamide as medical therapy. In certain cases, cerebral transverse sinus stenting, repeated lumbar puncture, and CSF shunting procedures are also considered [84].

Other Causes

Several other important central causes of nausea and vomiting such as motion sickness, chemotherapy-induced nausea, and postoperative nausea and vomiting (PONV) are beyond the scope of this chapter and book. Nausea and vomiting in motion sickness are complex processes mediated by several central and peripheral pathways such as vestibular system, cerebellum, chemoreceptor trigger zone, vomiting center, hypothalamus, and autonomic nervous system [85]. Nausea and vomiting in both chemotherapy-induced nausea and vomiting as well as PONV are in part mediated by chemoreceptor trigger zone in area postrema.

Conclusion

Nausea and vomiting are common symptoms in several central nervous system diseases and are usually associated with other neurological symptoms. Central pathway leading up to nausea and vomiting is generally activated by peripheral stimuli, but direct activation of these pathways could explain the presence of these symptoms in a myriad of central nervous system diseases.

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9 Pharmacological Causes and Treatments of Nausea and Vomiting

William L. Hasler

Introduction

Medication use can impact significantly on patient reports of nausea and vomiting. Numerous agents in several classes can elicit these symptoms in previously healthy individuals or can worsen them in patients with preexisting disorders with nausea and vomiting. Conversely, a variety of medications with actions to reduce vomiting (and nausea to a lesser degree) have been shown to provide benefits in diverse clinical settings.

Neurotransmitter Mediation of Nausea and Vomiting: Relation to Medication Effects

Vomiting is elicited by stimulation of well-characterized emetic receptor sites in the peripheral and central nervous systems followed by activation of brainstem nuclei which evoke the stereotypical motor responses that lead to oral expulsion of gut contents. Due to lack of good animal models, the neural pathways responsible for the sensation of nausea are less well understood but clearly involve cerebral cortical participation. Definition of a gamut of neurotransmitters and associated receptors involved in the initiation and suppression of vomiting has permitted development of a collection of medications to abort or prevent nausea and vomiting. Understanding these pathways can facilitate better management of these bothersome symptoms.

Neural Pathways of Nausea and Vomiting

Based mostly on animal models, the neural mechanisms involved in vomiting have been well characterized. Emetic stimulation promotes activation of several brainstem nuclei including the area postrema in the base of the brainstem fourth ventricle, the nucleus tractus solitarius, the dorsal motor nucleus of the vagus, phrenic and medullary nuclei involved with regulating respiration, the hypothalamus, and the amygdala. Most stimuli of vomiting activate emesis by action on one of four pathways—the cerebral cortex, the area postrema, the vestibular nuclei, and vagal afferent pathways projecting from the upper gut which then project to the nucleus tractus solitarius. Cortical pathways elicit vomiting in response to emotional factors as well as to severe pain and unpleasant olfactory, gustatory, or visual stimuli. The area postrema possesses a porous blood-brain barrier that permits access to toxins circulating in the bloodstream and cerebrospinal fluid.

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Emetic stimuli acting by area postrema stimulation include several medications (opiates, nicotine, digoxin, some cancer chemotherapeutic agents), endocrinologic and metabolic disorders (hypercalculemia, uremia, diabetic ketoacidosis, hypoxemia), and toxins associated with bacterial gastroenteritis. Vestibular nuclei respond to stimuli related to movement and activate vomiting in patients with motion sickness, labyrinthitis, labyrinthine tumors, and Meniere's disease. Gastric and small intestinal vagal afferent fibers elicit emesis in response to both circulating drugs and local toxins within the gut lumen.

Neural pathways underlying the sensation of nausea are less well established, because of the lack of a proven animal model. Given that nausea is experienced only in awake individuals, participation of cerebral cortical mechanisms must be involved. In healthy volunteers, induction of experimental motion sickness has been shown to activate several structures including the insular, anterior cingulate, orbitofrontal, somatosensory, and prefrontal cortex [1].

Neurotransmitters Involved in Nausea and Vomiting

A broad range of neurotransmitters participate in emesis elicited by activation of the different neural pathways described above. The most important receptor subtypes involved in vomiting are histamine H_1, acetylcholine muscarinic M_1 (or M_3/M_4/M5), dopamine D_2, serotonin 5-HT_3, neurokinin NK_1, and cannabinoid CB_1 [2]. Not coincidentally, many antiemetic therapies target these receptors. Other transmitter receptors involved in vomiting depending on the emetic stimulus include adrenoceptor, adrenocorticotropic hormone, μ and δ opioid, glucocorticoid, prostaglandin, γ-aminobutyric acid, N-methyl-D-aspartic acid, vasopressin, transient receptor potential vanilloid ($TRPV_1$), as well as other dopamine (D_3) and serotonin (5-HT_{1A}, 5-HT_4) subtypes [2, 3]. Motion stimuli and cold caloric irrigation of the ear promote histamine release in the hypothalamus and brainstem. Cholinergic pathways involve both peripheral and central mechanisms: presynaptic muscarinic receptors are present in vagal afferent fibers, whereas vomiting in response to M_1/M_4 receptor agonist administration and intravenous nicotine perfusion are partly blocked by area postrema ablation [4]. Involvement of central catecholamine pathways is evidenced by increase in plasma epinephrine, elevated activity of noradrenergic neurons in the locus coeruleus in different models of emesis, and area postrema medication of epinephrine, norepinephrine, and α_2 adrenoceptor agonist-induced emesis [5]. Vasopressin is released during experimental motion sickness and intravenous vasopressin evokes nausea in humans; vasopressin V_1 receptor antagonists prevent motion-induced emesis in monkeys. Extensive research has characterized the roles of serotonin, neurokinin, and cannabinoid receptors in several models of emesis.

Serotonin Pathways

Several serotonin receptor pathways participate in emesis in response to a number of emetic stimuli. Serotonin released by intestinal enterochromaffin cells or myenteric neurons acts on vagal afferent 5-HT_3 receptors as well as 5-HT_3 receptors in the area postrema and nucleus tractus solitarius. Vomiting caused by 5-HT_3 receptor agonist administration is reduced by vagotomy and splanchnicectomy but not by ablation of the area postrema. 5-HT_3 receptor antagonists show antiemetic actions by binding to vagal afferent nerves with lesser effects in the area postrema. 5-HT_3 receptor activation may result in acute vomiting or may cause more delayed emesis by sensitizing the vagus to other emetic mediators including substance P [6]. Other serotonin receptor subtypes participate in vomiting in different models. Motion sickness can be blunted by 5-$HT_{1A/7}$ receptor agonism or 5-HT_{2A} receptor antagonism, 5-HT_{1A} receptor agonists reduce emesis from resiniferatoxin in shrews, and emesis is elicited by 5-HT_4 receptor agonists while 5-HT_4 receptor antagonists show antiemetic effects in some experimental models [7].

Neurokinin Pathways

Several lines of evidence indicate important roles for neurokinin pathways in nausea and vomiting.

NK_1 receptors have been identified in the area postrema, nucleus tractus solitarius, the reticular area near the nucleus ambiguus, and the abdominal vagus [8]. Brainstem injection of substance P elicits vomiting, while NK_1 receptor antagonists delivered peripherally, into the area postrema, medial solitary nucleus, reticular formation, and dorsal vagal complex, prevent emesis to a range of stimuli. Peripheral pathways are also involved as substance P and other tachykinins have been localized to intestinal enterochromaffin cells and can be released by chemotherapeutic agents [8]. Furthermore, an abdominal vagal pathway for the antiemetic actions of NK_1 receptor antagonists has been suggested [9].

Cannabinoid Pathways

Roles for anti- and proemetic actions of cannabinoid receptor pathways have been proposed. CB_1 receptors are present in the cerebral cortex, hypothalamus, anterior cingulate gyrus, hippocampus, cerebellum, dorsal motor nucleus of the vagus, medial and dorsal subnuclei of the solitary nucleus, and area postrema [10]. Peripheral CB_1 receptors also are localized to enteric neurons. The importance of CB_2 receptor pathways in emesis is less well established. CB_2 receptors are expressed in ileal myenteric and submucosal ganglia as well as intestinal plasma cells and activated macrophages and have been proposed to participate in visceral pain perception and altered motor function with intestinal inflammation. However, CB_2 receptor participation in emesis has not been excluded as CB_2 receptors also have been identified in the dorsal vagal complex, amygdala, and other brain regions. Anandamide and 2-arachidonylglycerol have been characterized as endocannabinoids in the central and enteric nervous systems. Tetrahydrocannabinol has antiemetic action on central nervous system CB_1 receptors, as evidenced by decreases in C-fos expression in the nucleus tractus solitarius and dorsal motor nucleus of the vagus and reduced C-fos protein levels in the area postrema and dorsal subnucleus of the solitary nucleus [10]. However, the cannabinoid substance cannabidiol elicits a biphasic effect with antiemetic actions at low doses but stimulation of vomiting at higher doses in animal models [11].

The complex actions of cannabinoid agents are reflected in the poorly understood clinical entity cannabinoid hyperemesis syndrome. This disorder is characterized by recurrent episodes of relentless nausea and vomiting separated by asymptomatic intervals, similar to cyclic vomiting syndrome. Indeed, approximately one-third of patients with cyclic vomiting syndrome report significant marijuana use [11]. Cannabinoid hyperemesis syndrome typically occurs in men who use large quantities of cannabis daily over at least a 2-year period and resolves with cessation of marijuana use [12]. Delays in diagnosis as long as 9 years are frequently reported and emergency room visits prior to diagnosis are common (7.1 ± 4.3). The underlying pathophysiology of cannabinoid hyperemesis syndrome is not well defined. It has been postulated that this condition results either from accumulation of a toxic byproduct of the cannabis leaves or to divergent downregulation of different cannabinoid receptors [13].

Medication-Induced Nausea and Vomiting

Medications are common causes of nausea and vomiting and most often elicit these symptoms early in the course of therapy. Prescription and over-the-counter drugs have been reported to elicit these symptoms in 14 % of patients enrolled in clinical trials of novel pharmaceuticals [14]. The actions of emetogenic agents may relate to activation of one or more of the receptor-mediated pathways described above or to nonreceptor mechanisms.

Receptor-Mediated Medication Effects

Many medications cause nausea and vomiting by actions on receptors for neurotransmitters involved in genesis of emesis or by increasing levels of these neurotransmitters (Table 9.1).

Table 9.1 Medications that cause nausea and vomiting by receptor-mediated pathways

Drug class	Representative individual agents	Mechanisms of action	Percent with nausea or vomiting (%)
Opiates	Morphine Hydromorphone Codeine Hydrocodone Oxycodone	μ-opioid receptor agonists	5–70
	Tramadol Tapentadol	μ-opioid receptor agonists plus norepinephrine and/or serotonin reuptake inhibitors	
Anti-Parkinsonian/ antirestless legs drugs	Levodopa Bromocriptine Pergolide Cabergoline Ropinirole Pramipexole	D_2 receptor agonists	5–60
Antidepressants	Fluoxetine Sertraline Citalopram Escitalopram Paroxetine Vilazodone	Serotonin reuptake inhibitors	21–58
	Duloxetine Venlafaxine Dexvenlafaxine	Serotonin-norepinephrine reuptake inhibitors	
Fibromyalgia treatments	Milnacipran Levomilnacipran	Serotonin-norepinephrine reuptake inhibitors	5–37
Antidiabetic agents	Exenatide Liraglutide Dulaglutide	Glucagon-like peptide$_1$ receptor agonists	7–25
Smoking cessation drugs	Nicotine	Nicotine receptor agonist	6–40
	Varenicline	Nicotine receptor partial agonist	
Weight reduction agent	Lorcaserin	5-HT_{2C} receptor agonist	4–9
Alzheimer's disease/ myasthenia gravis medications	Neostigmine Pyridostigmine Physostigmine Donepezil Galantamine	Acetylcholinesterase inhibitors	3–25
	Rivastigmine	Combined butyryl- and acetylcholinesterase inhibitor	
Antibiotics	Erythromycin Azithromycin	Motilin receptor agonists	3–14

The three best evaluated causes of medication-induced nausea and vomiting, opiates, cancer chemotherapy, and postoperative nausea and vomiting, are discussed below. Acetylcholinesterase inhibitors (e.g., neostigmine, pyridostigmine, physostigmine) interfere with acetylcholine metabolism and lead to a cholinergic syndrome of nausea, vomiting, diarrhea, diaphoresis, bradycardia, and other symptoms. Medications in this class are employed during surgery and for selected neurologic conditions; newer drugs like donepezil and galantamine and agents which have combined butyrl- and acetylcholinesterase inhibiting effects like rivastigmine are prescribed to improve cognitive function in patients with dementia. Nausea and vomiting

may underlie the high dropout rates in clinical trials of acetylcholinesterase inhibitors for Alzheimer's disease [15]. Another agent active on cholinergic pathways, nicotine, has been reported to cause nausea, anorexia, and vomiting when used in clinical trials of Parkinson's disease [16]. Conversely, nicotine products elicit very little nausea in smokers because these individuals develop tolerance to this agent. The nicotine partial receptor agonist varenicline also is employed clinically for smoking cessation and has been reported to cause nausea and/or vomiting in up to 40 % of cases; gastrointestinal symptoms led to early discontinuation of therapy in clinical trials with this drug [17]. Dopamine receptor agonists such as levodopa, bromocriptine, pergolide, cabergoline, ropinirole, and pramipexole are used to treat Parkinson's disease and movement disorders such as restless legs syndrome. Such agents evoke nausea and vomiting in 5–60 % of patients. Antidepressants in the serotonin reuptake inhibitor (e.g., fluoxetine, sertraline, citalopram, escitalopram, paroxetine) and serotonin-norepinephrine reuptake inhibitor (e.g., duloxetine, venlafaxine, dexvenlafaxine) classes are associated with nausea and vomiting in 21–58 % of cases due to increases in serotonin acting on 5-HT_3 receptors on vagal afferent nerves and in the area postrema and nucleus tractus solitarius [18]. Related medications used for fibromyalgia (e.g., milnacipran, levomilnacipran) have similar actions. Several antidiabetic drugs including metformin and glucagon-like peptide-1 analogs (e.g., exenatide, liraglutide, dulaglutide) frequently induce nausea and vomiting in patients with type 2 diabetes. However, a recent report from a large multicenter database observed that these drugs did not worsen symptom severity in patients with gastroparesis [19]. Other medication causes of nausea and vomiting involving receptor pathways include macrolide antibiotics in high doses like erythromycin and azithromycin (motilin receptor agonists) and oral contraceptives (progesterone and estrogen compounds).

Opiate-Induced Nausea and Vomiting

Opiates are among the most common causes of medication-induced nausea and vomiting. Twenty-seven percent of patients with noncancer pain managed with opiates reported nausea in one recent study, while 9 % noted vomiting [20]. In a systematic review of randomized trials of opiate medications for pain control, nausea and vomiting were experienced by 32 and 15 % of patients, respectively [21]. Opiate drugs are believed to elicit these symptoms by actions within the central and peripheral nervous systems. These effects include binding to μ-opioid receptors in the area postrema, the nucleus tractus solitarius, the vestibular apparatus, and the gut myenteric and submucosal plexi where they stimulate uncoordinated contractile activity. Other receptor subtypes may participate in opiate-induced nausea and vomiting including k and δ-opioid, D_2, 5-HT_3, and NK_1 receptors. Furthermore, morphine can increase synthesis, release, and metabolism of serotonin [22]. Most investigators observe similar degrees of nausea and vomiting from use of all opiate medications when adjusted for potency. However, some reports suggest that some agents such as tapentadol and hydromorphone may elicit less nausea and/or vomiting compared to morphine or oxycodone [23].

Chemotherapy-Induced Nausea and Vomiting

Nausea and vomiting are very common complications of cancer chemotherapy. Chemotherapy-induced nausea and vomiting (CINV) is classified as acute, delayed, and anticipatory. Chemotherapy drugs have been stratified into four risk categories for CINV including those that are at high (90 % risk of CINV without antiemetic therapy), moderate (30–90 %), low (10–30 %), and minimal (<10 %) risk. Highly emetogenic agents include cisplatin, high-dose cyclophosphamide, streptozotocin, carmustine, and dacarbazine. Even with antiemetic prophylaxis, acute and delayed vomiting are reported by 35 and 50 % of patients receiving highly emetogenic drugs, respectively [24]. Anticipatory nausea and vomiting occur in 25–34 % of individuals within the first four courses of chemotherapy, especially in younger patients. Risk scores have been developed to predict the risk of CINV and include poor

social functioning, nausea before administration of chemotherapy, female sex, age <50 years, delivery of these highly emetogenic drugs, and prior history of CINV [25]. Compared to those at low risk, patients at high risk are three to four times more likely to experience CINV. Patients under treatment for hematologic malignancies appear to be a higher risk of CINV, perhaps secondary to their younger age and the emetogenicity of the chemotherapeutic agents employed in this setting [25].

Pathways underlying CINV have been extensively characterized in animal and human models and provide the rational basis for its prophylaxis and treatment. Acute vomiting after highly emetogenic agents like cisplatin is associated with elevations in plasma and ileal tissue serotonin, serotonin immunoreactive mucosal cells, and urinary levels of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) within hours of chemotherapy administration. Conversely, milder chemotherapeutic drugs do not increase plasma serotonin or urinary 5-HIAA concentrations. Mechanistic studies have observed release of serotonin from intestinal mucosal enterochromaffin cells which then bind to vagal afferent 5-HT_3 receptors projecting to the area postrema. Highly emetogenic agents like cisplatin also increase serotonin turnover in the brain and activate several structures including the dorsal vagal nuclei and central amygdala. The risk for acute CINV development is increased with some 5-HT_3 receptor gene polymorphisms, reflecting participation of serotonin pathways. Conversely, delayed CINV is mostly mediated by serotonin-independent pathways as there is little 5-HIAA excretion in the urine and poor responses to 5-HT_3 receptor antagonists. Rather, evidence suggests an important role for central NK_1 receptor-mediated mechanisms as suggested by the capability of central but not peripheral NK_1 receptor antagonists to reduce delayed CINV [3]. However, studies observing reductions in delayed CINV after treatment with the long-acting 5-HT_3 receptor antagonist palonosetron suggest there may be interactions between 5-HT_3 and NK_1 receptor pathways in this emetic phase [26]. In contrast to acute CINV, delayed emesis is prevented by ablation of the area postrema but is unaffected by vagotomy. Other pathways which may participate in delayed CINV include 5-HT_4 receptor, adrenoceptor, and peripheral muscarinic receptor pathways.

Postoperative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) occurs after 17–37 % of operations. Drug risk factors for this condition include general anesthesia with volatile agents or nitrous oxide, intraoperative neostigmine, and intra- and postoperative opiate use. Indeed, opiate use after anesthesia is one of 5 factors in a recently developed risk score predicting rates of PONV [27]. Non-medication-related risk factors for PONV include abdominal or orthopedic surgery, female sex, older age, obesity, anxiety previous PONV, histories of migraines or motion sickness, and prior *Helicobacter pylori* infection. Mechanisms underlying PONV have not been completely defined; however, some reports suggest that inhalational anesthestics (e.g., halothane, isoflurane) can modify 5-HT_3 receptor function [28]. A range of variants of genes encoding M_3, D_2, 5-HT_3, μ-opioid receptors, and α_2-adrenoceptors have been associated with PONV which may underlie susceptibility to this complication. Other polymorphisms associated with PONV may influence transport and metabolism of opiates or antiemetics like the 5-HT_3 receptor antagonist ondansetron.

Medication-Induced Nausea and Vomiting Unrelated to Receptor Activation

Several medications elicit nausea and vomiting by mechanisms unrelated to receptor activation or neurotransmitter release. Salicylates and nonsteroidal anti-inflammatory drugs are proposed to produce these symptoms by local mucosal irritation in the stomach and duodenum with subsequent activation of vagal afferent pathways. Similar local effects may be involved in nausea and vomiting after ingestion of potassium supplements or vitamin preparations. Medication

effects on ion channels may mediate nausea and vomiting evoked by some cardiac antiarrhythmics, antihypertensives, anticonvulsants, calcium channel antagonists, and diuretics.

Medications Used to Treat Nausea and Vomiting

Medications prescribed to treat or prevent nausea and vomiting include antiemetic agents acting on an assortment of receptor pathways in the central or peripheral nervous systems, prokinetic drugs that increase motor activity or accelerate transit in the stomach or small bowel, and medications that modulate neural activity to reduce noxious gut sensations.

Antiemetic Agents

Several antiemetic agents are available that act by effects on different receptor subtypes (Table 9.2).

Histamine Receptor Antagonists

Antihistamines such as meclizine, dimenhydrinate, and promethazine bind to H_1 receptors in the brainstem and vestibular nuclei and are useful for vomiting in disorders in which there is labyrinthine activation (e.g., motion sickness, labyrinthitis), gastroenteritis, uremia, and PONV. Prominent side effects with this drug class include sedation and mouth dryness. Second-generation histamine receptor antagonists with less sedation like cetirizine and fexofenadine are ineffective antiemetics [29].

Muscarinic Receptor Antagonists

Muscarinic receptor antagonists such as scopolamine and hyoscine bind to M_1 receptors in the vestibular nuclei and medulla to prevent or treat motion sickness with similar potency as antihistamines. Anticholinegic agents given alone or with other antiemetic classes also have documented efficacy in prophylaxis against PONV after orthopedic, plastic, gynecologic, abdominal, and otologic surgeries. However, these agents significantly slow gastric emptying thus they should be used with some caution in gastroparesis. One investigation reported no benefits of the peripherally active anticholinergic drug methscopolamine on motion sickness, indicating central actions of this drug class [30]. Muscarinic receptor antagonists elicit prominent dryness of the mouth and eyes and can also cause sedation, reduced concentration, constipation, and urinary retention (especially in older men).

Dopamine Receptor Antagonists

Dopamine D_2 receptor antagonists (with possible additional action on D_3 receptors) act in the area postrema and are frequently used as antiemetics in patients with vomiting secondary to acute gastroenteritis, PONV, radiation therapy, some medications, and some forms of CINV. These include phenothiazine (e.g., prochlorperazine, chlorpromazine, trimethobenzamide) and butyrophenone (e.g., droperidol, haloperidol) agents. Frequently reported side effects of these agents include sleep disturbances, anxiety, depression, movement disorders (e.g., akithisia, parkinsonism, tardive dyskinesia), and hyperprolactinemic effects (e.g., gynecomastia, lactation, amenorrhea, loss of libido). Many dopamine receptor antagonist antiemetics also bind to histaminic and muscarinic receptors as well. Consequently, patients treated with these agents may also report antihistamine and anticholinergic side effects. Among phenothiazines, prochlorperazine is several fold more selective for D_2 receptors compared to H_1 receptors while chlorpromazine shows no selectivity for the two receptor subtypes [2].

Serotonin Receptor Antagonists

Short acting oral, intravenous, and transdermal serotonin 5-HT_3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron) show prophylactic efficacy in a range of clinical conditions including acute CINV, radiation-induced vomiting, PONV, and medication-induced nausea and vomiting occurring with antidepressant treatment with selective serotonin reuptake inhibitors [31]. However, these agents are less effective for delayed CINV. Other patient subsets showing antiemetic responses to 5-HT_3 receptor antago-

Table 9.2 Antiemetic medications

Drug class	Representative individual agents (Antiemetic doses)	Side effects	Clinical indications
Histamine H_1 receptor antagonists	Meclizine (25 mg oral every day) Dimenhydrinate (50 mg oral every 4–6 h) Promethazine (12.5–50 mg oral/rectal every 4–6 h)	Dry mouth Sedation	Motion sickness Labyrinthine disorders PONV Uremia
Acetylcholine muscarinic M_1 receptor antagonists	Scopolamine (1.5 mg transdermal every 72 h)	Dry mouth and eyes Blurred vision Sedation Urinary retention Impaired concentration	Motion sickness Labyrinthine disorders PONV
Dopamine D_2 receptor antagonists	Prochlorperazine (5–10 mg oral 3–4 times daily; 25 mg rectal twice daily; up to 10 mg IM/IV 3–4 times daily) Trimethobenzamide (300 mg oral three times daily; 200 mg IV three times daily)	Sleep disturbances Anxiety Mood disturbances Constipation Dystonias Tardive dyskinesia Blurred vision Galactorrhea Sexual dysfunction	Gastroenteritis Toxins PONV CINV Radiation-induced nausea and vomiting
Serotonin 5-HT_3 receptor antagonists	Ondansetron (4–8 mg oral/oral dissolving tablet 2–3 times daily; 4 mg IV three times daily) Granisetron (1 mg oral twice daily; 3.1 g/24 h transdermal; 1 mg IV) Dolasetron (50–100 mg oral; 100 mg IV) Palonosetron (0.075–0.25 mg IV)	Headache Fatigue Constipation Cardiac arrhythmias Sudden cardiac death	CINV Radiation-induced nausea and vomiting PONV Hyperemesis gravidarum Emesis in AIDS
Neurokinin NK_1 receptor antagonists	Aprepitant (40–125 mg oral) Fosaprepitant (115–150 mg IV) Netupitant (300 mg with 0.5 mg palonosetron oral)	Fatigue Anorexia Diarrhea Constipation	CINV PONV
Cannabinoid CB_1 receptor agonists	Dronabinol (2.5–10 mg oral 2–4 times daily) Nabilone (1–6 mg oral 2–3 times daily)	Weight gain Somnolence Ataxia Hallucinations	CINV
Corticosteroids	Dexamethasone (4–12 mg oral, 4–5 mg IV)	Depression Anxiety Hyperglycemia Hypertension	CINV PONV
Benzodiazepines	Lorazepam (1 mg IV)	Sedation	Anticipatory nausea and vomiting

nists include those with hepatic impairment or renal failure, bulimia nervosa, pregnancy, and nausea and vomiting secondary to human inmmunodeficiency virus infection. One study reported comparable efficacy from intravenous 5-HT_3 antagonists as with the H_1 receptor antagonist promethazine [32]. 5-HT_3 receptor antagonists act by binding to receptors on peripheral vagal afferent terminals and in the brainstem in the area postrema, nucleus tractus solitarius, and dorsal motor nucleus of the vagus [3]. In most comparisons, the different short acting agents ondanse-

tron, granisetron, and dolasetron have similar efficacy and the intravenous formulations are not more effective versus oral preparations. Palonosetron is a second-generation 5-HT_3 antagonist with a longer half-life that triggers receptor alteration leading to persistent inhibition of receptor function after the drug is withdrawn [33]. Furthermore, palonosetron blunts cross-talk between NK_1 and 5-HT_3 pathways. Because of these different properties, palonosetron provides better prevention of delayed CINV compared to shorter acting 5-HT_3 receptor antagonists. Adverse effects of this drug class include headaches, constipation, abnormal liver chemistry values, as well as cardiac arrhythmias and increases in the risk of sudden cardiac death in patients with QTc interval prolongation on electrocardiography (EKG).

Neurokinin Receptor Antagonists

Oral aprepitant and intravenous fosaprepitant bind to neurokinin NK_1 receptors in the area postrema, nucleus tractus solitarius, and possibly the reticular formation and have shown efficacy in prophylaxis of acute and delayed CINV, PONV, and motion sickness [34]. Documented cross-talk between NK_1 and 5-HT_3 pathways suggests synergism of antiemetic effects of antagonists at both receptor subtypes [9]. The oral and parenteral formulations exhibit equivalent antiemetic efficacy. Side effects of NK_1 antagonist therapy include appetite suppression, altered bowel function, and singultus. Newer NK_1 antagonists (e.g., rolapitant, netupitant) exhibit stronger binding characteristics and longer duration of activity and may offer advantages over older agents in treatment of vomiting as well as severe nausea occurring with chemotherapy. Netupitant was recently approved as part of a combination drug with palonosetron by the United States Food and Drug Administration (FDA) to treat acute and delayed CINV.

Cannabinoid Receptor Agonists

Cannabinoids (e.g., dronabinol, nabilone) exert antiemetic effects by action as agonists on CB_1 receptors in the insular cortex of the brain, dorsal vagal complex, and other central and peripheral nervous system sites. Cannabinoids are best characterized as therapies for both acute and delayed CINV. In this setting, cannabinoid drugs are more potent antemetics than D_2 receptor antagonists for moderately emetogenic chemotherapy but are only equivalently effective for severely emetogenic regimens. The combination of dronabinol with the D_2 receptor antagonist prochlorperazine reduces the duration and severity of chemotherapy-induced nausea more than either agent alone, but dronabinol and the 5-HT_3 receptor antagonist ondansetron were equally effective in reducing CINV severity yet were not more effective in combination in another comparison study [35]. Other cannabis-based medicines have been released worldwide for treatment of nausea and vomiting. Cannabidiol is available as a sublingual spray; a second product combining cannabidiol and tetrahydrocannabinol (Sativex) showed efficacy in reducing delayed nausea and vomiting after chemotherapy in a phase II trial [36]. In this study, 57 % of patients on active drug reported no delayed nausea and 71 % had no delayed vomiting compared to 22 % for each symptom with placebo. In addition to their antiemetic effects, CB_1 receptor agonists have been employed as appetite stimulants. Cannabinoid drugs produce significant side effects, especially in elderly patients, including sedation, lethargy, euphoria, cognitive dysfunction, and rarely hallucinations. To date, prescription cannabinoids have not been identified as causes of cannabinoid hyperemesis syndrome.

Corticosteroids

Corticosteroids (e.g., dexamethasone) commonly are prescribed as prophylactic agent to prevent acute and delayed CINV and PONV. Glucocorticoid receptors are present in the area postrema and nucleus tractus solitarius. Additional antiemetic actions of dexamethasone may include modulation of vagal 5-HT_3 receptor activity [37]. When used as antiemetics, corticosteroids may cause severe side effects like insomnia, dyspepsia, and anxiety.

Other Medications

Benzodiazepines are often given for anticipatory nausea as part of CINV treatment, but it is not

clear they have true antiemetic actions. Medications which act on central and peripheral adrenoceptor pathways reduce nausea and vomiting in some scenarios. Ephedrine, the α_1 adrenoceptor agonist phenylephrine, and the centrally acting α_2 adrenoceptor agonists clonidine and dexmedetomidine can reduce PONV in selected settings. Clonidine also has shown antiemetic benefits in conditions with autonomic disturbances, and in cases with diabetic gastroparesis and in refractory cyclic vomiting syndrome [38]. Subcutaneous methylnaltrexone, approved for opiate-induced constipation, decreases nausea secondary to morphine administration in animal models [39]. Case reports also have reported improvements in patients with refractory nausea and vomiting with the anticonvulsant carbamazepine.

Prokinetic Agents

Several prokinetic agents are available that stimulate gastric emptying or small bowel propulsion by varied mechanisms (Table 9.3).

