HHS Public Access

Author manuscript

Curr Treat Options Gastroenterol. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Curr Treat Options Gastroenterol. 2016 December ; 14(4): 410–419. doi:10.1007/s11938-016-0113-z.

Chronic Unexplained Nausea and Vomiting or Gastric Neuromuscular Dysfunction (GND)? An Update on Nomenclature, Pathophysiology and Treatment and Relationship to Gastroparesis

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Keywords

Nausea; Vomiting; Gastroparesis; Chronic unexplained nausea and vomiting; Gastroparesis-like dysfunction

Introduction

Definitions

Both patients and clinicians use the terms nausea and vomiting; however, these terms are commonly employed to define a broad range of symptoms. It is important to delineate patients with true nausea and vomiting from patients with other disorders such as regurgitation, belching, or gastroesophageal reflux.

Nausea is the subjective, unpleasant sensation of the need to vomit, and vomiting is the forceful expulsion of gastric contents out of the mouth.[1] It is important to differentiate vomiting from regurgitation as the etiology, diagnostic evaluation, and treatment of the two conditions differs significantly. Vomiting differs from regurgitation or GERD in that vomiting involves a forceful process with expulsion of gastric contents from the mouth, whereas regurgitation and GERD involve the effortless and passive movement of gastric contents into the esophagus or oral cavity.[1]

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Kimberly N. Harer declares no conflict of interest.

Classification

Chronic nausea and vomiting disorders have been referred to by many names in the literature including chronic unexplained nausea and vomiting (CUNV), gastroparesis-like syndrome (GLS), functional vomiting, and vomiting of unexplained etiology (VUE).[2–4] Chronic nausea and vomiting disorders are also included in the classification of functional gastrointestinal disorders (FGIDs). The sections below will discuss the FGID classification based on the recently published Rome IV criteria, as well as the difficulties with classification due to symptom overlap between disorders such gastroparesis, chronic nausea and vomiting, and functional dyspepsia.

Classification of Functional Gastrointestinal Disorders (FGIDs)

FGIDs are classified based on the Rome criteria, recently updated in May 2016[1]. Rome IV classifies nausea disorders into three categories (Table 1): Chronic Nausea and Vomiting Syndrome (CNVS), Cyclic Vomiting Syndrome (CVS), and Cannabinoid Hyperemesis Syndrome (CHS).[1] These classifications differ from the prior Rome III criteria by combining two disorders, 1) Chronic Idiopathic Nausea and 2) Functional Vomiting, into the composite disorder of Chronic Nausea and Vomiting Syndrome (CNVS). This change was implemented due to the lack of evidence demonstrating a difference in the diagnostic and management approach between the two disorders.[1]

CNVS is defined as having nausea or vomiting at least 1 day per week, the absence of self-induced vomiting, and no evidence of organic disease on routine investigations. Cyclic Vomiting Syndrome (CVS) is defined by having at least 3 episodes in the past year of acute onset vomiting lasting less than 1 week, with 2 episodes in the past 6 months which occur at least 1 week apart. Cannabinoid Hyperemesis Syndrome (CHS) is defined as experiencing episodes resembling CVS, which occur after prolonged excessive cannabis use and resolve after sustained cessation of cannabis. For all three categories, the criteria must be fulfilled for the previous 3 months with the onset of symptoms at least 6 months prior to the time of diagnosis.[1]

Functional dyspepsia is listed under a separate category of gastroduodenal disorders.[1] Functional dyspepsia diagnostic criteria include suffering from at least one symptom of postprandial fullness, early satiation, epigastric pain, or epigastric burning, in addition to meeting criteria for one of the two sub-classes. The two sub-classes of functional dyspepsia are postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). PDS criteria include bothersome postprandial fullness and/or early satiation at least 3 days per week over the last 3 months with symptoms for at least 6 months; whereas, EPS includes bothersome epigastric pain and/or burning at least 1 day a week over the last 3 months with symptoms for at least 6 months.

