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REVIEW ARTICLE

A link between gastrointestinal disorders and migraine: Insights into the gut–brain connection

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Abstract

Background: Migraine is a complex, multifaceted, and disabling headache disease that is often complicated by gastrointestinal (GI) conditions, such as gastroparesis, functional dyspepsia, and cyclic vomiting syndrome (CVS). Functional dyspepsia and CVS are part of a spectrum of disorders newly classified as disorders of gut–brain interaction (DGBI). Gastroparesis and functional dyspepsia are both associated with delayed gastric emptying, while nausea and vomiting are prominent in CVS, which are also symptoms that commonly occur with migraine attacks. Furthermore, these gastric disorders are comorbidities frequently reported by patients with migraine. While very few studies assessing GI disorders in patients with migraine have been performed, they do demonstrate a physiological link between these conditions.

Objective: To summarize the available studies supporting a link between GI comorbidities and migraine, including historical and current scientific evidence, as well as provide evidence that symptoms of GI disorders are also observed outside of migraine attacks during the interictal period. Additionally, the importance of route of administration and formulation of migraine therapies for patients with GI symptoms will be discussed.

Methods: A literature search of PubMed for articles relating to the relationship between the gut and the brain with no restriction on the publication year was performed. Studies providing scientific support for associations of gastroparesis, functional dyspepsia, and CVS with migraine and the impact these associations may have on migraine treatment were the primary focus. This is a narrative review of identified studies.

Results: Although the association between migraine and GI disorders has received very little attention in the literature, the existing evidence suggests that they may share a common etiology. In particular, the relationship between migraine, gastric motility, and vomiting has important clinical implications in the treatment of migraine, as

Abbreviations: ANS, autonomic nervous system; AUC, area under the curve; CGRP, calcitonin gene-related peptide; CI, confidence interval; CNS, central nervous system; CVS, cyclic vomiting syndrome; CUNV, chronic unexplained nausea and vomiting; DGBI, disorders of gut–brain interaction; EPS, epigastric pain syndrome; GCSI, Gastroparesis Cardinal Symptom Index; GI, gastrointestinal; IBS, irritable bowel syndrome; NTS, nucleus tractus solitarius; OR, odds ratio; PDS, postprandial distress syndrome; SD, standard deviation; SEM, standard error of the mean; TGV, trigeminovascular; TNFα, tumor necrosis factor-alpha.

delayed gastric emptying and vomiting may affect oral dosing compliance, and thus, the absorption and efficacy of oral migraine treatments.

Conclusions: There is evidence of a link between migraine and GI comorbidities, including those under the DGBI classification. Many patients do not find adequate relief with oral migraine therapies, which further necessitates increased recognition of GI disorders in patients with migraine by the headache community.

KEYWORDS
cyclic vomiting syndrome, disorders of gut–brain interaction, functional dyspepsia, gastric motility, gastroparesis, migraine

INTRODUCTION

Migraine is defined by the International Classification of Headache Disorders (3rd edition) as a common, disabling primary headache disorder.[1] According to the Global Burden of Disease Study in 2016, migraine was the sixth most prevalent disorder, afflicted ~1 billion individuals, and was more predominant in women (18.9%) compared to men (9.8%) globally.[2] Migraine is defined as a recurrent headache disorder with moderate or severe headache attacks that can last for 4–72 h and are accompanied by nausea and/or photophobia and phonophobia.[1] In particular, the nausea that accompanies migraine strongly contributes to the burden and disability associated with migraine.[3] The American Migraine Prevalence and Prevention study conducted in 2009 revealed that patients with migraine who experienced high-frequency nausea had significantly higher odds of occupational disability or taking medical leave, and increased headache pain severity and impact.[3] In addition to nausea, other gastrointestinal (GI) symptoms may be present with migraine and include vomiting, diarrhea, reflux, and constipation.[4,5] A large survey in the United States completed by 29,727 participants reported that 73% and 29% of patients with migraine experienced nausea and vomiting, respectively.[5] In a large analysis of women with migraine, nausea and vomiting were reported by 61.6% of those with migraine with aura and 66.0% without aura.[6] Furthermore, a variety of GI conditions have been associated with migraine, such as inflammatory bowel disease, celiac disease, irritable bowel syndrome (IBS), *Helicobacter pylori* infection, cyclic vomiting syndrome (CVS), functional dyspepsia, and gastroparesis.[7–13] The Rome Foundation recently introduced the term, disorders of gut–brain interaction (DGBI), which is defined as "a group of disorders classified by GI symptoms related to any combination of motility disturbances, visceral hypersensitivity, altered mucosal and immune function, gut microbiota, and/or central nervous system (CNS) processing."[14] The Rome Foundation is an independent not-for-profit organization that provides support for science-based activities to assist in DGBI diagnosis and treatment.[15] Functional dyspepsia and CVS are included under the DGBI classification, thus, suggesting that an interaction between the brain and gut exists in these common disorders.[14] There is significant overlap between idiopathic gastroparesis and functional dyspepsia such that both are associated with delayed gastric emptying in the absence of a mechanical obstruction, as well as impaired fundic accommodation and gastric hypersensitivity in functional dyspepsia,[16,17] while episodic nausea, vomiting, and abdominal pain are present in CVS.[18] In our recently completed Phase 3 STOP 301 study,[19] 38.4% of our patients (N = 354) had comorbid GI disorders at study entry. Gastroesophageal reflux disease was the most prevalent (20.3%), followed by IBS (5.6%), constipation (4.0%), and dyspepsia (3.1%). There is evidence of an association between migraine and GI disorders in the literature. In this paper, we will review the historical and current state of scientific evidence that exists for a relationship between migraine and GI comorbidities, and how their association may impact migraine treatment.