Metoclopramide

Metoclopramide accelerates gastric emptying by activating 5-HT_4 receptors and antagonizing D_2 receptors in the GI tract. This agent has additional central antiemetic actions as a D_2 receptor antagonist in the area postrema, as well as antagonist effects on H_1 and 5-HT_3 receptors. The motor stimulatory properties of metoclopramide are restricted to the proximal gut, thus this drug is not effective for small bowel or colonic transit propulsion. Central nervous system complaints (e.g., anxiety, depression, sleep

Table 9.3 Prokinetic medications

Available agents (Prokinetic doses)	Mechanisms of action	Side effects	Clinical indications
Metoclopramide (5–10 mg oral/oral dissolving tablet/IM/IV 3–4 times daily before meals)	Dopamine D_2 receptor antagonist Serotonin 5-HT_4 receptor agonist Serotonin 5-HT_3 receptor antagonist	Anxiety Mood disturbances Sleep disturbances Dystonias Tardive dyskinesia Galactorrhea Sexual dysfunction	Gastroparesis Functional dyspepsia
Domperidone (10 mg oral three times daily before meals)	Peripheral dopamine D_2 receptor antagonist	Galactorrhea Sexual dysfunction Cardiac arrhythmias Sudden cardiac death	Gastroparesis Functional dyspepsia
Erythromycin (125 mg oral suspension/IV 3–4 times daily before meals) Azithromycin (125 mg oral suspension/IV 3–4 times daily before meals)	Motilin receptor agonist	Abdominal pain Nausea and vomiting Diarrhea Cardiac arrhythmias Sudden cardiac death	Gastroparesis Intestinal pseudoobstruction
Pyridostigmine (30–120 mg oral three times daily)	Acetylcholinesterase inhibitor	Abdominal pain Salivation Nausea Diaphoresis Cardiac arrhythmias Heart block	Gastroparesis Intestinal pseudoobstruction Diabetic constipation
Octreotide (50–100 mcg subcutaneous at bedtime)	Somatostatin analog	Diarrhea Altered glycemic control Cholelithiasis Hypothyroidism	Intestinal pseudoobstruction with bacterial overgrowth

disruption, movement disorders) and hyperprolactinemic complications (e.g., gynecomastia, amenorrhea, impotence) are commonly reported and may preclude use of the drug in up to one-third of patients. The United States Food and Drug Administration issued a Black Box Warning in 2009 for the risk of irreversible tardive dyskinesia with chronic metoclopramide use. This adverse event has been most often observed with longstanding use (>20 months), most commonly with daily doses exceeding 30 mg and while being taken by women and individuals over age 70 years [40]. Likely as a consequence of this warning, prescription rates for metoclopramide have fallen from 70 to 24 % of patients [41]. Because this condition can develop insidiously and can be irreversible, the risks should be explained in detail and the discussions documented in the medical records; furthermore, patients should be examined several times yearly.

Motilin Receptor Agonists

Motilin receptor agonists including erythromycin and other macrolide antibiotics like azithromycin and clarithromycin are potent stimulants of phasic antral contractions and accelerants of gastric emptying. Unlike metoclopramide, there are no proven central actions for erythromycin although recent animal models of motion sickness raise the possibility of such antiemetic capabilities of this class of drugs [42]. Motilin agonists have two main drawbacks as prokinetics. First, they have a narrow therapeutic range, failing to elicit contractions at low doses but generating spastic activity at higher doses that are associated with induction of abdominal pain and vomiting. Second, patients commonly develop tolerance to the prokinetic effects of erythromycin. Consequently, some have reserved this drug class for acute rather chronic therapy of gastroparesis. In addition to their GI side effects, macrolide agents increase the risk of sudden cardiac death more than twofold through induction of ventricular arrhythmias relating to QTc interval prolongation [43]. This risk increases to fivefold among patients who additionally are prescribed CYP3A inhibitors.

Domperidone

Domperidone is a peripheral D_2 antagonist which exhibits both prokinetic effects on the stomach and antiemetic activity by effects in the brainstem, thereby providing benefits to both patients with gastroparesis and functional dyspepsia. Unlike metoclopramide, domperidone does not cross the blood-brain barrier and is not associated with an increased risk of movement disorders. However, hyperprolactinemic side effects may occur because of the relatively porous nature of this barrier in the anterior pituitary. Recent case-control series document three- to fourfold increases in sudden cardiac death in patients with prolonged QTc intervals on EKG testing. These risks are increased at daily domperidone doses >30 mg and in patients over 60 years old [44, 45]. As a consequence, recent worldwide policy statements are now advocating limiting the dose and duration of domperidone therapy and restricting its use in high risk populations. The drug is not approved by the FDA, but still can be obtained from foreign pharmacies and pharmacy websites. Currently, the FDA permits domperidone prescription under the auspices of an Investigational New Drug program for clinicians who receive both FDA and local Institutional Review Board approval. Patients participating in this program must be willing to undergo frequent testing with EKG and electrolyte determinations and to avoid intake of other pharmaceuticals that prolong QT intervals.

Other Medications

Other medications with prokinetic action on the proximal gut have been prescribed for selected cases of gastroparesis or intestinal pseudoobstruction with nausea and vomiting. Cholinesterase inhibitors such as pyridostigmine have reported efficacy in autoimmune intestinal dysmotility by effects to increase gastrointestinal contractility [46]. The somatostatin analog octreotide elicits aborally propagating contractile complexes in the small intestine and has been employed as a prokinetic in some patients with chronic intestinal pseudoobstruction with associated small intestinal bacterial overgrowth [47]. However, this agent inhibits antral contractions

and delays gastric emptying and may not be advocated in patients with symptoms predominantly relating to gastroparesis. Other prokinetic agents in use worldwide but unavailable in the United States include the 5-HT_4 receptor agonists mosapride and prucalopride, the D_2 receptor antagonist levosulpiride, the acetylcholinesterase inhibitor acotiamide, and the combined D_2 receptor antagonist/acetylcholinesterase inhibitor itopride.

Neuromodulatory Agents

Neuromodulatory medications are purported to reduce nausea and vomiting by actions to decrease gut sensitivity (Table 9.4).

Tricyclic Antidepressants

Tricyclic antidepressants have a range of pharmaceutical actions including norepiphrine reuptake inhibition with variable inhibition of serotonin and dopamine reuptake. In uncontrolled case series, tricyclic agents have been reported to reduce emesis in functional vomiting, cyclic vomiting syndrome, and in diabetics with refractory nausea and vomiting [48]. In this latter study, symptoms decreased in 88 % and resolved in one-third of patients while two-thirds noted that tricyclics were their most effective therapy at median daily doses of 50 mg. Because of the promise shown by these patient series, a controlled trial of the tricyclic drug nortritpyline was conducted in patients with idiopathic gastroparesis [49]. However, nortriptyline was not superior to placebo in the primary outcome of the trial—a 50 % reduction in symptoms over two consecutive study visits—although secondary improvements in anorexia and body mass index were observed. Tricyclic side effects can limit therapy in patients with functional GI symptoms and include dryness of the mouth, blurred vision, urinary retention (especially in older men), constipation, cognitive impairments, lightheadedness, palpitations, and weight gain. This drug class also can prolong the QTc interval on EKG testing and may promote cardiac arrhythmia generation.

Mirtazapine

The tetracyclic antidepressant agent mirtazepine has a complex pharmacology including indirect agonism on central nervous system 5-HT_{1A} receptors, inverse agonism on 5-HT_{2C} and H_1 receptors, and antagonism on 5-HT_2, 5-HT_3, and α_2 receptors. In individual reports, mirtazapine has been reported to exhibit antiemetic efficacy in CINV and PONV. Several uncontrolled case reports have noted decreases in gastroparesis symptoms with mirtazapine [50]. The effects of mirtazapine on gastric emptying in humans are uncertain. The agent accelerated gastric emptying in healthy dogs and in a canine model of delayed emptying and reduced gastric residuals in a patient on gastrostomy feedings [51]. Common side effects of mirtazapine include sedation, constipation, dryness of the mouth, appetite stimulation, and weight gain.

Olanzapine

The atypical antipsychotic olanzapine has a broad pharmaceutical profile with antagonism of H_1, muscarinic cholinergic (M_1, M_2, M_3, and M_4), dopamine (D_1, D_2, D_3, D_4), serotonin (5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6), and α_1 receptors. Olanzapine has been best characterized as an antiemetic in CINV where it exhibits prophylactic effects and can be used as a rescue antiemetic with efficacy greater than metoclopramide [52]. This drug also has shown benefits in opiate-induced nausea in an open label study of patients with cancer-related pain with associated improvements in quality of life [53]. The most common side effect of olanzapine therapy is weight gain; other adverse effects include worsening glycemic control in diabetics, cognitive effects, depression and suicidality, and hallucinations.

Other Medications

Other neuromodulatory medications have proposed antiemetic actions. Although the 5-HT_{1A} receptor agonist buspirone has shown benefits in functional dyspepsia with enhancement of gastric accommodation after meal ingestion and reductions in postprandial fullness, early satiety, and bloating, the drug has not exhibited efficacy as an antiemetic in human disorders with nausea and

Table 9.4 Neuromodulatory medications for treatment of nausea and vomiting

Drug class	Available agents (GI neuromodulator doses)	Mechanisms of action	Side effects	Clinical indications
Tricyclic antidepressants	Amitriptyline, nortriptyline, desipramine (10–75 mg oral at bedtime)	Norepinephrine reuptake inhibitors with variable serotonin (and dopamine) reuptake inhibition	Sleep disturbance Constipation Lightheadedness Palpitations Cardiac arrhythmias Sudden cardiac death	Cyclic vomiting syndrome Functional nausea and vomiting Functional dyspepsia
Tetracyclic antidepressant	Mirtazapine (15–45 mg oral at bedtime)	"Indirect" CNS serotonin 5-HT_{1A} receptor agonist, 5-HT_2 receptor antagonist, 5-HT_{2C} inverse receptor agonist, 5-HT_3 receptor antagonist, α_2-adrenoceptor antagonist, histamine H_1 inverse receptor agonist	Sedation Weight gain Constipation	Hyperemesis gravidarum PONV CINV ?Gastroparesis ?Functional dyspepsia
Atypical thienobenzo-diazepine antipsychotic	Olanzapine (5–20 mg oral at bedtime)	Serotonin 5-HT_2 inverse receptor agonist, 5-HT_3 receptor antagonist, acebylcholine muscarinic M_1 receptor antagonist, M_3 receptor antagonist, dopamine D_2 receptor antagonist, histamine H_1 inverse receptor agonist	Weight gain Sedation Peripheral edema Tremor Dizziness	CINV
Azapirone anxiolytic	Buspirone (5–10 mg three times daily before meals)	Serotonin 5-HT_{1A} partial receptor agonist	Sedation Headache Lightheadedness Dizziness	Functional dyspepsia

vomiting [54]. The γ-amino butyric acid analog gabapentin has shown potential in reducing nausea in cancer patients when given in combination with the 5-HT_3 receptor antagonist ondansetron and dexamethasone [55].

Medication Management in Selected Clinical Situations

Nausea and vomiting are prominent symptoms in a diverse range of clinical situations. Distinct management approaches employing antiemetic, prokinetic, or neuromodulatory agents have been devised to treat these symptoms in the different settings.

Gastroparesis and Functional Gastroduodenal Disease

Most gastroparesis patients unresponsive to dietary and lifestyle measures are managed with prokinetic and/or antiemetic drugs. There have been 7 randomized controlled trials for metoclopramide and 3 for erythromycin in gastroparesis that support their use. However, these trials have small sample sizes and exhibit trial design flaws.

Two-thirds of 11 publications and 16 meeting abstracts noted symptom improvements with domperidone in gastroparesis; however, there was insufficient evidence to recommend this drug because of similar study deficiencies [56]. Both metoclopramide and domperidone reduce symptoms over prolonged periods of therapy even when initial prokinetic actions wane, reflecting the importance of their antiemetic actions. Standard antiemetics are commonly prescribed in gastroparesis, being used by 61 % of patients with idiopathic gastroparesis, 70 % of type 1 and 66 % of type 2 diabetics with gastroparesis [57]. Among antiemetics, the transdermal 5-HT_3 antagonist granisetron decreased symptoms in half of gastroparesis patients in an open label series while the NK_1 receptor antagonist aprepitant was reported to produce benefits in individual gastroparesis cases [58]. Other antiemetics acting as D_2 receptor antagonists, NK_1 receptor antagonists, and glucocorticoid receptor agents have been reported to reduce gastroparesis symptoms in individual case reports. However, no controlled trials have been performed assessing antiemetic drug efficacy in gastroparesis. Likewise although case reports have suggested benefits of neuromodulatory agents like mirtazapine in gastroparesis, no randomized trials of neuromodulators have been conducted in this condition. Strategies for improving therapy for patients with more difficult to control symptoms include combination treatment with two medications in different drug classes or delivery of drugs as an orally dissolving tablet, in liquid oral form, as a rectal suppository, as a transdermal patch (e.g., granisetron), or subcutaneously (e.g., metoclopramide).

Very little investigation has been performed into studying the usefulness of antiemetics in functional gastroduodenal diseases. Patients with functional dyspepsia do report modest reductions in nausea and vomiting in older trials of 5-HT_3 receptor antagonists [59]. Tricyclic antidepressants show benefits in uncontrolled functional vomiting studies [48]. Furthermore, in a retrospective report of 94 patients fulfilling Rome III criteria for chronic idiopathic nausea or functional vomiting, 72 % experienced at least moderate symptom decreases and 22 % noted remission on neuromodulators (tricyclics in 66 patients, norepinephrine dopamine reuptake inhibitors in 10 patients, selective serotonin reuptake inhibitors in five patients, serotonin norepinephrine reuptake inhibitors in 5 patients, and others in 9 patients) [60].

Cyclic Vomiting Syndrome

Several strategies have been employed to manage acute cyclic vomiting syndrome (CVS) attacks and to prevent future episodes (Table 9.5). 5-HT_3 receptor antagonists have assumed a prominent role in treating CVS attacks, although antidopaminergic agents like prochlorperazine, metoclopramide, and haloperidol also have been used. Intravenous benzodiazepines (e.g., lorazepam) also provide relief likely in part by promoting sedation. 5-$HT_{1B,1D}$ agonists (e.g., sumatriptan) may be useful especially for patients with personal or family histories of migraines, given the proposed relation of CVS to some cases of migraines. Fifty-four percent of adult patients responded to this drug class in one study [61]. Prophylactic therapy is recommended for CVS patients with frequent attacks (at least monthly) who present with dehydration or electrolyte disturbances or who require numerous emergency room visits or hospitalizations for management. Tricyclic antidepressants most often are used to prevent recurrent CVS attacks, and are effective in 76 % of adults and 68 % of children with associated reductions in frequency and duration of episodes and decreases in emergency room visits [62]. Patient subgroups less responsive to tricyclic therapy include those with severe psychiatric disease, migraine headaches, and dependence on marijuana or opiates. When tricyclic prophylaxis fails, patients may be offered a range of other therapies including anticonvulsant medications (e.g., levetiracetam, zonisamide, carbamazepine, topiramate, valproate, phenobarbital, phenytoin), β – adrenoceptor antagonists (e.g., propranolol), cyproheptadine (an antihistamine with anticholinergic and antiserotonergic activity), mitochondrial stabilizers (e.g., L-carnitine, co-enzyme

Table 9.5 Medication strategies for cyclic vomiting syndrome

Treatment of acute attacks		Prophylaxis against future attacks	
Antiemetics	5-HT_3 receptor antagonists (ondansetron) D_2 receptor antagonists (prochlorperazine, metoclopramide)	Antidepressant neuromodulators	Tricyclic agents (amitriptyline) Tetracyclic agents (mirtazapine)
Sedatives	Benzodiazepines (lorazepam)	Anticonvulsants	Levetiracetam Zonisamide Carbamazepine Topiramate Valproate Phenobarbital Phenytoin
Antimigraine therapies	5-$HT_{1B,1D}$ receptor agonists (sumatriptan)	Antimigraine therapies	β-adrenoceptor antagonists (propranolol) Cyproheptadine
Treatments for associated pain	Nonsteroidal anti-inflammatory drugs (ketorelac) μ-opioid receptor agonists (tramadol, hydromorphone)	Mitochondrial stabilizers	L-carnitine Co-enzyme Q10

Q10), and cognitive behavioral therapy. Three quarters of patients in one study reported decreases in vomiting episodes over 9 months of therapy with levetiracetam or zonisamide; however, side effects were prominent in 45 % [63].

Chemotherapy- and Radiation Therapy-Induced Nausea and Vomiting

Most antiemetic programs for prophylaxis of CINV include multiple agents which bind to distinct receptor sites. Many regimens combine a 5-HT_3 receptor antagonist, an NK_1 receptor antagonist, and a corticosteroid to provide control of both acute and delayed CINV [34]. In a meta-analysis comprised of 16 studies, all first-generation 5-HT_3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron) were calculated to be equally effective for preventing acute CINV after highly emetogenic treatments [64]. However, such agents are relatively ineffective against delayed CINV. Studies of the second-generation 5-HT_3 receptor antagonist palonosetron have reported similar efficacy as first-generation antiemetics for acute CINV and superiority over these older 5-HT_3 antagonists for delayed CINV prophylaxis [65]. NK_1 receptor antagonists (e.g., aprepitant, fosaprepitant) are effective as single agents for prevention of some cases of acute and delayed CINV and provide additional synergistic antiemetic control after highly or moderately emetogenic chemotherapies versus antiemetic regimens not containing an NK_1 antagonist [66]. A meta-analysis of 32 studies reported that dexamethasone is an effective prophylactic agent against both acute and delayed CINV after highly or moderately emetogenic chemotherapeutic treatments [67]. Other therapies with benefits in CINV include D_2 receptor antagonists, CB_1 receptor agonists, olanzapine, and gabapentin. Anticipatory CINV typically responds poorly to antiemetic medication therapy. This phase typically is managed with intravenous benzodiazepines and nonmedication options (e.g., relaxation therapy, systematic desensitization techniques, hypnotherapy).

Prevention of radiation therapy-induced nausea and vomiting is accomplished by regimens similar to those used with CINV. Prophylaxis with a 5-HT_3 receptor antagonist plus dexamethasone is offered to patients at high risk of this complication while those at lower risks may

receive either prophylaxis or rescue with a 5-HT_3 antagonist.

Postoperative Nausea and Vomiting

Several regimens have been proposed as PONV prophylaxis or treatment. Published guidelines have advocated no antiemetic prophylaxis for patients at low risk for PONV, while those at moderate risk should be given one or two agents and individuals at high risk should be considered for double or triple antiemetic protocols. A large systematic review of 737 studies in 103,237 subjects concluded that prophylactic antiemetic therapy only provides benefit for 28% of patients [68]. Antiemetic treatment with ondansetron, dexamethasone, and droperidol each had similar efficacy in a factorial trial of 6 interventions for PONV [69]. Other agents effective in some cases of PONV include the NK_1 receptor antagonist aprepitant and transdermal scopolamine, whereas H_1 receptor antagonists appear to be less effective [68].

Acute Gastroenteritis

Despite the prevalence of acute gastroenteritis as a presenting diagnosis in emergency departments and primary care offices, little study has been conducted of antiemetic management of this condition. The greatest volume of investigation has been on 5-HT_3 receptor antagonists like ondansetron which have been reported to reduce vomiting, needs for supplemental hydration, and rates of hospitalization in both children and adults to greater degrees than placebo [70]. In another study in children and adolescents, the H_1 receptor antagonist dimenhydrinate shortened the time of active emesis from acute gastroenteritis by 0.34 days although others have not observed similar benefits with this agent [71].

Nausea and Vomiting of Pregnancy

Nausea and vomiting are reported by approximately 70% of women in the first trimester of pregnancy. Evidence supporting utility of antiemetic medication therapy (H_1, D_2, 5-HT_3 receptor antagonists) of nausea and vomiting of pregnancy was limited in a recent Cochrane review of 37 trials comprised of 5049 women [72]. Corticosteroids have been employed for some cases of hyperemesis gravidarum, although benefits of this practice have not been uniformly observed. Antiemetic therapy has been associated with minor increases in adverse pregnancy outcomes in some older reviews (OR 1.03) [73]. More recently, ondansetron use during pregnancy was associated with cleft palate development [74].

Relative Medication Effects on Nausea Versus Vomiting

Clinical investigations of many available antiemetic treatments have indicated that most agent are much better at controlling vomiting than reducing nausea. This has been best characterized in CINV and PONV studies of 5-HT_3 receptor antagonist therapy. However, this phenomenon has not universally been observed. One systematic review calculated that the 5-HT_3 receptor antagonist is more effective as an antiemetic than an antinausea drug, but relative risk analyses in a second article reported similar effectiveness for the two symptoms [75, 76]. Initial investigations reported that NK_1 receptor antagonists exhibit potent antinausea actions in addition to their antiemetic effects; however, others subsequently commented that this drug class also offers superior antiemetic control compared to their benefits in nausea [77]. Conversely, the D_2 receptor antagonist droperidol was reported to be more effective at decreasing nausea compared to vomiting; however, this differential effect on the two symptoms disappeared upon relative risk analyses [78, 79]. Regardless, no medication has been developed or approved to treat nausea.

Clinical Implications and Future Directions

Clinicians managing any patient with unexplained nausea and vomiting should carefully examine the medication list on the initial evalua-

tion, given the highly prevalent use of opiates and other agents that cause these symptoms. New pharmaceuticals are introduced each year for diverse indications that may inadvertently elicit nausea and vomiting, especially those used to treat depression, type 2 diabetes, dementia, movement disorders, migraines, and tobacco dependence. Prior to recommending an antiemetic or antinausea regimen for individuals on such treatments, it is appropriate to attempt to avoid (or at least reduce doses of) offending medications. Understanding the neurotransmitter pathways by which medications cause nausea and vomiting is helpful in this era of pharmaceutical advances.

There is an assortment of options which are available to treat nausea and vomiting for patients who require medication therapy. The selection of the appropriate antiemetic or antinausea drug is dependent on several factors including the underlying clinical scenario, the side effects of the agent being considered, interactions of this agent with other drugs being taken by the patient, and (unfortunately) cost issues. The existing pharmacopeia is relatively mature, although active research is ongoing into novel agents that act by previously characterized receptor mechanisms but which offer advantages pertaining to other pharmacologic properties. An area in need of further investigation is on therapies specifically targeting control of nausea for individuals whose vomiting is adequately controlled.

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10 Gastric Electrical Stimulation, Pyloroplasty, Gastrectomy, and Acustimulation for the Treatment of Nausea and Vomiting in the Setting of Gastroparesis

Ihsan Al-Bayati, Irene Sarosiek, and Richard W. McCallum

Introduction

This chapter addresses gastric electrical stimulation (GES), pyloroplasty in the setting of GES, total gastrectomy, and acustimulation as approaches for the treatment of patients with gastroparesis (GP) refractory to standard medical therapies. Jejunal tube feeding and other nutritional measures may accompany these treatments but are not discussed in this chapter, as they are covered in Chap. 11 of this book.

Gastroparesis (GP) is a delay in gastric emptying which results in nausea, vomiting, early satiety, epigastric discomfort, and bloating in the postprandial setting when mechanical obstruction of the upper gastrointestinal tract has been excluded. Initial therapy consists of modification in diet, maintaining nutrition and hydration, tight glycemic control in patients with diabetes mellitus as well as antiemetic medications to reduce nausea/vomiting, prokinetics to accelerate gastric emptying, and utilization of drugs that modify abdominal pain. Novel treatment approaches were developed as it became apparent that traditional measures were limited, based either on suboptimal efficacy of the agents or the accompanying adverse events [1, 2]. It is estimated that up to 30 % of patients with gastroparesis will fail to respond to medical therapy based on subjective and objective criteria and require these additional interventions. Therefore, surgical approaches are required in the treatment of GP when medical management fails to control the symptoms.

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Basic Myoelectric Stomach Activity

Different regions in the stomach control gastric emptying. The proximal part of the stomach, mainly the fundus, initially relaxes to accommodate and store an ingested food bolus. Subsequently, these contents are slowly delivered into the distal stomach by phasic contractions propagating from the gastric body to the antrum at a maximal frequency of three cycles per minute (cpm) [3]. The process of mixing and grinding up of the food into small particles (approximately <5 mm in size) is termed trituration. These particles can then pass through the pylorus and into the

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small bowel for calorie absorption [4]. In gastroparesis, impaired motor activity in the antrum results from decreased peristalsis and coordination. Gastric slow waves are rhythmic electrical oscillations occurring at a rate of 2.5–3.5 cpm and generated by the interstitial cells of Cajal, which are located in the gastric muscularis propria. The slow waves are propagated down the stomach beginning at a site, which has been termed the "pacemaker zone," located in the proximal stomach regulating the direction and frequency of gastric motor activity [5, 6]. In gastroparesis, there can be loss of interstitial cells of Cajal as well as damage to enteric neuron, resulting in gastric dysrhythmias [7]. This causes impaired electromechanical coupling and hence weak motor activity slowing gastric emptying of food.

Gastric Electrical Stimulation

Based on similar cardiac pacing principles, the concept of gastric pacing was initially proposed for strengthening and regulating slow waves and overcoming dysrhythmias [1]. There are currently two methods for electrical stimulation, only one of which is FDA approved as a compassionate treatment option (Fig. 10.1). The first method utilizes a low-energy pulse width of 300 μs and a frequency of 12 cpm, higher than physiologic, to alleviate symptoms, specifically nausea and vomiting, but does not always alter gastric slow wave dysrhythmia or accelerate gastric emptying and is referred to as neurostimulation [1, 8]. The second is termed gastric pacing and, as the name implies, it entrains the slow wave and reverses dysrhythmias, utilizing physiologic frequencies of approximately 3 cpm with high-energy pulse widths in the 300 ms range [9, 10]. This activates smooth muscle contractions, resulting in accelerated gastric emptying.

Physiologic Frequency Electrical Stimulation (Pacing)

High-energy stimulation with a pulse width of 10–600 ms and a frequency similar to the physiologic stomach frequency of 2.5–3.5 cpm was shown to "pace" the stomach through entrainment of the stomach slow waves. Studies showed correction of the gastric dysrhythmias, better control of symptoms, and faster gastric emptying in a dog model as well as in humans [9, 11].

Historically, gastric emptying was not accelerated in pacing experiments on vagotomized dogs done by one of the pioneers, Keith Kelly [12]. Subsequently, the effect of gastric pacing on

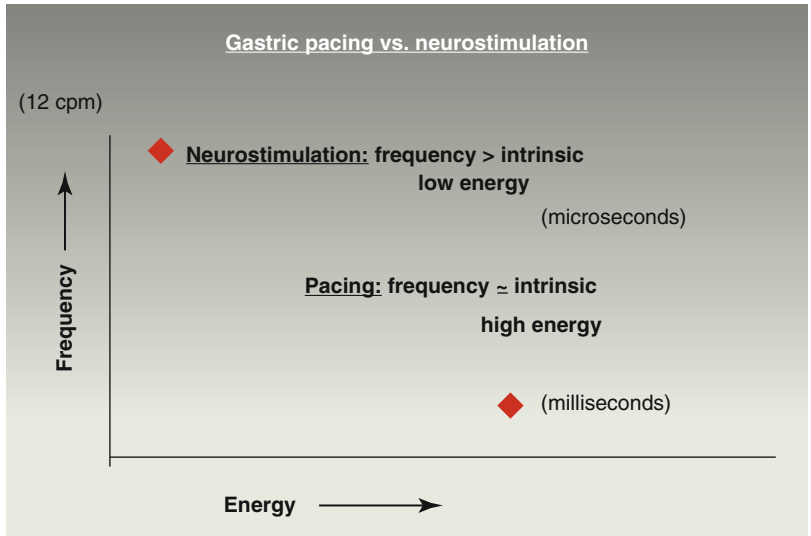

Fig. 10.1 The two different gastric electrical stimulation parameters being used in clinical and animal research

gastric emptying and gastrointestinal symptoms was studied in nine patients with severe gastroparesis [9]. Four pairs of temporary pacing wires were placed surgically 4 cm apart, and the most distal pair was located 2–4 cm proximal to the pylorus. The proximal pair was used for electrical stimulation, while the three distal pairs recorded the effects. Gastric dysrhythmias were identified in two patients. Using a gastric pacing frequency 10% higher than the intrinsic slow wave frequency, gastric slow waves were entrained in all patients. In the distal antrum, the amplitude of the gastric slow wave was higher during electrical stimulation compared with the sham stimulation [9]. Some unique points need to be mentioned about this study. All the patients in this study were referred for treatment of severe gastroparesis and had failed standard medical therapy. It was established that entrainment of gastric slow waves was always achieved even when initial dysrhythmia was present by optimizing the pacing parameters. At the end of the 4 weeks of gastric pacing, a gastric emptying study was performed, which confirmed an accelerated rate of emptying and patients were also symptomatically improved.

A clinical trial in patients with severe GP secondary to diabetes compared an external pacing device with high energy and low frequency to an implantable low-energy, high-frequency neurostimulator (Enterra System) [13]. The study investigated primarily the effect of two-channel gastric pacing on the stomach myoelectric activity and energy consumption with the secondary goal of evaluating the patients' symptoms and monitoring gastric emptying. Four pairs of temporary pacing wires were inserted and secured in the serosa of the stomach at the time of placing the Enterra System (Fig. 10.2). Nineteen patients with severe GP who did not respond to medical therapy were included in the pacing group. Electrical stimulation was provided through two pairs of wires 16 and 8 cm from the pylorus, and the other two pairs 12 and 4 cm from the pylorus were utilized for recording of the slow waves. Serosal recording measured the optimal pacing parameters in each patient for entrainment of gastric slow waves 5 days after the surgery. Gastric pacing was initiated for 6 weeks using an external multichannel pulse generator during the day, while the battery was charged overnight. It was concluded that two-channel, low-frequency gastric electrical stimulation at 1.1 times the intrinsic frequency was able to entrain gastric slow waves, improve symptoms, significantly accelerate the mean 4-h gastric retention rate, normalize gastric dysrhythmia, and decrease tachygastria in fasting and postprandial states in severe diabetic GP patients with an excellent safety profile. These results confirmed earlier studies of multichannel gastric pacing performed in dogs [14, 15]. The advantage of the two-channel gastric pacing system is mainly to improve energy consumption.

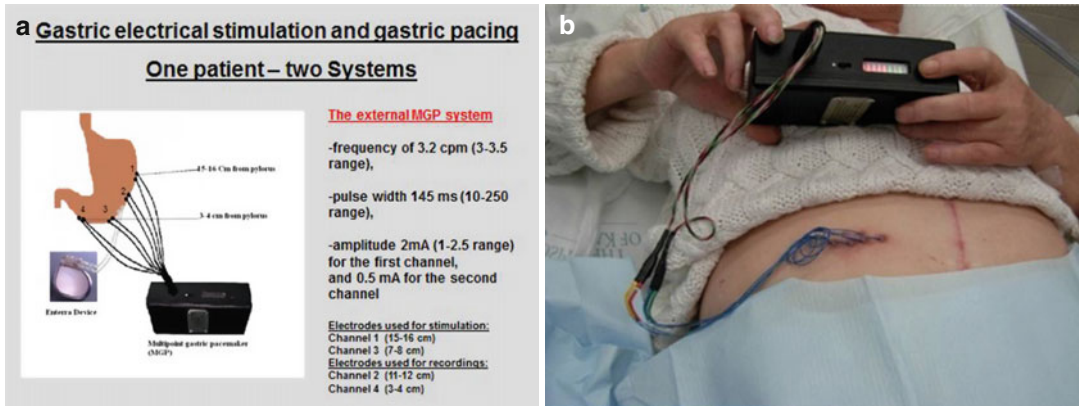

Fig. 10.2 (**a**) The Enterra neurostimulator pulse generator surgically placed as well as an external gastric pacemaker unit connected to four pairs of electrodes on the serosa of the stomach; (**b**) patient with multichannel pulse generator connected to the stomach by external wires

For a single-channel pacing system, high energy is needed to entrain gastric slow waves and normalize dysrhythmias. The electrode being placed in the proximal stomach to avoid reverse pacing makes it necessary to consume very high energy enough to get the pulses to travel a distance of more than 20 cm to reach the distal antrum. In the two-channel gastric pacing, there is much less energy required to entrain slow waves as each channel is responsible for a smaller distance, approximately 8 cm, thus saving the battery life.

