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REVIEW ARTICLE

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Evidence-based review and frontiers of migraine therapy

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Abstract

Background: Cyclic vomiting syndrome (CVS) is identified as one of the "episodic syndromes that may be associated with migraine," along with benign paroxysmal torticollis, benign paroxysmal vertigo, and abdominal migraine. It has been proposed that CVS and migraine may share pathophysiologic mechanisms of hypothalamic activation and altered dopaminergic signaling, and impaired sensorimotor intrinsic connectivity. The past decade has brought groundbreaking advances in the treatment of migraine and other headache disorders. While many of these therapies have yet to be studied in episodic syndromes associated with migraine including CVS and abdominal migraine, the potential shared pathophysiology among these conditions suggests that use of migraine-specific treatments may have a beneficial role even in those for whom headache is not the primary symptom.

Purpose: This manuscript highlights newer therapies in migraine. Calcitonin gene-related peptide (CGRP) and its relation to migraine pathophysiology and the therapies that target the CGRP pathway, as well as a 5HT1F receptor agonist and neuromodulation devices used to treat migraine are briefly discussed as they may potentially prove to be useful in the future treatment of CVS.

KEYWORDS
calcitonin gene-related protein (CGRP) therapy, cyclic vomiting syndrome, migraine, migraine treatment, neuromodulation, serotonin receptor agonist

1 | INTRODUCTION

Cyclic vomiting syndrome (CVS) was first recognized by the International Classification of Headache Disorders in its second edition, when it was identified as one of the "childhood periodic syndromes that are commonly precursors to migraine."[1] As it is reported that recurrent gastrointestinal (GI) disturbances including cyclic vomiting can have onset in both adulthood and childhood,[2–4] the 3rd edition of the International Classification of Headache Disorders (ICHD-3)[5] now identifies CVS as one of the "episodic syndromes that may be associated with migraine," along with benign paroxysmal torticollis, benign paroxysmal vertigo, and abdominal migraine.[5] Follow-up studies of children with CVS have demonstrated that 40%–50% will develop migraine[6–9] and family history of migraine is also common.[10,11] It has been proposed that CVS and migraine may share pathophysiologic mechanisms of hypothalamic activation and altered dopaminergic signaling, and impaired sensorimotor intrinsic connectivity.[9,12,13] As such, the treatment of CVS has historically utilized migraine-directed acute therapies, such as sumatriptan, as well as medications commonly used in the preventive treatment of migraine (e.g., cyproheptadine, amitriptyline, and topiramate), though treatment studies are limited.[14–16]

The past decade has brought groundbreaking advances in the treatment of migraine and other headache disorders. While many of these therapies have yet to be studied in episodic syndromes associated with migraine including CVS and abdominal migraine,[5]

the potential shared pathophysiology among these conditions suggests that use of migraine-specific mechanisms may have a beneficial role even in those for whom headache is not the primary symptom.

Migraine has historically been viewed as a result of disturbances in intracranial blood flow. However, imaging studies have demonstrated that changes in intracranial vessels do not explain the dynamic experience of migraine or its response to treatment.[17] It is now understood that migraine results from a complex disruption in pain processing involving numerous pro-nociceptive and inflammatory signaling molecules, neurovascular fluctuations, and activation of cortical and subcortical anatomic circuits.[18] As a part of the proceedings of the 2022 Third International Symposium on Cyclic Vomiting Syndrome (CVS) and Cannabinoid Hyperemesis Syndrome (CHS), this article will highlight newer therapies in migraine, as they may potentially prove to be useful in the future treatment of CVS. We include a brief discussion on calcitonin gene-related peptide (CGRP) and its relation to migraine pathophysiology and the therapies that target the CGRP pathway, as well as a $5HT_{1F}$ receptor agonist and neuromodulation devices used to treat migraine (summarized in Table 1).