METHODS

For this narrative review, a literature search of PubMed with no restriction on the publication year for articles relating to the relationship between the gut and the brain was performed. Search terms included gut-brain connection, gut-brain axis, gastric disorders AND migraine OR headache, gastroparesis AND migraine OR headache, functional dyspepsia AND migraine OR headache, and CVS AND migraine OR headache. Studies of primary focus were manually identified, which included those that investigated the association of migraine with three gastric disorders (gastroparesis, functional dyspepsia, and CVS) as well as studies reporting an impact of GI symptoms on migraine therapies. Since the objective of this narrative review was to provide historic and current scientific evidence linking gastric disorders with migraine and their effect on migraine management, inclusion criteria included all study types (i.e., case reports, randomized-controlled trials, reviews, etc.). Manual reads of the reference section of articles were also completed. All authors reviewed the identified studies reported in this review.

PATHOPHYSIOLOGICAL SIMILARITIES BETWEEN GI COMORBIDITIES AND MIGRAINE

The pathophysiology of both migraine and GI comorbidities, including DGBI, is complex and neither has been fully elucidated[20]; however, scientific evidence does show an overlap in pathophysiology

between these complex disorders. Investigating this overlap can help shed light on a common pathophysiological abnormality or biological mechanism. Currently, there is evidence to implicate a shared pathophysiology between migraine and GI disorders, which is believed to occur via an interaction of numerous factors including inflammatory mediators, gut microbiota, neuropeptides, and the serotonin pathway.[21] Particularly, the autonomic nervous system (ANS) is thought to play an important role in the association between migraine and GI dysfunction due to the similarities in their symptom profiles, which both include nausea, vomiting, dyspepsia, and gastroparesis.[20,22] Further, ANS abnormalities have been described in migraine[23–25] and various upper GI disorders, such as diabetic and idiopathic gastroparesis,[26,27] CVS,[28,29] and functional dyspepsia[30,31] (Figure 1). Under normal conditions, digestion is regulated by a bidirectional interaction between the gut and brain through an interplay of the enteric nervous system, the interstitial cells of Cajal, fibroblast-like cells, gastric smooth muscle, the CNS, and the ANS.[32,33] Afferent sensory information from the GI tract is transmitted by the vagus nerve to the nucleus tractus solitarius (NTS) of the brainstem, which then leads to efferent sympathetic or parasympathetic innervation of the GI tract to modulate GI function by either decreasing or increasing GI secretion and motility, respectively.[27,34] Under pathological conditions, delayed gastric emptying (i.e., gastroparesis) may occur either due to a loss or injury to the interstitial cells of Cajal, which may result from macrophage-driven immune dysregulation and oxidative stress, and/or in some individuals, can involve the loss of enteric nerves and fibrosis in muscle layers.[33]

Nausea, vomiting, and delayed gastric emptying are part of the migraine symptom profile.[1,4,5,7,59] The NTS is involved in regulating vomiting, and in migraine it is suggested that the activation of the trigeminovascular (TGV) system during a migraine attack leads to neuronal activation in the NTS, which may cause nausea and vomiting.[60,61] The pathophysiology of migraine, especially the nausea and vomiting and alterations in gastric emptying, involves serotonergic signaling. Serotonin, both a vasodilator and vasoconstrictor, acts as a modulator of nociceptive pain, and decreased activity of 5-$HT_{1B/1D}$ receptors has been thought to activate the TGV system involved in the initiation of a migraine attack.[35–37] The gut contains ~95% of the body's total serotonin, and numerous studies utilizing serotonergic pharmacologic agents have reported that serotonin may play a role in regulating gastric emptying and symptoms associated with GI dysfunction.[38–41] Serotonin acting on 5-HT_{1P} receptors initiates peristaltic and secretory reflexes, while stimulation of 5-HT_4 receptors enhances the release of neurotransmitters in reflex pathways. 5-HT_3 receptors activate extrinsic sensory nerves, regulating information transmitted from the gut to the brain, and blocking their activity can delay intestinal motility, while activating 5-HT_3 receptors on visceral afferent fibers can result in emesis.[40,62] Furthermore, a decrease in serotonergic signaling in mucosa occurs during inflammation.[40,63] Studies assessing the effects of 5-HT_{1A} agonists have shown enhanced gastric accommodation and improvement in postprandial symptoms in patients with functional dyspepsia as well as improvements in common gastroparetic symptoms such as nausea and vomiting in patients with gastroparesis.[42,43] In addition to the serotonergic receptors mentioned above, other receptor subtypes that are expressed in the GI tract have also been implicated in the pathogenesis of migraine, which include adrenergic and dopaminergic receptor subtypes, and are summarized in Table 1.