High-Frequency Electrical Stimulation (Neurostimulation)

The short-pulse high-frequency stimulation parameters are a pulse width of few hundred microseconds (300 μs) and a frequency of 12 cpm, which is about four times the physiologic gastric slow wave frequency [16]. Studies in humans had initially showed stronger gastric contractions could be induced using these programming parameters as well as accelerated gastric emptying [1, 17]. Based on these principles of high-frequency and low-energy parameters, the implantable device named Enterra therapy (Medtronic, Inc, Minneapolis, MN) was developed (Fig. 10.3). A number of clinical trials ensued and the consistent outcome was that gastric electrical stimulation with the Enterra device showed both sustained and significant improvement in symptoms in most patients with severe gastroparesis refractory to medical therapy [10]. The initial double-blind crossover study using Enterra System was named World Anti-Vomiting Electrical Stimulation Study (WAVESS) [10]. The system was either turned on or shammed after implantation. After 1 month of this therapy, patients were then crossed over to the other arm of treatment for another month utilizing a randomized double-blind approach. This study was positive as far as significant differences observed in symptoms of nausea and vomiting in Enterra versus Sham arm. In the year 2000, Enterra electrical stimulation was approved by the United States Food and Drug Administration for treatment of patients with gastroparesis refractory to other therapies under the umbrella of Humanitarian Device Exemption (HDE) [18].

In the WAVESS trial, 33 patients (17 diabetic GP; 16 idiopathic GP) were randomized to a dou-

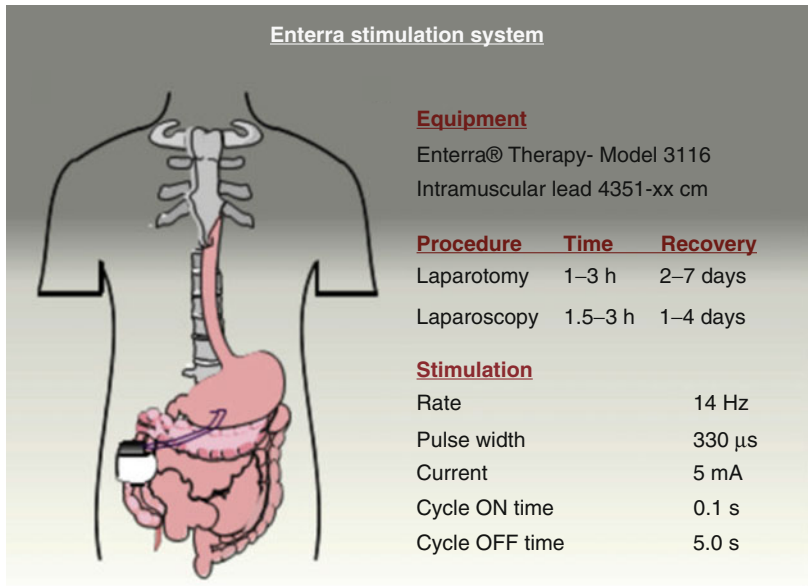

Fig. 10.3 Demonstration of the location of the two electrodes in the stomach and the subcutaneously placed pulse generator as well as its programming parameters

ble-blind crossover study, initially, followed by 10 months open label phase when all patients had their devices activated. The weekly vomiting frequency (WVF) is a monitoring parameter set as a primary objective in many studies. After the total 12-month follow-up, 80 % of patients had more than 50 % improvement in symptoms [10]. A subsequent trial studied 55 diabetic patients with GP utilizing a different study design [19]. All patients had their devices activated after surgery for 6 weeks. Then they were randomized in a double-blind fashion to two groups, ON or OFF, for 3 months followed by crossing over to the other treatment for a further 3 months. The devices then were activated in all patients and they were followed for up to 1 year. After the initial 6 weeks, the WVF showed a median reduction of 57 % compared to baseline. Interestingly enough, during the 3-month randomization period to sham or active stimulation, the WVF was similar for the two arms. At 1-year follow-up, when all patients had the devices turned ON, there was a median reduction of 67 % in WVF in all patients, associated with improvement in total symptom scores, gastric emptying, and their overall quality of life.

Subsequently, a similar multicenter, randomized, crossover study evaluated the efficacy of GES in 32 idiopathic GP patients using the same study design as in the diabetic GP trial. For 6 weeks after surgery, all devices were activated. This was followed by a double-blinded randomized crossover phase, each of 3 months' duration with the device either ON or OFF. A total of 25 patients completed the crossover periods and 21 patients continued a 1-year follow-up with the device activated. During the first 6-week period, there was a significant reduction in WVF of 61 %. Again, during the crossover period, the improvement was not significant in the treatment phase versus sham (17 % median reduction of WVF). At 1 year, there was a median reduction of 87 % in WVF from the initial baseline with improvement of GP symptoms, gastric emptying, and with reduction in days of hospitalization [20]. Collectively, these two studies showed that at 12 months of continuing stimulation, there was a significant improvement of symptoms, reduction in hospitalization days, and better quality of life in patients with severe refractory GP unresponsive to medical therapy (Fig. 10.4) [19, 20].

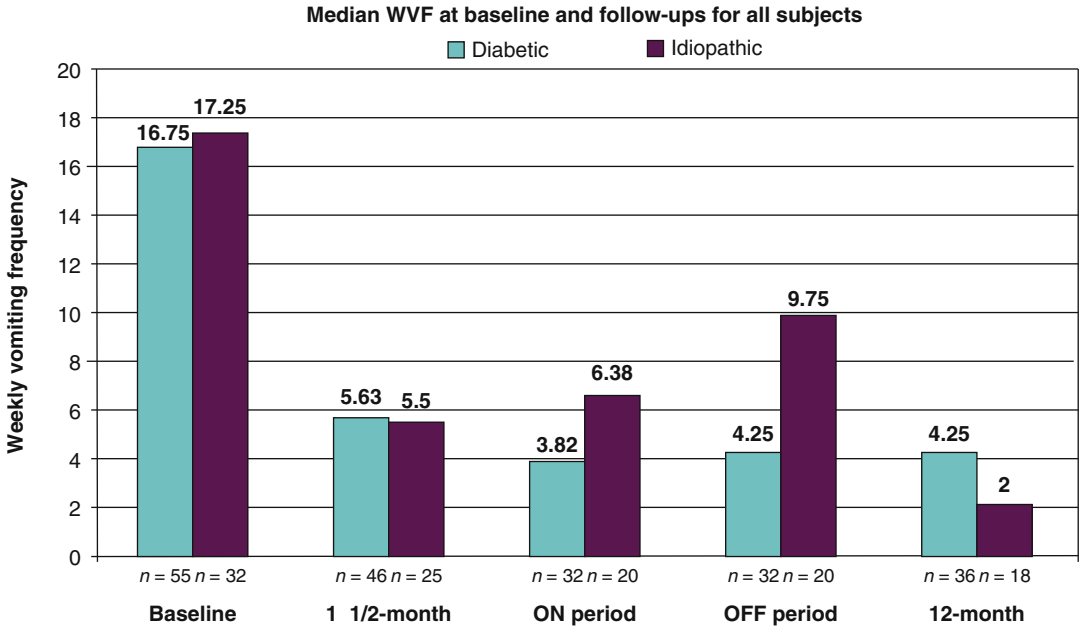

Fig. 10.4 Two double-blind crossover studies, one in diabetic gastroparesis and the other in idiopathic gastroparesis. Results show improvement in the first 6 weeks when the device was ON. There were no differences during 3-month crossover period when comparing active stimulation to sham. One year follow-up with the device being activated showed significant and sustained reduction in nausea and vomiting

The reason why these two trials did not meet the primary goal still needs to be investigated since there was no difference between Enterra therapy and sham during the crossover period. One possibility is that the initial 6 weeks of GES preceding the crossover phase induced a sustained symptom response resembling a memory or "imprinting" effect that continued despite the device being deactivated. The lesson for future trials is to randomize GES patients at the time of surgery to stimulation versus sham arm, without introducing a crossover phase.

The largest series with long-term follow-up of Enterra treatment describes 221 patients: diabetic (64 %), idiopathic (22 %), and postsurgical (14 %) gastroparetic subjects who were followed for up to 10 years with the GES device being always activated. The total symptom score was improved more than 50 % in 54 % of patients overall, while diabetic GP improved the most (58 %) and the least impressive results were seen in idiopathic GP patients (48 %). The study is considered the largest and longest in the world. It concluded that electrical stimulation achieved significant improvement in patients with severe GP and the efficacy was sustained for up to 10 years. In addition, 89 % of patients who were requiring a jejunostomy tube at time of GES implantation could stop their tube feeding and have the jejunostomy tube removed within 12 months. Most importantly, there was good tolerance and safety profile [21]. An explanation for the idiopathic GP patients to be the least responders is that those patients represent a heterogeneous mixture of patients who have more complaints of abdominal pain than other groups [22, 23]. Unfortunately, abdominal pain is the least likely symptom to improve with electrical stimulation [1].

Mechanisms of Symptom Improvement with Gastric Neurostimulation

Although several studies have showed clinical improvement in symptoms and quality of life in patients with severe GP not responding to medical therapy, it is also established that there is no consistent improvement in gastric emptying and no reduction in gastric dysrhythmias. Three main mechanisms are identified to explain symptomatic improvement with GES [24]:

1. Central nervous system control mechanism: Positron emission tomography (PET) scanning technique documented the activation of the thalamus following an active stimulation with the Enterra System. This observation reflected stimulation of the visceral afferent component of the vagal nerve fibers transmitting impulses to the nucleus tractus solitarius, which then project to the thalami via the reticular formation and in turn exert an inhibitory influence on nausea and vomiting control mechanisms.
2. Increase in vagal activity as determined by the power spectral analysis of the heart rate variability (R-R interval).
3. Increased gastric accommodation demonstrated by utilizing a Barostat methodology. This finding could explain the enhancement of food intake, better postprandial adaptation, and decreased gastric sensitivity to distension. These effects are probably mediated by the enhanced vagal autonomic function.

Surgical Implantation of the GES

Both laparotomy and laparoscopic approaches are utilized as implantation techniques of the GES depending on the expertise and training of the surgeon (Fig. 10.3) [9]. The laparoscopic technique has the benefit of less need for postoperative pain medication and briefer hospital stay. In both approaches, two leads are inserted in the muscularis propria. They are sutured on the greater curvature 9 and 10 cm from the pylorus and connected by 35 cm long leads to the pulse generator implanted subcutaneously in the abdominal wall, mostly in the right upper quadrant. Using an external programmer, the device is interrogated to standardized parameters termed the "default setting" (5 mA, 14 Hz, 330 μs, cycle on and cycle off 0.1 and 5 s, respectively).

Voltage and current parameters are then reevaluated at varying times postoperatively. There are no controlled trials regarding the best stimulation parameters to be adopted [21]. In the 10-year trial data that were published [21], the voltage was increased in increments of approximately 20–30 % during follow-up visits if the clinician and the patient felt that symptoms were still not well controlled and more energy was required.

Adverse Events Associated with GES

Infection of the generator site is the most common complication with incidence of about 6 %. It occurs more in diabetic patients or due to trauma or falls [1]. Other complications include dislodgement of the electrodes or their penetration through the gastric mucosa, lead insulation damage, erosion or migration of the device and bowel obstruction, or discomfort at the site of the pulse generator.

Removal of the Enterra System may be necessary in some cases of infection (6 %), persistence of symptoms (2 %), lead dislodgement, skin penetration, bowel obstruction, and when gastrectomy is performed due to failure of treatment (4 %). Repositioning and/or replacement of the lead(s) due to dislodgment from trauma or twisted wires (2 %) and device migration (1 %) may also necessary if these complications were radiologically documented.

Batteries can be changed if depleted without changing the electrodes. The life expectancy of the battery is 8–10 years but may be shortened if high parameters (voltage, rate, pulse width) are sustained.

Response Predictors

Studies have attempted to identify factors that predict the response to GES. It is very well established that patients with diabetic GP represent a homogenous group in terms of pathophysiology and are the ones who benefit the most from GES [21]. Making the right diagnosis is a very important outcome predictor. GES will not improve nausea and vomiting caused by rumination syndrome, dumping syndrome, cyclic vomiting syndrome, or bulimic/anorexic vomiting.

Other factors that will reduce the response to GES and impair the outcome are concomitant migraine headaches, endometriosis, and the menstrual cycle. When abdominal pain is the major presenting symptom, this is a red flag. GES controls nausea that may lead to less abdominal pain because of reduced vomiting episodes. However, controlling abdominal pain by GES is not the primary goal. Idiopathic GP is less responsive than diabetic group of GP patients, and one reason could be the very strong component of abdominal pain in their clinical presentation. Narcotic use to control abdominal pain or for other reasons like fibromyalgia, back pain, or migraine is more common in idiopathic patients. Narcotic use inhibits gastric motility and increases nausea and vomiting. Finally, the presence of dysrhythmias found by performing an electrogastrogram as a marker for the loss of interstitial cells of Cajal (ICC) has been reported to be associated with less long-term symptom improvement [1]. Recent data now indicate that up to 50 % of patients have depleted ICC population based on smooth muscle biopsies obtained at the surgery [7].

The Application of Pyloroplasty in the Setting of GES

The implantation of the gastric electrical stimulator alone has no positive effects on improving gastric motility and gastric emptying or correcting electrical dysrhythmias [25]. This therapeutic deficiency of continued slow gastric emptying can be overcome by performing the Heineke-Mikulicz pyloroplasty as a supplementary surgery in severe GP patients undergoing implantation of the gastric electrical stimulation system. In a recent abstract submitted to Digestive Disease Week 2016, the mean retention of isotope during gastric emptying was decreased after GES combined with pyloroplasty and 62 % of patients actually normalized their emptying. There were also significantly reduced days of

subsequent postoperative hospitalization from 78 to 10 days per patient/year. No postsurgical complications were observed during the long-term follow-up, indicating the addition of pyloroplasty was safe. At Texas Tech University Health and Science Center in El Paso, simultaneous placement of GES and pyloroplasty began in 2012, and our experience now exceeds 40 patients. Currently, the laparoscopic robotic approach (Fig. 10.5) further reduces the risks of postsurgical complications, due to the improved wrist-like articulation that facilitates suturing and electrode placement. The incidence of wound infections and abscess or enteric fistulas did not increase with this procedure. An intraoperative EGD exam is performed in all cases to confirm placement of GES stimulator leads and examine the effect of pyloroplasty on the pylorus. This series demonstrated the safety and efficacy of combining pyloroplasty with implantation of the gastric electrical stimulator, achieving a 50% improvement in overall gastroparesis score in 71% of patients during long-term follow-up (Table 10.1) [25]. This compares to only 50% achieving this response by GES alone.

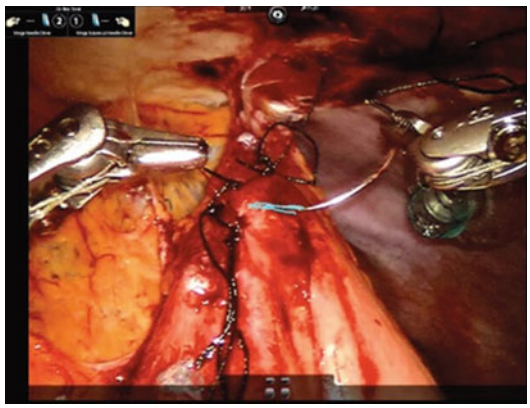

Fig. 10.5 Demonstration of laparoscopic placement of electrodes for Enterra as well as pyloroplasty by robotic technique

Combining the benefits of pyloroplasty that can normalize gastric emptying, with the reduction in nausea and emesis achieved by gastric neurostimulation, explains the great success of this approach. Evolution of this treatment technique will include endoscopic (nonsurgical) approaches, for example, pyloromyotomy [25].

The Role of Gastrectomy for Treating Gastroparesis

If all pharmacological and surgical resources, including GES therapy, have been exhausted to control nausea and vomiting, then performing a sub- or total gastrectomy may be considered [1]. The history of total gastrectomy began in the era of peptic ulcer disease and antral resections. Gastrectomy was reported to be effective in eight patients who failed to improve after medical therapy with prokinetics and antiemetics for gastroparesis in the setting of Billroth I or II for peptic ulcers. This surgery was termed "completion" gastrectomy [26]. On the other hand, in the era of placing GES devices in intact stomachs, there are different indications for total gastrectomy. There was a report of 9 out of 200 patients (4.5%) who already were receiving GES therapy, who were narcotic dependent, but were not sufficiently responsive (<20% symptom improvement) and subsequently underwent a total gastrectomy with simultaneous placement of jejunostomy tube [27]. All these postgastrectomy patients had

Table 10.1 Mean results before and after surgery (Gastric Electrical Stimulation and pyloroplasty). The severity of each symptom was graded by the patients as 0, absent; 1, mild (not influencing usual activities); 2, moderate (diverting from, but not requiring modifications of usual activities); 3, severe (influencing usual activities, severely enough to urge modifications); and 4, extremely severe (requiring bed rest)

	N	V	B	F	ES	EP	TSS	GET 2 h%	GET 4 h%	Weight (Pounds)	DOH
Before surgery	3.9	3.5	2.7	2.8	3.3	2.8	19	64	42	143	57
After surgery	1.2	0.7	0.8	0.8	0.9	1.2	6	16	3	157	11

N nausea, *V* vomiting, *B* bloating, *F* fullness, *ES* early satiety, *EP* epigastric pain, *TSS* total symptom score, the sum of all reported scores, *GET* gastric emptying time, *DOH* days of hospitalization

reduction in their of nausea and vomiting by 55 %, while also their emergency room visits were reduced and the jejunostomy tube was removed when patients' nutrition status adequately improved.

In 2013, a comparison was made between GES and subtotal gastrectomy, which is a surgical procedure that involves resection of 70 % of the stomach (including the antrum and pylorus) and Roux-en-Y jejunal loop anastomosis [28]. Thirty-one patients out of 103 underwent laparoscopic subtotal gastrectomy, while 72 received GES. At 30 days the morbidity was significantly higher in the first group compared to the GES group (23 % versus 8 %), a finding that decreased over time. Later on, a total of 63 % of the patients in the GES group reported symptomatic improvement, while 87 % of the patients in the gastrectomy group had significant improvement in symptoms.

It was also observed that after bariatric surgery with longitudinal sleeve gastrectomy in GP patients, gastric emptying was faster. This surgery involves the removal of the gastric body and fundus with stapling along the lesser curvature to architect a tubular stomach. Sleeve gastrectomy was performed on four patients with diabetic GP [29]. At 6 months follow-up, it was reported that three out of four patients had symptom resolution. Another similar report showed symptom improvement as well as increased gastric emptying in nine morbidly obese diabetic patients after laparoscopic longitudinal sleeve gastrectomy [30].

In summary, obese diabetics who have failed medical therapy for severe gastroparesis, there is consideration for a bariatric procedure that could overcome both morbid obesity and diabetes, while subsequently reducing nausea and vomiting of gastroparesis.

Acustimulation

Minimally invasive techniques such as acupuncture have frequently been used for the treatment of GI symptoms in Eastern countries. The most commonly used acupuncture points (acupoints) for treating GI symptoms, especially nausea and vomiting, are the Neiguan (PC6) and the Zusanli (ST36) points (Fig. 10.6). Application of electroacupuncture (EA) to these acupoints provides peripheral electrical stimulation with a band not a needle. It is as effective as manual needling [31]. It is established that EA application at the acupoints has reduced nausea and vomiting induced

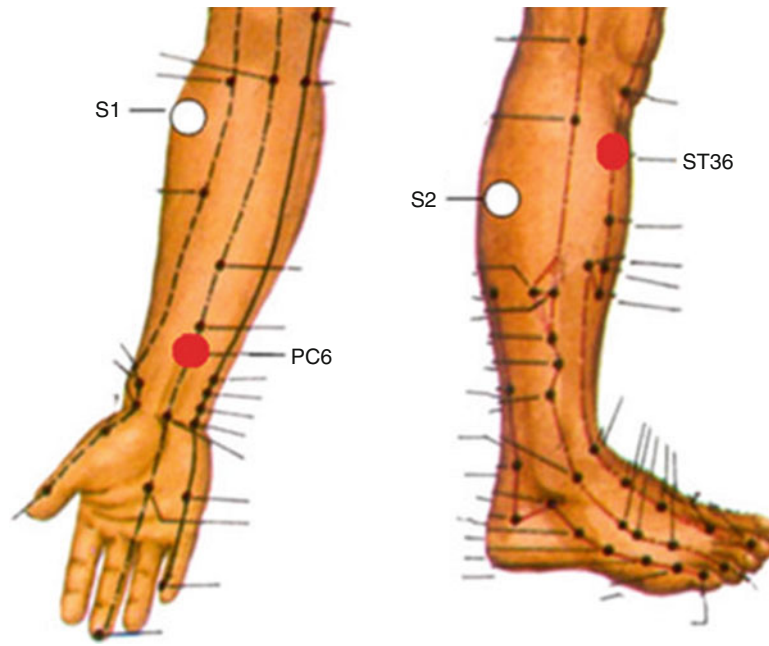

Fig. 10.6 Locations of acupuncture points (PC6 Neiguan and ST36 Zusanli). The *lines* on the leg and arm are meridians and the dots are various acupuncture points. *S1* and *S2* are used as sham points in clinical trials

by chemotherapy compared to sham acupoints [31, 32]. Recent reports addressed the feasibility and efficacy of transcutaneous electroacupuncture (TEA) in healthy volunteers [33] as well as patients with gastroparesis using a sham controlled trial [34] where electrical stimulation was applied to acupoints via surface electrodes without needles. This completely noninvasive method was well tolerated by the patients, and it resulted in good efficacy while proving it is applicable to the outpatient setting and allows for frequent use in nauseated/vomiting patients.

As far as we know, no studies have assessed the anatomical function of the central nervous system (CNS) in diabetics with nausea. However, several studies have investigated abdominal pain in diabetes, utilizing the electroencephalography (EEG) and evoked potentials (EPs) [35, 36]. These studies have provided some insight into the nature of diabetes-related gastrointestinal complications, suggesting some critical roles for the CNS in symptom generation. Inferior frontal lobe asymmetry association with pleasant and unpleasant feelings has been reported by Craig [37]. The author summarized imaging results and described how right inferior frontal is more active during unpleasant stimuli, for example, nausea, in contrast to left inferior frontal being more dominant during pleasant stimuli, for example, improvement of nausea symptoms.

Based on this background overview, a recent pilot study was conducted to investigate the central and peripheral responses to TEA in diabetic gastroparetic patients with predominant symptoms of nausea and vomiting. Results have shown a significant reduction in nausea by introduction of TEA therapy. Another interesting observation was documented during electroencephalography (EEG) recordings. TEA therapy was accompanied by predominant left inferior frontal lobe activity. This effect of TEA was associated with the reduction in nausea (Fig. 10.7) [38, 39].

Electrogastrography (EGG) has previously been shown to be an accurate and reliable measure for studying gastric myoelectrical activity (GMA), which in turn regulates gastric motility [40, 41]. Imai et al. demonstrated an increase in tachygastria accompanied with a decrease in the percentage of normal slow waves induced by optokinetic motion sickness [42], while Chen et al. [43] and Riezzo et al. [44] showed that audio stimulation (noise), stress, such as cold water and arithmetic task, may decrease the percentage of normal gastric slow wave in humans also. We have shown that the application of TEA, a noninvasive method for electrical stimulation, improved EGG recordings as well as the nausea.

The most recent introduction of Synchronized TEA (STEA), a novel method when breathing is synchronized with the electrical stimulation, was

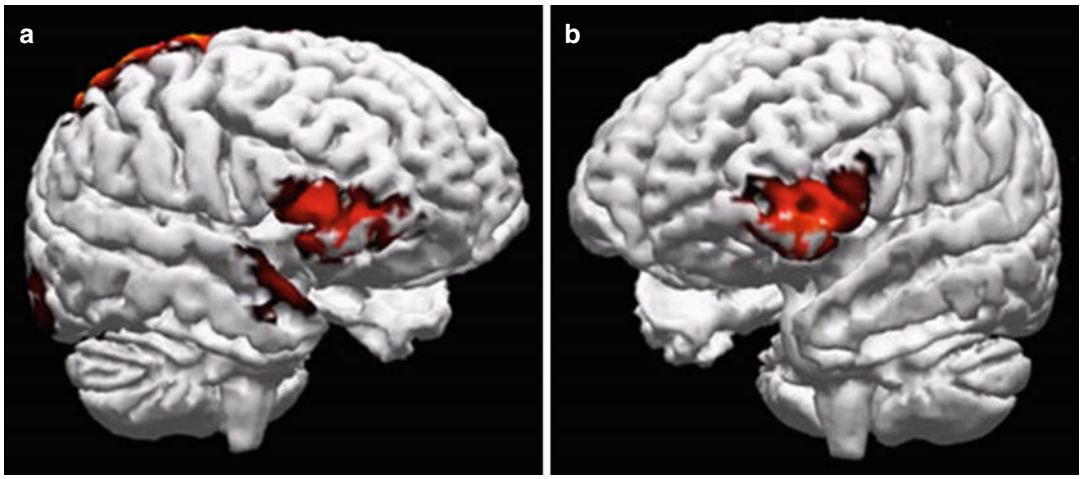

Fig. 10.7 (**a**) Neural activity source reconstruction during the induction of nausea. A large activation of the right inferior frontal gyrus can be seen. Activation of parietal lobe is also evident. (**b**) Neural activity source reconstruction during and post TEA treatment. The Left Inferior Frontal Gyrus activity was observed

shown to be more potent than TEA alone in enhancing vagal activity in normal subjects. Therefore, the investigation of efficacy and mechanisms of acute STEA therapy for treating nausea in gastroparesis could be a future direction to explore both in gastroparesis and other dyspepsia-related nausea and vomiting conditions.

Conclusion and a Look into the Future

Managing gastroparesis has definitely progressed. Promising ongoing research is evolving in the technology of electrical stimulation [1]. Progress is being made in developing endoscopic methods of implantation with smaller size electrodes. Therapeutic responses have been reported after endoscopic placement of temporary gastric electrical stimulator leads for 4–5 days. Further studies are required with larger numbers to ascertain if this response could be a predictor to a positive sustained outcome to long-term therapy with GES [45]. High-resolution gastric mapping is another evolving modality that may provide better understanding to how GES controls nausea and vomiting and how it affects and treats dysrhythmias. This would be more relevant if a major jump in the technology of GES took place making it possible to provide both neurostimulation and true gastric pacing in one device. This would allow for alternating stimuli of low- and high-frequency pulses to improve symptoms and accelerate gastric emptying in the same time. The low-frequency and high-energy parameters are required in the postprandial setting to improve gastric emptying, while the chronic nausea persisting between meals could be reduced by low-energy and high-frequency parameters.

In the area of addressing pyloric dysfunction in the therapy of GP, it is predicted that nonsurgical procedures will be pursued. Endoscopy will focus on pyloric sphincter dilation and possible stent placement. Also nonsurgical endoscopic pyloromyotomy has been proposed with similar principle to the peroral endoscopic myotomy (POEM) procedure which is now being utilized in achalasia treatment. However, for the present time we have a surgical approach, namely, GES placement and pyloroplasty, that provides essentially total symptom relief for gastroparesis.

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11 Nutritional Management for Patients with Nausea and Vomiting and Gastroparesis or Dumping Syndrome

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Introduction

There are many diseases and disorders associated with nausea. These diseases and disorders include, but are not limited to, gastroparesis, gastroesophageal reflux disease, mechanical obstructions, carcinomas, metabolic or endocrine disorders, postsurgical, medications, dumping syndrome, chronic cholecystitis, small bowel bacterial overgrowth, postprandial distress syndrome, dyspepsia, and irritable bowel syndrome [1]. The focus of this chapter is on patients who have gastroparesis or dumping syndrome. We emphasize the importance of pathophysiological abnormalities of the stomach in helping patients to appreciate how their food choices can provoke more nausea, which leads to nutritional deficiencies as fewer and fewer foods are ingested. This becomes a classic vicious cycle. Very few drugs are available to treat gastroparesis at this time [2, 3]. Although scant literature is available regarding the effect of dietary interventions on symptoms of chronic nausea and vomiting, dietary interventions, in our view, oftentimes are as effective as medication in reducing nausea or vomiting in patients with gastroparesis or dumping syndrome.

The gastroparesis diet, which is reviewed below, reduces the symptoms of nausea, fullness, and early satiety in our experience [3]. We review this diet with all of our patients with gastroparesis. Interestingly, the Gastroparesis Clinical Research Consortium found that a minority of patients with gastroparesis received any formal dietary education; only 32 % of patients were referred to a dietitian to receive nutritional counseling, and they were more often hospitalized or diabetic patients [4]. Nutritional management of gastroparesis in conjunction with medications can help control postprandial symptoms associated with gastroparesis. Nutritional management addresses not only the patient's specific nutritional deficiencies, but also should provide counseling about volume of meals and liquid versus solid nutrients in the context of the patient's understanding of the neuromuscular dysfunction of the stomach [5].

Nutritional Management for Patients with Gastroparesis

Nutritional management of gastroparesis patients begins with restoring fluids and electrolytes if dehydration is an issue. Nutritional and caloric

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deficiencies must be assessed and blood glucose levels must be controlled in the diabetic patients. Calorie goals and protein requirements should be determined for each patient. There are several formulas available for determining calorie goals. The daily energy expenditure equation that we use is as follows: for normal maintenance, 25–28 kcal/kg; for mild-moderate stress, 30–35 kcal/kg; for severe stress, 40 kcal/kg. Protein intake should be 15–20 % of total daily caloric intake. Protein needs are estimated as follows: for normal maintenance, 0.80–10 g/kg; for moderate stress, 1.2–1.5 g/kg; for infection or major surgery, 1.3–1.6 g/kg. Patients with chronic illness need approximately 20–25 calories per kg of body weight [7], 0.8-1.0 g of protein per kg of body weight, and 25 ml per kg of body weight of fluids daily. However, malnourished or underweight patients may need up to 30–40 calories per kg per day. The patient's ideal body weight in a euvolemic state should be used when assessing calorie and protein needs and then compared with the patient's current body weight. A nutrition consultation should be obtained to calculate patients' specific nutritional requirements and to educate patients regarding how to choose foods that will meet their nutritional needs, but also be appropriate choices given poor gastric relaxation (accommodation) and poor mixing and emptying of food that occurs with gastroparesis. (See Chap. 3 for detailed review of gastric neuromuscular dysfunction in gastroparesis.)

Dietary coaching helps patients reach the daily fluid intake they need to avoid dehydration. It is surprising how many patients who are underweight and borderline hypovolemic drink only water during the day. Water provides neither calories nor salt nor potassium. Some patients are confined to bed because of dehydration symptoms and then become deconditioned. Patients are coached to take small sips of an electrolyte replacement solution every hour to a goal of 60–90 ml each hour in order to hydrate as described below in the gastroparesis diet.

Many patients with gastroparesis and chronic nausea and vomiting may gain weight; others lose weight. Over 45 % of patients with gastroparesis are overweight or obese [4]. The postprandial symptoms and weight changes may result in frustration and depression. The patients who are overweight often feel their nausea and vomiting symptoms are met with skepticism by doctors. Social interactions and the enjoyment of eating food disappear. Patients often express to us that they "want their life back." This really means that they want to be able to enjoy meals together with friends and family again. We have found that helping patients make diet choices that take into account their stomach neuromuscular dysfunction results in fewer postprandial symptoms and better calorie intake.