Key points

- The past decade has brought groundbreaking advances in the treatment of migraine and other headache disorders.
- Novel therapies for migraine target the CGRP pathway, 5-HT receptor subsets, and/or neuromodulation that interrupt the neurophysiologic mechanisms of the migraine attack.
- Newer therapies in migraine have resulted from further understanding of migraine pathophysiology and may prove to be useful in the future treatment of Cyclic Vomiting Syndrome (CVS) due to the potential overlap in the pathophysiology of the two diseases.

2 | CALCITONIN GENE-RELATED PEPTIDE

The evolution of understanding of the role of CGRP in migraine exemplifies the progress in translational research in the field. CGRP derives from the family of calcitonin peptides and is formed from differential splicing of the calcitonin gene.[60,61] In the central nervous system, CGRP is released from nerve endings and acts at receptors throughout the trigeminovascular system leading to local vasodilation as well as release of other pro-nociceptive neuropeptides.[18,62,63] While the alpha-isoform of CGRP is the primary form in the central nervous system, the beta-isoform is found throughout the enteric nervous system. CGRP acts at both the canonical CGRP receptor and the amylin 1 subtype[64] receptor; binding at these sites may have differential impact on CGRP function and blockade.[19,62,63]

CGRP was identified as playing a role in the pathophysiology of migraine when it was demonstrated that CGRP levels were elevated in jugular venous blood samples of patients with migraine during a migraine attack.[65] CGRP levels could also be restored to interictal (i.e., between attack) levels following administration of sumatriptan, demonstrating that sumatriptan's effects may be mediated by reversal of CGRP signaling.[65,66] Later work in this area demonstrated that levels of CGRP are persistently elevated in the plasma, blood, Cerebral Spinal Fluid (CSF), and saliva of adult and pediatric patients with migraine,[67–71] and that infusion of CGRP could cause both an immediate and delayed headache in patients with migraine.[72,73] As a result of these studies, CGRP was recognized as a potential treatment target in migraine, leading to the development of two novel categories of CGRP pathway therapies: anti-CGRP monoclonal antibodies ("mAbs") and small-molecule CGRP receptor inhibitors ("gepants"). Three of the monoclonal antibodies act on CGRP itself, while one binds to the canonical CGRP receptor. All the gepants antagonize the canonical CGRP receptor.

Importantly, CGRP is not exclusively localized to the nervous system and plays numerous roles in other organ systems including the GI system. Our understanding of the role of CGRP in the GI system is summarized nicely elsewhere by Ailani et al.[19] Briefly, in animal studies, CGRP has been shown to affect gut motility, gastric secretion, inflammation, and nociception.[19,74] In humans, infusion of CGRP in healthy controls resulted in prominent GI symptoms including nausea, stomach discomfort, urge to defecate, and defecation. Notably, these symptoms were not attenuated by pretreatment with sumatriptan.[75,76] In contrast, antagonism of CGRP via anti-CGRP antibodies or gepants did prevent or attenuate, respectively, CGRP-induced diarrhea in mice.[77]

There are now four anti-CGRP monoclonal antibodies and four "gepant" medications approved by the United States Food and Drug Administration (FDA) for treatment of migraine (Table 1). The anti-CGRP mAbs are approved for prevention of both episodic migraine (headache <15 days per month) or chronic migraine (headache ≥15 days per month for ≥3 months, with ≥8 meeting criteria for migraine) in adults. Among the gepants, three (rimegepant dissolvable tablet, ubrogepant oral tablet, and zavegepant nasal spray) are approved for acute treatment, while two (rimegepant and atogepant) are approved for prevention of migraine in adults. Rimegepant is approved for prevention of episodic migraine whereas atogepant is approved for prevention of both episodic and chronic migraine.[39] There are no anti-CGRP targeted therapies approved yet in the pediatric population, but retrospective chart review studies have suggested these medications may be safe and effective in adolescent patients with refractory headache disorders.[78,79]

In 2021, the American Headache Society (AHS) published an initial consensus statement for integration of these novel migraine therapeutics into clinical practice.[80] It was recommended that "gepants" be considered for acute treatments for patients who have tried at least two triptan medications with insufficient benefit, bothersome side effects or contraindication to/intolerance of triptans. For

TABLE 1 Newer migraine treatment and Triptans.