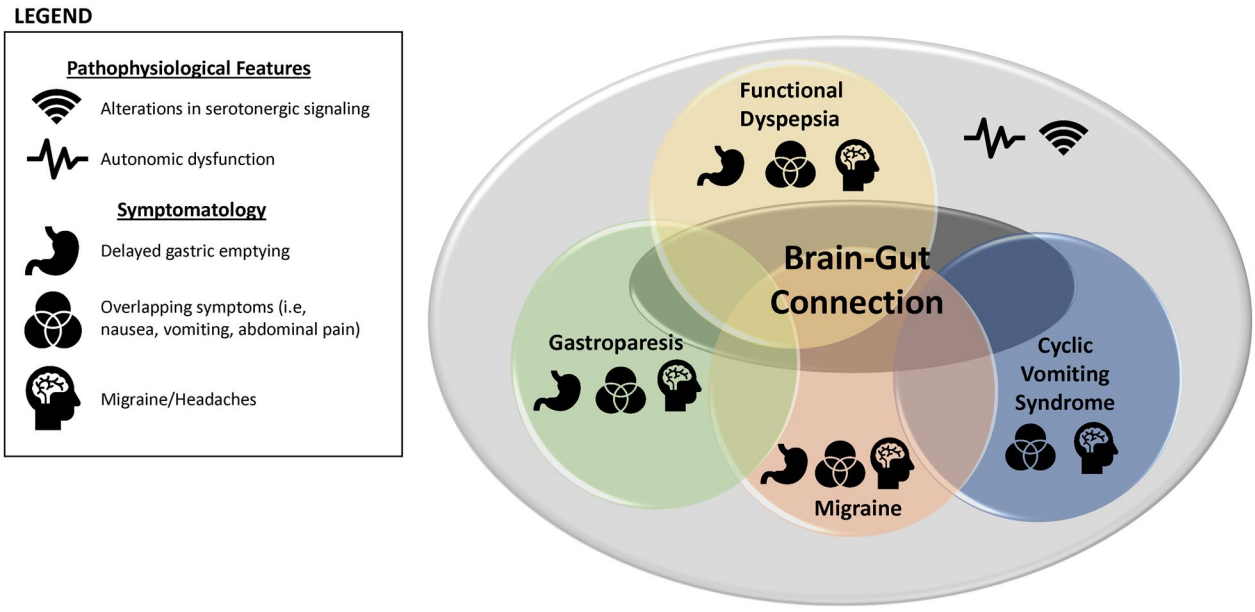

FIGURE 1 A brain–gut connection between migraine and gastric disorders. There is evidence in the literature supporting a brain-gut connection.[21] This review further corroborates this association by providing evidence of shared pathophysiological features, such as alterations in serotonergic signaling[35–43] and autonomic dysfunction,[20,22–24,26–28,30,31] and overlapping symptomatology between migraine,[1,4,5,7,11,14,18,44–53] and GI disorders including gastroparesis, functional dyspepsia, and cyclic vomiting syndrome, often presenting as comorbidities in either condition[7,10,11,54–58] [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Selective receptors implicated in migraine pathophysiology are expressed in the GI tract

Major receptors	Expression in the GI tract	Evidence supporting implication in migraine pathogenesis
Serotonergic[40,62–85]	5-HT_{1A}, 5-HT_{1P} 5-HT_{2A}, 5-HT_{2B} 5-HT_3 5-HT_4 5-HT_7	5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1F} 5-HT_{2A}, 5-HT_{2B}
Adrenergic[86–94]	α_2 β_1 β_2 β_3	α_2 β_1 β_2
Dopaminergic[80,95–106]	$D_{1\text{-}5}$	$D_{2\text{-}5}$
CGRP[107–109]	CLR/RAMP1	CLR/RAMP1

Note: This table includes a list of key receptors located in the GI tract that are also implicated in the pathogenesis of migraine in both animal and human studies.

Abbreviations: 5-HT, 5-hydroxytryptamine; CGRP, calcitonin gene-related peptide; CLR, calcitonin-like receptor; GI, gastrointestinal; RAMP1, receptor activity modifying protein 1.

The neuropeptide calcitonin gene-related peptide (CGRP) has been implicated in migraine pathophysiology based on biological mechanisms as well as clinical trials demonstrating efficacy in migraine patients treated with pharmacologic agents that target CGRP and its receptors.[110–114] αCGRP and βCGRP are isoforms of CGRP that are predominantly expressed in sensory and enteric neurons, respectively, and have been shown to innervate a variety of areas within the digestive system.[114–116] Both the release of CGRP from parasympathetic perivascular and trigeminal fibers in migraine and the alterations in intestinal microbiota and gut permeability in response to stress factors can lead to the release of proinflammatory mediators. These, in turn, can affect nociceptive responses in the trigeminal pathway and lead to migraine development.[22,117–120] The release of proinflammatory molecules can also result in increased susceptibility to inflammatory disorders via the activation of the hypothalamic–pituitary–adrenal axis, such as those affecting the GI system.[21,117,118] In particular, high levels of CGRP and low pain thresholds for gastric distention have been reported in patients with functional dyspepsia who are positive for *Helicobacter pylori*, highlighting a potential role for CGRP in pain mechanisms in functional dyspepsia pathophysiology.[121] Additionally, CGRP has been shown to inhibit gastric acid secretion and may suppress food intake, and alterations in gut microbiota may affect signaling of CGRP.[122,123] A summary of the biologic mechanisms that may contribute to the relationship between migraine and gastric disorders can be found in Figure 2.

A pathophysiological relationship between migraine and gastric disorders is further supported by overlap in some pharmacological agents used in the treatment of both disorders. Domperidone, a dopamine receptor antagonist with gastrokinetic and antiemetic features, is used for the treatment of gastroparesis and was shown to prevent a majority of migraine attacks with early administration (i.e., at the time of early warning symptoms) at the higher doses.[132–134] Used to treat gastroparesis and nausea, metoclopramide is a dopamine receptor antagonist that was reported to be effective as an intravenous acute treatment of migraine at multiple doses.[134–136] CVS and migraine also overlap with regard to medications used to prevent or treat both conditions, which include tricyclic antidepressants and antiepileptic drugs as prophylaxis, and triptans and antiemetics as abortive therapies.[18] Similarly, agents used to treat migraine may also be efficacious in treating some GI disorders. One study reported the effectiveness of propranolol, a beta-blocker used for migraine prevention, in increasing colonic motility in 10 patients with IBS.[137,138] Tricyclic antidepressants are used for migraine prevention and as first-line therapy for pain-predominant DGBIs such as functional dyspepsia, IBS, and CVS.[138–140] Noninvasive vagal nerve stimulation, which stimulates myelinated sensory afferent vagal fibers, is approved by the Food and Drug Administration as abortive therapy in patients with migraine and cluster headache.[141,142] Two separate open-label pilot studies using the same device in patients with gastroparesis demonstrated improvement in gastroparesis symptoms and acceleration of gastric emptying.[142,143] While there are indications that the pathophysiologies of migraine and gut disorders are linked in many individuals, there is still work to be done to elucidate the mechanisms involved. Early research into the pathogenesis and links between these two disorders is sparse. A recent in vivo study utilizing several monogenic mouse models with mutations of genes linked to migraine phenotypes reported no presence of gastroparesis or delayed small intestinal motility, suggesting an absence of heritable characteristics between migraine and gastroparesis.[144] One recent in vivo mouse model that explicitly evaluated the role of the gut microbiome in the development of migraine-like pain demonstrated that antibiotic treatment prolonged nitroglycerin-induced acute migraine-like pain, but this pain prolongation was completely blocked by genetic deletion of tumor necrosis factor-alpha (TNFα) or injection of a TNFα receptor antagonist. These results suggest that gut microbiota dysbiosis contributes to migraine-like pain by upregulating TNFα levels in the trigeminal nociceptive system, supporting