Gastroparesis: Accommodation and Trituration are Keys to Understanding the Gastroparesis Diet

The dietitian called upon to help patients with gastroparesis must understand the key elements of normal gastric emptying and the dysfunctions that are present in gastroparesis. Patients with gastroparesis need to consume foods that are easy for the stomach to mill and empty; and, although some patients intuitively choose appropriate foods, most patients are not familiar with what foods to choose. Table 11.1 lists the three-step gastroparesis diet that we review with patients with nausea and vomiting and gastroparesis who are seen in clinic. The basic concepts can be reviewed in 5 min to at least get the patient to begin to consider these diet changes (see Table 11.1). The neuromuscular "work" of the stomach is briefly summarized and foods that will provide minimal neuromuscular work for the stomach are described.

As reviewed in Chap. 3, the normal stomach first relaxes to receive the ingested food and then mills or triturates the meal into fine particles before gastric emptying actually begins. Some patients with gastroparesis may have severe fundic accommodation dysfunction and the stomach does not relax properly to accommodate a normal volume of food. As the patient eats, they feel full and often nauseated due to poor gastric relaxation and stretch on the stomach walls. Patients must

Table 11.1 Gastroparesis diet guidelines: brief summary for clinic visits

Step 1. Gatorade and bouillon	
Diet:	Patients with severe nausea and vomiting should sip small volumes of salty liquids such as Gatorade or bouillon in order to avoid dehydration. Any liquid to be ingested should have some caloric content. A multiple vitamin supplement should be prescribed.
Goal:	To ingest 1000–1500 cc per day in multiple servings, e.g., twelve 4 oz servings over the course of 12–14 h.
Avoid:	Citrus drinks of all kinds and highly sweetened drinks.
Step 2. Soups	
Diet:	The diet may be advanced to include a variety of soups with noodles or rice and crackers. Peanut butter, cheese, and crackers may be tolerated in small amounts. Caramels or other chewy confections may be tried. These foods should be given in at least six divided meals per day. A multivitamin should be prescribed.
Goal:	To ingest approximately 1,500 calories per day. Patients who can accomplish this will avoid dehydration and will hopefully ingest enough calories to maintain their weight.
Avoid:	Creamy, milk-based liquids. The fat in the meal will delay emptying of the stomach.
Step 3. Starches, chicken, and fish	
Diet:	Starches such as noodles, pasta, potatoes, and rice are easily mixed and emptied by the stomach. Thus, soups, mashed potatoes or baked potatoes, pasta dishes, rice and baked chicken breast and fish are usually well-tolerated sources of carbohydrates and protein. These solids should also be ingested in six small meals per day. A one-a-day vitamin should be prescribed.
Goal:	To find a diet of common foods that the patient finds interesting, satisfying, and that evoke minimal nausea/vomiting symptoms.
Avoid:	Fatty foods that delay gastric emptying and red meats and fresh vegetables that require considerable nutrition. Avoid pulpy fibrous foods that promote formation of bezoars.

Modified from Ref. [3]

be helped to understand this basic principle of gastric relaxation or accommodation. It then makes sense to the patient when they are coached to choose smaller volumes of food and liquids and then to eat these small-volume meals four to six times per day [3, 8]. This approach reflects understanding the gastroparetic stomach and sets the physiological rationale for the patient to follow through with the dietary advice.

A recent study showed that meals comprised of small particles reduced upper gastrointestinal symptoms in patients with diabetic gastroparesis [9]. This randomized, controlled-trial demonstrated that a diet with small particle foods improved the upper gastrointestinal symptoms associated with gastroparesis in patients with diabetes mellitus compared with the standard ADA diet [9]. Nausea/vomiting, postprandial fullness, early satiety, and bloating improved significantly in the small particle size meal group. The meals were small-volume and low in fat and fiber content and were consumed four to five times a day [9]. The diet is similar to the three-step diet suggestions shown in Table 11.1.

After solid foods are ingested and accommodated by the stomach, they must be milled. Recurrent three per minute peristaltic waves move through the stomach body and corpus and produce the milling of the food. After solid foods are milled to 1–2 mm in diameter particles, the emptying of the food particles then begins [3]. Liquids are emptied much earlier and easier with less neuromuscular work compared with solid foods because trituration is not required. Caloric liquids are emptied slower than noncaloric liquids. The gastroparetic stomach is unable to mill and empty solid foods normally because of loss of interstitial cells of Cajal (the pacemaker cells) and the presence of gastric dysrhythmias. It is extremely important to help patients understand the poor milling and emptying that occurs in gastroparesis. Patients can then appreciate why they must select "easy" foods that their weak stomach can mix and empty. A meal with fibrous or pulpy

foods, for example, will require more peristaltic contractions (more "work") to mill compared with starches like mashed potatoes (an "easy to empty" food). As patients appreciate these aspects of stomach physiology, we have found they make better food choices that result in fewer postprandial symptoms and better caloric intake.

Most patients with gastroparesis learn to alter their diets because they identify what foods increase or decrease their nausea. Others, however, continue to consume foods rich in fat and fiber. Patients are coached that fatty or fried foods delay gastric emptying and fibrous foods are the most difficult foods for a weak stomach to mill and empty. Patients with diabetic gastroparesis may not appreciate that salads with lettuce, carrots, and other fresh, fibrous vegetables are difficult foods for the stomach to mill and empty. These foods are standard ADA diet recommendations for diabetic patients with normal gastric emptying, but are very difficult foods for the diabetic patients with gastroparesis [3, 6]. The fruits, vegetables, and beans are choices that require much more gastric work to empty (compared with other choices) and often evoke early satiety, prolonged fullness, and nausea and vomiting. Patients with gastroparesis may also form phytobezoars, masses of fibrous food that are retained in the fundus or corpus, because the weak stomach cannot empty these foods. Foods known to form bezoars include coconuts, berries, apples, sauerkraut, figs, legumes, oranges, and potato peels [10, 11]. Thus, patients need to be advised that these and any fibrous, pulpy foods are to be avoided.

The Gastroparesis Diet

The dietitian and the patient need to understand the key gastric neuromuscular abnormalities in the gastroparetic stomach. Then patients with gastroparesis understand the reasons to eat smaller-volume meals of foods that their weak stomachs can mill and empty and thereby achieve nutritional goals *and* reduce postprandial nausea and noxious fullness, symptoms that can lead to vomiting episodes [12]. We help patients understand that they need to choose foods in a three-step fashion and the choice of steps depends upon the intensity of their nausea and fullness symptoms throughout the day [12]. For example, if a patient is having a difficult day with frequent vomiting, then he or she should choose only liquids, such as Gatorade™, bouillon, or ginger ale that day (see Table 11.1, Step 1). The patient is coached to consume at least 1–1.5 l of an electrolyte solution in small quantities (60–90 ml per hour) on such a day to prevent dehydration and to avoid a visit to the hospital for intravenous hydration. The patient understands gastric accommodation may be impaired and learns that by taking very small sips (60–90 ml or 2–3 oz) of electrolyte-containing liquids every hour that the nausea and vomiting symptoms and dehydration can be limited.

Citrus juices and highly sweetened beverages are to be avoided because they are acidic and may irritate gastritis or esophagitis if present and thereby worsen nausea. Carbonated beverages or sodas are avoided because release of carbon dioxide may increase gastric distension and result in bloating, fullness, or heartburn. Foods that lower LES pressure and thereby increase heartburn include peppermint, chocolate, fat, and caffeine. A chewable vitamin should be taken to maintain vitamin levels. Some patients may tolerate clear liquid caloric supplements such as Ensure Clear™, Boost Breeze™, or Enlive™ during Step 1. Weight should be monitored twice a week at home. If weight is trending downward, then nutritional supplements described in Step 2 below should be added. Overall, the goal of Step 1 is to consume enough electrolyte solutions to maintain hydration and avoid increasing postprandial nausea and vomiting.

If the Step 1 diet is tolerated and nausea and vomiting decreased, then patients can decide to move to Step 2. The Step 2 phase is basically *liquid nutrition* as provided by soups and smoothies, which require little trituration. Step 2 foods include, for example, chicken noodle soup, chicken and rice soup, and small amounts of cheese, crackers, peanut butter, or soft caramels or soft chewy fruit candies. Milk-based liquids

that contain fat are often not tolerated, but the patient may try almond milk, soy milk, or Lactaid™ milk. Some of our patients have lactose intolerance and lactose-free milk products or almond or soy milk products are appropriate for them. The goal of Step 2 is for the patient to consume at least 1,500 calories in six or more meals or snacks of small volume in order to maintain or gain weight while selecting foods that align with dysfunction in gastric accommodation and peristalsis. Some patients need to remain on Step 2 for long periods of time because the solid foods in Step 3 are not tolerated. Protein and calorie intake goals can be achieved with Step 2 if the patient adds protein supplements like soy or whey and uses complete vitamin products.

In addition to soups, the patient may try smoothies with soy milk, Lactaid™ milk, or almond milk products and vegetables and fruits blenderized into very small particles. Liquid nutrient suspensions require gastric peristaltic contractions for proper emptying from the stomach, but they do not require the trituration that solid foods require before emptying. Thus, the liquid caloric meals can be tasty, require less gastric work to empty than solid foods, and hopefully elicit few postprandial symptoms. Patients are reminded that the supine position may contribute to delayed emptying since ingested nutrients pool in the fundus. Thus, patients are encouraged to remain sitting up after even small-volume meals for at least 1 h. Patients with gastroparesis may consider elevating the head of the bed onto 6–8 in. blocks to prevent regurgitation and gastroesophageal reflux when sleeping. Thus, the goal of Step 2 is to find liquid nutritional foods that are tasty, provide calories to maintain weight, and evoke minimal postprandial symptoms.

If patients tolerate the Step 2 phase and nausea and vomiting are controlled, then they can advance to Step 3. Step 3 emphasizes solid foods that are low in fat and fiber because these foods delay gastric emptying. In other words, the easy foods to empty are basically the starches since starches do not require extensive trituration. Thus, Step 3 includes foods such as rice, pasta, and potatoes. Mashed potatoes would be a choice example for patients to appreciate as a food that requires almost no milling and is easy for their weak stomach to mix and empty. Small portions (e.g., 3–4 oz) of broiled, baked, or grilled lean meats such as chicken, turkey, or fish may be tolerated if diced or chewed thoroughly. Other solid foods recommended in small portions include canned fruit in its own juice, applesauce, or cooked, fork-tender vegetables. Puddings and yogurts are also semisolid foods that require little milling and elicit less postprandial symptoms.

A consultation with a registered dietitian is highly recommended because he or she can calculate patients' individual nutritional needs, tailor the patients' diet according to their specific concerns, and ensure that the patients are meeting the individualized nutritional goals at follow-up visits. Based on consultation and follow-up visits, the patient can continue to introduce new foods and add or subtract foods to their list with help of the dietitian. The patient can revise or tailor their diet after he or she has tried various foods or liquids that were suggested. In our practice, there is a wide variation of food tolerances. The spectrum ranges from the patient who can eat every type of food as long as the portion is very small to the patient who can tolerate no foods whatsoever and survives only on enteral feeding. The dietitian must be creative in helping these patients select a nutritious set of foods that also elicits minimal postprandial symptoms.

Patients who follow low fat dietary guidelines may develop essential fatty acid deficiency. Unsaturated fats, which are liquid at room temperature, are considered healthier fats because they can improve blood cholesterol levels and can reduce inflammation [13, 14]. Unsaturated fats are predominantly found in plant foods such as vegetable oils, nuts, and seeds. It may be difficult for patients with gastroparesis to meet daily fat requirements, since 25–30 % of daily calories should be provided in the form of unsaturated fat. The two types of "good" unsaturated fats are listed below and some of these foods may be tolerated by the gastroparesis patient. Monounsaturated fats are found in high concentrations in (a) olive, peanut, and canola oils; (b) avocados; (c) nuts such as almonds, hazelnuts,

and pecans; (d) seeds such as pumpkin and sesame seeds; and polyunsaturated fats are found in high concentrations in (a) sunflower, corn, soybean, and flaxseed oils; (b) walnuts; (c) flax seeds; (d) fish; and (e) canola oil (although canola oil is higher in monounsaturated fat, it is also a good source of polyunsaturated fat) [13, 14].

Patients with gastroparesis should avoid most nuts and seeds because they will be difficult to mill and empty; however, patients can try peanut butter or almond butter in small quantities and use small amounts of canola or olive oils when cooking. Baked or broiled fish contain fats, but these foods in small quantities are recommended [10]. Patients with gastroparesis can also increase fat in a liquid form in small volumes of supplements, shakes, or whole milk products sipped throughout the day. High calorie liquid supplements, such as Boost Plus™, Boost Very High Calorie™, Mighty Shakes™, and Ensure Plus™ can be added from Step 2 if needed to meet daily caloric requirements.

The three-step diet for patients with nausea and vomiting is low in protein and fat and therefore it is not a "complete diet." Almost 32 % of patients with gastroparesis have diets deficient in calories, vitamins, and minerals; and, unfortunately, only one-third of these patients were taking multivitamins on a daily basis [4]. Patients with idiopathic gastroparesis were more likely to have diets with deficiencies in vitamins B_6, vitamin K, and iron and less likely to have seen a dietitian compared with patients with diabetic gastroparesis. Baseline vitamin levels such as vitamin D, iron panel, zinc, vitamin B12, and folate should be obtained and vitamins or minerals that are deficient should be treated. Laboratory tests should be repeated 3–6 months later to assure repletion. A chewable multivitamin should be added to the daily diet regimen for all patients with gastroparesis. The chewable vitamin should say "complete" on the label. Some of the gummy vitamins lack certain vitamins and minerals. Chewable or gummy vitamins are liquids when they enter the stomach and elicit no gastric symptoms compared with the large standard adult vitamin tablets. Table 11.2 illustrates in more detail a list of foods that are recommended and those to avoid with the three-step gastroparesis diet and sample menus.

Multivitamins cannot substitute for a healthy, balanced diet and should be regarded as a supplement to foods. The following guidelines are helpful when selecting a multivitamin. Patients should not exceed the daily values (DVs), which were developed by the US Food and Drug Administration (FDA) and are listed on the right side of the nutrition facts label [15]. DVs were not designed according to gender or age and were established at the maximum recommended amount for a particular group [16–18]. Selecting a multivitamin that contains 100 % of DVs is the way to ensure the patients' daily recommendation is met. A multivitamin should contain both vitamins and minerals. Some chewable vitamins contain vitamins but no minerals. A reputable multivitamin should provide "Proof of External Certification." Certification programs are voluntary, but they do indicate that an independent organization has tested the product for quality [19]. Two examples of seals to look for are USP (United States Pharmacopeia) and CL (ConsumerLab.com). Most multivitamins have a shelf life of about 2 years, but they do tend to degrade over time [20]. The expiration date should be checked to assure the full potency of the product. Ingesting mega doses of any vitamin or mineral is not recommended because certain vitamins and minerals are toxic [21–24].

Soluble fiber supplements may be tolerated by patients with gastroparesis in low doses and with slow, upward titration over several weeks. Soluble fiber has an important role in health by lowering cholesterol and helping irritable bowel syndrome, diverticulosis, and hemorrhoid diseases. Patients with gastroparesis often have IBS or constipation and soluble fiber may have a role in treatment. The average American consumes 10–15 g of fiber per day, but the recommendation for older children, adolescents, and adults is 20–35 g of fiber each day [11]. Trials of fiber supplements for gastroparesis with constipation or diarrhea can be initiated on a patient-by-patient basis. We typically recommend starting with only 3–6 g of soluble fiber for 3 weeks and then increase to 6–9 g daily for 3 weeks and eventually

Table 11.2 Gastroparesis diet: expanded list of foods and suggested menus

Step 1. Electrolyte-containing liquids for hydration		
Allowed foods: Electrolyte-containing liquids, crackers		
Avoid: Citric juices		
Step 2. Soups and smoothies for liquid nutrition		
	Recommend	*Avoid*
Soups	Fat-free consommé and bouillon, soups made from skim milk, fat-free broths with pasta, noodles, rice, or allowed vegetables	Soups made with cream, whole milk, or broths containing fat
Beverages	Gatorade, soft drinks (sipped slowly throughout the day), tea, water	All others (such as citrus juices, drinks with high fructose corn syrup)
Breads & grains	Breads and cereals, cream of wheat, grits, pasta, white rice, egg noodles, low-fat crackers	Oatmeal, whole-grain or brown rice, whole-wheat pasta
Sweets & desserts	Hard candies, puddings and custards made from skim milk, frozen yogurt, fat-free ice cream, fruit ice, gelatin, ice milk, jelly, honey, syrup, caramel	High-fat desserts such as cakes, pies, cookies, pastries, ice cream, fruit preserves
Meats & protein foods	Eggs, peanut butter (max 2 tbsp per day)	Beef, chicken, turkey, pork, seafood, dried beans/peas, lentils
Vegetables	Vegetable juices	Raw vegetables, cooked vegetables with skins; corn, eggplant, peas, pea pods, broccoli, Brussel sprouts, cabbage, cauliflower, peppers, onions, sauerkraut, turnips, zucchini
Fats & oils	Small amounts of vegetable oil or margarine	Butter, salad dressing, fried or greasy foods
Step 3. Solid foods selected for gastric neuromuscular dysfunction of gastroparesis		
	Recommend	*Avoid*
Breads and grains	Breads and cereals, cream of wheat, grits, pasta, white rice, egg noodles, crackers	Oatmeal, whole-grain or brown rice, whole-wheat pasta
Meats and protein foods	Eggs, small amounts of smooth peanut butter, chicken, turkey, fish/shrimp, lean ground beef	Fibrous meats such as steaks, roasts, chops, etc., dried beans/peas, lentils
Fats and oils	Small amounts of vegetable oil or olive oil, margarine, low-fat mayonnaise	Butter, salad dressing, fried or greasy foods
Vegetables	Well-cooked vegetables without skins: potatoes, squash, beets, carrots, spinach, yams, strained tomato sauce	Raw vegetables, cooked vegetates with skins; corn, eggplant, peas, pea pods, broccoli, Brussel sprouts, cabbage, cauliflower, peppers, onions, sauerkraut, turnips, zucchini
Sweets and desserts	Hard candies, puddings and custards made from skim milk, frozen yogurt, fat-free ice cream, fruit ice, gelatin, ice milk, jelly, honey, syrup, caramel	High-fat desserts such as cakes, pies, cookies, pastries, ice cream, fruit preserves
Fruits	Canned fruits without skins	Citrus fruits or juices, fresh fruits, dried fruits/raisins, canned fruits with skins (apricots, cherries, blueberries, fruit cocktail, oranges, grapefruit, pineapple)
Sample menus		
Step 1		
Breakfast	*Lunch*	*Dinner*
1/2 cup Gatorade	1/2 cup Gatorade	1/2 cup Gatorade
1/2 cup ginger ale	1/2 cup cola	1/2 cup Sprite

(continued)

Table 11.2 (continued)

3/4 cup broth	3/4 cup broth	3/4 cup broth
6 saltine crackers	6 saltine crackers	6 saltine crackers
Mid-morning snack	*Mid-afternoon snack*	*Evening snack*
1/2 cup Gatorade	1/2 cup Gatorade	1/2 cup Gatorade
6 saltine crackers	6 saltine crackers	6 saltine crackers
(Approximately 1,350 calories, 206 g carbohydrate, 52 g protein, 35 g fat, 2.6 g sodium, 1.4 g potassium)		
Step 2		
Breakfast	*Lunch*	*Dinner*
1/2 cup skim milk	2 oz mozzarella cheese	1 tbsp. peanut butter
1 scrambled egg	6 saltine crackers	6 saltine crackers
1 slice white toast	3/4 cup chicken noodle soup	1/2 cup vanilla pudding
1/2 cup apple juice	1/2 cup Gatorade	1/2 cup grape juice
Mid-morning snack	*Mid-afternoon snack*	*Evening snack*
1/2 cup ginger ale	1/2 cup skim milk	1/2 cup frozen yogurt
1/2 cup canned pears	1/2 cup corn flakes	6 saltine crackers
	2 tsp sugar or sugar substitute	
Step 3		
Breakfast	*Lunch*	*Dinner*
1/2 cup skim milk	2 oz. tuna	2 oz. baked chicken
1/2 cup cream of wheat	2 tbsp. low-fat mayonnaise	1/2 cup white rice
1 tsp sugar/ sugar substitute	2 slices white bread	1/2 cup cooked carrots
1/2 cup apple juice	1/2 cup canned peaches	1 dinner roll, margarine
1 tsp margarine	1/2 cup Gatorade	1/2 cup skim milk
Mid-morning snack	*Mid-afternoon snack*	*Evening snack*
1/2 cup Sprite	1/2 cup ginger ale	1/2 cup fat-free ice cream
1 cup low-fat yogurt	1/2 cup vanilla pudding	2 pretzels
(Approximately 1,800 calories, 285 g carbohydrate, 75 g protein, 42 g fat, 2.2 g sodium, 2.5 g potassium)		

reach 12–15 g per day to achieve the goal of a bulky, soft, formed stool every day. Examples of soluble fiber supplements are Benefiber™, Citrucel™, and Metamucil™. Generic products are also available and may be less costly for patients.

Enteral Nutrition

Gastroparesis presents a number of challenges for patients to consume adequate calories and balance fat, protein, vitamin, and mineral requirements. Enteral nutrition support may be indicated when patients have severe persistent symptoms of nausea and vomiting or early satiety or fullness that regularly inhibits adequate oral intake. If patients experience significant weight loss of 5–10% of body weight over 3–6 months, frequent hospitalizations with intractable nausea and vomiting, inability to maintain adequate calorie intake, and evidence of protein calorie malnutrition (low albumin or prealbumin, hair loss, brittle nails, or vitamin and mineral deficiencies), then enteral support is the next step in nutritional management. The guidelines for the identification of patients at nutritional risk are BMI less than 20 kg/m^2 and unintentional weight loss of 5–10% over 3–6 months [10, 24]. Unintentional weight loss is one of the most important parameters to assess regardless of the patient's overall appearance. Enteral nutrition support is preferred over total parenteral nutrition (TPN) because line infections and sepsis are avoided and expenses are fewer. Enteral feeding also provides physiological delivery of nutrients into the small bowel, enhances glucose control, and utilizes the gut. TPN is rarely necessary for patients with gastroparesis and should be reserved for those who have had small bowel resections, small bowel motility abnormalities, or who failed enteral therapy [24].

A trial of nasojejunal feeding prior to placement of permanent enteral access is recommended for 2–4 weeks to determine if enteral feeding is tolerated. However, these tubes can migrate back into the stomach, which may require multiple tube placements and X-rays to confirm placement. If enteral feeding results in minimal GI symptoms and some weight gain, then proceeding to surgical jejunostomy is reasonable for long-term enteral feeding. A percutaneous endoscopic gastrostomy tube with a jejunal extension (PEG-J) is not recommended for long-term enteral feeding because gastroparesis patients frequently vomit and the J-tube extension reverts to the stomach. Therefore, a feeding jejunostomy tube, which bypasses the gastroparetic stomach, is a much more dependable access to the small bowel for predictable enteral nutrition.

Enteral feeding can be started with standard formulas at 1.0, 1.2, or 1.3 kcal/ml. On the other hand, formulas with 1.5–2.0 calorie/ml may not be tolerated due to the caloric density. Diluting enteral formulas is generally not recommended because the risk of contamination or spoilage of the formula increases and instructions about diluting formulas may also be confusing for the patient. If there is evidence of malabsorption or delayed small bowel transit, then the formula should be changed to a semi-elemental or elemental formula such as Vital, Peptamen, or Vivonex. There is little or no literature describing efficacy of diabetic-specific enteral formulas [24].

To initiate enteral feedings, patients may start their feeds at 10 ml per hour for 1–2 days and then increase by 10 ml every 2–3 days as tolerated until they reach a goal rate that has been calculated by the dietitian for weight gain or weight maintenance. A dietitian consultation is recommended to determine energy and protein needs and identify the most appropriate formula for the patient and to follow-up, monitor weight trends, and to assess tolerance of feedings. Patients can utilize infusion pumps or gravity feedings. Water flushes are very important to keep the feeding tube patent and should be done for medication administration and to provide additional free water because typically free water needs are not met by enteral formula alone. Proper hydration with free water or Gatorade™ is just as important as infusion of adequate calories and protein. In order to allow the patient freedom during the daytime to ambulate and work, enteral nutrition can be infused 8–12 h at night if calorie goals can be met.

In summary, dietary modification should always be individualized for the patient with gastroparesis according to their needs for hydration and nutrition *and* with an appreciation of their postprandial symptoms and an understanding of the key pathophysiological abnormalities of gastroparesis. Understanding what is meant by gastric accommodation and trituration or milling is extremely important for patients with gastroparesis. The patient's own list of tolerated foods, achieved by trial and error, is usually very limited, but knowing how their stomach works will help and encourage the patient to continue to introduce new foods into the diet in a rational manner. Understanding poor gastric accommodation and the wide variations and the severity of delayed gastric emptying helps the dietitian and the patient design realistic goals for food choices that also limit postprandial symptoms [4].

Nutritional Management for Patients with Dumping Syndrome

Dumping syndrome, or rapid gastric emptying, is another cause of nausea and vomiting. Like gastroparesis, dumping syndrome can adversely affect a patient's quality of life due to debilitating postprandial symptoms including nausea. Patients who have rapid gastric emptying often have surprisingly similar symptoms to patients with gastroparesis. Dumping syndrome occurs after gastric operations such as Roux-en-Y or Whipple procedures, but many patients have idiopathic dumping syndrome.

Dumping syndrome occurs when food is emptied too quickly from the stomach and rapidly fills the duodenum and jejunum with undigested food that is not properly milled into small particles as described above. Absorption of nutrients in the small intestine is inefficient for this reason and the intraluminal particles create an osmotic gradient that draws increased fluids into the lumen of the small intestine [25]. Thus, dumping syndrome can result in symptoms of postprandial nausea, fullness, bloating, and diarrhea. Patients often report loud noises in the abdomen after meals and crampy pain that moves through different areas of the abdomen. In addition, these patients may develop weakness, cold sweats, or dizzy spells after eating due to postprandial hypoglycemia [26]. The vomiting of ingested food may mimic gastroparesis. In contrast to patients with gastroparesis, patients with dumping syndrome are frequently very hungry.

Patients with dumping syndrome benefit from dietary counseling and management. Patients are advised to consume four to six small-volume (3–4 oz) meals a day. They are coached to "eat dry." This means they ingest small volumes of liquids like Gastorade™ about 30 min after the meal and in small volumes between meals [25]. Liquids consumed with a meal may increase the rate of emptying (dumping) and create more abdominal symptoms. Simple sugars contained in candy bars, cookies, table sugar, fruit juice, sweet tea, milk, yogurt, honey, molasses, maple syrup, and brown sugar should be avoided since rapid increases in blood glucose and subsequent surges of insulin occur when those foods are dumped into the small intestine. The surge in insulin then results in a rapid decrease in blood glucose and the sweating, shakiness, and lightheadedness of hypoglycemia. The high osmolality of the simple sugars may also lead to bloating and diarrhea. Complex carbohydrates (e.g., whole wheat bread and pasta, oats, fruits, vegetables) should be consumed instead of simple carbohydrates. Some patients with dumping syndrome do not have any postprandial changes in bowel habits.

Because fat is known to delay gastric emptying, patients should include a source of a heart-healthy fat with every meal or snack. For example, patients can drizzle olive oil on almost all foods and the oil will delay gastric emptying time, at least to some degree, which hopefully will decrease postprandial symptoms. Small, frequent sips of an electrolyte replacement solution are recommended to enhance absorption of the liquid and to prevent dehydration in patients with dumping and diarrhea. By carefully designing dietary choices, postprandial symptoms can be reduced.

By reclining to some degree after meals, the ingested food may pool in the fundus and thereby slow the rate of gastric emptying.

Conclusion

To summarize, chronic nausea and vomiting are devastating to patients with gastroparesis or dumping syndrome. Caloric and vitamin deficiencies are common in patients with gastroparesis. Surprisingly few patients with gastroparesis are referred for dietary consultations, but an individualized, high-carbohydrate, small-volume diet with frequent meals can help to maintain hydration, caloric goals, and weight while reducing postprandial symptoms in patients with gastroparesis. Patients with dumping syndrome have similar symptoms, but a very different approach to dietary management may help to reduce postprandial symptoms.

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Complementary and Alternative Medicine for Nausea and Vomiting

12

Linda Anh Nguyen and Linda Lee

Introduction

Complementary and alternative medicines (CAM) are commonly used in the general population. The allopathic view of nausea and vomiting is that it is a reflex that results from a complex interaction of peripheral and central mechanisms, involving neurotransmitters and receptors. Pharmacologic antiemetic therapies have been developed that antagonize serotonin and NK1 receptors involved in these pathways. Antiemetics, approved for the use of chemotherapy-induced nausea and vomiting, may not be as effective when used off-label for the treatment of nausea and/or vomiting from other causes. This may be in part due to the fact that nausea is subjective, may be anticipatory, and in some clinical scenarios, tends to cluster with other symptoms, such as fatigue, drowsiness, and anorexia, which may independently predict responses to therapy [1].

Other whole health systems, such as Traditional Chinese Medicine, incorporate personal factors, like the patient's feelings, the appearance and odor of the emesis, and the sound the patient makes when vomiting, which help to establish highly individualized treatment plans that may incorporate diet, herbal therapies, and/or acupuncture [2]. Some plant-based therapies used for thousands of years have recently been found to possess activity against the same serotonin and NK1 receptors targeted by antiemetic therapies. More clinical studies are needed in most cases to establish their safety and usefulness in an integrative approach. This review will describe commonly used herbal remedies and acupuncture for the relief of nausea and vomiting.

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Herbal Remedies for Nausea and Vomiting

Ginger, *Zingiber officinale Roscoe*

Ginger is prescribed in many cultures as a remedy for abdominal discomfort, nausea, and flatulence and has been studied as a potential treatment for motion sickness, postoperative nausea and vomiting, pregnancy-induced nausea and vomiting, and chemotherapy-induced nausea and vomiting (CINV) [3]. It has the advantage of the fresh root being widely available, and not being associated with significant side effects. However, some caution is necessary when using commercially prepared ginger root powder, because among manufacturers there is wide variation in the concentration of bioactive compounds and suggested serving sizes [4]. Several bioactive compounds found in ginger include gingerol, shogaol, and zingerone [5], and these appear to act through

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serotonin and NK1 receptors in the gut and central nervous system. In a mink model of chemotherapy-induced nausea, gingerol reduced the frequency of cisplatin-induced retching and vomiting in a dose-dependent manner [6]. Gingerol did this in this model by inhibiting the expression of substance P and NK(1) receptors induced by cisplatin in the ileum and area postrema in the medulla. Like the $5HT_3$ antagonist, ondansetron, ginger extract and its individual compounds antagonized serotonin-evoked current responses in visceral vagal afferent neurons, with a relative inhibitor potency of [6]-shogaol > [6]-gingerol > zingerone [7].