Medication	Indication in migraine	Formulation	Mechanism	Common side effects
Anti-CGRP monoclonal antibodies				
Erenumab	Prevention	SC monthly	Anti-CGRPr mAb	Constipation, injection site reaction, hypersensitivity, hypertension[19–25]
Galcanezumab	Prevention	SC monthly	Anti-CGRP mAb	Injection site reaction, possible constipation (<2%), hypersensitivity reaction[19,26–30]
Fremanezumab	Prevention	SC monthly or quarterly	Anti-CGRP mAb	Injection site reaction, possible constipation (<1%), hypersensitivity reaction[19,24,31–34]
Eptinezumab	Prevention	Intravenous quarterly	Anti-CGRP mAb	Nasopharyngitis, nausea, fatigue, hypersensitivity reaction[19,35–38]
Gepants				
Atogepant	Prevention	Oral tab	CGRPr small-molecule inhibitor	Nausea, constipation, dizziness, drowsiness, weight loss[39–43]
Rimegepant	Prevention, acute	ODT	CGRPr small-molecule inhibitor	Nausea, abdominal pain/dyspepsia[19,44–48]
Ubrogepant	Acute	Oral tab	CGRPr small-molecule inhibitor	Nausea, drowsiness, dizziness, dry mouth[19,46,47,49–52]
Zavegepant	Acute	NS	CGRPr small-molecule inhibitor	Nausea, dysgeusia, nasal irritation[53–55]
Tritpans	Acute	Oral tab, ODT, NS, SC	5-$HT_{1B/1D/1F}$ agonism	Nausea, malaise, dizziness, paresthesia, flushing, neck/jaw/chest tightness; contraindicated in those with uncontrolled hypertension, vascular disease, hemiplegic migraine or basilar aura[56,57]
Sumatriptan[c]		Oral tab[a], NS[a], SC		
Rizatriptan		Oral tab, ODT[b]		
Zolmitriptan		Oral tab, ODT, NS[a]		
Eletriptan		Oral tab		
Almotriptan		Oral tab		
Naratriptan		Oral tab		
Frovatriptan		Oral tab		
Ditans (lasmiditan)	Acute	Oral tab	5-HT_{1F} agonism	Dizziness, somnolence, nausea, paresthesia, fatigue[46,47,58,59]

Abbreviations: CGPRr, CGRP receptor; IV, intravenous; mAb, monoclonal antibody; NS, nasal spray; ODT, oral dissolving tablet; SC, subcutaneous.

[a]FDA-approved in age ≥ 12.

[b]FDA-approved in age ≥6.

[c]ǂStudied in CVS [20, 62] in case series.

preventive treatments, it was recommended that anti-CGRP directed therapy be considered in patients who have had adequate trials of at least two oral preventive agents (anti-convulsant, anti-hypertensive, and/or anti-depressant and/or onabotulinumtoxinA for those with chronic migraine) with insufficient benefit, bothersome side effects or contraindication to standard medications. However, based on accumulation of evidence for their efficacy and tolerability, in 2024 the AHS published an updated position statement asserting that CGRP targeted therapy (whether a monoclonal antibody or a gepant) should be considered a first-line treatment option for migraine prevention.[81] The Pediatric Special Interest Group of the AHS has similarly published an expert opinion on use of anti-CGRP medications in pediatric populations, including special considerations in this population and indications for considering off-label use.[82]

Given its prominent role in GI function, it is perhaps unsurprising that the predominant side effects of the anti-CGRP medications have been GI. In phase 2 and 3 clinical trials of the anti-CGRP receptor monoclonal antibody erenumab, constipation was reported by 1%–4% of patients taking erenumab (vs. 1%–2.1% taking placebo), with higher rate of constipation reported at higher dose of erenumab.[20–22] In phase 3 clinical trials of anti-CGRP monoclonal antibodies targeting CGRP, constipation was also seen in 0%–1.5% of participants on galcanezumab (vs. 0.6% of patients taking placebo)[26–29] and 0-<1% of participants on fremanezumab monthly