Symptom overlap and the gastroparesis spectrum hypothesis

Unfortunately, these arbitrary classifications, including the most recent Rome categories, continue to not only add to our confusion but also obscure the fact that many, if not most, of these cases do not represent a “black box” but can be readily understood within an

acceptable and established clinical framework. The term gastroparesis-like syndrome was first coined by the senior author of this paper precisely because these patients are clinically indistinguishable from those with so-called “classical” gastroparesis.[6] Thus, these patients do not complain of nausea and vomiting exclusively; instead these symptoms occur along with early satiety, fullness, bloating and pain-all cardinal features of gastroparesis. By current Rome criteria, these patients cannot be labeled as either gastroparesis (since their gastric emptying is normal) or functional dyspepsia (as nausea and vomiting are prominent are not predominant syndromes). However, by calling them CNVS, the Rome criteria ignore their other symptoms that strongly suggest a gastric origin (early satiety, postprandial fullness etc.).

We propose a more rationale, clinically meaningful, and relatively simple classification to chronic nausea and vomiting. We suggest “**gastric neuromuscular dysfunction (GND)” as an umbrella term** for patients presenting with nausea, vomiting, early satiety, fullness, bloating, and pain-all pointing to a gastric origin of their symptoms. This can be further sub-classified as type A (GND-A) where gastric emptying is delayed (otherwise known as gastroparesis) and type B (GND-B) where gastric emptying is normal (also known as gastroparesis-like syndrome or CUNV). GND-B is almost identical to what had been described in Rome III as “functional dyspepsia-postprandial distress subtype”. However, GND does not include patients who present with only nausea and vomiting and no other features that indicate a gastric origin-such patients require a robust investigation to rule out non-gastrointestinal causes such as vestibular or central nervous system dysfunction or medications. GND also does not include cyclic vomiting syndrome, which is now a well-established and sufficiently distinctive syndrome.

Under this classification, the unifying theme for GND is therefore an underlying gastric dysfunction that may or may not manifest in delaying gastric emptying. A lack of correlation between the severity of gastric emptying delay and patient symptoms severity scores has been confirmed by the GpCRC and others several years ago,[2, 7–9] and recently reproduced again by another prospective observational study.[10] Thus, our proposed nomenclature appropriately relegates gastric emptying to a descriptive feature rather than a defining pathophysiological element in the approach to suspected gastric dysmotility. Under this scheme, the overlap between gastroparesis and “functional dyspepsia” which includes both clinical and pathophysiological similarities (such as decreased accommodation)[11–12] is easier to understand. Although our proposed nomenclature may represent a radical departure from the current paradigm, we believe it is time to move forward taking into account accumulated clinical experience and emerging knowledge that supports such an approach.

Update and discussion of recent studies

Studies evaluating symptoms and pathophysiology

There has been increasing interest in understanding the role interstitial cells of Cajal (ICC) play in disorders such as gastroparesis with characteristic decreases in ICC density reported.[13–15] More recently, researchers investigated the hypothesis that decreased numbers of interstitial cells of Cajal were also associated with chronic unexplained nausea and vomiting.[16] Investigators performed a case-control study of nine CUNV and nine age-

matched controls that were scheduled to undergo bariatric surgery. Of the nine CUNV patients, four were diabetic and all nine had normal gastric emptying. Gastric biopsies were collected from seven of the nine CUNV cases and high-resolution electrical mapping was performed in all patients. CUNV patients demonstrated a significantly lower ICC density along with dysrhythmic slow wave activity.

In another abstract presented by GpCRC investigators at DDW this year,[17] of 804 patients presenting with gastroparesis or gastroparesis like symptoms, 231 had normal gastric emptying of which 86% of patients met Rome III criteria for functional dyspepsia with postprandial distress syndrome (PDS) phenotype. At 48 weeks, both groups showed similar improvements in Gastroparesis Clinical Severity Index (GCSI), hospitalizations and quality of life measures. In 64 patients with normal solid gastric emptying, 9 (14%) had delayed emptying of liquids, as compared with 46 of 66 (69%) of patients with delayed solid gastric emptying. Of 126 patients who had a solid emptying test at baseline and at 48 weeks, 65% had no change in status; 22% with normal baseline testing showed a delay and 13% with delayed baseline testing normalized on testing at 48 weeks. Histological analysis in the subset of patients who had a full thickness biopsy showed ICC loss (Kit staining) in both patient groups but no significant change in neurons (PGP9.5 staining). Further, there was a significant decrease in myenteric plexus CD206 positive staining, implying loss of the anti-inflammatory M2 phenotype of macrophages. The investigators concluded that patients with CUNV fit criteria for FD/PDS and have similar 48-week clinical outcomes and histopathological changes as patients with gastroparesis. Further a single measurement in time of solid gastric emptying is an imperfect marker for these conditions. These results therefore suggest that patients with FD/PDS may be part of the same pathobiological and clinical spectrum as patients with gastroparesis and raise questions about the “functional” nature of this condition. Taken together this supports the proposed grouping of both gastroparesis and this syndrome under the term “gastric neuromuscular dysfunction” (GND).