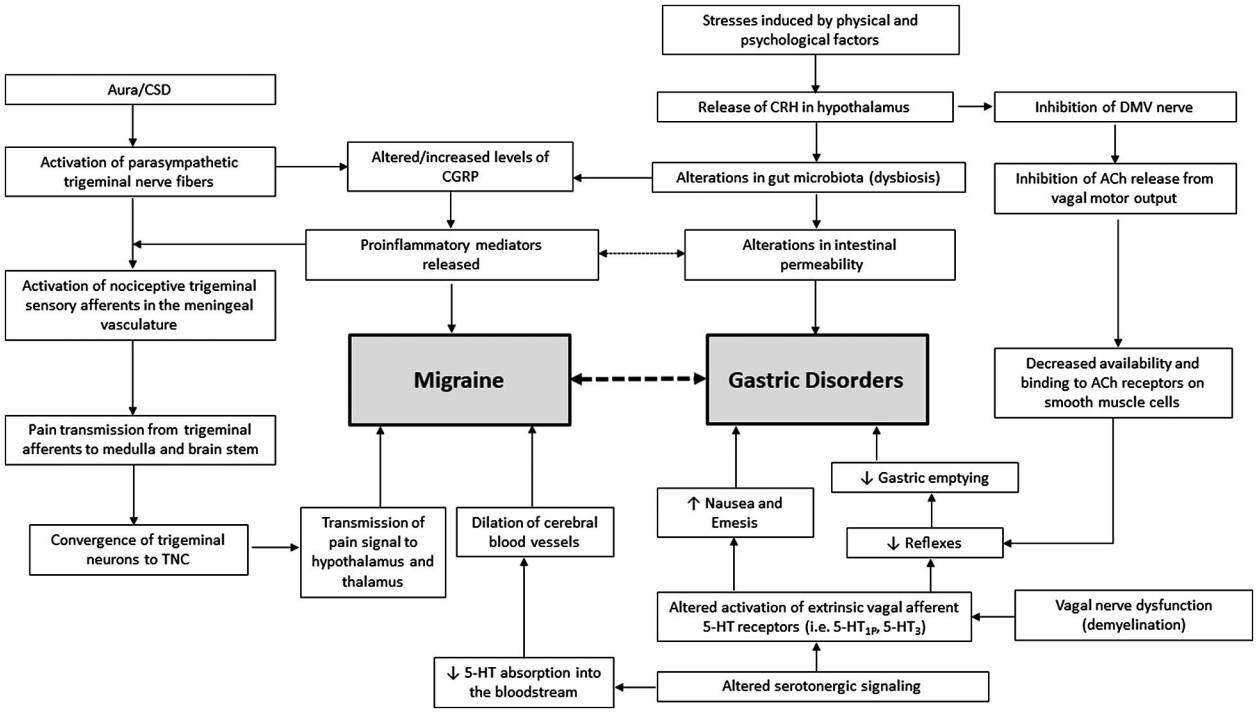

FIGURE 2 Proposed mechanisms explaining the relationship between migraine and gastric disorders.[21,22,34,35,40,62,124–131] A bidirectional relationship exists between migraine and gastric disorders, which is influenced by autonomic dysfunction; specifically, altered sympathetic and parasympathetic activity and changes in the gut microbiota profile, which are mediated by various cytokines, hormones, and neurotransmitters.[21] In migraine, cortical spreading depression (CSD) activates pain pathways that originate from the parasympathetic trigeminal nerve fibers and results in the release of calcitonin gene-related peptide (CGRP) and proinflammatory mediators, which are implicated in both migraine and gastrointestinal (GI) disorder pathophysiology.[22,124] In gastric disorders, it is suggested that stress induced by physical and psychological factors causes the release of corticotrophin-releasing hormone (CRH), which leads to alterations in gut microbiota and intestinal permeability, the release of proinflammatory mediators, and the inhibition of acetylcholine release, resulting in GI dysfunction. Another major factor contributing to this relationship is an alteration in serotonergic signaling, which can activate the TGV system involved in the initiation of a migraine attack and lead to the development of symptoms of gastric disorders including nausea, emesis, and delayed gastric emptying by altering GI reflex pathways or activating GI serotonin receptors.[21,22,35–43,62] Abbreviations: 5-HT, 5-hydroxytryptamine; ACh, acetylcholine; DMV, dorsal motor nucleus of the vagus; TGV, trigeminovascular; TNC, trigeminal nucleus caudalis

a proposed link between these disorders.[145] We look forward for future studies elucidating this potential pathophysiologic link between migraine and gut disorders.