The effect of ginger compounds on gastrointestinal motility has been studied. In the intestine, it has a spasmolytic effect. Ginger extract inhibits $5HT_3$ receptor activation to reduce isotonic contractions of isolated guinea pig ileum [8]. It exerts antispasmodic effects in isolated rabbit jejunum and rodent ileum by inhibiting 5-HT and K+ induced contractions, but at the same time, appears to stimulate gastric motility [9]. A gastric prokinetic effect has been observed in healthy volunteers, in which ginger extract increased interdigestive antral motility during phase III of the migrating motor complex [10]. Gastric emptying half-time was less after ginger, with increased frequency of antral contractions [11]. In human models of nausea and vomiting, ginger exerts slow wave antiarrhythmic effects to reduce tachygastria triggered by circular vection [12]. It also decreases slow wave dysrhythmias induced by hyperglycemia [13]. These studies suggest that its effects on gastric motility may be related to inhibition of vasopressin release [12] or blunting of endogenous prostaglandin production [13].

In contrast to preclinical studies, clinical trials of ginger for the treatment of nausea and/or vomiting have produced conflicting results. In patients with functional dyspepsia, ginger stimulated gastric emptying and antral contractions, but there was no significant improvement in symptoms [14]. Powdered or fresh ginger root did not improve motion sickness in one study [15], but in another study, volunteers with a history of motion sickness who were pretreated with 1000 mg of a commercial preparation of a ginger supplement experienced a delay in the onset of nausea and it was less severe [12]. In the case of CINV, a recent review of randomized controlled or crossover trial identified seven studies with variable methodological quality and produced variable results [16]. In most studies, patients were administered 1–2 g of ginger divided into four to eight capsules and consumed over a period of up to 10 days. The first dose was typically given within 1 h of the first chemotherapy session. Five of the studies used standard antiemetic medication in conjunction with ginger. Three studies demonstrated a positive effect when compared to placebo with a reduction in measures of CINV by 16–47 %; two gave positive results when compared to metoclopramide but had no placebo arm; and the remaining two yielded negative results [16].

Studies on the effect of ginger on postoperative nausea and vomiting have been mostly conducted in patients undergoing gynecologic surgery and have also yielded inconsistent findings. Typically, ginger is administered 1 h prior to surgery. The studies have been small in numbers of subjects [17–23].

Ginger is one of the most commonly used supplements by pregnant women in a multinational study to manage nausea symptoms of colds and flu, and to promote health and treat other GI disorders [24]. A meta-analysis based on six randomized placebo controlled trials with extractable data found that 1 g of ginger daily for at least 4 days is associated with fivefold likelihood of improvement in symptoms [25]. Another meta-analysis, published that same year, identified 12 randomized controlled trials and found that although ginger significantly improved the symptoms of nausea when compared to placebo, it did not reduce the number of vomiting episodes [26]. Importantly, the authors did not find that ginger had significant side effects or risk for spontaneous abortion [26].

Ginseng

Ginseng is used in traditional Chinese medicine for the alleviation of nausea and vomiting. Its antiemetic effects have been attributed to sapo-

nins. Indeed, saponin has been demonstrated to inhibit current flow in a concentration-dependent manner through the 5HT(3A) receptor using the voltage-clamp technique [27]. Preclinical studies using Korean red ginseng extract in ferrets attenuated nausea and vomiting [28]. Saponin and the non-saponin fraction of ginseng were associated with less cisplatin-induced pica in a rat model [29, 30]. No human studies on nausea and vomiting have been done.

Cannabis Sativa L

Cannabis has a long history of use for the treatment of nausea and other GI ailments, but psychotropic side effects and regional legal issues have limited its use. More than 60 tepernophenols have been isolated from this plant, but the most studied has been the major psychoactive substance, delta-9-tetrahydrocannabinol (THC). Synthetic analogues of THC, which suppress vomiting by binding to CB1 brainstem receptors, are approved for the treatment of chemotherapy-induced nausea and vomiting and are discussed elsewhere in this volume. New combination formulations of THC and cannabidiol, a non-psychoactive marijuana constituent that suppresses vomiting through 5-HT1A receptors, as an oromucosal spray are under investigation [31]. Endogenous cannabinoids like anandamide and 2-arachidonyl glycerol suppress nausea and are stimulating development of pharmacologic agents that target enzymes that interfere with the degradation of endogenous cannabinoids [32, 33].

Despite the availability of THC analogues, many patients still prefer using medical marijuana, which may be inhaled by smoking or vaporization, eaten or drunk as a tea, or topically applied [34]. The pharmacokinetics are likely to differ depending on each mode of administration, and the potential pulmonary and other health effects of smoking it require further investigation [35, 36]. However, in contrast to the number of trials using cannabinoid derivatives, there are very few clinical studies that examine the antiemetic effect of medicinal or crude marijuana [37] despite the interest expressed by patients. An observational study of inhalation marijuana showed improvement in 78 % of 56 cancer patients with intractable nausea and vomiting [38]. Another study of 13 healthy volunteers in which emesis was induced by Ipecac, found that marijuana smoked 2 h before administration of Ipecac, reduced "queasiness" modestly and only slightly reduced vomiting compared to a placebo cigarette. Ondansetron [39], on the other hand, entirely blocked the emetic effects of Ipecac.

Rikkunshito

A traditional Japanese phytomedicine that contains eight herbal constituents: *Aurantii* pericarpium (bitter orange), *Ginseng* radix (Ginseng root), *Zingiberis* rhizoma, *Jujubae* (zizyphi) fructus (Jujubae fruit), *Pinellia* tuber (Crowdipper), *Atractylodis* rhizoma, *Glycyrrhiza* radix (licorice root), *Porio cocos*. Its antiemetic effect had been attributed to ginger, but a recent study demonstrated glycyrrhiza as the most potent inhibitor of current flow in 5HT3A-expressing Xenopus oocytes using the two-electrode voltage clamp technique; the flavanoid (−)-liquiritigenin is the putative component responsible for this effect [40]. *Ginseng, Atractylodis, and Aurantii* extracts also inhibited 5HT3A in this model. Another Rikkunshito component, hesperidin derived from *Aurantii*, had previously been shown to inhibit 5HT3 receptor activation with an effect as great as ondansetron in rats [41]. These represent candidates for future investigation.

Artichoke Leaf (*Cynara scopymus*)

Artichoke has been used since ancient Greece and Rome to aid digestion [42]. Cynaropicrin, a sesquiterpene lactone derived from artichoke, demonstrated antispasmodic activity against guinea pig ileum, with similar potency to papaverine [43]. In a double-blind, randomized

controlled trial of 247 patients with functional dyspepsia, patients received 640 mg of artichoke leaf extract (ALE) or placebo. The ALE group demonstrated significantly improved symptoms and improvement in quality of life scores. The intensity of dyspeptic symptoms was also evaluated, and while there were statistically significant differences in fullness and flatulence, there was no significant difference in nausea or vomiting between ALE and placebo groups [44]. In a multicenter, double-blind, randomized placebo-controlled trial over 4 weeks using ALE with ginger [45], patients receiving the supplements reported more symptomatic improvement than the placebo group. Secondary outcomes included intensity of individual symptoms; there was a significant reduction in intensity score for nausea, but not for vomiting.

Padma Digestin®

A blend of 5 herbs manufactured in Switzerland based on Tibetan Traditional formula, Se 'bru, prescribed for digestive problems and malabsorption. Capsules contain derivatives of pomegranate seed, lesser galangal, long pepper, cardamom fruit, and cassia bark. Its physiologic effects have been described in only one study in which the formulation increased contractility in muscle strips derived from the antrum and pylorus but decreased it in duodenal and jejunal strips. An open-label observational study of 31 patients with functional dyspepsia found significant improvement in nausea and postprandial fullness without significant adverse events related to the formulation [46].

STW 5 (Iberogast®)

A blend manufactured in Germany consisting of nine herbs: Angelica root, milk thistle fruit, caraway fruit, celandine herb, licorice root, chamomile flower, lemon balm leaf, peppermint leaf and bitter candytuft. STW 5 has been studied in the treatment of functional dyspepsia and irritable bowel syndrome. STW 5 exhibits spasmolytic activities in isolated guinea pig ileum stimulated with either acetylcholine or histamine [47]. In human physiology studies, STW 5 increased gastric accommodation and antral contractility, but did not accelerate gastric emptying of solids [48]. In a multicenter, placebo-controlled double-blind study of 103 patients with functional dyspepsia and gastroparesis demonstrated significant symptom improvement when compared to placebo, but no significant change in gastric emptying [49]. In addition to its effects on gastrointestinal motility, STW 5 reduces afferent sensitivity in the rat small intestine [50, 51]. Ethanolic extracts of celandine herb and chamomile flower selectively bound to 5-HT4, and licorice root to 5-HT3 receptors in the intestine [52].

Acupuncture, Acupressure and Acustimulation

Acupuncture and acupressure aim to correct the imbalance in "yin-yang" and "qi" that causes symptoms, by inserting needles (acupuncture) or applying hand pressure (acupressure) on specific points on the body. Acupuncture has been used in Chinese medicine before the first century BC, but did not populate "Western medicine" until the 1970s [53]. In 1997, an NIH Consensus Development Panel reviewed the available literature and concluded that acupuncture yielded "promising results" in the treatment of postoperative and chemotherapy-induced nausea and vomiting in adults [54]. Neiguan or P6 is the most commonly studied acupuncture point for nausea and vomiting. It is located approximately 3 finger breadths proximal to the wrist between the tendons of the flexor carpi radialis muscle and the palmaris longus muscle [55–57].

The mechanism of action of acupuncture is still unknown. The analgesic effects of acupuncture may be related to release of endogenous opioids, activation of the hypothalamus and pituitary gland, and/or alterations in neurotransmitters and immune function [53, 54]. There is also evidence that stimulation of acupuncture sites affects gastric myoelectrical activity. Gastric slow waves originate in the proximal stomach and determine the frequency and direction of gastric contractions. Gastric dysrhythmias have been

associated with impaired gastric motility and gastroparesis [58]. Hu et al. demonstrated that acupressure at the P6 point decreased nausea related to visually induced motion sickness and gastric dysrhythmias measured by electrogastrography (EGG) [59]. Similarly, combined acupuncture of P6 (*Neiguan*), SP4 (*Gong sun*), and DU20 (*Baihui*) improved symptoms of nausea and improved gastric dysrhythmias in an uncontrolled group of patients with refractory nausea and/or abdominal pain/bloating [60]. Acupuncture stimulation of P6 in healthy controls resulted in increased vagal modulation, with evidence of decreased heart rate (increased R-R interval) and increased high-frequency power measured by heart rate variability, which is a measure of cardiovagal tone [61]. Stimulation of the ST36 (*Zu San Li*) point below the knee has been shown to affect gastrointestinal motility, including decrease transient lower esophageal sphincter relaxation, increase gastric accommodation, decrease gastric dysrhythmias, and increase antral and colonic contractions [62].

Since the first description of acupuncture for the prophylaxis of postoperative nausea and vomiting in 1986 [63], there have been a number of controlled trials that have shown benefit of P6 stimulation in PONV and chemotherapy-induced nausea and vomiting (CINV), which have included acupressure, acupuncture, electroacupuncture, and transcutaneous electrical stimulation [56, 57]. A Cochrane Review of P6 acupoint stimulation (acupressure, needle acupuncture, electroacupuncture, transcutaneous electrical stimulation) for prevention of postoperative nausea and vomiting was updated in 2015 (initially published in 2004) [55]. This review included 59 trials involving 7667 patients comparing acupoint stimulation versus sham or antiemetics or P6 stimulation plus antiemetic versus antiemetic alone. Compared to sham, this review found that P6 stimulation decreased nausea (RR = 0.68, 95 % CI = 0.60–0.77), vomiting (RR = 0.60, 95 % CI = 0.51–0.71), and need for rescue antiemetics (RR = 0.64, 95 % CI = 0.55–0.73). There were no differences in symptom reduction when P6 stimuation alone or P6 stimulation plus antiemetic were compared to various antiemetics (metoclopramide, cyclizine, prochlorperazine, droperidol, ondansetron, and dexamethasone). Stimulation of P6 is similar to antiemetic therapy in reducing symptoms of nausea and vomiting. The effect of combined P6 stimulation plus antiemetic therapy versus either therapy alone is unclear. Adverse events related to acupuncture are transient and mild, including forgotten needles, orthostasis/dizziness, needling site pain/hematoma, minor bleeding, and skin irritation [53, 55, 56].

Acupressure

Pressure stimulation to P6 can be applied manually with the fingers or by wearing an elastic wristband with an embedded plastic button or pearl that provides constant pressure (SeaBand™, Sea-band Ltd., Leicestershire, England). Studies on the use of acupressure for PONV and CINV have had conflicting results with heterogeneity in study design [56]. However, pooled analysis of six trials in PONV involving 292 acupressure and 288 sham controls found that acupressure significantly reduced postoperative nausea (30.8 % vs. 43.4 %, RR = 0.71, 95 %CI 0.57–0.87, $p = 0.001$) and vomiting frequency (24.2 % vs. 38.8 %, RR = 0.61, 95 %CI 0.49–0.80, $p < 0.001$) [64]. Acupressure reduces acute nausea but not vomiting in CINV [65]. The effectiveness of P6 acupressure for nausea and vomiting in early pregnancy is conflicting; however, there were no significant adverse events associated with this therapy [66].

Acupoint stimulation is also commonly used for GI diseases with nausea and vomiting as part of the constellation of symptoms, including functional dyspepsia and gastroparesis [67, 68]. Studies of functional dyspepsia and gastroparesis most commonly evaluated the stimulation of the ST36 (*zusanli*) site, which in general increased gastric accommodation [69], increased antral contractions [70], improved gastric dysrhythmias [71], and reduced visceral hyperalgesia [72]. Studies comparing acupuncture to domperidone and/or sham found that acupuncture improved gastroparesis symptoms but not gastric emptying or glycemic control in patients with diabetic gastroparesis [73, 74].

Key Points

1. Herbal therapies, such as ginger and ginseng, can be helpful with symptoms of nausea and vomiting.
2. Herbal blends, such as STW5 and Rikkunshito, have been found to be efficacious in treating symptoms of nausea and/or vomiting related to functional dyspepsia and gastroparesis; however, they have not been studied in other causes of nausea and vomiting.
3. Acupuncture, acupressure and electroacupuncture are methods of acupoint stimulation that have been studied in the treatment of nausea and vomiting related to surgery, chemotherapy, motion, and pregnancy. Different modalities have varying effects depending on the underlying cause of nausea and vomiting.
4. The mostly commonly studied acupoint for nausea and vomiting is the P6 acupoint.
5. Stimulation of the ST36 acupoint can affect gastric motility and may benefit patients with gastroparesis or functional dyspepsia.

Electrical Acupressure/ Transcutaneous Electrical Stimulation

The ReliefBand® (Woodside Biomedical Systems, Carlsbad, CA) is a wristband worn like a watch that provides transcutaneous electrical stimulation of the P6 acupoint. Although difficult to compare given the differences in the control groups (electroacupressure vs. sham or antiemetic plus sham) across various studies, electroacupressure was effective in PONV, variably effective for motion sickness, and ineffective for CINV and nausea and vomiting in pregnancy [56].

Transcutaneous electrical stimulation at ST36 and P6 in functional dyspepsia patients twice a week for 2 weeks decreased dyspeptic symptoms and increased parasympathetic activity and heart rate variability [75].

Needle Acupuncture

Traditional needle acupuncture involves stimulation of acupoints manually with a fine needle. Manual acupuncture is effective in PONV but not CINV or nausea and vomiting of early pregnancy [55, 65, 66].

Electroacupuncture

Electroacupuncture involves connecting acupuncture needles to electrodes providing both mechanical and electrical stimulation of the acupoint. The current is generally adjusted until patients feel a tingling and numb sensation with a set alternating waveform of 2–100Hz. Electroacupuncture alone or as an adjunct to antiemetics is effective in treating and preventing PONV [55]. Unlike traditional needle acupuncture, electroacupuncture may be effective in preventing CINV [65].

Conclusions

Complementary and alternative medicine (CAM) is commonly used in the general population, with prevalence rates ranging from 5 to 75 % [76]. The rate of CAM use has increased over the past decade, with gastrointestinal disorders among the most common conditions treated with CAM [76]. Nausea and/or vomiting are debilitating symptoms resulting from a complex interplay of peripheral, central, and psychological factors. Traditional pharmacologic therapies for various causes of nausea and vomiting have limited efficacy and significant side effects. Herbal therapies and acupuncture have demonstrated efficacy in decreasing symptoms of nausea and vomiting.

The mechanisms of action of these therapies need to be further elucidated; however, there is evidence that these therapies act on serotonin, NK1, and/or opiate receptors in the gut or central nervous system to affect symptoms and gastric myoelectrical function. CAM is being used and desired by patients. Although the quality of studies is poor for many of these therapies, herbal therapies and acupuncture are safe and effective. Thus, CAM can play a role in the treatment of nausea and vomiting. Clinicians should keep an open mind and be able to discuss these treatment options with their patients.

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Vomiting and Nausea in the Pediatric Patient

13

John E. Fortunato and Sally E. Tarbell

Abbreviations

CIPO	Chronic intestinal pseudo-obstruction
CVS	Cyclic vomiting syndrome
FGID	Functional gastrointestinal disorder
GI	Gastroenterological
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
OI	Orthostatic intolerance
POTS	Postural orthostatic tachycardia syndrome

Epidemiology of Chronic Nausea and Vomiting in Children

Nausea and vomiting are frequent symptoms among children of all ages and are associated with common pediatric conditions. These include both primary gastrointestinal conditions such as anatomic anomalies, inflammatory conditions, and motility disorders, but also secondary manifestations of conditions outside the gastrointestinal (GI) tract such as metabolic abnormalities, drugs (e.g., chemotherapy, analgesics), central/peripheral/autonomic disorders, migraine headaches, vestibular disorders, and motion sickness. Both nausea and vomiting are included among the broad category of functional gastrointestinal disorders (FGIDs), but in the absence of a clear mechanistic etiology of these symptoms, it is unclear whether to attribute them to a primary GI origin. With the exception of idiopathic nausea, functional vomiting, and cyclic vomiting syndrome, nausea and vomiting are typically considered as symptoms of other disorders or treatments, rather than as separate medical conditions.

Estimates of the prevalence of nausea and vomiting in pediatric gastrointestinal conditions are hindered by the limited diagnostic criteria for primary nausea and vomiting disorders. Rome III criteria are used for the diagnosis of functional gastrointestinal disorders, which are defined as conditions where there are chronic and/or recurrent gastrointestinal symptoms for which no organic cause has been identified [1]. Standard diagnostic criteria for these disorders have guided research to improve treatment, but the application of these criteria in clinical practice is at times difficult as patients often present with symptoms that overlap diagnoses [2]. Further, diagnoses defining a range of nausea or vomiting disorders are absent

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or unavailable for pediatric patients. Cyclic vomiting syndrome (CVS) is the only pediatric vomiting disorder defined by Rome III [3]. Several population-based studies have found the prevalence rate of CVS to be approximately 2 % [4]. Another factor limiting our knowledge of the prevalence of nausea and vomiting in pediatric gastrointestinal disorders is the paucity of literature providing information on the frequency of these symptoms. Recently, a few studies have begun to address these issues. For example, a school-based study of FGIDs found 23 % of children reported nausea [5]. Kovacic and colleagues evaluated the presence of nausea in the setting of pain-associated FGIDs, where 60 % of children presenting to a GI clinic were found to experience co-occurring intermittent (53 %) or chronic (29 %) nausea [6]. To date, no population studies have set out to estimate the prevalence of idiopathic/primary nausea or vomiting. Although functional vomiting and chronic idiopathic nausea are disorders included in Rome III as diagnoses in adults, they are conspicuously absent when defining functional GI disorders in the pediatric population.

This chapter will focus on nausea and vomiting within the context of pediatric GI disorders. It is beyond its scope to discuss all pediatric conditions in which nausea and vomiting occur due to the extensive number of diagnoses included (traumatic brain injury, CNS malignancies, disorders of the inner ear, viral and bacterial infections, toxin ingestions, motion sickness, medication side effects). Instead, we will focus on primary GI problems in children frequently associated with nausea and vomiting and elaborate on potential causes for nausea and vomiting in FGID. We will emphasize mechanisms for nausea and vomiting for each of these conditions with the goal of determining appropriate diagnostic and treatment strategies.

Vomiting

Mechanisms and Initial Approach

Wang and Borison first proposed the notion of a vomiting center in which two anatomic regions in the medulla were identified controlling vomiting: the chemoreceptor trigger zone (CTZ) located specifically in the area postrema and the central vomiting center [7]. It was thought that receptors in the CTZ were activated by proemetic agents in serum or cerebrospinal fluid, transmitted to the central vomiting center after which the mechanical process of vomiting was initiated via the abdominal vagus nerve. Subsequent studies have not supported the concept of a simple vomiting center that could be manipulated with pharmacological intervention or surgery [8]. However, the concept of chemoreceptors in the area postrema as the major site involved in triggering vomiting as well as the idea that integrity of the vagus nerve is essential for the mechanical process of emesis to occur have been upheld.

While there is understanding of the central and peripheral neural circuitry and the neurohumoral response providing the gastrointestinal motor basis for vomiting, the underlying conditions triggering this cascade of events are extremely diverse. Among the initial challenges in approaching the pediatric patient with vomiting is, first, a huge differential diagnosis that must be considered. Second, determination must be made as to which potential diagnoses are most relevant to effectively approach and treat the underlying cause. Vomiting can be the presenting symptom for Various disorders ranging from self-limited illness to long-standing chronic conditions to acute life-threatening conditions. Common causes of vomiting in pediatric pediatrics are listed in Table 13.1.

Overall, focusing the differential diagnosis is often contingent on the patient's age and whether the etiology is directly related to the GI tract. For instance, congenital and metabolic abnormalities are generally more commonly observed in infants; whereas, inflammatory, motility, and functional disorders are more prominent in older children and adolescents. While most of these conditions are age-specific, a detailed history and physical is imperative in all children as delayed diagnosis can have serious consequences – most notably, for anatomical anomalies such as malrotation. While 90 % of cases can present symptoms prior to 1 year of age, several congenital

Table 13.1 Causes of vomiting in pediatric patients

Categories	Examples
Infectious	Viral, bacterial, or parasitic gastroenteritis
Neurological	Meningitis
	Functional neurological syndromes: migraine headache, vertigo
	Brain tumor
	Intracranial bleed
	Concussion
Mechanical/obstructive	Pyloric stenosis
	Congenital small bowel atresia
	Intestinal malrotation with volvulus
	Intra-abdominal adhesions
	Intussusception
	Superior mesenteric artery syndrome
Functional and motility gastrointestinal disorders	Gastroesophageal reflux
	Cyclic vomiting syndrome
	Gastroparesis
	Dyspepsia
	Hirschsprung's disease
	Constipation/stool impaction
	Autonomic disorders e.g., postural orthostatic tachycardia syndrome (POTS)
Inflammatory disorders	Crohn's disease
	Ulcerative colitis
	Peptic ulcer disease
	Appendicitis
	Pancreatitis
	Hepatitis
	Gastrointestinal eosinophilic disorders, e.g., eosinophilic esophagitis
Intra-abdominal malignancy	Small bowel lymphoma
	Renal obstructive tumors
Metabolic/endocrine	Diabetic ketoacidosis
	Adrenal insufficiency
	Inborn errors of metabolism
Genitourinary	Gonadal torsion
	Urinary tract infection
	Hemolytic uremic syndrome
	Nephrolithiasis
	Ureteropelvic junction (UPJ) obstruction
Psychiatric/psychological conditions	Eating disorders
	Rumination syndrome
	Factitious disorder and Factitious Disorder imposed on another
Toxins/drugs	Poison ingestion
	Medication reactions
	Cannabis hyperemesis syndrome
Pulmonary/ENT	Pneumonia
	Post-tussive emesis
	Otitis media

anomalies of the GI tract are still being diagnosed later in life, which can result in serious consequences in some cases [9].

Conditions Requiring Immediate Attention

Bilious emesis at any age requires immediate attention as it is potentially indicative of intestinal obstruction and need for early surgical intervention. For patients with previous abdominal surgery, adhesive small bowel obstruction is a significant cause of long-term morbidity occurring more commonly after laparotomy, but may also follow laparoscopic procedures [10, 11]. In patients without prior abdominal surgery, the presence of bile-tinged emesis raises concern for acute bowel obstruction secondary to unrecognized congenital abnormalities, most notably malrotation. Intestinal malrotation is due to abnormal fixation of the bowel, which can predispose patients to midgut volvulus. While the majority of patients present early in life, symptoms related to volvulus may present later in life, underscoring the need to always rule out malrotation when bilious vomiting is present [12].

Diagnosis of small bowel obstruction is based on a thorough history and detailed physical examination as well as the use of selective imaging studies. In addition to vomiting, small bowel obstruction is frequently associated with symptoms of abdominal pain, distension, and obstipation. Emergent surgical exploration is indicated for patients with evidence of peritoneal signs or clinical evidence of bowel ischemia. For those without signs and symptoms of acute bowel ischemia, bowel decompression with a nasogastric tube, fluid resuscitation, and close observation are appropriate initial measures. CT imaging is highly sensitive for diagnosing small bowel obstruction in children [13]. In children without acute symptoms, but a previously reported bilious emesis, upper gastrointestinal series is an appropriate step toward ruling out malrotation.

While most acute conditions associated with vomiting involve the GI tract, special consideration for central nervous system abnormalities is essential in any child with persistent nausea and vomiting. This is particularly relevant to those with associated headaches, most notably occurring in the morning or awakening from sleep as well as evidence of visual symptoms or signs or neurological impairment. A child whose differential diagnosis includes a potential intracranial space-occupying lesion requires prompt attention and CNS imaging [14]. This further supports the need for both pediatricians and specialists to conduct a full physical examination including neurological assessment in patients with complex symptoms that include vomiting.

Motility and Functional Disorders Associated with Vomiting

Gastroparesis

Gastroparesis is a motility disorder defined by delayed emptying of gastric contents into the duodenum in the absence of an anatomic or mechanical obstruction. The pathophysiology of gastroparesis is not well understood, particularly in children in whom its prevalence rates are unknown. Proposed mechanisms in children range from exaggerated fundic accommodation and relaxation, weak or absent antral contractions, to incomplete relaxation of the pylorus (pylorospasm). Gastroparesis may present with a variety of symptoms in children including vomiting of undigested food, nausea, bloating, early satiety, abdominal discomfort, anorexia, and weight loss. While diagnosis is based primarily on clinical assessment, diagnostic tools such as gastric emptying scintigraphy and antroduodenal manometry provide objective measures of gastric emptying and gastric motor function [15]. For example, the use of antroduodenal manometry may allow differentiation between weak antral contractions (myopathic or neuropathic gastroparesis) versus higher amplitude antral contractions, which may be attributed to incomplete pyloric relaxation or pylorospasm (Fig. 13.1). For the latter, the use of pyloric botulinum toxin (Botox) injection or balloon dilatation may have a role with reported symptom response rates around 51 % for Botox [16].

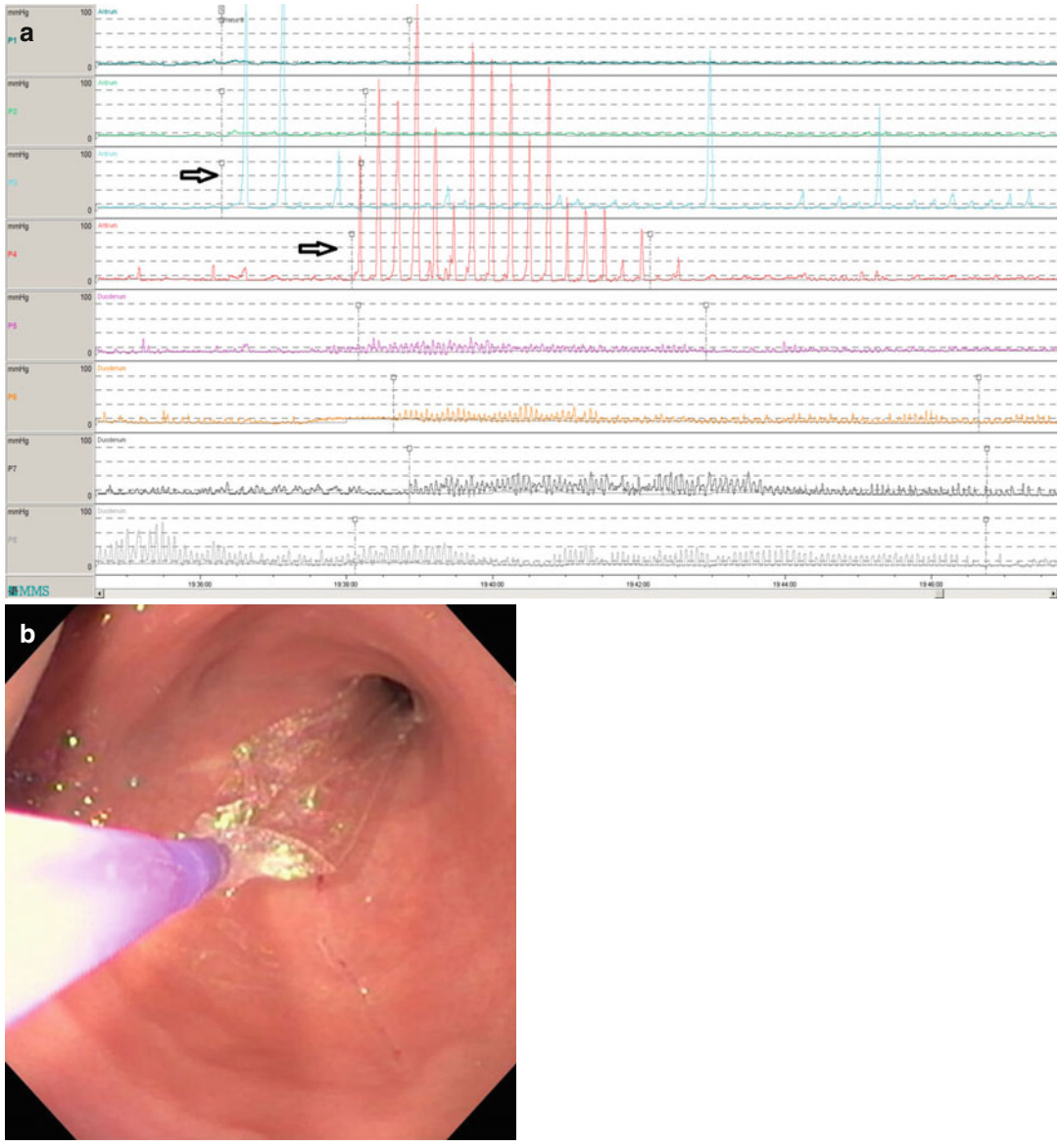

Fig. 13.1 Antroduodenal manometry of a 2-year-old child with persistent vomiting, gastroparesis, and high volume output from gastrostomy (**a**). High-amplitude antral contractions, some measured in excess of 400 mmHg, were observed (see *arrows*). Balloon dilatation of the pylorus (**b**) resulted in marked improvement in vomiting and feeding tolerance

Chronic Intestinal Pseudo-Obstruction

Chronic intestinal pseudo-obstruction (CIPO) represents a more severe and heterogeneous motility disorder with common symptoms including vomiting, abdominal pain, and either constipation or diarrhea. Patients often present with profound abdominal distension and malnutrition due to long-standing symptoms. The etiology of CIPO is likely multifactorial, but includes a spectrum of abnormal gastric, small bowel, and colonic myoelectrical activity and contractions resulting in insufficiency of intestinal peristalsis [17]. CIPO may be congenital or acquired. In the

latter, there exists a large number of conditions resulting in either transient or permanent manifestations including endocrine disorders such as hypothyroidism, certain viral infections, including herpes simplex and Epstein-Barr virus, as well as connective tissue disorders such as scleroderma [18]. Assessment of CIPO includes the use of abdominal imaging, which may demonstrate dilated small bowel loops and potentially air-fluid levels. Both manometry and transit studies may also assist in better defining neuropathic versus myopathic motility patterns as well as the potential site of functional obstruction (Fig. 13.2).