Studies evaluating treatment options

Current treatment options—Although numerous antiemetic and prokinetic pharmacologic therapies are employed to treat chronic nausea and vomiting, there is a dearth of data regarding their efficacy in the chronic nausea and vomiting patient population. 5-HT_3 antagonists (ondansetron and granisetron) and phenothiazines (prochlorperazine, promethazine, chlorpromazine) have been used; however, there are no randomized clinical trials evaluating their use in chronic unexplained nausea and vomiting patients. Metoclopramide and domperidone, which are D2, 5-HT_4, and 5-HT_3 receptor antagonists, are commonly used due to their mixed antiemetic and prokinetic properties. Dronabinol, a cannabinoid, is also used; however, no trials regarding its use in chronic nausea and vomiting patients have been published. Finally, olanzapine, a 5-HT_2, 5-HT_3, D2, M_1, M_3, H_1, and alpha-2 receptor antagonist, has also been used for patients with nausea and vomiting; however, efficacy studies have only been performed in chemotherapy and palliative care trials.[18–20]

Update in treatment options

Unfortunately, there are few randomized, placebo controlled clinical trials evaluating pharmacologic or procedural treatments in these patients, partly due to a paucity of agents and partly due to the inconsistency with nomenclature mentioned above. However, given the above discussion, it is reasonable to extrapolate from trials on gastroparesis and functional dyspepsia/PDS type, especially focusing on the endpoints of nausea and vomiting.

Mirtazapine—Mirtazapine, a 5-HT_2, 5-HT_3, alpha-2, and H_1 receptor antagonist, has also been a therapy of interest to treat chronic nausea and vomiting. Interestingly, mirtazapine has been shown to improve gastric emptying in dogs.[21] A randomized, placebo-controlled pilot study evaluated mirtazapine versus placebo in 34 functional dyspepsia patients.[22] Rome III criteria would have classified 17 with postprandial distress syndrome, 9 with epigastric pain syndrome, and 8 with both postprandial distress syndrome and epigastric pain syndrome. The intervention period was 8-weeks, with a 2-week run-in period. Of the 34 patients, 28 patients reported nausea, 10 patients reported vomiting, and 30 patients reported early satiety. Although a statistically significant reduction in dyspepsia symptom severity and early satiety were noted in the mirtazapine group compared to baseline measurements, there was not a statistically significant difference in symptoms compared to the placebo group at week 4 or week 8 ($p = 0.059$ and $p = 0.55$). Statistically significant improvements in weight loss, quality of life, and visceral specific anxiety scores were noted in the mirtazapine group compared to the placebo group. In another study, 60 patients with functional dyspepsia (based on Rome III criteria), depression, and weight loss were randomized to mirtazapine, paroxetine, or placebo therapy for 8 weeks.[23] Mirtazapine worked best with improvement in both functional dyspepsia symptoms (measured by the Nepean index) and depressive symptoms compared to placebo or paroxetine, as well as resulting in significant weight gain ($p < 0.05$ for all aforementioned comparisons).

Escitalopram and amitriptyline—A randomized double-blind, placebo controlled trial evaluated the effects of amitriptyline and escitalopram compared to placebo in treating functional dyspepsia symptoms.[24] The study included 292 functional dyspepsia patients who were randomized to either placebo, amitriptyline 50mg, or escitalopram 10mg therapy for 10 weeks. 75% were female, and 21% had delayed gastric emptying at baseline. The primary endpoint was adequate relief of symptoms (binary yes/no outcome) for at least 50% of the time during treatment. Of the participants, 40% of placebo subjects, 53% of amitriptyline subjects, and 38% escitalopram subjects reported adequate relief ($p = 0.05$, after adjustment for sex, body mass index, race, anxiety, dyspepsia subtype, gastric emptying, meal-induced satiety, and recruitment site). Investigators found no statistically significant difference between amitriptyline or escitalopram compared to placebo in treating nausea symptoms in functional dyspepsia patients. Subgroup analysis of the ulcer-like functional dyspepsia participants demonstrated statistically significant increased odds of symptoms improvement with amitriptyline therapy compared to placebo (OR 3.1, [95%CI: 1.1–9.0]). Analysis of daily symptoms diaries did not demonstrate a statistically significant improvement in upper abdominal pain, nausea, bloating, fullness, or early satiety. Of note, the symptom of vomiting was not assessed.