GI COMORBIDITIES AND MIGRAINE: GASTROPARESIS, FUNCTIONAL DYSPEPSIA, AND CYCLIC VOMITING SYNDROME

Gastroparesis and migraine

A diagnosis of gastroparesis is confirmed with a 4-h gastric emptying evaluation by scintigraphy and exclusion of other etiologies.[146,147] To assess symptom severity, the Gastroparesis Cardinal Symptom Index (GCSI), a subset of the Patient Assessment of Upper Gastrointestinal Symptoms, can be used. It comprises three subscales (nausea and vomiting, postprandial fullness and early satiety, and bloating) that the patient scores based on the past 2 weeks.[148] The Gastroparesis Cardinal Symptom Index – Daily Diary, a more accurate and comprehensive version of the GCSI that allows patients to record symptoms daily, is also available.[149] The natural history of gastroparesis is largely unknown, and the prevalence is difficult to estimate; however, the prevalence of diagnosed gastroparesis in the US population has been estimated at 24.2 per 100,000 persons.[150,151] According to population-based studies, individuals are predominantly female and the most common symptoms, either persistent or episodic, are nausea and vomiting, but can also include abdominal pain, bloating, weight loss, postprandial fullness, and early satiety.[44,45,150] Importantly, abdominal pain is a common but underrecognized symptom that contributes to a decrease in quality of life.[46,47] In individuals with idiopathic gastroparesis and abdominal pain, those with severe abdominal pain were more likely to have overlapping migraine than those with milder symptoms.[54] Major etiologies of gastroparesis are diabetic, post-surgical, and idiopathic, and in general, an idiopathic etiology is the most common.[45,150,152] A National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) study that characterized 243 patients with idiopathic gastroparesis reported that delayed gastric emptying was mild (≤20% gastric retention) in 45%, moderate (>20%–35% retention) in 27%, and severe (>35% retention) in 28% of patients.[44] Historical evidence supporting an

association between migraine and delayed gastric emptying emerged from early reports of alterations in gastric motility in patients experiencing a migraine attack.[153,154] Later, experimental studies by Volans reported a delay in effervescent aspirin absorption during a migraine attack, but not during the headache-free period, suggesting that delayed gastric emptying occurs during spontaneous migraine attacks.[59] A comprehensive summary of key studies assessing gastric emptying in patients with migraine is provided in Table 2. Boyle et al.[48] examined delay in gastric emptying utilizing the epigastric impedance method in 46 patients with migraine and 64 individuals without migraine. There was no difference in the mean time to half gastric emptying in those without migraine (mean ± standard deviation [SD]: 9 ± 5 min) compared to those with migraine outside an attack (mean ± SD: 10.1 ± 5.3 min). However, in 14 patients who experienced severe or moderate migraine attacks that were sometimes associated with pain, nausea, and photophobia, the mean time to half gastric emptying ranged from 6 to >60 min.[48] The hypothesis that gastric emptying was delayed only during a migraine attack was questioned when studies decades later demonstrated delay in gastric emptying during visually induced migraine and during the headache-free, interictal period.[7,49] Aurora et al. evaluated gastric emptying using gastric scintigraphy in 10 patients with migraine during the ictal and interictal period and 10 age- and sex-matched individuals without migraine. In patients with migraine, the time to half emptying after a visually induced migraine attack was delayed ictally (78%) and interictally (80%), and the mean time to half emptying during the interictal period was significantly longer in patients with migraine (mean ± SD: 188.8 ± 100.6 min) compared to patients without migraine (mean ± SD: 111.8 ± 38.6 min; $p = 0.0168$).[7] In a subsequent case report, Aurora et al. replicated these findings when assessing gastric emptying by gastric scintigraphy in a single patient with spontaneous migraine (124 min), a single patient with induced migraine (182 min), and a single patient with migraine during the interictal period (243 min) compared to normative values (112 min).[49] These results suggest that individuals with migraine may experience a delay in gastric motility both during and outside of a migraine attack, challenging previous theories that delays occur only during an attack.[48,49,59] However, when Yalcin et al. assessed liquid phase gastric emptying in seven patients with migraine during the interictal period, seven patients with migraine during the ictal period, and seven individuals without migraine, findings contradictory to those of Aurora and colleagues were reported. The mean time to half gastric emptying was similar between patients with migraine outside a migraine attack (mean ± SD: 26.29 ± 9.45 min) and those without migraine (mean ± SD: 26.14 ± 5.61 min), compared to patients with migraine during an attack (mean ± SD: 48.00 ± 18.72 min).[50] The difference in methodology used to evaluate gastric emptying during the liquid phase in this study may explain the observation of delayed gastric emptying only in patients with migraine during an attack and not interictally. More recent and extensive evidence is provided

TABLE 2 Experimental studies assessing gastric emptying in patients with migraine

Study	*N*	Subject group	$T_{1/2}$ (min)[a]	Detection method
Boyle 1990[48]	46	Patients with migraine—outside of attack	10.1 ± 5.3	Epigastric impedance
	14	Patients with migraine—during attack	6–<60	
	64	Individuals without migraine—controls	9 ± 5	
Aurora 2006[7]	10	Patients with migraine—interictal	188.8 ± 100.6	Gastric scintigraphy
	9	Patients with migraine—ictal	149.9 ± 69.4	
	10	Individuals without migraine—controls	111.8 ± 38.6	
Aurora 2007[49]	1	Patients with migraine—interictal	243	Gastric scintigraphy
	1	Patients with migraine—spontaneous migraine	124	
	1	Patients with migraine—induced migraine	182	
	N/A	Control—normative value	112	
Yu 2012[52]	27	Patients with migraine without GI symptoms interictally	100.82 ± 23.94	Gastric scintigraphy
	32	Functional dyspepsia patients	125.51 ± 52.55	
	12	Healthy individuals—controls	95.23 ± 23.29	
Yalcin 2012[50]	7	Patients with migraine—interictal	26.29 ± 9.447	Liquid phase gastric scintigraphy
	7	Patients with migraine—ictal	48.0 ± 18.717	
	7	Individuals without migraine—controls	26.14 ± 95.610	

Note: This table includes a comprehensive list of experimental studies assessing gastric emptying in patients with migraine utilizing different methodologies and patient populations.