Cyclic Vomiting Syndrome

Cyclic vomiting syndrome (CVS) is characterized by recurring episodes of high-intensity vomiting lasting hours to days, accompanied by

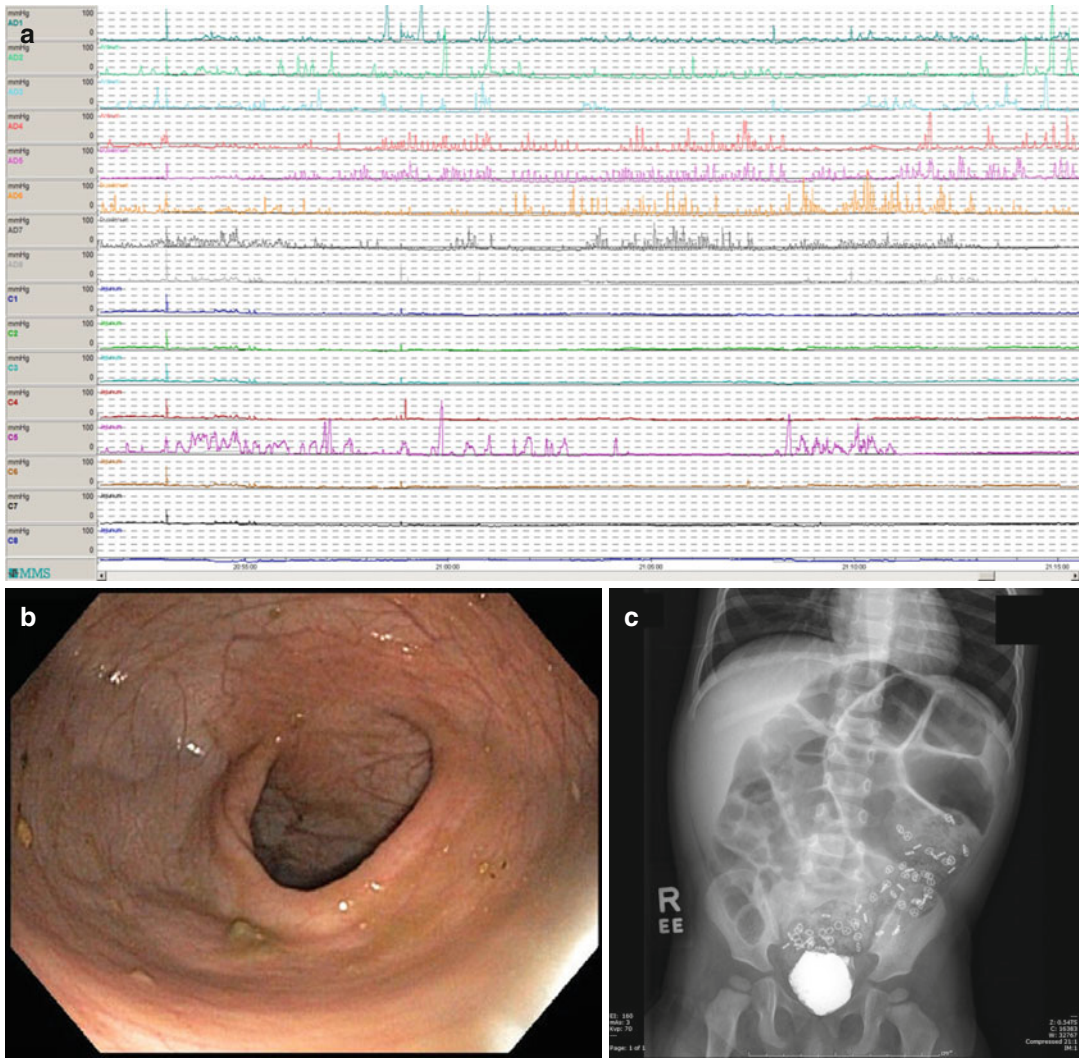

Fig. 13.2 Combined antroduodenal and colonic manometry (**a**) with CIPO demonstrating duodenal peristalsis (channels AD4-8) and absence of high-amplitude propagating contractions (HAPCs) despite stimulation with bisacodyl (channels C1-8). Marked dilatation of the recto-sigmoid colon was observed during colonoscopy (**b**), which corresponded to the location of Sitz markers (**c**) measured 5 days after swallowing the radiopaque markers

severe, persistent nausea, retching, and abdominal pain [19]. CVS diagnostic criteria include: (1) five episodes in any interval, or three or more episodes over 6 months; (2) stereotypic episodes with regard to onset, duration, and associated symptoms, and (3) return to baseline health between episodes [20]. CVS is diagnosed only after other serious medical conditions that may mimic its symptoms (e.g., intestinal malrotation) are excluded [19]. Although CVS involves intense vomiting, requiring intravenous hydration in about 60 % of affected children, the lack of an identified pathophysiology has led to its classification as a functional disorder [21]. CVS prodromal symptoms can include appetite loss, nausea, pallor, lethargy, social withdrawal, and irritability [22]. Onset of the vomiting can occur at anytime but early morning onset or upon awakening is commonly described by patients [22]. Notably, vomiting does not relieve symptoms of nausea and abdominal discomfort in CVS, as is typically the case for influenza or gastroenteritis. Associated signs and symptoms can include fever, diarrhea, light and noise sensitivity, vertigo, headache, and increased salivation [19, 22]. The generally poor recognition of CVS leads to an average delay in diagnosis of 2.5 years [19]. The median age of onset of CVS is 4.8 years, but it can also begin in adolescence or adulthood [19].

The etiology of CVS is unknown, but several mechanisms are under investigation. A majority of children with CVS (82 %) have a subtype considered to be a migraine variant due to similarities in symptoms, response to anti-migraine therapies, and family history of migraines [22, 23]. CVS episode triggers are also similar to those for a migraine headache. These include both positive events (e.g., birthdays, holidays) [22] and negative stressors (e.g., school or family problems, sleep changes, missed meals, inadequate fluid intake) [21]. Episodes tend to be less frequent in the summer, perhaps due to the reduction in school-related stressors and infections and increased sleep duration [22]. CVS onset at a young age and co-occurring headaches, are associated with an increased risk for the development of migraine headaches [24].

Other CVS subtypes have been identified and include: children with disorders of energy metabolism (mitochondropathies), who experience an earlier onset of CVS (i.e., ≤1 year of age) [25]; menstrual-related episodes [22]; the Sato's subtype, which is characterized by profound lethargy, hypertension, and is associated with the most prolonged (6 days) and intense episodes (92 emesis/episode) [19]; and timed or calendar-based CVS, wherein attacks reliably occur after a specific number of days [19]. Autonomic abnormalities also have been identified in children with CVS. Chelimsky and Chelimsky (2007) found abnormal sympathetic function and orthostatic intolerance in a small sample of children with CVS [26]. To and colleagues [27] assessed heart rate variability in children with CVS and found an enhanced sympathetic and diminished parasympathetic modulation of the heart.

Children with CVS have a high prevalence of internalizing psychiatric symptoms [28], especially anxiety [29]. There is also evidence of an increased prevalence of anxiety and depression in parents of children with CVS, especially mothers [29]. Anxiety has also been reported as a trigger for CVS episodes [30]. In adult CVS patients, uncontrolled nausea has been reported to increase anxiety about further cyclic vomiting attacks facilitating fear conditioning, leading to anticipatory nausea and vomiting [31].

The diathesis-stress model may help explain the relationship between CVS and anxiety symptoms. The premise of this model is that stress activates a diathesis, which is an enduring, endogenous predisposition to illness [32]. Endogenous vulnerabilities for anxiety in children with CVS are not yet known. However, the associations found between pediatric CVS and maternal anxiety [29], family histories of migraine and mitochondrial dysfunction, both known to be associated with psychiatric comorbidity [33, 34], suggest biological or genetic vulnerabilities. It is noteworthy that anxiety has been found to be a stronger predictor of health-related quality of life than disease characteristics in youth with CVS [35], suggesting that psychiatric screening of youth with CVS is integral to the development of a comprehensive treatment plan.

Cannabis use has been reported in CVS, especially among adolescent and young adult males, which users report ameliorates their symptoms of nausea and vomiting [36]. There are also published reports linking cannabis use to hyperemesis [37], but it is unclear as to whether the emesis is attributable to the cannabis use or the presence of CVS, and the patient's use of cannabis to self-manage symptoms of nausea.

Impact of CVS on Child Functioning and Health-Related Quality of Life CVS can have a significant negative impact on the affected child and the family as a whole. Children miss several days of school (median number of days = 11), compromising not only their education but also interfering with their social and recreational activities [38]. Parents looking after their sick child both at home and during hospitalization spend time away from their other children, miss days at work, and, in some cases, lose or quit their jobs due to multiple absences related to caring for their sick child. Quality of life in CVS is significantly poorer than that for children with irritable bowel syndrome and healthy children, with school functioning the lowest domain, and social functioning a relative strength [38].

Failure to diagnose CVS can make it difficult to obtain appropriate educational support for the child. Modest adjustments, such as a delayed school start time can be quite helpful given the onset of symptoms during sleep or upon awakening. Informing schools that the child is not suffering from a contagious illness should allow for the child to return to school as soon as symptoms have resolved. Useful information for families can be obtained from the Cyclic Vomiting Syndrome Association (CVSA) (www.cvsaonline.org).

Medical intervention can reduce the duration and frequency of CVS episodes, but children may continue to have intermittent CVS attacks. Medical treatment includes preventive, abortive, and palliative strategies [20]. Generally, the sooner medical intervention is offered in the setting of an acute attack, the better the chance of symptom control. For children who cannot be managed as outpatients, emergency room visits or hospital admissions are used to restore electrolyte imbalances, provide IV hydration, and symptom relief. There is generally poor recognition of CVS in emergency departments, which can lead to delays in the diagnosis and treatment of CVS [39]. The annual medical costs for a child with CVS were estimated to be $17, 035 in 2000 [21], a sum that has likely increased in the ensuing years, placing a significant financial impact on the family and the health-care system. Some families report that bringing recommendations for CVS management provided by their physician improves recognition of CVS and expedites treatment in the emergency department.

Functional Vomiting

The Rome III diagnostic criteria for functional vomiting include: one or more episodes of vomiting per week, absence of an eating disorder, rumination or major psychiatric disorder, and absence of self-induced vomiting, central nervous system or metabolic disorders or chronic marijuana use. These criteria need to be fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis [40]. Children and adolescents who present with intermittent vomiting typically describe vomiting only once per incident, with the vomiting occurring prior to or during exciting or stressful events such as competitive athletic meets, exams, performances, vacations, and holiday parties. Functional impairment in youth with this intermittent vomiting pattern is significantly less than that described for CVS; however, these children can be sent home from school or miss activities due to concerns about infectious illness. There is sparse literature on this condition in children, and the authors' clinical experience with these youth is that comorbid anxiety symptoms are often present but do not meet criteria for a psychiatric diagnosis. Clinically, these children have responded to cognitive and behavioral intervention focused on lowering arousal during times of anticipated stress (cognitive restructuring, biofeedback-assisted relaxation training). No treatment

literature exists for the behavioral management of this condition in children and there is no evidence that psychotropic medications are particularly useful for this condition.

Nausea

Approach to Chronic Nausea

Nausea is a common symptom with a prevalence of up to 10 % in otherwise healthy adolescents in the community [41]. It is often a difficult symptom to define and locate. It is usually described as a sense of queasiness often perceived in anticipation of imminent vomiting. While patients most notably localize their nausea in the epigastrium, other regions such as the head, throat, or lower abdominal may be considered the predominant site. This heterogeneous presentation underscores the need for a thorough assessment elaborating on the quality, duration, location, and associated symptoms related to the nausea.

When nausea is chronic and unexplained, the patient's and family's daily activities are often profoundly disrupted with loss in quality of life. The origin of nausea is often difficult to define objectively due to multifactorial causes with precipitating triggers and mechanisms not well described. Thus, it is imperative for the general clinician as well as for specialists to take a comprehensive history and perform a detailed examination for considerations both within and outside the GI tract. Oftentimes, when routine diagnostic testing fails to identify a cause for the nausea, patients are generally treated with empiric therapy in an attempt to alleviate their symptoms.

There are no specific diagnostic criteria for chronic idiopathic nausea in children, necessitating the use of adult criteria as defined by the Rome III definitions of functional gastrointestinal disorders. Chronic idiopathic nausea is diagnosed when there is a report of bothersome nausea, occurring at least several times per week, not typically associated with vomiting, in the absence of medical abnormalities that would explain the nausea (e.g., peptic ulcer disease, gastritis, celiac disease, delayed gastric emptying). These criteria need to be fulfilled for the past 3 months, with symptom onset at least 6 months prior to diagnosis [40]. This condition has received little attention in pediatrics until recently. Kovacic et al. [42] compared medical records of children seen in a pediatric GI clinic that had nausea as a primary complaint to youth with functional abdominal pain and associated nausea. The former group was significantly more likely to be Caucasian adolescent females with severe daily nausea that peaks in the morning. The nausea was of sufficient intensity to interfere with daily activities, including school.

Comorbidities Associated with Nausea

The medical comorbidities in youth with chronic nausea are diverse once again supporting the complex nature of the mechanisms underlying these symptoms. Common comorbidities include migraines (62 %), family history of migraines (71 %), postural orthostatic tachycardia syndrome (36 %), and cyclic vomiting syndrome (27 %) [42]. Children presenting with chronic nausea as a primary complaint compared to those with abdominal pain and nausea, have been found to have more comorbid symptoms such as anxiety, dizziness, and fatigue [42]. Chronic nausea has also been found in youth with orthostatic intolerance (i.e., symptoms made worse upon standing and improve with recumbence) [43–45].

Psychiatric and Psychological Aspects of Nausea

There is limited literature on psychiatric comorbidity in children with nausea. Pediatric subjects presenting with chronic nausea as a primary complaint, compared to those with abdominal pain and nausea, have been found to have more symptoms of anxiety and to have greater functional disability [42]. Nausea is also a common symptom in pediatric patients with POTS, CVS, Systemic exertional intolerance disease (SEID)

(formally Known as myalgic encephalomyelitis/chronic fatigue syndrome), and functional abdominal pain [6, 20, 46], and these youth are reported to have an increased prevalence of anxiety symptoms. [29, 47–50]. Furthermore, in adolescents with orthostatic intolerance, nausea has been found to be significantly associated with both state and trait anxiety symptoms [43]. Explanations for the relationships among anxiety and nausea symptoms have not been established in these conditions, although there is preliminary research suggesting that the perception of intense nausea leads to activation of brain areas involved in the processing of fear conditioning [51]. Napadow et al. also found that increases in nausea were associated with enhanced interoceptive awareness of the stomach, and it is known that individuals with anxiety are hypervigilant of and differentially attend to interoceptive sensory information [52]. Nausea is also one of the most common symptoms of panic disorder in adolescents [53]. Panic is the only anxiety disorder to include nausea as a diagnostic criterion [54]. Although the presence of nausea is clinically observed in children and adolescents with generalized anxiety and fear-based anxiety disorders such as phobias and social anxiety, there is no mention of nausea as a comorbidity or as a diagnostic criterion for other anxiety disorders.

Nausea and the Autonomic Nervous System

Dysautonomia manifesting as orthostatic intolerance is found in nearly 500,000 Americans with approximately 15 % of all children experiencing syncope before the end of adolescence [41, 55]. There is increasing recognition that autonomic disorders such as POTS are frequently associated with GI complaints including nausea, abdominal pain, and constipation [56]. For example, in subjects with functional dyspepsia, increased sympathetic nervous system reactivity was associated with higher nausea scores, and those with decreased parasympathetic flexibility demonstrated a higher incidence of tachygastria on electrogastrogram (EGG) [57]. In pediatric patients with POTS, abnormal gastric myoelectrical activity has been observed during head-upright tilt (HUT) table testing compared to those without POTS [58]. In addition, for pediatric subjects with chronic upper GI complaints and reported orthostatic symptoms such as dizziness, 42 % exhibited reproducible GI systems when challenged with HUT [59].

In one pediatric study, diagnostic workup for chronic idiopathic nausea revealed underlying cardiovascular instability manifesting primarily as postural orthostatic tachycardia syndrome (POTS) in 68 % of subjects [45]. When a similar cohort of subjects was treated with fludrocortisone for their orthostatic symptoms, nausea, abdominal pain, and dizziness improved by over 30 %, and school attendance improved by 44 % [44]. Despite the close link between the autonomic nervous system and gastrointestinal symptoms and motility, determining the presence of dysautonomia symptoms is not part of routine GI clinical assessment.

Autonomic abnormalities, especially neurally mediated syncope and POTS, are also highly prevalent in adolescents with ME/CFS where nausea is common [60]. Nausea is particularly prevalent in those with a migrainous phenotype [47]. Studies of heart rate variability in SEID have found sympathetic predominance of heart rate control, with increased vagal withdrawal during orthostatic stress [61, 62]. Nausea has also been found to be negatively associated with heart rate variability in a sample of adolescents with a primary complaint of chronic nausea [43].

Assessment of Nausea in Pediatric Patients

Patients with chronic nausea very often undergo extensive and, at times, invasive diagnostic testing to determine a source for their symptom. The majority of these subjects demonstrate unrevealing laboratory, radiographic, endoscopic, and sometimes surgical assessment [42]. These findings suggest that an extensive diagnostic workup may not be indicated in these patients. Instead, a meticulous clinical history including family

history as well as a detailed physical examination, which should also consist of a brief neurological and psychological assessment may help better elucidate the origins of a patient's nausea. "Red flags" identified during, history taking including bilious or bloody emesis, malnutrition, morning headaches, or other focal neurological signs do warrant further investigation. However, under these circumstances, the differential diagnosis is generally more objective, thereby, prompting a more focused diagnostic strategy.

Symptom Questionnaires

In keeping with the tenet that history is the crucial component to defining the causes underlying nausea, it is the opinion of the authors that a clinical model integrating one or more disciplines in the initial evaluation of patients is optimal when feasible. Furthermore, in order to consistently obtain categorical data from subjects, the use of symptom questionnaires can be very useful particularly if administered before the clinic visit.

Self-Report of Nausea
Few scales have been validated for assessing nausea and vomiting in children and adolescents. A pictorial nausea intensity rating scale developed for children ages 7–18 has preliminary evidence of validity [63]. The Nausea Profile, a 17-item scale for the assessment of the somatic, gastrointestinal, and emotional dimensions of nausea developed for use in adults [64] has demonstrated internal reliability in a sample of adolescents [43], but its validity has not yet been established in the pediatric population. The frequency and intensity of the nausea and/or vomiting episodes can be assessed by paper or electronic symptom diaries similar to those used for children with chronic pain [65]. These scales can be used to facilitate standard assessment of nausea symptoms and treatment response in children.

Symptom Impact
As chronic nausea and vomiting can be debilitating for the pediatric patient, assessment of functional disability and health-related quality of life can provide useful information about the impact of such symptoms on the child, and family, as well as assess treatment impact. The Functional Disability Inventory is a validated scale to assess the impact of somatic symptoms on child functioning [66]. A quality of life scale such as the PedsQL™ can be used to assess the impact of illness across physical, psychosocial, and school domains and provides a general assessment of overall of quality of life [67].

Psychiatric Comorbidity
Due to the prevalence of psychiatric comorbidity in disorders where nausea and vomiting are prominent symptoms, it may be prudent to assess for such psychiatric comorbidity to optimize treatment. There are several brief mental health screeners, including the Revised Child Anxiety and Depression Scale (RCADS) [68] and the Screen for Anxiety-Related Emotional Disorders (SCARED) [69] that are available in the public domain. These scales can be completed by parents and children and scored in a few minutes, making them feasible for use in the medical setting.

Role of Electrogastrogram and Head-Upright Tilt (HUT) Test

As previously discussed, the etiology of chronic nausea can often be determined with a thorough history and physical examination as well as the use of symptom questionnaires to better define both primary and comorbid symptoms. While orthostatic intolerance is a clinical symptom, which can be identified by history, the significance between the relationship of cardiovascular and gastrointestinal symptoms during orthostatic challenge is unclear. Recently, it has been shown that distinct neurohumoral profiles such as changes in catecholamine and vasopressin levels may exist in children, which are related to the specific type of cardiovascular response elicited on HUT [70]. The impact of these neurohumoral changes on gastric myoelectrical activity and nausea requires further study. In light of previous

studies in which HUT provocation was associated with GI symptoms [59] and EGG changes [58], the HUT and EGG may serve as future biomarkers toward defining the phenotype of chronic nausea and orthostatic intolerance. The noninvasive nature of both these diagnostic tests may increase their feasibility in a pediatric population.

Treatment Strategies for Nausea

Drugs

Due to its poorly understood etiology, treatments for chronic nausea are empirical and often ineffective. This is likely attributed to the existence of multiple mechanisms involved in causing nausea. For this reason, traditional antiemetic agents such as ondansetron, a serotonin 5-HT_3 antagonist, while effective for acute nausea from chemotherapy and postoperative anesthesia, tend to have little impact in chronic nausea [48, 71]. Tricyclic antidepressants in lower dosages have also been used to a variety of function gastrointestinal disorders including chronic abdominal pain and cyclic vomiting syndrome. A recent retrospective review demonstrated at least 50 % improvement when pediatric subjects with chronic nausea were treated with amitriptyline, but this response was only observed in 44 % of subjects studied. Prospective placebo-controlled trials are needed to objectively determine the impact of these drugs in the treatment of chronic nausea.

The use of herbal drugs such as ginger (*Zingiber officinale Roscoe*), which target muscarinic M_3 receptors and both 5-HT_3 and 5-HT_4 receptors have been shown to be somewhat effective for pregnancy-associated nausea and chemotherapy, but only modestly helpful for chronic nausea [72]. Furthermore, in the advent of increased legalization, marijuana is becoming increasingly available for treatment of a variety of medical conditions including severe nausea [73]. However, there still remains very little evidence to support its use particularly in pediatrics.

When assessment of a patient's nausea reveals other clinical features such as orthostatic intolerance, focusing on treatment of these coexisting symptoms may result in mitigating the nausea itself. For conditions such as POTS, both nonpharmacologic and pharmacologic treatment strategies alone or in combination may be effective in treating the orthostatic symptoms. These include cardiovascular and upper/lower extremity conditioning exercises as well as increasing fluid and salt intake. Pharmacologic treatment should be individualized and may be guided both by characteristics of symptoms as well as specific response to HUT [74]. Common drugs used include mineralocorticoid agents (e.g., fludrocortisone) to increase blood volume, β-blocking agents to blunt tachycardia associated with orthostasis, and α-adrenergic agents, which increase peripheral vascular resistance. Effective treatment of orthostatic intolerance as the primary condition has been associated with improvement in what may be considered secondary GI symptoms [44].

Psychological Treatments

Literature on the psychological treatment of these conditions is very limited. One case report describes the successful treatment of CVS in an adolescent resulting in a durable improvement in symptoms [75]. The intervention included: (a) education on the association between psychological stress and episodes; (b) identification of modifiable triggers for episodes, such as decreased sleep; (c) cognitive restructuring to address anticipatory anxiety related to vomiting attacks and beliefs related to control of symptoms; (d) biofeedback-assisted relaxation training to address sympathetic arousal; and (e) parent training to coach the child in the use of self-management skills. Psychological treatment for youth with CVS that combines the evidence-based techniques used for the behavioral treatment of pediatric headache [76] and the cognitive-behavioral methods for treating anxiety and depression in children and adolescents [77–79] may best meet the needs of these medically and psychiatrically vulnerable youth.

No evidence-based psychological treatments have been developed for the management of idiopathic nausea and functional vomiting; however, emerging treatments for the management of CVS and other disorders where nausea can be a prominent symptom such as POTS may be considered for idiopathic nausea and vomiting, given similarities in hypothesized etiology (autonomic dysfunction, migraine) and comorbid anxiety [80]. As an example, the lifestyle recommendations for increasing fluid intake, improving exercise tolerance, regular meals and snacks, and sleep hygiene have been applied to youth with autonomic dysfunction as well as those with migraine headaches [46, 81, 82]. These lifestyle changes can be difficult for youth who are debilitated by their nausea and vomiting symptoms, and thus consultation with a pediatric psychologist may be helpful in assisting with implementation of the recommendations.

Surgical Intervention

Despite efforts to avoid invasive treatment approaches for children with chronic nausea, it is sometimes unavoidable as nausea in addition to other functional GI disorders are often refractory to both pharmacologic treatment and psychological intervention. Children with intractable nausea are frequently underweight, putting them at risk for malnutrition. Under these circumstances, consideration must be given to placement of short-term enteral access catheters including nasogastric or nasojejunal tubes as well as more permanent conduits such as gastrostomy or jejunostomy tubes to provide adequate caloric intake. Under more serious conditions, some patient may require administration of parenteral nutrition. The use of permanent gastric electrical stimulation remains a relatively new approach in the treatment of nausea more commonly utilized in the context of underlying gastroparesis [83]. A recent study in children demonstrated success in the treatment of children with medically refractory nausea and vomiting meeting Rome III criteria for functional dyspepsia using an implantable gastric electrical stimulator [84]. The long-term safety and efficacy of the gastric electrical stimulator device requires further study.

Conclusions

Vomiting and nausea disorders in pediatric patients are conditions with significant medical and psychosocial morbidity. These disorders often involve extensive medical care utilization that may or may not improve the symptoms of these disorders and expose these children to the risk of iatrogenic complications. Research and clinical care of these disorders are hindered by the lack of pediatric diagnostic criteria. Nausea in particular is a symptom that often is overlooked in clinical encounters unless it is presented as a primary complaint, further reducing opportunities to understand and treat this highly prevalent and aversive symptom. Given the significant functional impairment associated with idiopathic nausea and vomiting, the establishment of pediatric diagnostic criteria for these disorders will facilitate efforts to develop an evidence base for both medical and behavioral interventions for these conditions. Interdisciplinary teams may be the best suited to optimize the treatment of vomiting and nausea disorders in children, given the significant comorbidities found in these conditions. A biospychosocial model of care likely has the greatest potential to improve health-care outcomes, reduce health-care utilization, and improve the patient and family experience for these highly aversive and disabling conditions.

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The Psychophysiology of Nausea

14

Max E. Levine

Introduction

Nausea is a debilitating and decidedly aversive subjective experience. Despite the fact that people use different terms to describe the sensation, and refer to a wide range of physiological signs and symptoms in its context, it seems clear that everyone knows from personal experience exactly what it feels like. After all, nausea serves a tremendous adaptive function for most of those who suffer from it; it warns us that we have ingested something potentially dangerous, or that we have been infected by an antigen or toxin, and that we should probably stop eating. That nausea usually precedes vomiting is understandable for the same adaptive reasons. With regard to conditioned taste aversion, nausea reminds us to avoid whatever food has been ingested recently when the opportunity presents itself again in the future. Like pain, nausea is entirely unpleasant, but protects us from additional harm. It should come as no surprise, therefore, that nausea is a regular occurrence for millions of people around the world.

Given how common nausea is, one might rationally assume that a comprehensive understanding of its causes, effects, and characteristics already exists; this is unfortunately not the case. Though a great deal of ambitious scientific explorations of the phenomenon of nausea have been conducted, including assessments of various treatment strategies, we continue to struggle to explain the physiological aspects of nausea, not to mention the psychosocial influences on its incidence and severity. Such an understanding is essential, of course, for the development of successful interventions for those who struggle with severe nausea on a daily basis, for whom nausea no longer serves an adaptive purpose.

Differential Susceptibility to Nausea

That all people are strongly motivated to avoid its onset or diminish its severity is unquestionable, yet some unfortunate individuals appear to be particularly prone to the development of nausea in a variety of evocative contexts. Some appear to be more sensitive to perceptions of disgust [1], for example, whereas the stomachs of others seem to be more vulnerable to the presence of toxins, or to the effects of pathological conditions that are ultimately diagnosed as functional gastrointestinal disorders [2]. Cancer patients undergoing chemotherapy exhibit a wide range of nausea responses [3], and while the nausea experienced by pregnant women is much more common and intense than many might otherwise believe [4], their experiences are considerably variable as well. The nausea of motion sickness,

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which is thought to result from a sensory mismatch that is mistakenly interpreted as the result of an ingested toxin [5], is a condition that is well known for the individual differences with which it is experienced. For instance, nausea and other symptoms of motion sickness are typically experienced by only 50% of healthy people exposed to a rotating optokinetic drum [6]. Individuals who are susceptible to nausea evoked in one context tend to be susceptible to nausea evoked in others, suggesting that their thresholds for nausea are consistent across a variety of nauseogenic settings (e.g., [7]).

Many theories have been advanced to explain differential susceptibility to nausea, and several factors have been proposed to mediate differences both between individuals and within one person from one point in time to another, in terms of their thresholds for nausea. Stern [8] proposed the idea of a "dynamic nausea threshold" that is determined by both stable, inherent characteristics such as age, gender, and race, and more variable, conditional factors such as anxiety, expectation, and recent experience. Inter- and intra-individual differences also exist in terms of physiological responses to nauseogenic stimuli. Variations in autonomic nervous system responsivity, the development of gastric dysrhythmia, and increases in plasma vasopressin may very well underlie differences in subjective reports of nausea symptoms.

Nausea, like pain and other aversive subjective conditions, appears to be a function of a complex interaction of physiological states, individuals' perceptions or interpretations of those states, and psychological variables [8]. In order to develop a valid and comprehensive theory to improve our understanding of the causes of nausea, to account for differential susceptibility to nausea, and to provide effective relief to individuals suffering from nausea, each of these factors and their interactions with each other must therefore be carefully considered. Such an endeavor certainly has been, and will continue to be a significant and challenging one, but one that must be undertaken in light of the universality of nausea, and the absence of consistently effective therapeutic strategies.

Studying Nausea from a Psychophysiological Perspective

A psychophysiological approach to studying nausea offers the unique opportunity to explore the interacting influences of psychosocial, behavioral, and physiological factors on the development and intensity of nausea symptoms. Consideration of the multitude of influences on nausea that relate to psychophysiological mechanisms underlying its incidence may be critical to effectively managing this debilitating condition. A complicating matter is that it is not necessarily that one's thoughts, emotions, and motivations directly affect physiological functions that underlie nausea, nor is it certain that the physiological factors that have been implicated have an influence on subjective perceptions of symptoms, but understanding the interaction of the two may provide invaluable insight into this elusive phenomenon.

The observation that nausea is often reported by individuals experiencing stress and anxiety emphasizes the importance of considering the psychophysiology of nausea. The physiological stress response is marked by a pattern of autonomic nervous system (ANS) activation that involves increased sympathetic nervous system (SNS) activity, and decreased parasympathetic nervous system (PNS) activity. This response profile is regarded as adaptive given that it facilitates an immediate fight-or-flight response to a threatening situation, in part by diverting energy to exercising muscle including the heart, and away from expensive, long-term maintenance functions like digestion. The response becomes maladaptive, however, when activated repeatedly or over long periods of time, since the stomach and other significant organs do not receive an adequate supply of energy to perform their essential functions properly. Neglect of the gastrointestinal system during stress and anxiety is thought to give rise to sensations of nausea [9]. The direct physiological effect of ANS responses to stress and anxiety on the stomach is the reduction or complete termination of gastric motor activity, and the introduction of gastric dysrhythmias [10]. This pattern of autonomic and gastric

myoelectrical response to psychological stress is identical to the one observed in patients experiencing chemotherapy-induced nausea [11], the nausea of pregnancy [12], and the nausea of motion sickness [6]. Psychosocial events, therefore, appear to have the capacity to induce the same physiological changes and corresponding subjective symptoms as those induced by more biomedical circumstances. The aim of psychophysiological explorations of nausea is to consider the interactive effects of both biomedical and psychosocial influences in an effort to develop a more comprehensive, biopsychosocial model of nausea.