Intranasal metoclopramide—In addition to numerous previously published trials demonstrating improvement in symptoms and gastric motility with oral metoclopramide, metoclopramide nasal spray has recently been studied as an alternative administration modality in gastroparesis patients. This modality is of particular interest given the frequent intolerance of orally administered medications within this patient population. An open-label trial was performed that compared metoclopramide nasal spray (10mg and 20mg treatment arms) to oral metoclopramide administration among 89 patients with symptoms of gastroparesis.[25] Investigators demonstrated statistically significant improvement in control of symptoms with nasal spray administration, in both the 10mg and 20mg intranasal groups, compared to oral administration ($p = 0.026$ and $p = 0.008$ respectively). In a subsequent study of 287 diabetic patients performed by the same investigators,[26] a statistically significant difference in symptoms was not demonstrated between the intranasal metoclopramide 10mg or 14mg arms and placebo groups ($p = 0.1504$ and $p = 0.3005$ respectively).

5-HT$_4$ receptor agonists—Revexepride, a 5-HT$_4$-receptor agonist with prokinetic effects, was studied in a phase 2, double-blind, randomized, placebo-controlled trial in 100 patients with symptoms suggestive of gastroparesis, which plausibly would include GND-B patients.[27] Unfortunately, the drug had no significant effect on symptoms when compared with placebo. This is not surprising considering that many patients may have had normal emptying to begin with, along with the now well-established lack of correlation between a prokinetic effect and improved symptoms.

Prucalopride is a 5-HT$_3$ and 5-HT$_4$ agonist used to treat constipation. In a recent placebo controlled trial in 28 patients with idiopathic gastroparesis,[28] prucalopride was shown to improve nausea/vomiting ($p = 0.01$), bloating/distention ($p < 0.0005$), and gastric emptying ($p < 0.05$) compared to placebo. However, there was no correlation between improvement in gastric emptying and improvement in symptoms, suggesting mechanisms other than a prokinetic effect may be responsible. No studies have been reported yet in patients with normal gastric emptying at baseline.

Emerging endoscopic therapies

Pylorospasm and failure of pyloric relaxation have been postulated to be important in the pathogenesis of gastroparesis.[29,30] Along with improvements in technology, this has led to an “irrational exuberance” amongst endoscopists to try and eliminate pyloric resistance by any means, despite demonstrated failure of a similar approach in the past using botulinum toxin.[31,32] Two retrospective uncontrolled case series have been conducted investigating transpyloric stenting.[33,34] The largest case series[34] included 30 patients who underwent transpyloric stent placement for refractory nausea and vomiting. The study did not demonstrate a statistically significant difference in clinical symptoms with treatment, despite the presence of a statistically significant improvement in gastric emptying. Stent migration was a significant barrier, with 100% of non-anchored, 50% of endoclip anchored, 71% of over-the-scope-clip anchored, and 48% of endostitch anchored stents migrating.

Another technique to tackle the pylorus is gastric per-oral endoscopic myotomy (G-POEM). A few case reports and case series have been published,[35–40] with the largest being a multicenter, retrospective case series, with results that were not meaningfully interpretable in an objective manner, and can be at best regarded as proof of technical feasibility.[40]

In an attempt to identify a specific gastroparesis phenotype that may benefit from pyloric intervention, a retrospective study evaluated 33 patients with scintographically confirmed gastroparesis, a normal or increased amplitude 3 cpm gastric myoelectrical pattern on electrogastrography, and at least one previous pyloric intervention with either botulinum toxin injection (n=25) or balloon dilation (n=8).[41] Based on the documented gastric emptying delay despite normal gastric myoelectrical activity, this subset of patients was hypothesized to represent a gastroparesis phenotype with pyloric neuromuscular dysfunction. Of the 33 patients, 25 (75.8%) experienced partial or complete improvement in symptoms after one intervention. Subsequently, of the 25 patients who underwent a second intervention and 17 patients who underwent a third intervention, 18 (72%) and 13 (76.5%) experienced partial or complete improvement in symptoms respectively. Although this study investigated an interesting hypothesis regarding different gastroparesis phenotypes, a randomized, double-blind controlled trial is required to further investigate these findings given the considerable placebo effect associated with pyloric interventions, which has been shown to be as high as 56%.[31]