Abbreviations: GI, gastrointestinal; N/A, not available.

[a]$T_{1/2}$ is the time to half gastric emptying; values presented as mean ± standard deviation for all studies with the exception of the Aurora 2007 study.

TABLE 3 Prevalence of comorbidities in patients with gastroparesis or CUNV

	Gastroparesis[a] (*N* = 516)	CUNV[b] (*N* = 195)	Total (*N* = 711)	*p* value[c]	Population estimates (US)
Severe abdominal pain[d]	237 (45.9%)	66 (33.9%)	303 (42.6%)	0.004	
Migraine headache	189 (36.6%)	69 (35.4%)	258 (36.3%)	0.79	15.3%
Endometriosis[e]	71 (16.6%)	20 (12.5%)	91 (15.5%)	0.25	6.1%
Fibromyalgia	67 (13.0%)	24 (12.3%)	91 (12.8%)	0.90	1.75%
Chronic fatigue syndrome	44 (8.5%)	11 (5.6%)	55 (7.7%)	0.27	0.52%–1.04%
Interstitial cystitis	18 (3.5%)	7 (3.6%)	25 (3.5%)	1.00	1.9%–6.53%[f]

Note: This table presents the prevalence of the most frequent comorbidities associated with patients with gastroparesis and CUNV from the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium study.[55,155–160]

Abbreviation: US, United States.

[a]Gastroparesis based on delayed gastric emptying scintigraphy >60% retention at 2 hours or >10% retention at 4 hours; [b]CUNV is defined as chronic unexplained nausea and vomiting, based on non-delayed gastric emptying scintigraphy; [c]*p*-values derived from Fisher's exact tests; [d]Severe abdominal pain based on a score of 4 (severe) or 5 (very severe) on the patient assessment of upper gastrointestinal symptom severity (PAGI-SYM) questionnaire (scale of 0–5); [e]89 males excluded from endometriosis counts; [f]Range includes calculated prevalence estimates based on definitions spanning a range of sensitivity and specificity for both men and women.

in a retrospective study that evaluated gastroparesis-like symptoms in patients from the NIDDK Gastroparesis Clinical Research Consortium. A total of 711 patients were studied, including 516 patients with gastroparesis and 195 patients with chronic unexplained nausea and vomiting (CUNV). 36.6% of patients with gastroparesis reported having migraine attacks (Table 3). Patients with migraine headaches also had a more severe GCSI (odds ratio [OR] 1.24, 95% confidence interval [CI] 1.05–1.45, $p = 0.009$), increased trait anxiety (OR 1.16, 95% CI = 1.03–1.32, $p = 0.02$), and were less likely to be diabetic (OR = 0.67, 95% CI = 0.48–0.94, $p = 0.02$) compared to those without migraine headaches.[55] These data suggest that the comorbid association of migraine and GI disorders is indeed common and worthy of more detailed investigation.

Functional dyspepsia and migraine

According to the Rome IV criteria, functional dyspepsia is subdivided into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). Functional dyspepsia is defined by bothersome early satiety or postprandial fullness ≥3 days per week (PDS) or bothersome epigastric pain or epigastric burning ≥1 day per week in the past 3 months (EPS) with a ≥6-month history, respectively.[161] Additional symptoms may also include bloating, belching, and nausea.[14] A delay in gastric emptying of solids and liquids is also present in 23% and 35% of patients with functional dyspepsia, respectively.[51] Further, there is an overlap in symptomatology between gastroparesis and functional dyspepsia. According to the Gastroparesis Registry of 106 patients with gastroparesis, the majority of patients also met Rome criteria for the PDS subtype of functional dyspepsia.[46] While the etiology of functional dyspepsia remains to be determined, the prevalence varies between geographic location and diagnostic criteria, ranging from ~5% to 40% globally.[161,162] Di Stefano et al. observed that migraine is a common comorbidity in patients with functional dyspepsia and postprandial symptoms. In a study of 60 patients with functional dyspepsia, 38 with PDS and 22 with EPS, 68% experienced migraine without aura. Of those with EPS, 54% experienced migraine without aura, which was not correlated with ingesting a meal, while 76% of patients with PDS experienced migraine, where 89% of migraine attacks were correlated with meal ingestion. Interestingly, patients with PDS and moderate to severe migraine experienced significantly greater fullness (2.2 ± 0.7 vs. 1.9 ± 0.7; $p = 0.02$) and early satiety (2.0 ± 0.8 vs. 1.7 ± 0.8; $p = 0.01$) compared to PDS patients with mild or no migraine, while patients with EPS and severe migraine experienced less severe epigastric burning (0.7 ± 0.7 vs. 1.6 ± 0.8; $p = 0.008$) and bloating (1.3 ± 1.0 vs. 2.3 ± 0.7; $p = 0.01$) compared to EPS patients with mild or no migraine. However, the mean time to gastric emptying in patients with PDS and EPS was similar irrespective of migraine severity.[10] Pucci et al. observed meal-induced hypersensitivity of the stomach in patients with functional dyspepsia and migraine. Visceral sensitivity was evaluated by assessing sensitivity thresholds to mechanical distention by utilizing an instrument called the barostat following a liquid meal. The discomfort threshold following a liquid meal was significantly lower in seven patients with functional dyspepsia and migraine without aura (mean ± SD: 7 ± 4 mm Hg; $p < 0.01$) compared to seven patients with functional dyspepsia without migraine (mean ± SD: 11 ± 4 mm Hg) and seven healthy

