



Review

Methodologic considerations for studies of chronic nausea and vomiting in adults and children



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ABSTRACT

Methods to characterize and quantify severity of chronic nausea and vomiting and to elucidate their underlying mechanisms have received significant attention for both adult and pediatric patients. Validated dyspepsia symptom surveys include measures of nausea and vomiting intensity in relation to other upper gut symptoms. Visual analog scales quantify nausea intensity in real-time in physiologic studies and have been employed as enrollment criteria in clinical trial settings. A new nausea and vomiting survey has been administered to gastroparesis patients to provide insight into timing, triggers, and autonomic and psychological correlates of these symptoms. Several gastric sensorimotor and extragastric abnormalities are proposed to contribute to nausea and vomiting pathogenesis, but their relations to symptom severity are either limited or uninvestigated. Gastric emptying delays are prevalent in patients with chronic nausea and vomiting, as are blunting of fundic accommodation, aberrant gastric slow wave rhythms, and heightened perception of noxious and physiologic luminal stimulation. Potential extragastric correlates of nausea and vomiting include transit delays distal to the stomach, autonomic abnormalities, altered central nervous system activation, metabolic dysregulation, and psychological dysfunction. One goal of novel survey development will be to relate these physiologic correlates to specific symptom presentations to gain insight into mechanisms of nausea in different clinical conditions. Pediatric patients represent special challenges because of the different disorders that cause nausea and vomiting in children and differences in understanding disease manifestations, the ability to communicate symptom intensity and characteristics, and immature coping mechanisms compared to adults.

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1. Introduction

Nausea and vomiting have significant socioeconomic effects in many clinical disorders. Patients with gastroparesis consume diets which satisfy only 58% of total energy requirements, report dramatic impairments in quality of life, and present frequently for emergency department or inpatient care (Parkman et al., 2011a, 2011b; Koch et al., 2016). Patients receiving cancer chemotherapy report nausea and vomiting as the most bothersome complications of therapy, often to the point of stopping treatment, with reductions in quality of life in roughly 40% of chemotherapy cycles (Lindley et al., 1999; Fernandez-Ortega et al., 2012). These consequences mandate expanded investigation into better clinical characterization and improved understanding of symptom pathogenesis in patients with nausea and vomiting.

Many symptom questionnaires have been utilized to define the intensity and properties of chronic nausea and vomiting, while several physiologic methods are available to characterize potential mechanisms underlying symptom genesis. Questionnaires for assessing a range of gastrointestinal symptoms have been validated for use in conditions such as gastroesophageal reflux disease and functional dyspepsia but also contain questions pertaining to nausea and vomiting. Numerical scales for nausea intensity are most often used for research studies, which require assessment of current symptoms, but also have been adopted for pharmaceutical trials of antiemetic and antinausea therapies. Others have devised novel surveys to characterize profiles of nausea and vomiting to better understand their impact in selected clinical conditions.

Mechanisms underlying development of nausea and vomiting are poorly understood for most clinical disorders. Pathophysiologic roles have been proposed for a number of motor and sensory functions involving the stomach and more distal intestinal regions as well as the autonomic and central nervous systems, including gut transit abnormalities, impaired gastric relaxation, heightened sensitivity to stimulation, dysautonomias, and altered brain processing of gut information. Proof of many of these functional abnormalities as causes of nausea or vomiting is lacking in most instances. Potential extragastric correlates of nausea and vomiting include transit delays distal to the stomach, autonomic and central nervous system (CNS) abnormalities, metabolic dysregulation including hyperglycemia, and psychological dysfunction.

This topic review discusses methodologic considerations for studying chronic nausea and vomiting in disorders of presumed gastrointestinal origin, as symptom pathogenesis in these conditions is poorly understood. These include gastroparesis as well as the recently

described condition chronic unexplained nausea and vomiting (CUNV), a disorder which mimics gastroparesis but with normal gastric emptying (Pasricha et al., 2011). This contrasts with the extensive body of literature in clinical conditions with established causes such as chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting. It is also recognized that some disorders have no peripheral mechanisms which mediate nausea, including anticipatory nausea prior to chemotherapy administration and motion sickness. These conditions are not a focus of this article. Special attention also is given to children with chronic nausea and vomiting for several reasons. First, the diagnoses that present with this symptom complex are somewhat distinct from those in adults. Second, children (particularly infants, toddlers, and preschoolers) may not be able to convey the intensity or specific characteristics of their symptoms to either their parents or care providers. Finally, pediatric patients may lack the appropriate perspective to cope with chronic nausea and vomiting.

2. Symptom scoring systems for nausea and vomiting

Several symptom scales have been utilized to quantify nausea and vomiting severity in a range of upper gastrointestinal disorders (Table 1). The Patient Assessment of Upper Gastrointestinal Disorders Symptoms (PAGI-SYM) instrument was initially developed to measure symptom severity and profiles in patients with gastroesophageal reflux disease (GERD), dyspepsia, and gastroparesis. This survey quantifies 20 symptoms referable to the upper and lower gut recalled over the prior 2 weeks on a numerical scale ranging from 0 (no symptoms) to 5 (most severe symptoms) (Rentz et al., 2004). The PAGI-SYM is comprised of 6 subscales including nausea/vomiting, heartburn/regurgitation, fullness/early satiety, bloating, upper abdominal pain, and lower abdominal pain recalled over the prior 2 weeks. The Gastroparesis Cardinal Symptom Index (GCSI) is a survey specifically designed to assess gastroparesis severity and includes 9 questions from the PAGI-SYM in 3 subscales (nausea/vomiting, fullness/early satiety, bloating/distention) (Revicki et al., 2003). This survey recently has been expanded to 11 questions including two new questions relating to upper abdominal pain and discomfort and can be administered daily (Cardinal Symptom Index-Daily Diary) (Revicki et al., 2012). An older survey, the Leeds Dyspepsia Survey, contains 8 items in two stems which describe the frequency and intensity of dyspeptic symptoms including nausea, vomiting, epigastric and retrosternal pain, regurgitation, belching, early satiety, and dysphagia over the prior 6 months (Moayyedi et al., 1998). Some have questioned specifically grading vomiting severity, as it may be difficult to provide a definition of severe vomiting that is

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