We feel strongly that at the present time, these approaches cannot be recommended. Indeed, given the dubious rationale and lack of evidence of efficacy, along with the highly invasive nature of these treatments, high cost and the potential for serious adverse events, there is currently no justification for doing these studies for chronic unexplained nausea outside of a controlled clinical research setting.

Conclusion

Patients with chronic unexplained nausea and vomiting provide a clinical challenge, both diagnostically and therapeutically. It is vital to appreciate the symptom overlap between disorders termed gastroparesis, Chronic Unexplained Nausea and Vomiting, Chronic Nausea and Vomiting Syndrome, and functional dyspepsia. The clinically indistinguishable presentation of chronic unexplained nausea and vomiting patients compared to gastroparesis and functional dyspepsia patients, in concert with the repeatedly proven lack of correlation between gastric emptying delay severity and nausea and vomiting symptom severity, indicates that many chronic nausea and vomiting syndromes may be part of a spectrum of disorders driven by a common underlying pathophysiologic process (that does not necessarily delay gastric emptying) instead of separate entities. Thus, we propose changing the nomenclature to “gastric neuromuscular dysfunction (GND)” as an umbrella term for patients presenting with nausea, vomiting, early satiety, fullness, bloating, and pain. GND can be further sub-classified as type A (GND-A) where gastric emptying is delayed (otherwise known as gastroparesis) and type B (GND-B) where gastric emptying is normal.

Despite our current knowledge of the gut-brain axis and the interplay between the central, peripheral, autonomic and vestibular systems; further investigation into the underlying

pathways that drive gastric neuromuscular dysfunction is required. Future investigation is needed to elucidate the underlying pathophysiology driving GND and identify new therapeutic targets. In addition, studies with rigorous methodology are needed to evaluate the currently available therapies within this population. It is our hope that new research endeavors will be undertaken that strive to elucidate the pathophysiologic cause of gastric neuromuscular dysfunction and identify effective therapeutic options to treat the debilitating symptoms affecting this important patient population.

Acknowledgments

Pankaj J. Pasricha has received a grant from the NIH, is a cofounder of Neurogastrx and ETx, is a consultant for Vanda Pharma, and has received sponsored research fees from Theravance.

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•• Of major importance

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Opinion Statement

Chronic unexplained nausea and vomiting is a debilitating condition that dramatically decreases patient quality of life and creates diagnostic and treatment challenges for healthcare providers. Additionally, the significant overlap in symptoms between disorders such as chronic unexplained nausea and vomiting, gastroparesis and functional dyspepsia has resulted in a blurring of diagnostic lines and added confusion to the therapeutic approach. The identified overlap in clinical symptoms also suggests a common underlying pathophysiological mechanism may drive these conditions, indicating they could possibly be part of a spectrum of gastric neuromuscular disorders instead of discrete processes. This article will discuss the classification, updates in pathophysiology and therapeutic research, and future directions of research in the treatment of chronic unexplained nausea and vomiting.

Table 1

Rome III vs Rome IV criteria for nausea and vomiting disorders and functional dyspepsia[1,5]

Rome III			Rome IV	
Nausea and vomiting disorders	**1**	Chronic Idiopathic Nausea	**1**	Chronic Nausea and Vomiting Syndrome (CNVS)
	2	Cyclic Vomiting Syndrome	**2**	Cyclic Vomiting Syndrome (CVS)
	3	Functional Vomiting (criteria included cannabinoid use)	**3**	Cannabinoid Hyperemesis Syndrome (CHS)
Functional Dyspepsia	**1**	Postprandial Distress Syndrome (PDS)	**1**	Postprandial Distress Syndrome (PDS)
	2	Epigastric Pain Syndrome (EPS)	**2**	Epigastric Pain Syndrome (EPS)