Physiological Factors in the Development of Nausea

Psychophysiological research generally involves the noninvasive assessment of the ongoing function of various organ systems through the evaluation of electrical signals received at the surface of the skin, and relating those signals to some aspect of cognition, emotion, or subjective experience. As manipulations are employed, the effects of them can be ascertained in terms of physiology, psychology, and their interaction. For studying the psychophysiology of nausea, attention has primarily been focused on the activity of the stomach, cardiovascular system, respiratory system, and eccrine sweat glands as it relates to the experience of symptoms. Thanks to a number of significant efforts to identify potential pathophysiological mechanisms underlying nausea, data are now available to begin to formulate ideas about how this subjective experience is physiologically mediated [13]. Evidence from gastric neuromuscular studies, in particular, has permitted the advancement of theories relating gastric dysrhythmia to the development of nausea [14]. Other studies have attempted to correlate endocrine and ANS responses to the experience of the same symptoms (e.g., [10, 15]). More recently, patterns of brain activation during the experience of nausea have been explored as well (e.g., [16]).

One approach to understanding the pathophysiological mechanisms of nausea is to consider what differentiates susceptible individuals from those who tend to remain free of symptoms despite exposure to the same stimulation. A compelling case has been made that an individual's response to a nauseogenic stimulus may be influenced by both prestimulus (baseline or resting) physiological levels and by physiological reactions to that stimulus (e.g., [17–19]). Although researchers have been unable to establish a purely physiological profile that unmistakably characterizes variations, either within individuals or between them, in susceptibility to nausea, it may simply be that the precise pattern of physiological activity that represents nausea remains to be revealed. It is perhaps even more likely that until psychosocial and behavioral influences on nausea and their interactions with physiological responses are considered, we will continue to fall short of satisfactorily explaining and successfully managing nausea.

Nausea and Gastric Dysrhythmias

Nausea has consistently been observed to be accompanied by gastric dysrhythmias (e.g., [20]). Such observations have led researchers to suggest that disturbed gastric neuromuscular function may play a causal role in the development of nausea. While it is reasonable to suspect that gastric dysrhythmias give rise to subjective experiences of nausea, studies of this concurrence have been largely correlational in nature, and therefore unable to establish direct cause-and-effect relationships. Studies in which gastric neuromuscular activity is experimentally manipulated, and the effects on reports of nausea are observed, are needed to improve our understanding of this relationship.

The electrogastrogram (EGG) has been extremely useful as a physiological marker for the subjective experience of nausea [21]. By monitoring and later analyzing the EGG of participants exposed to nauseogenic stimulation, the relative severity of the nausea that a participant experiences may be inferred. Although the

strength of the correlation between subjective reports of nausea and the EGG is not perfect, the relationship is a highly significant one, and should be regarded as noteworthy given the variable nature of the subjective interpretation of sensations arising from the viscera [22]. When experimental groups can be distinguished on the basis of the severity of their nausea, they typically can be distinguished by their EGGs as well (e.g., [23–25]).

In contrast to other intrusive methods of measuring gastrointestinal system activity, the cutaneous EGG is a noninvasive method of recording the electrical activity of the stomach. Three electrodes are placed on the surface of the skin over the abdomen. The electrodes record signals from the muscular walls of the stomach that reflect gastric myoelectrical activity [26]. The frequency of the EGG signal is identical to the frequency of the contractions of the stomach when they occur [27]. The frequency of the EGG is also identical when it is recorded from the serosal surface of the stomach as when it is recorded cutaneously. Recording from the surface of the skin rather than from the serosa of the stomach allows for the collection of reliable, accurate, physiological data using a painless, noninvasive procedure.

Through spectral analysis, the EGG signal is broken down into its component frequencies and power values are assigned to each of the frequency ranges of interest of gastric myoelectrical activity. In healthy humans, the stomach normally contracts approximately three times every minute; the EGG signal that reflects this normal, "slow wave" gastric activity is generally referred to as three cycles per minute (3 cpm). During nausea, the frequency of the EGG signal typically increases to approximately four to nine cycles per minute (4–9 cpm), and generally becomes dysrhythmic. This abnormal dysrhythmia is referred to as gastric tachyarrhythmia, and is directly related to the severity of nausea reported by participants exposed to a rotating drum [22, 26].

Most studies conducted with a motion sickness simulator have yielded similar associations between subjective reports of nausea and the EGG (e.g., [28, 29]). However, dissociation of the electrical activity of the stomach from the subjective experience of nausea has occasionally been observed, particularly when pharmacological agents are introduced. For example, Levine et al. [30] examined the effect of serotonin (5-HT_3) receptor-antagonist antiemetics on gastric tachyarrhythmia, nausea, and the symptoms of motion sickness. While these drugs, especially granisetron, prevented the development of gastric tachyarrhythmia during exposure to the rotating drum, they did not prevent the development of the subjective experience of nausea. Some participants experienced nausea in the absence of abnormal dysrhythmias in the stomach. It was apparent from these results that there are multiple pathways for the development of nausea, and that gastric tachyarrhythmia is not absolutely necessary for the development of nausea. Stern et al. [31] also found a dissociation between gastric tachyarrhythmia and subjective reports of nausea while studying the effects of phenytoin on nausea and motion sickness. The possibility was raised that reluctance to admit symptoms and response biases may have produced such a dissociation. It may also be that a certain threshold of difference in gastric tachyarrhythmia between experimental groups must be reached in order for concomitant differences in subjective symptoms to be observed. Whatever the case may be, it is clear that the association between gastric tachyarrhythmia and nausea is a complex and intriguing one.

There are, of course, many more stimuli than provocative motion that are capable of eliciting nausea. The nausea of motion sickness can be presumed to reflect the recognition of a sensory mismatch in the central nervous system, while the nausea of pregnancy is more likely to be due to hormonal variations [13]. Cancer chemotherapy-induced nausea is likely a consequence of the presence of toxins in the bloodstream, and nausea reported by patients with one of the many gastrointestinal diseases in which it is a common symptom (e.g., functional dyspepsia) may be a more direct effect of neuromuscular disorders of the stomach [32]. The critical neural or hormonal mechanisms that underlie the development of these different forms of nausea probably vary according to the nature of the nauseogenic stimulus. The one unifying theme of all of these forms of nausea is

that each tends to be accompanied by gastric dysrhythmias. Where in the causal pathway between a nauseogenic stimulus and reports of nausea these dysrhythmias fit remains poorly understood.

Nausea is reported by approximately 80 % of women during the first trimester of pregnancy, with the severity of nausea varying from mild nausea to hyperemesis gravidarum, the latter of which generally requires hospitalization [15]. Gastric dysrhythmias have been documented in women reporting nausea during pregnancy [33], and interventions that have effectively reduced the nausea of pregnancy have also reduced the presence of gastric dysrhythmias [34]. The physiological basis for the development of gastric dysrhythmia and the accompanying nausea during pregnancy deserves considerably more attention.

Dysrhythmic gastric myoelectrical activity has also been exhibited by cancer patients who experienced nausea after a chemotherapy treatment [35, 11]. Interestingly, the presence of gastric dysrhythmia before treatment begins is most predictive of nausea reported after the treatment ends. Statistically significant differences in the presence of gastric dysrhythmias between patients with and without nausea after their chemotherapy treatment have not been observed.

Patients with functional dyspepsia often exhibit gastric dysrhythmias [2], as do patients with other gastrointestinal diseases like gastroparesis (diabetic and idiopathic). These dysrhythmias are thought to contribute not only to symptoms of nausea, but also to early satiety, fullness, bloating, and abdominal discomfort. Drugs like metoclopromide that are given to treat dyspepsia symptoms appear to do so, at least in part, by reducing gastric dysrhythmias [14]. This body of evidence makes a strong case for the importance of gastric dysrhythmias in the pathophysiology of nausea in various contexts.

Nausea and the Autonomic Nervous System

Interest in the treatment, prevention, and general understanding of the phenomenon of nausea has led psychophysiologists to consider the involvement of the ANS. Measures of ANS activity, particularly the parasympathetic branch, have been linked to both risk for development, and subsequent severity of nausea and motion sickness symptoms during exposure to a rotating drum (e.g., [18, 28]). Vagal withdrawal (loss of parasympathetic activation) and increased SNS activation have been shown to accompany the development of nausea.

Hu et al. [18] examined several physiological correlates of nausea, and the extent to which they change as an individual experiences adaptation to motion sickness. Heart rate variability (HRV) is an estimate of autonomic activation that is derived from the electrocardiogram (EKG). Unlike heart rate, which is determined by both branches of the ANS [36], HRV is a rough index of PNS activation [37]. Conversely, skin conductance level (SCL), or electrodermal activity, can be used to assess SNS activation since it is predominantly mediated by sympathetic cholinergic innervation [38]. Hu et al. [18] demonstrated significantly greater increases in both gastric tachyarrhythmia and SCL among participants who developed nausea. Additionally, HRV decreased significantly more in participants who experienced nausea.

The changes in individuals' physiological profiles as they adapt to motion sickness offer additional insight. In the same study, increases in gastric tachyarrhythmia and SCL during exposure to the rotating drum became significantly attenuated with repeated exposures, as did reports of nausea [18]. Decreases in HRV also became significantly smaller with each exposure. Given that these changes accompanied decreases in nausea, these data seem to indicate that adaptation to motion sickness is accompanied by a recovery of autonomic balance.

Uijtdehaage et al. [39] examined the effects of eating a meal on nausea, gastric myoelectrical activity, and autonomic responses. Cardiac vagal tone was assessed by respiratory sinus arrhythmia (RSA), which is a more accurate index of PNS activation at the level of the heart than heart rate or other measures of cardiovascular function [40]. Subjective reports of nausea were significantly less severe among participants who received a

meal prior to exposure to a rotating drum than among participants who did not. This difference was accompanied by significantly greater RSA and significantly less gastric tachyarrhythmia during drum exposure among fed than nonfed participants. When all participants were collapsed across groups, significant negative correlations were observed between RSA and gastric tachyarrhythmia, and between RSA and reports of nausea. The implications of these results are that increased gastric tachyarrhythmia and nausea are accompanied by cardiac vagal withdrawal, or decreased PNS activation. Increased vagal tone, therefore, might be advantageous for reducing or preventing nausea and its dysrhythmic gastric underpinnings.

Levine et al. [41] provided additional support for the theory that vagal tone possesses a relationship with susceptibility to the development of nausea. Participants were fed either a protein-predominant meal, a carbohydrate meal, or nothing immediately before exposure to a rotating drum. Participants in the protein condition developed the least severe symptoms of nausea and motion sickness. Not only did they exhibit less gastric tachyarrhythmia during drum rotation, but they also displayed greater estimates of RSA during a post-meal baseline. In another study, Gianaros et al. [10] found that baseline RSA values were negatively associated with nausea developed during exposure to a rotating drum. These data suggest that having greater PNS activation before being exposed to provocative motion might offer protection from the development of nausea and gastric tachyarrhythmia.

Based on the studies mentioned so far, a somewhat consistent picture of the autonomic correlates of the nausea of motion sickness begins to emerge. It seems nausea is more likely to develop when vagal withdrawal occurs, and/or when SNS activation increases. However, this impression is called into question by the fact that scopolamine, a potent anti-motion sickness agent, is a muscarinic anticholinergic drug. Therefore, it can be considered a PNS antagonist. However, since scopolamine has been shown to increase cardiac vagal tone and induce bradycardia, it has been reasoned that scopolamine may stimulate vagal motor nuclei in the central nervous system, the effect of which overrides scopolamine's anticholinergic effects in the periphery.

Uijtdehaage et al. [28] systematically investigated the effects of scopolamine on ANS profiles underlying nausea and motion sickness susceptibility. Participants who received scopolamine experienced significantly less nausea than did participants who received placebo. In addition, RSA was significantly higher, and gastric tachyarrhythmia was significantly lower among scopolamine group participants during exposure to the rotating drum than among placebo group participants. Once again, increased cardiac vagal tone was found to be associated with less severe nausea and less gastric tachyarrhythmia among participants in both groups. It appears again from these results that higher vagal tone prior to drum rotation (possibly aided by the administration of scopolamine) offers protection from nausea and motion sickness by initiating a pattern of gastric myoelectrical stability.

The counterintuitive observation that scopolamine, presumably a PNS antagonist, protects individuals from the development of nausea and motion sickness while motion sickness symptoms are frequently accompanied by decreases in vagal tone was further explored by Hasler et al. [42]. The effects of various pharmacological agents with different influences over the ANS on gastric dysrhythmias and the nausea of motion sickness were examined. The only agents that were found to reduce gastric dysrhythmias and nausea provoked by a rotating drum were atropine, a primarily central muscarinic-anticholinergic agent, and phentolamine, an α-adrenergic antagonist. Neither methscopolamine, a primarily peripheral muscarinic-anticholinergic, nor propanalol, a β-adrenergic antagonist, had any effect on dysrhythmias or nausea. The authors concluded that central cholinergic pathways are mediators of dysrhythmias, with additional modulation by α-adrenergic neural pathways. Given that atropine acts primarily as a central anticholinergic, and like scopolamine, also reduced nausea and gastric dysrhythmias, it seems unlikely on the basis of these results that scopolamine acts by exerting a central excitatory effect on vagal efferents that overrides its peripheral anticholinergic effects. The suggestion has been made, instead, that the

prevention of vagal withdrawal is accomplished by blocking PNS activation, and that this action may be at the heart of anti-motion sickness agents' effectiveness. A reasonable explanation of these findings and a satisfactory solution to this enigma remains to be achieved.

The evidence discussed thus far suggests that the prevention of vagal withdrawal during exposure to a nauseogenic stimulus, and/or high vagal tone prior to exposure to the stimulus offer protection from the development of nausea. The employment of manipulations that increase vagal tone, or make vagal withdrawal less likely, should therefore be helpful for people exposed to a rotating drum. Uijtdehaage et al. [39] and Levine et al. [41] demonstrated support for this reasoning with the effects of the presentation of a meal to participants before entering a rotating drum. Levine and Stern [43] extended the exploration of this hypothesis by testing the effects of facial cooling, which increases PNS activation, on gastric tachyarrhythmia, nausea, and the symptoms of motion sickness. Gastric tachyarrhythmia increased significantly with exposure to the rotating drum only in participants without facial cooling. Maintaining or augmenting vagal tone appears again to offer protection from the development of nausea and gastric dysrhythmias.

The contribution of the ANS to the pathophysiology of chemotherapy-induced nausea has also been investigated. The development of nausea either in anticipation of, or during recovery from chemotherapy treatment has been demonstrated to be associated with baseline autonomic activity and autonomic reactivity to the treatment [44]. HRV increased in cancer patients who experienced nausea as the chemotherapy agent was infused, but then began to decrease before the nausea was actually reported. Clearly, more research in this area is needed to determine the nature of autonomic contributions to the development of nausea.

Nausea and the Endocrine System

Far less research on hormonal influences on nausea has been conducted than on gastric myoelectrical and autonomic influences. Vasopressin, however, is one hormone that has received considerable attention (e.g., [15, 19, 45]). Plasma vasopressin levels correlate positively with the intensity of nausea reported during exposure to provocative motion. In what were reported as carefully timed studies, the appearance of gastric dysrhythmias preceded increases in vasopressin concentration, which coincided with the first reports of nausea. Revealing the temporal associations between reports of nausea and the appearance of these physiological markers allows for speculation concerning the causal relationships underlying the pathophysiology of nausea. However, until controlled experimental studies are carried out in which physiological responses are manipulated, and the effects of those manipulations on nausea are observed, an acceptable pathophysiological theory of nausea cannot be achieved. In one study of a small number of participants, infusions of very high levels of vasopressin were observed to induce reports of nausea and gastric dysrhythmias [46].

Hormones other than vasopressin may also be involved in the pathogenesis of nausea. The high frequency of reports of nausea during the first trimester of pregnancy implicates the involvement of pregnancy hormones such as human chorionic gonadotropin. Digestive hormones like cholecystokinin (CCK) are secreted in response to some foods more than others, and may explain variations in the extent to which certain foods induce nausea. More work in this area as well as in the exploration of gastric myoelectrical and autonomic influences on nausea desperately needs to be done in order to better appreciate the pathophysiology of nausea.

Nausea and the Central Nervous System

The recent integration of brain imaging approaches with psychophysiological recording is providing for a greater understanding of the neural bases of nausea and motion sickness

susceptibility. Results of one fMRI study demonstrated reports of nausea to be preceded by activation of brainstem and limbic regions (e.g., amygdala, putamen, and dorsal pons), and followed by changes in interoceptive, limbic, somatosensory, and cognitive networks (e.g., insular, anterior cingulate, orbitofrontal, somatosensory, and prefrontal cortices) [16]. Kim et al. [47] showed that nausea-related changes in visceromotor regions of the medial prefrontal cortex (ventromedial prefrontal cortex and perigenual anterior cingulate cortex) were associated with heart rate and HRV responses consistent with a pattern of increased sympathetic and decreased parasympathetic cardiac autonomic control.

In addition to functional brain imaging studies that have identified the neural correlates of nausea and associated changes in autonomic function, recent structural brain imaging studies are beginning to identify the morphological neural correlates of nausea susceptibility. For example, it has been shown with diffusion tensor imaging recently that decreased white matter integrity along the inferior fronto-occipital fasciculus predicts greater motion-induced nausea [48]. In sum, both functional and structural brain imaging studies that integrate psychophysiological recordings with experimental (e.g., motion sickness) paradigms are providing new insights into central nervous system contributions to nausea.

Psychosocial and Behavioral Influences on Nausea

Given the dynamic and inseparable relationship between the "mind," or higher-order cognitive and emotional processes, and the "body," or its physiological characteristics, one must consider psychosocial and behavioral influences on nausea in addition to pathophysiological factors in order to truly understand its incidence. The following discourse addresses the potential role of psychological factors, and evidence that suggests they are meaningful determinants of one's nausea experience.

Modeling Nausea with Motion Sickness

Identifying the influence of psychosocial and behavioral variables on nausea, and experimentally manipulating them at various levels can be challenging. In order to study both the subjective experience of nausea and the associated physiological changes in a controlled environment, useful methods of modeling nausea in the laboratory with motion sickness have been developed. A rotating optokinetic drum has been designed to effectively induce nausea and motion sickness in susceptible participants [26]. The rotating drum is a cylindrical chamber inside which a participant sits on a stationary stool (Fig. 14.1). The inside of the drum is covered with alternating black and white vertical stripes. The drum slowly rotates around the participant as the participant stares straight ahead at the vertical stripes passing through the field of view. Observing the motion

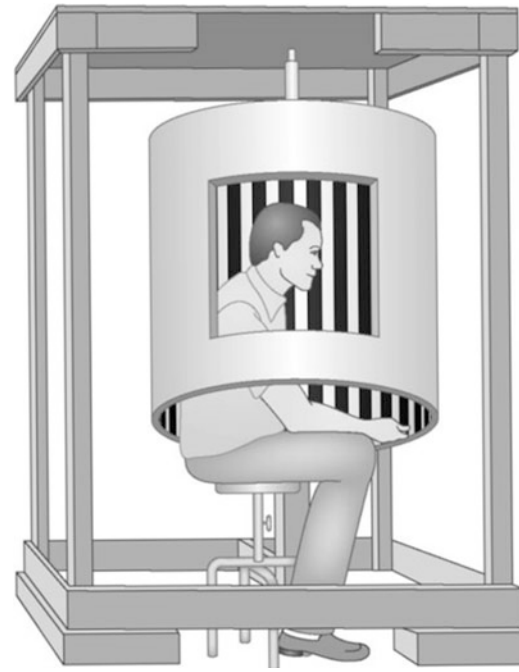

Fig. 14.1 The rotating optokinetic drum. The drum is a cylindrical chamber inside which participants sit on a stationary stool. The inside of the drum is lined with alternating black and white vertical stripes. As the drum rotates, it induces the illusion of self-motion, which is sufficient to elicit nausea in susceptible individuals

of the stripes induces the sensation of illusory self-motion. Participants consistently have the feeling that they are spinning on the stool in direction opposite the drum's rotation. For participants who are susceptible to motion sickness, this sensation is sufficient to evoke the discomforting symptoms of nausea [49].

The modeling of nausea through the use of the rotating drum offers a unique opportunity to examine the subjective and physiological aspects of nausea in otherwise healthy individuals. In most other studies of nausea, which often take place in hospital settings, there is the major obstacle of controlling for the effects of various concomitant illnesses or for the occurrence of emesis. Participants in many studies of nausea are patients receiving treatment for any of a number of conditions in which nausea is a major component. Of course, certain conditions, such as cancer, have profound physiological and psychological aspects aside from nausea; therefore, it is difficult to conclude that what is observed represents a phenomenon associated with nausea rather than an aspect of the coexisting illness, condition, or disorder. Studies of nausea that utilize healthy participants exposed to the rotating drum are not confounded with this problem.

Another drawback of many studies of nausea is that they combine nausea and vomiting into one behavioral and physiological entity. A common misunderstanding among many researchers is that vomiting simply represents an extreme point along the nausea continuum. Nausea and vomiting are certainly correlated; however, nausea is neither necessary nor sufficient for vomiting. Emesis sometimes occurs in the absence of nausea, and nausea is frequently not accompanied by vomiting. Nausea and vomiting also appear to have distinct neurophysiological profiles. Roscoe et al. [50] demonstrated that while cancer chemotherapy patients treated with serotonin receptor-antagonist antiemetics reported a significant reduction in posttreatment vomiting episodes, they did not experience a matching reduction in posttreatment nausea. In studies employing the rotating drum, nausea is induced, but emesis is avoided. Consequently, it can unequivocally be concluded that responses that are observed are not influenced by the emetic response.

Expectation/Anticipation

Perhaps nowhere else is the role of cognitive processes on the development of nausea more evident than in the context of expectations. Numerous observations have been made under a variety of nauseogenic circumstances of expectations' effects on the development of nausea, and on the physiological changes that accompany reports of symptoms. The dramatic impact of placebos on both symptoms and physiological function has been interpreted to be the effect of manipulation of one's expectations of the effect of a given treatment. It is important to emphasize that placebo effects are not simply matters of symptom perception; they are accompanied by measurable changes in physiological indices of health.

Response expectancy theory attributes the placebo effect to the forming of expectations that an ingested substance will produce both subjective and physiological changes in accordance with the supposed effect of that substance [51]. Response expectancy is defined as the anticipation of the occurrence of nonvolitional, automatic responses. For instance, if an individual expects a treatment to produce relief from pain or any other response that is not under that individual's direct control, the effect is much more likely to take place than if no such expectation exists. Individuals can learn to expect certain outcomes simply by listening to others' descriptions of a treatment to be administered or by observing the behavior of others who supposedly have experience with the treatment [52]. Kirsch suggested that the single-most influential determinant of the placebo response is one's expectation that some change in bodily state will be achieved through the administration of a placebo treatment.

Internal states such as mild nausea tend to be somewhat ambiguous, particularly during the early stages of their development. This ambiguity may underlie the strong association between response expectancy and involuntary, automatic

responses to stimuli [51]. A response expectancy may induce a perceptual set that is employed for the interpretation of ambiguous bodily sensations. Once an interpretation has been made that a set of vague physiological sensations is representative of the anticipated condition, an unspecified psychophysiological mechanism is initiated that produces the expected physical symptoms that otherwise may not have developed.

Several studies suggest expectations play a meaningful role in the development of nausea symptoms. Chemotherapy patients exhibit direct relationships between expectations for nausea before their first treatment and nausea that actually develops [53, 54]. In addition, patients who expect nausea side effects of the treatment report significantly more severe nausea than those who do not. Eden and Zuk [55] conducted a study of naval cadets undergoing training on rough seas that often promote the development of nausea and motion sickness. Those provided with a "verbal placebo" that they would not suffer from severe symptoms because of their psychological and physiological profiles developed significantly less nausea than those who were not.

Mearin et al. [56] administered placebos to patients with functional dyspepsia, a disorder marked by abdominal pain or discomfort centered in the upper abdomen and/or nausea, bloating, and early satiety following meal ingestion [13]. The condition lacks a substantiated structural or biochemical explanation but is often accompanied by disturbed gastric motility. After 8 weeks of placebo treatment, scores on a global symptom index were significantly reduced in 80 % of the patients. The reduction in symptoms was accompanied by a return of normal gastric motility. The placebo's effect on subjective symptoms could not, therefore, be attributed solely to a response bias. In a series of studies exploring the use of acustimulation for the management of nausea and gastric dysrhythmia, significant placebo effects were observed (e.g., [57]).

The idea that the placebo response represents a specific biological phenomenon is based on the assumption that mental experience can somehow affect physiology. According to Fields and Price [58], the administration of a placebo alters the interacting neural representations of memory, environmental context, and specific sensory stimuli. This aggregate of neural activity translates into a subjective experience that simultaneously affects physiology. Indeed, cognitive factors like attribution, belief, desire, motivation, and expectation may be potent mediators of the placebo response [59]. That placebo effects of greater magnitude are achieved by more believable and technically sophisticated agents seems to support this idea. For instance, placebo injections elicit greater placebo responses than placebo pills, and larger pills are associated with stronger placebo responses than smaller pills; the number of pills taken is also directly related to the magnitude of the placebo response [60]. Also, when there is a strong desire for a given treatment to produce a certain effect, as when pain is extraordinarily intense, the placebo effect tends to be augmented.

The results of a study employing the rotating drum in order to induce the nausea of motion sickness demonstrated the powerful effect of placebo-induced expectations on nausea and gastric dysrhythmia [61], albeit in a different manner than what was predicted. All participants were given placebo pills prior to their exposure to the rotating drum, but were led to believe different things about what the effects of the pills would be. One group of participants was led to believe that the pills would essentially prevent the development of nausea, while another was told the pills would actually intensify their symptoms. Surprisingly, nausea was significantly less severe among participants told their experience would be made more unpleasant by the administration of the pills than among participants who were assured that their experience would be relatively innocuous (Fig. 14.2). This reverse placebo effect was also revealed by EGG data that were collected; participants who believed they would not experience nausea developed significantly more gastric dysrhythmia during their exposure to the motion stimulus. These results are consistent with those of Williamson et al. [62], who demonstrated high expectations of motion sickness symptoms produced by a rotating drum to be

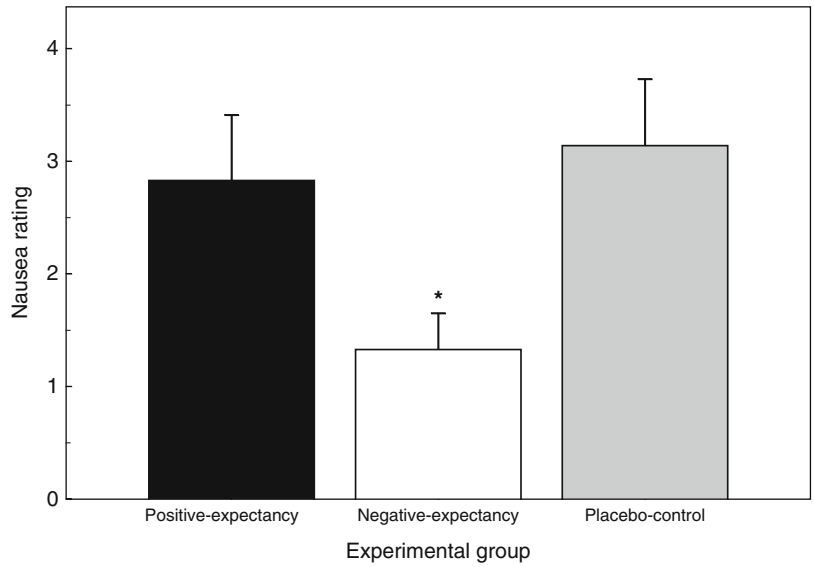

Fig. 14.2 Effects of placebo-induced expectations on ratings of nausea. Nausea ratings were significantly lower among Negative-Expectancy Group participants, who were led to believe that placebo pills they took prior to their exposure to a rotating drum would aggravate the nausea they developed, than among Positive-Expectancy Group participants, who were led to believe the pills would keep them free of symptoms, and Placebo-Control Group participants, who knew the pills they took would have no effect

associated with the inhibition of the development of gastric tachyarrhythmia.

Although the results of Levine et al. [61] did not confirm the hypothesis of a traditional placebo effect, they dramatically demonstrate the ability of expectation to influence nausea. In retrospect, the startling results were not difficult to interpret. It was speculated that participants who were told they should anticipate a sickening ordeal may have experienced something far more innocuous than they had expected. Participants who were led to believe their experience in the rotating drum would be fairly benign due to the pills they were given soon realized it would be much more unpleasant than they came to expect. These important differences may have resulted in very different experiences for these two groups of participants. Those who unnecessarily braced themselves for a torturous ordeal may have been calmed or relaxed by what they experienced, whereas those who expected to feel fine may have been alarmed by or unprepared for what they confronted. These differences may have differentially influenced the development of nausea and gastric dysrhythmia. Presumably, participants in each group experienced the same ambiguous, somewhat unsettling sensations during the early minutes of exposure to the nauseogenic stimulation. Those who were alarmed by the sensations probably interpreted them as relatively severe and may have activated an unspecified psychophysiological mechanism that intensified the nausea and gastric dysrhythmia they were already experiencing. Those who were relieved by the sensations likely interpreted them as relatively mild, thereby leading to the minimization of nausea symptoms.

Expectation appears to have a significant impact on the nausea experienced by cancer patients undergoing chemotherapy as well. Several studies have demonstrated that patients expecting to experience nausea during or after their chemotherapy treatment are more likely to suffer from nausea (e.g., [63]). Anticipatory nausea is experienced by approximately 25 % of cancer patients who had previous treatments during which they experienced nausea [64]. Classical conditioning models have been used to explain the occurrence of anticipatory nausea; neutral stimuli such as the drive to the hospital, and the

sights, sounds, and smells of the treatment facility are associated by patients with the chemotherapy agents that are administered. If nausea develops during or after the treatment, the previously neutral stimuli acquire the ability to induce symptoms on subsequent visits to the hospital even before the chemotherapy agent is administered. Levine et al. [65] demonstrated support for this idea in a sample of 49 cancer patients receiving chemotherapy. Both acute and delayed nausea experienced during prior chemotherapy treatments were significant predictors of anticipatory nausea experienced before the next administration. Presumably, patients who suffered from nausea during and/or after earlier treatments anticipated more of the same in the context of subsequent treatments, perhaps because their anticipation induced physiological changes consistent with the development of nausea.

Control/Predictability

The perception of control may be conceived of as the belief that one has the power to dictate the outcome of a situation. Perceived control over a potentially aversive situation has been repeatedly demonstrated to have a significant favorable impact on an individual's subjective and physiological response to stress (e.g., [66–68]). It is not entirely clear how perceptions of control minimize stress, but most theorists advocate the position that maintaining a belief that the outcomes one experiences are contingent upon one's actions allows the person to more effectively cope with and hence reduce the unpleasantness of stress.