volunteers (mean ± SD: 11 ± 6 mm Hg).[163] In a study by Yu et al.[52] gastric emptying was assessed by gastric scintigraphy in 27 patients with migraine without GI symptoms during the interictal period, 32 patients with functional dyspepsia, and 12 healthy volunteers. The mean gastric half emptying time in patients with functional dyspepsia (mean ± SD: 125.51 ± 52.55 min) was longer than in patients with migraine (mean ± SD: 100.82 ± 23.94 min; $p = 0.035$) and healthy volunteers (mean ± SD: 95.25 ± 23.29 min; $p = 0.021$). Further, in patients with migraine, the gastric half emptying time was similar in patients who did experience vomiting (mean ± SD: 98.1 ± 22.8 min) or nausea (mean ± SD: 103.8 ± 22.1 min) compared to those who did not experience vomiting (mean ± SD: 103.5 ± 24.7 min) or nausea (mean ± SD: 95.0 ± 29.9 min), suggesting that gastric half emptying time was not associated with vomiting or nausea experienced during the interictal period (Table 1).[52] It is important to note that the grading criteria of gastric emptying used in this study has been questioned, since the proportions of gastric emptying in the functional dyspepsia patients and healthy volunteers do not align with previous studies. Further, it had been suggested that the exclusion of patients with migraine who experience GI symptoms during the interictal period does not allow for an accurate assessment of an association between migraine and functional dyspepsia.[164]

CVS and migraine

According to the Rome IV criteria, CVS is defined by stereotypical episodes of acute-onset vomiting lasting <1 week, ≥3 discrete episodes in the prior year, and 2 episodes in the past 6 months, occurring ≥1 week apart; and absence of vomiting between episodes, although milder symptoms can be present. Symptoms are also required to have been present for the past 3 months with onset at least 6 months prior.[53] Although CVS is typically regarded as a pediatric condition, it is also present in adults,[11,18] and although few data have been published, the prevalence of CVS in adults has been reported to range from 0.7% to 2% in the United States, Canada, and the United Kingdom.[53] Depending on the stage of CVS, common symptoms may include nausea, sweating, epigastric pain, fatigue, feeling hot or cold, GI disturbances, and/or violent attacks of vomiting or retching. Some individuals may experience little to no symptoms during the inter-episodic phase.[11,18] The etiology of CVS is unclear and it may arise from stress triggers, and less frequently dietary triggers, but an association with migraine is suggested based on similarities in triggers and symptomatology, which include antecedent auras, associated headaches, phonophobia, and photophobia.[18,28] Migraine is also a frequent comorbidity present in individuals with CVS, including children.[56,57] In a retrospective study by Fleisher et al. of 40 adult patients with CVS, 70% experienced migraine headaches during or between CVS episodes.[11] In a large, retrospective study by Bhandari et al. in adult patients with CVS ($N = 20{,}952$) and age-matched patients without CVS ($N = 44{,}262$), migraine was a comorbidity observed more frequently in CVS patients (9%) compared to patients without CVS (3%; $p < 0.001$).[165] Additionally, Kumar et al. observed that 43% of adult patients with CVS experienced migraine in a retrospective analysis.[58] Further, a whole-brain analysis of patients with CVS and episodic migraine by Ellingsen et al. revealed that patients with CVS and episodic migraine showed reduced sensorimotor connectivity in the mid/posterior insula, an area important for nausea and viscerosensory processing, compared to healthy controls, highlighting a shared pathophysiology between these conditions.[166]

THE IMPACT OF GI COMORBIDITIES ON MIGRAINE TREATMENT

Nausea is an extremely disabling symptom of migraine and may impact when in an evolving attack a patient uses an oral treatment. In a large survey of 500 patients with migraine, nausea and vomiting were reported to affect a patient's willingness to take an oral medication in 30.5% and 42.2% of patients with migraine, respectively.[167,168] Gastric motility dysfunction and vomiting may also affect the rate and efficiency of absorption of drugs with high intestinal permeability.[167] Early studies assessing the pharmacokinetics of migraine treatment demonstrated that the absorption rates of oral formulations of headache medications were impaired in patients with migraine compared to the same patients with migraine during the headache-free period or to patients without migraine. Volans[59] assessed effervescent aspirin absorption by measuring plasma salicylate levels at 30 and 60 min after ingestion of aspirin in 42 migraine patients. Compared to patients without migraine at 30 min (mean: 7.88 ± 0.40 mg/100 mL), patients with migraine demonstrated a statistically significant impairment in the mean rate of aspirin absorption during an acute attack (mean: 4.77 ± 0.43 mg/100 mL) but not during the headache-free period (mean: 7.04 ± 0.64 mg/100 mL). At 30 min, 19 out of 42 migraine patients experienced plasma salicylate levels below the 2.5% lower confidence limit for individuals without migraine (i.e., 4.42 mg/100 mL), and delayed absorption was present more frequently with increasing headache and GI symptom severity.[59] Tokola and Neuvonen assessed the absorption of paracetamol in 9 female outpatients with migraine and determined that the mean peak serum concentration of paracetamol was significantly lower during the migraine phase (mean ± standard error of the mean [SEM]: 109 ± 14 μmol/L) than it was during the migraine-free period (mean ± SEM: 144 ± 16 μmol/L; $p < 0.05$). During a migraine attack, the area under the curve $(AUC)_{0\text{-}2\ h}$ was decreased by 17%, the $AUC_{0\text{-}4\ h}$ by 14%, and the $AUC_{0\text{-}6\ h}$ by 12% ($p < 0.05$) compared to the headache-free period. There was also a significant correlation between nausea at the beginning of the study and the decrease in the AUCs during a migraine attack at 0–3, 0–4, and 0–6 h ($p < 0.05$–<0.01).[169] Tokola and Neuvonen[170] also assessed the absorption of tolfenamic acid, a nonsteroidal anti-inflammatory drug, in 7 patients with migraine and reported that mean $AUC_{0\text{-}2\ h}$ was significantly lower during the migraine phase (mean ± SEM: 2.00 ± 0.66 mg*h/L) compared to the headache-free period (mean ± SEM: 4.07 ± 0.61 mg*h/L; $p < 0.05$), while the t_{max}

was significantly higher during the migraine phase (mean ± SEM: 2.86 ± 0.36 h) compared to the headache-free period (mean ± SEM: 1.69 ± 0.20 h; $p < 0.05$). Pre-treatment with metoclopramide, a p-aminobenzamide derivative that increases gastric motility and emptying, during migraine attacks increased the serum concentration of tolfenamic acid at 1.5 h. There was also no association between impairment in tolfenamic acid absorption during a migraine attack and attack duration or severity.[170]

There is also evidence that oral administration of some triptans results in varying plasma concentrations among patients with migraine during and outside of an attack. Thomsen et al. demonstrated that zolmitriptan was less rapidly absorbed during a migraine attack (median $C_{max0\text{-}4}$: 7.9 ng/mL; $n = 20$), which included those patients who vomited, compared to the migraine-free period (median $C_{max0\text{-}4}$: 12.6 ng/mL; $n = 18$), which is consistent with a delay in gastric emptying.[171] Further, the efficacy of triptans in treating migraine is increased when combined with medications that enhance GI motility. Schulman and Dermott[172] reported the efficacy of combining orally administered sumatriptan with either metoclopramide or placebo to treat moderate to severe migraine in 16 patients with migraine with or without aura. A headache response, defined as moderate or severe to mild or no pain at 2 h, was observed in 7/16 (44%) of patients receiving sumatriptan with metoclopramide compared to 5/16 (31%) with placebo. Three additional patients who received sumatriptan and metoclopramide reported meaningful migraine relief, as defined by the patient. Therefore, meaningful relief was achieved in 10/16 (63%) headaches treated with sumatriptan and metoclopramide compared to 5/16 (31%) headaches treated with sumatriptan and placebo, suggesting that adding metoclopramide to sumatriptan may benefit those patients who do not receive adequate relief with triptans alone.[172] Krymchantowski et al.[173] assessed whether combining rizatriptan with trimebutine (β-[dimethylamino]-β-ethylfenethylalcohol-3,4,5-trimetoxibenzoate), an opioid derivative that can activate receptors in the GI tract, would improve pain freedom compared to rizatriptan alone. Rizatriptan with trimebutine resulted in complete resolution of 30 out of 64 migraine attacks (46.8%) 1-h post-dose, compared with only 8 out of 64 attacks (12.5%) in patients treated with rizatriptan alone ($p < 0.01$). Complete resolution of migraine attacks was observed at even higher rates at 2 h (73.4% vs. 31.2%; $p < 0.001$) and 4 h (79.7% vs. 31.2%; $p < 0.001$) post-dose, respectively.[173] Interestingly, there are several reports of delayed gastric motility associated with the use of sumatriptan in healthy volunteers. Sakamoto et al. demonstrated that the time to gastric half emptying, as measured by a continuous ^{13}C breath test (BreathID system; Exalenz Bioscience Ltd.) in healthy individuals following ingestion of a liquid meal was a median of 131.84 (range: 103.13–168.70) minutes in the group receiving oral sumatriptan compared to 120.27 (range: 89.61–138.25) minutes in the control group ($p = 0.0166$).[174] Houghton et al. reported that in healthy individuals administered intravenous sumatriptan, the time to half gastric emptying, as measured by gamma scintillation, was delayed following a liquid meal (mean ± SD: 96 ± 40 min) compared to those who received placebo (mean ± SD: 76 ± 33 min).[175] Further, acute migraine therapies that are CGRP receptor antagonists or CGRP monoclonal antibodies have also been shown to cause constipation in some patients, suggesting that these agents are unable to provide patients relief from GI symptoms; however, data on the effect these molecules have on gastric emptying are not yet available.[176] Recognition of GI and DGBI comorbidities in patients with migraine is important for patients who experience GI symptoms and do not have relief from migraine symptoms using an oral abortive treatment. Non-oral routes of administration should be considered in these patients as they may positively impact them.[167,177] Importantly, efficacious, non-oral abortive therapies may also reduce the need for patients to seek chronic migraine medications that can be expensive or oral daily preventives that are suboptimal with regard to efficacy and tolerability.

CONCLUSION

The association between GI comorbidities, including those under the DGBI classification, and migraine may be underrecognized. Very few studies assessing DGBI, specifically gastroparesis, functional dyspepsia, and CVS, in patients with migraine have been performed, but the similarities and frequent comorbid presentation suggest a strong physiological link connecting these disorders that remains to be elucidated. It is evident that there is significant overlap with migraine and GI symptoms, which has been shown to affect the timing of drug administration by a patient due to nausea and fear of vomiting as well as the absorption of oral migraine medications. Attention to GI disorders and DGBI as comorbidities of migraine may be particularly important if patients with symptoms of nausea, vomiting, and/or abdominal pain do not experience relief from migraine symptoms using an oral migraine medication. Specifically, if a patient has cycled through several different orally administered migraine therapies without adequate relief, an assessment of GI comorbidities should be warranted. Non-oral routes of administration and formulation of migraine therapies should be considered early in migraine management.

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CONFLICT OF INTEREST

Sheena K. Aurora, Sutapa Ray, and Stephen B. Shrewsbury are full-time employees of Impel NeuroPharma and are stockholders in Impel NeuroPharma. Nada Hindiyeh serves on advisory boards for Amgen,

Eli Lilly, Lundbeck, and Zosano Pharma. Linda Nguyen serves on an advisory board for Gemelli and consults for Pendulum, Neurogastrx, Ironwood, Eli Lilly, and Alnylam.

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