Predictability is the capacity to accurately anticipate future events. Many studies have demonstrated the availability of predictive information to diminish the subjective and physiological response to stress as well (e.g., [69, 70]). The ability to foresee how a stressful situation will develop can be advantageous for generating an adaptive coping response; knowing when, and for how long a stressful period will last allows people to prepare themselves to cope more effectively with the stressor. Perhaps more importantly, a sense of predictability allows a person to take comfort in the awareness of when it is no longer necessary to engage a coping response and relax given the absence of a stressor [71]. One feature of the perception of control that might allow it to be effective for reducing stress is its relationship with being able to predict and anticipate the development of a challenging situation. An individual who knows he or she can dictate future events related to a potentially aversive interaction can, by definition, predict the course of those events. The beneficial effect of perceived or actual control on responses to various forms of stress may therefore, in varying degrees, be attributed to the predictability that it provides.

Levine et al. [72] explored the extent to which perceptions of control and predictability could both individually and collectively affect the development of nausea, motion sickness, and gastric dysrhythmia during exposure to a motion sickness stimulus. Perceived control was manipulated by providing some participants with the means to start and, more importantly, stop their exposure to a rotating optokinetic drum at their discretion by simply flipping a switch. Other participants were told that in order to terminate the session if their symptoms became intolerable, they needed to request the drum's rotation to be stopped by an experimenter from an adjacent room. Predictability was provided with and without control of the motion sickness stimulus. Some participants were informed of the duration of their exposure to the rotating drum and were also given regular updates regarding how much time remained. Although the provision of control of the drum itself made the situation somewhat more predictable, the availability of temporal information made the experience considerably more predictable for some participants.

As predicted, the development of nausea was significantly attenuated in participants given control of the rotating drum, and also in participants given predictability concerning the timing of their exposure (Fig. 14.3). The significant main effects of control and predictability on ratings of nausea suggest that providing participants with the means to start and stop the drum's rotation and, to a lesser extent, providing them with

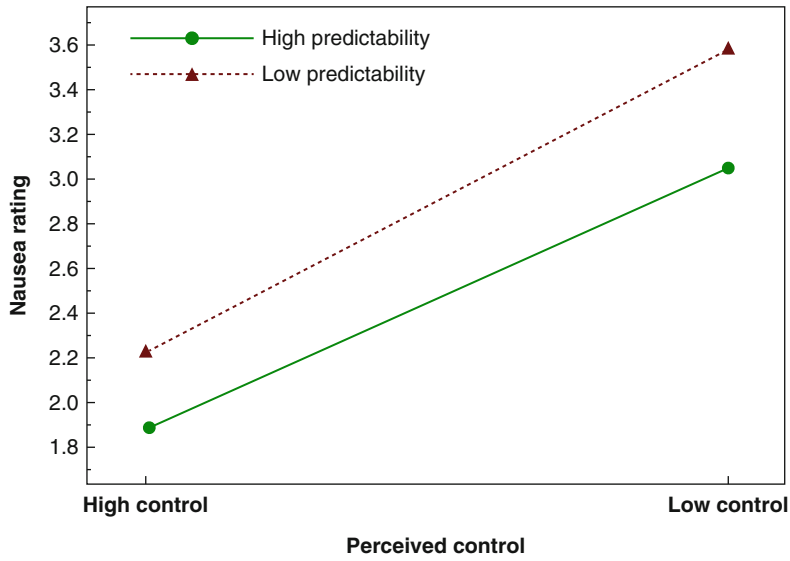

Fig. 14.3 Effects of perceived control and expectation on ratings of nausea. Significant main effects of enhanced perceptions of control and receiving predictive information on nausea severity were observed. Having the ability to manually terminate the rotation of an optokinetic drum, and knowing for how long the nauseogenic stimulation would continue were effective for arresting the development of nausea. A significant interaction effect was not observed

predictive information about the duration of the drum rotation period was each effective for reducing the intensity of nausea and other symptoms of motion sickness. That the interaction effect of perceived control and predictability on nausea ratings scores was not statistically significant suggests that these protective effects were additive rather than interactive. In other words, perceived control and predictability appeared to act as distinct psychological factors in the attenuation of the subjective experience of nausea. Having both control and predictability appeared to offer the most protection to participants from the development of nausea, but the effect of one did not depend on the availability of the other. The protective effects of control and predictability were also revealed by their influence on gastric myoelectrical activity [72]; gastric dysrhythmias were least evident in those provided with both control and predictability.

That providing individuals with the opportunity to escape from the stimulation that might bring them discomfort results in the experience of less unpleasant consequences makes great intuitive sense. However, it still is not entirely clear why perceptions of control are so valuable in situations like the rotating drum where noxious stimulation must be coped with effectively. One possibility is that control exerts its protective effects against nausea through its ability to reduce stress and anxiety, and the accompanying physiological responses [66, 68]. The issue remains unresolved, though it is likely that through some as yet unspecified psychophysiological mechanism, perceived control motivates an individual to engage in some form of coping, whether active or passive, which adaptively reduces the stress and negative consequences that result from an aversive situation. Explaining predictability's capacity to provide relief to those enduring stressful conditions is somewhat more intuitive. Knowing exactly when, and for how long a stressful event will take place will certainly facilitate effective coping with the situation. Without such predictive information, coping resources might seem far too scarce to deal with what could go on for a considerable time longer. This sort of thought process might begin a cascade of negative cognitions that could serve to worsen the stressful nature of the situation, both subjectively and physiologically [69–71]. Having the capacity to predict the unfolding of future events may

stimulate positive thinking that facilitates successful adjustment to stressors of all kinds, including those that tend to promote the development of nausea.

Stress/Anxiety

As mentioned earlier, nausea is often reported by individuals struggling with stress and anxiety. Reports of nausea have been shown to be common among patients with anxiety disorders such as generalized anxiety disorder [73]. Cancer patients with a great deal of anxiety have been reported to suffer from more side effects of chemotherapy, including nausea and vomiting [74]. In a thorough review of the role of anxiety in chemotherapy-induced nausea, Andrykowski [75] concluded that anxiety contributes to the development of both anticipatory and posttreatment nausea.

Gianaros et al. [10] presented participants with two laboratory stressors and evaluated their effects on gastric myoelectrical activity and ANS responses. Both stressors caused an increase in gastric dysrhythmia, an increase in SNS activation, and a decrease in PNS activation. The extent to which SNS activation increased, in particular, was predictive of nausea that developed during subsequent exposure to a rotating optokinetic drum, suggesting that one's physiological response to stress plays a role in susceptibility to nausea evoked by a motion stimulus.

If stress exacerbates nausea, then efforts to limit stress should presumably reduce the intensity of nausea, or help prevent it from developing. Relaxation has often been demonstrated to have beneficial effects on individuals' subjective well-being and stress level, and on a variety of health-related outcomes (e.g., [76, 77]). The physiological mechanism that mediates the purported influence of interventions such as mindfulness meditation and progressive muscle relaxation remains elusive, but likely involves the central and autonomic nervous systems. Levine et al. [78] examined the effects of a brief session of progressive muscle relaxation on reports of nausea made by individuals exposed to a rotating drum, and on the development of gastric tachyarrhythmia. Participants assigned to the relaxation group were guided through a 10 min progressive muscle relaxation program prior to their exposure to the rotating drum. As predicted, participants who engaged in the progressive muscle relaxation program prior to their exposure to the motion stimulus experienced significantly less severe nausea (Fig. 14.4). Analysis of the physiological data is ongoing, and may contribute to the elucidation of the physiological mechanism responsible for relaxation's beneficial effect.

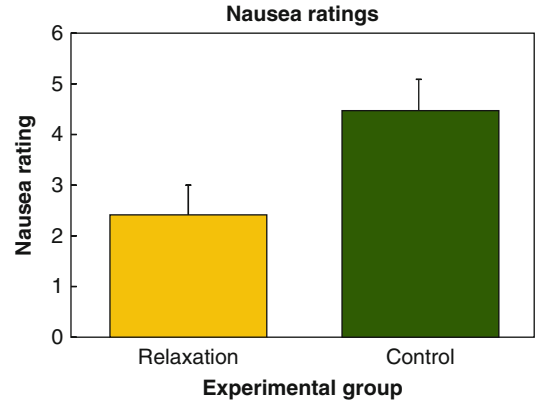

Fig. 14.4 Effects of progressive muscle relaxation on ratings of nausea. Participants who were led through a 10-min progressive muscle relaxation exercise prior to their exposure to a rotating drum reported significantly less severe nausea than participants who were not

Distraction

Distraction has been found in many instances to have a beneficial effect on pain; for instance, those who are engaged in a cognitive task that is demanding of one's attention, or an activity they find interesting and enjoyable tend to report pain as less severe (e.g., [79, 80]). Levine et al. [81] examined the effects of two sorts of distraction on nausea and gastric dysrhythmia induced by exposure to a rotating drum. A randomized, independent-groups design was employed in which 60 participants were assigned to one of three experimental groups. Distraction was manipulated in two ways in an effort to determine whether one is more effective than the other at reducing nausea and its

physiological underpinnings. Each was compared to a no-distraction control group. The first version of distraction was a cognitive/attentional distracting task called shadowing that was completed during exposure to the nauseogenic stimulus. Shadowing consists of repeating back the words being read to the participant from a recorded message in a continuous manner. The second version of distraction was an interest/engagement task that combines attentional distraction with a source of emotional enjoyment. Participants in this group were permitted to listen to their favorite variety of music while they were exposed to the rotating drum. It was hypothesized that participants in each of the distraction groups would report less severe nausea and other symptoms of motion sickness than participants in the control group. It was also expected that participants in each of the distraction groups would exhibit less gastric tachyarrhythmia than participants in the control group. Specific differences between the shadowing and music groups were not anticipated, as each distraction manipulation was expected to be effective for reducing nausea.

As predicted, participants who were permitted to listen to music during their exposure to the motion stimulus experienced significantly less severe nausea; contrary to the hypothesis, however, participants in the shadowing group experienced significantly more severe nausea than the music group. Control group participants reported nausea of intermediate intensity relative to the two distraction groups (Fig. 14.5).

The emotional distraction of listening to familiar and preferred music appeared to have had the desired effect of redirecting the focus of participants away from the negative experience of nausea and toward the positive experience of enjoying a familiar tune. Although the harmful effects of shadowing were not anticipated, they are understandable given the difficult nature of this cognitive task. As mentioned earlier, stress tends to aggravate the intensity of the symptoms experienced, and amplify the physiological responses that often accompany nausea. These results suggest that for individuals likely to suffer from nausea, it is important to find an activity or task that is interesting and enjoyable that can serve as a distraction from whatever is likely to cause the nausea, but not one that is excessively demanding of one's cognitive resources.

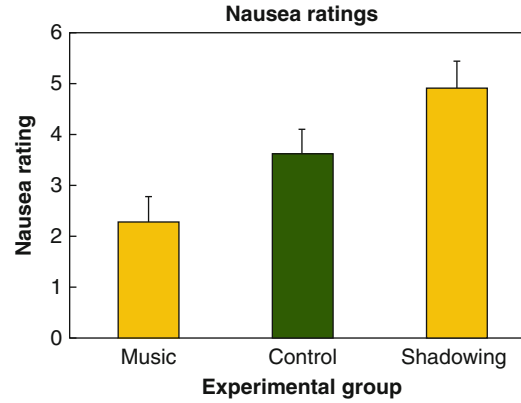

Fig. 14.5 Effects of cognitive and emotional distraction on ratings of nausea. Participants who listened to their favorite type of music during exposure to a rotating drum reported significantly less nausea than participants who completed the challenging cognitive task of shadowing during their exposure. Participants who were not distracted by either manipulation experienced nausea of intermediate severity

Adaptation

Adaptation to nausea and the symptoms of motion sickness upon repeated exposures to a rotating drum has been well documented [18, 82]. As described earlier, a person who was at first made quite ill during exposure to the rotating drum becomes less nauseated with each exposure so long as the time between exposures does not exceed 2 days. More recently, an intervention involving adaptation to the rotating drum was employed for individuals who were so susceptible to motion sickness that their condition prevented them from traveling in cars and other ordinary forms of transportation without severe nausea [83]. After a sufficient number of sessions in the rotating drum to allow adaptation to that particular form of nauseogenic stimulation, participants were also found to report significantly less nausea while engaged in travel that had previously been entirely unpleasant. That these individuals were able to generalize their adaptation from the motion

sickness simulator to real-world environments is extremely encouraging for future applications of this therapeutic approach; furthermore, it raises the possibility that adaptation to the rotating drum's stimulation could generalize to other nauseogenic experiences, such as anticipatory nausea associated with cancer chemotherapy or the nausea of pregnancy.

Conclusion

Nausea is the result of a complex psychophysiological mechanism that remains to be satisfactorily elucidated. Studies of the physiological aspects of nausea have provided invaluable insight into the biomedical factors involved with its incidence and severity. However, psychosocial and behavioral impacts on nausea have also been demonstrated to deserve careful consideration. Additional exploration of patterns of brain activation associated with nausea are likely to contribute a great deal to our understanding of this unpleasant phenomenon, and may help establish links between psychology and physiology in the context of nausea. How psychosocial and biomedical factors combine and interact to influence nausea remains to be clearly understood, as does their contribution to individual differences in susceptibility to nausea in a variety of nauseogenic contexts, but it is imperative that efforts to clarify their relationship continue to be made. Until that goal is realized, we may continue to struggle to effectively manage the nausea that millions of people suffer from on a daily basis.

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15 Future Directions in Understanding Nausea and Vomiting

Saraswathi Arasu and Henry P. Parkman

Introduction

Nausea and vomiting are debilitating symptoms for most patients. These symptoms can also be frustrating for the physicians taking care of these patients, as treatments currently available are not optimal. The impact of nausea and vomiting in health care utilization was highlighted in a recent report on the burden of gastrointestinal diseases in the United States [1]. Abdominal pain was the most common gastrointestinal (GI) symptom that prompted an ambulatory doctor's visit, but nausea and vomiting were also among the most frequent GI symptoms leading to ambulatory visits to physician offices [1].

Advances are occurring in understanding acute and chronic nausea and vomiting from pathophysiologic and treatment standpoints and particularly in nausea and vomiting related to chemotherapy, postoperative ileus, and gastroparesis. This chapter will review specific aspects of our current understanding of nausea and vomiting and then discuss future directions.

Pathophysiology

Nausea is the unpleasant sensation that occurs often before vomiting. Nausea can be accompanied by changes in heart rate, blood pressure, and cold sweating. Nausea is a sensation that usually, but not always, precedes vomiting. In many patients, nausea can occur separately from vomiting. In contrast to nausea, vomiting is a specific, physical event; a complex act that requires central neurologic coordination with both voluntary and involuntary components. More is known about vomiting mechanisms than nausea, as vomiting is studied from pathophysiologic aspects more so than nausea. There are animal models for vomiting, such as the shrew (*Cryptotis parva*), but not for nausea. The various components of the vomiting reflex include (1) afferent neural pathways that carry activating signals from the periphery from various sites to the central nervous system; (2) the chemoreceptor trigger zone (CTZ), located in the area postrema on floor of the fourth ventricle, which (at least in part) is located outside the blood–brain barrier; (3) nucleus solitarus, where afferent neural impulses are relayed to and then from here to the emetic center; and (4) emetic center (or vomiting center), which is located in the medulla. These peripheral and central pathways are discussed in Chap. 1.

The neural circuitry involved with nausea and vomiting involves a variety of receptors. Vagal and spinal afferents convey the sensory information to the CNS. 5-hyroxytriptamine type 3 (5-HT_3) receptors are present in the periphery and along the vagal afferents. Release of dopamine stimulates dopamine D_2 receptors in the emetic center. Histamine H_1 and muscarinic M_1

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receptors are abundant in the vestibular center and solitary nucleus. These H_1 and M_1 receptors are target receptors especially for motion sickness, vestibular nausea, and pregnancy-related emesis. Cannabinoid CB_1 reports are present in the dorsal vagal complex and inhibit the emetic reflex. Cannabinoid agonists can also modulate the 5-HT_3 ion channels. Neurokinin-1 (NK_1) receptors are located in the area postrema and the solitary nucleus. Substance P binds to these NK_1 receptors and is involved in the terminal emetic pathways. NK_1 receptor antagonists reduce emesis induced by peripherally and centrally acting emetogens. This is different than 5-HT_3 receptors, which appear to be involved to a greater extent in centrally induced emesis. NK1 receptor agonists may be more efficacious than 5-HT_3 receptors inhibitors in reducing vomiting induced by a variety of causes.

Vomiting occurs when somatic and visceral components are activated simultaneously. Vomiting results from brisk contraction of the diaphragm and abdominal muscles with relaxation of the lower esophageal sphincter. A forceful retrograde peristaltic contraction in the jejunum pushes enteric contents into the stomach and from there toward the mouth. At the same time, protective reflexes are initiated protecting individuals from aspirating. The soft palate is raised to prevent gastric contents from entering the nasopharynx. Respiration is inhibited momentarily and the glottis is closed to prevent pulmonary aspiration.

Disorders Causing Nausea and Vomiting

In this section, our current understanding of nausea and vomiting related to gastroparesis, postoperative ileus, and chemotherapy are reviewed.

Gastroparesis

Gastroparesis is defined as objective evidence for delayed gastric empting in the absence of mechanical obstruction [2]. Nausea and vomiting are important symptoms in patients with gastroparesis [3, 4]. However, the symptoms of nausea and vomiting have been poorly characterized in these patients. The author has undertaken several studies to help better understand these symptoms of nausea and vomiting in this disorder.

In the first study, we compared nausea in diabetic gastroparesis (DG) versus idiopathic gastroparesis (IG) [5]. Muth and colleagues developed a Nausea Profile (NP) that characterizes the multiple dimensions of nausea, not only from a gastrointestinal experience, but also from somatic and emotional domains [6]. Diabetic gastroparetic subjects reported significantly higher somatic distress, gastrointestinal distress, and higher total nausea scores compared with IG patients. The increased symptoms in DG may be attributed to differences in their mechanism of disease, since DG is based on glucose toxicity and autonomic nervous system dysfunction. The sensation of nausea is thought to originate from internal signals or external stimuli transmitted via the parasympathetic and sympathetic visceral afferent pathways to the nucleus tractus solitarius in the medulla [7]. Vagal nerve dysfunction may be implicated as a contributing mechanism of DG. Our studies showed that diabetic subjects not only experience a more heightened sensation of nausea, but also perceive their nausea in terms of somatic changes. We hypothesize that the somatic distress factor would correlate with autonomic dysfunction. Thus, an area for future study of DG should include autonomic nervous system measurements and correlate the results with Nausea Profile scores.

In this study, there was no correlation between the NP scores and the degree of gastric retention in DG patients. Our findings are consistent with previous observations that symptom severity does not necessarily correlate with the severity of gastric stasis [8]. The severity of nausea correlated with the low quality of life scores in DG. While the severity of nausea was not well differentiated by the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM) scale [9], the Nausea Profile distinguished the differences in character and degree of nausea in DG versus IG.

In our second study, we further characterized nausea and vomiting in patients with DG and IG [10]. In this study, nausea and vomiting were assessed with the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM); the Nausea Profile, which was initially used in vection-induced nausea [6]; and the Functional Living Index-Emesis (FLIE), which is used in chemotherapy-induced nausea and vomiting [11]. Nausea was present in 90 % of patients with DG and IG. Vomiting was present in 60 % of patients, with vomiting being more severe in patients with DG. Both nausea and vomiting had significant impacts on quality of life. There was a mild correlation between vomiting and 4-h gastric retention, indicating that gastric retention may contribute to severity of vomiting. There was no correlation between glycosylated hemoglobin and severity of vomiting, unlike the relationship of symptoms with more acute glucose control reported previously [12].

Although nausea is a common symptom, it is very difficult to quantitate. We asked patients to record the number of hours of nausea per day and the episodes of vomiting per day that they experienced. The number of hours of nausea per day correlated with the PAGI-SYM severity of nausea score and the number of vomiting episodes correlated with the PAGI-SYM severity of vomiting score. These two more quantitative measures, number of hours per day with nausea and number of vomiting episodes per day, may be useful in future clinical trials for gastroparesis. Patients seem to remember the exact number of times they vomit per day, but the hours of nausea per day might be difficult for patients to recall and may be overestimated by patients. However, a daily diary, rather than a weekly recall survey, should help to improve accurate nausea reporting. A prospective assessment of quantifying nausea and vomiting is needed to determine clinical value with drug or device studies.

There are few validated questionnaires to assess nausea and vomiting in patients with gastroparesis. The Gastroparesis Cardinal Symptom Index (GCSI) is often used and has nine symptoms associated of gastroparesis. The recent FDA guidance on gastroparesis also reports on a daily diary [13]. This study used two additional nausea measures developed for other nausea disorders: the Nausea Profile used in vection-induced nausea [6] and the Functional Living Index- Emesis (FLIE) used in chemotherapy-induced nausea and vomiting [11]. The FLIE questionnaire assesses the impact of nausea and vomiting on the patient's ability to maintain the activities of daily life. Nausea related to stomach disorders is reviewed in Chap. 3.

Other GI disorders causing nausea and vomiting are cyclic vomiting syndrome, rumination, and the superior mesenteric artery syndrome and are important to consider. *Cyclic Vomiting Syndrome* (CVS) refers to clustered episodes of vomiting lasting from 1 day to several days separated by weeks to months of no symptoms at all. CVS has no gender predilection, but sometimes is linked to menstrual cycle. A history of migraine headache is elicited in about 25% of patients. CVS was originally described in children but is also increasingly seen in adults. Mitochondrial DNA mutations may be involved in the pathogenesis in children. There appears to be an association between CVS and chronic cannabis use. These patients take hot baths or showers for symptoms relief and those who discontinue cannabis may recover completely. About 1 in 5 adult patients with CVS have an anxiety disorder or other psychiatric disease. Tricyclic antidepressants, especially amitriptyline, is used as a chronic treatment, with use of ondansetron for symptoms of vomiting. Sumatriptan and topomax might help reduce symptoms in patients with migraines.

Rumination Syndrome is characterized by repetitive effortless regurgitation of small amounts of recently ingested food into the mouth which may be confused with vomiting. However, the patients usually re-chew and swallow the regurgitated food. Nausea is not reported. Rumination occurs in men and women with equal frequency. Organic diseases such as achalasia, other esophageal motility disorders, gastric outlet obstruction, and gastroparesis must be excluded. In equivocal cases, antroduodenal manometry is performed occasionally with esophageal pH testing. The pathophysiology of rumination is

thought to include adaptation of the belch reflex or learned transient relaxation of the LES in combination with a voluntary increase in intra-abdominal pressure and relaxation of diaphragmatic crura may relax, which allows the normal postprandial increase in intra-gastric pressure to overcome the resistance of the LES. Treatment is patient education, behavior modification, and diaphragmatic breathing techniques.

Superior Mesenteric Artery (SMA) Syndrome If the angle between the aorta and SMA becomes more acute than normal, then the duodenum can become partially obstructed and results in the SMA syndrome. Factors that increase the acute angle include increased lordosis, loss of abdominal muscle tone, rapid weight loss, and abdominal surgery followed by prolonged bed rest. Symptoms include epigastric pain and pressure after meals, nausea, and bilious vomiting. Upper GI barium contrast study or CT scan may reveal the duodenal obstruction. Treatment is to correct underlying precipitating factors. Stasis proximal to the site of the duodenal obstruction should be demonstrated before operation is considered. A feeding catheter should be passed across the obstruction into the proximal jejunum to demonstrate that vomiting does not occur during enteral feeding. Proximal duodenojejunostomy is the surgical treatment. Nausea and vomiting due to non-esophageal and non-gastric diseases are reviewed in detail in Chap. 4.

Non-GI Disorders Causing Nausea and Vomiting

Chronic or relapsing nausea and vomiting can be seen in a number of non-GI disorders, which are highlighted and reviewed in detail in Chap. 4.

Nausea and Vomiting During Pregnancy Nausea and vomiting occurs in approximately three-quarters of all pregnancies. The nausea and vomiting occurs primarily in the morning, develops early in pregnancy, peaks at nine weeks gestation, and rarely continues beyond 22 weeks gestation. Nausea with vomiting is more common in women with multiple gestations than with a single gestation. Drugs for nausea of pregnancy that appear to be safe include vitamin B_6, ondansetron and related 5-HT_3 antagonists, and metoclopramide. Diclegis, similar to the medication Bendectin, was recently approved for this disorder. Concern about 5-HT_3 antagonists and fetal cardiac defects has been raised, but the literature is conflicting. *Hyperemesis gravidarum* (HG) is unusually severe nausea and vomiting that leads to complications (dehydration, electrolyte imbalance, malnutrition) and occurs in 1–5 % of pregnancies. Multiparous overweight women are at increased risk for HG. Treatment includes antiemetics, glucocorticoids, erythromycin, and powdered ginger root.

Chemotherapy-Induced Nausea and Vomiting Nausea has been well characterized among chemotherapy recipients in terms of frequency, severity, and duration. *Acute* chemotherapy-induced nausea and vomiting (CINV) occurs within 24 h of chemotherapy. Risk factors include lower socioeconomic status, prechemotherapy nausea, female gender, administration of highly emetogenic chemotherapy, absence of antiemetic therapy. Chemotherapeutic drugs causing this include cisplatinum, nitrogen mustard, and dacarbazine. CINV may occur from the increase in plasma serotonin levels. *Delayed* PCNV can also occur after 24 h. Principal risk factor is poor control of symptoms. Age, tumor burden, and gastroparesis can contribute. *Anticipatory* PCNV occurs in 25–50 % pts by fourth course of chemotherapy, especially among young patients with underlying anxiety and adverse drug experiences in the past. Current antiemetic agents prevent or markedly reduce nausea and vomiting, but 10–20 % of patients continue to suffer CINV and total control of nausea and vomiting remains the subject of ongoing research.

Postoperative ileus (POI) is an abnormal pattern of gastrointestinal motility characterized by nausea, vomiting, abdominal distension, and/or delayed passage of flatus or stool, which may occur after surgery. The cause of POI is

Table 15.1 Future directions for understanding nausea and vomiting

Better characterization of neural pathways and receptors mediating sensation of nausea and vomiting:	
Gender differences	
Similarities and differences for nausea compared to vomiting	
Similarities and differences for different disorders	
CINV vs. NVP vs. Gastroparesis, CUNV, CVS	
Development of animal models for nausea	
Improving evaluation of patients with chronic nausea and vomiting:	
What is proper evaluation of patients with nausea and vomiting	
Different specialties perform different tests and treat differently	
Better definition for nausea	
Determining relationships of gastric dysmotility to symptoms of nausea and vomiting	
Improving treatments:	
Are antiemetics also antinauseants	
How well do antinauseants and antiemetics used in one condition work in another	
Use of CNS imaging to demonstrate the therapeutic action of therapeutic agents	
Use of pharmacogenomics to guide treatment choices and dosing of antiemetics	
Targeting the gastric ENS/ICC as treatment	
Enhancing Drug development:	
Improve outcome measures for clinical trials	
Nausea	
Vomiting	
Explore use of agents for treatment of nausea and vomiting that are approved for other disorders	
Toperimate Olanzepine Mirtazepine Buspiorone	Gabapentin Corticosteroids Cannabinoids
Expand use of agents approved for CINV to treatment of nausea and vomiting from other disorders	
5-HT_3 receptor antagonists	
NK_1 receptor antagonists	

CINV chemotherapy-induced nausea and vomiting, *NVP* nausea and vomiting of pregnancy, *CUNV* chronic unexplained nausea and vomiting, *CVS* cyclic vomiting syndrome, *CNS* central nervous system, *ENS* enteric nervous system, *ICC* interstitial cells of Cajal

multifactorial, with principal mediators being inflammatory cell activation, autonomic dysfunction, activation of gut opioid receptors, modulation of gastrointestinal hormone activity, and electrolyte derangements. A final common pathway for these effectors is impaired contractility and motility of the gastrointestinal tract. Alvimopam is approved for POI.

Future Directions

Better understanding of nausea and vomiting is needed for better treatments for patients with these symptoms. Table 15.1 lists areas for future directions we have identified to lead to better understanding and treatment of nausea and vomiting.

The neural pathways and receptors mediating the sensation of nausea need better characterization. For example, are the neural pathways the same for nausea as for vomiting? Since gastroparesis is much more common in women than in men, what gender differences are present in the relevant neural pathways that result in nausea? How similar or different are the pathways mediating nausea for different disorders, such as gastroparesis or cyclic vomiting syndrome. Is vomiting elicited differently in these disorders? Do agents that are efficacious for CINV also

improve nausea and vomiting from gastrointestinal disorders? Should more of these agents be evaluated in GI diseases with prominent nausea and vomiting? In addition, are the pathways mediating nausea and vomiting in GI disorders, such gastroparesis or gastroparesis-like syndromes, similar to that for cyclic vomiting syndrome? To study the pathways in nausea and vomiting, animal models need to be developed. The shrew is an animal model in which vomiting can be studied. Currently, nausea is assessed only indirectly in animal models.

What is the proper clinical evaluation for these patients with nausea and vomiting? Currently, patients may seek care for their symptoms from their family medicine physician or internist and are then often referred to either a gastroenterologist, neurologist, or ENT physician. Each type of specialty might perform different tests and might treat patients differently. Better understanding of the evaluation of patients with chronic nausea and vomiting by different physicians may be helpful for all physicians. One area that is emerging is that for patients with gastroparesis, the symptoms do not correlate well with gastric emptying delays. Perhaps the symptoms that we attribute to delayed gastric emptying are from other gastric causes or non-gastric causes as reviewed in Chaps. 1, 3, and 4.

New treatments are emerging. The endpoints generally used for FDA approval are vomiting-free days, but these patients also have nausea. Agents designed as antiemetics may or may not also be antinauseants that improve nausea. How well do antinauseants and antiemetics used in one condition work in another? Some medications that are approved for other indications are being tried by physicians for nausea and vomiting because few drugs are specifically available. These include toperimate in CVS, olanzapine in CINV, and mirtazepine in gastroparesis. How can the physician select an appropriate medication to use other than trial by error? Pharmacogenomics may allow guidance of treatment choices and dosing of antiemetics. CNS imaging to demonstrate the therapeutic potential of therapeutic agents could be used. It may be that the doses or even agents used to control episodes of nausea and vomiting may be greater than those needed to prevent the onset of nausea and vomiting. These are areas that need more delineation for improved patient care.

In gastroparesis, there are cellular changes in the enteric nervous system (ENS), specifically a decrease in nitric oxide (NO)-containing nerves and a decrease in interstitial cells of Cajal (ICCs) accompanied by an increase in the resident macrophages. Targeting these abnormalities for treatment will be of interest.

Drug development with potent, selective agents and new primary endpoints focused on nausea are needed. Better endpoints for vomiting, rather than the absence of vomiting, are needed. Endpoints for nausea, itself, need to be generated. To do this, we may need better definitions of nausea for patients. We should explore the use of agents for treatment of nausea and vomiting that are approved for other disorders. Examples include toperimate, olanzapine, mirtazapine, buspiorone, gabapentin, cannabinoids, and corticosteroids. Agents that are approved for CINV should be further studied for ultimate approval for treatment of nausea and vomiting from other disorders, such as gastroparesis.

Conclusions

Our understanding of nausea and vomiting, both from pathophysiologic and treatment standpoints, has advanced. Future directions in understanding nausea and vomiting include: (1) better characterization of neural pathways and receptors mediating sensation of nausea and vomiting; (2) improving evaluation of patients with chronic nausea and vomiting; (3) improving treatments; and (4) enhancing drug development.

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