(vs. 0-<1% placebo).[31–33] As reported by Ailani et al., constipation is the most common GI side effect reported to the FDA Adverse Event Reporting System by patients prescribed anti-CGRP monoclonal antibodies and has been reported by up to 20% of patients in prospective post-marketing and safety studies of anti-CGRP monoclonal antibodies.[19]

Atogpepant may also cause constipation when taken for prevention (reported by 7%–11% of participants in the pivotal phase 3 clinical trial, vs. 0.53% in the placebo group) in addition to nausea (4%–10% in the atogpepant group vs. 2%–4% in the placebo group).[39,40] Weight loss has been seen with atogepant.[41] Among the other gepants, nausea is more commonly reported. In the pivotal phase 2/3 clinical trials of rimegepant, 3% of participants taking rimegepant for prevention (vs. 1% in the placebo group) and 2% taking rimegepant for acute treatment (vs. 1% in the placebo group) reported nausea; constipation was not reported.[44,45] Nausea was also reported by 3% of participants taking zavegepant (vs. 1% taking placebo)[53] and by 2%–4% of participants taking ubrogepant (vs. 2% taking placebo).[49,50] However, in addition to having nausea as a possible side effect, when nausea is driven by migraine pathophysiology, gepants may actually reduce nausea. For example, in participants treated with rimegepant, nausea was the "most bothersome symptom" accompanying attacks in 30%, and nearly 40% achieved freedom from the most bothersome migraine symptom following rimegepant administration.[44]

While we are not aware of any published literature on the use of CGRP-targeted therapies for the treatment of CVS, if CGRP signaling is involved in CVS pathophysiology it is possible that these treatments could be useful. For acute treatment, zavegepant may be particularly useful as nasal administration precludes the need for gastric absorption during severe vomiting attacks.

3 | SEROTONIN RECEPTOR AGONISTS: LASMITIDAN

Historically, triptan medications have been the most frequently utilized migraine-specific treatment available for the acute treatment of migraine. Triptans have also been used in treatment of CVS[61,83,84]; in a prospective study, sumatriptan resulted in ≥50% reduction of vomiting in 54 treated attacks and family history of migraine predicted response to treatment[61]; in a cross-sectional survey-based study, the majority of patients reported sumatriptan use prevented ED visits (64%) and hospitalization (60%).[61,83]

Triptans are predominantly agonists at the 5-$HT_{1B/1D}$ serotonin receptors; agonism at the 1B receptor results in vasoconstriction, while agonism at the 1D receptor is proposed to decrease release of CGRP and other pro-nociceptive neuropeptides and neurotransmitters.[63,85–87] It is thought to be the 5-HT_{1B} vasoconstrictive effect that accounts for the cardiovascular and cerebrovascular morbidity associated with triptan use and precludes its use in populations with significant vascular risk factors. Some triptans also have affinity to the 5-HT_{1F} receptor and sumatriptan was used in studies to show the presence of the 5-HT_{1D} and 5-HT_{1F} receptor subtypes in the human frontal cortex, globus pallidus, periaqueductal gray, and the trigeminal nucleus caudalis.[88] Interestingly, 5-HT_{1F} may also play a role in mitochondrial biogenesis.[89,90]

In contrast, the novel migraine acute treatment lasmitidan is a selective 5-HT_{1F} receptor agonist.[91] Through binding of the pre-synaptic 5-HT_{1F} receptor, lasmitidan is proposed to decrease release of CGRP from the pre-synaptic vesicles. As a result of its inaction at the 1B receptor, there has been less concern for vascular effects of this medication and there were no additional adverse events reported in patients with cardiovascular risk factors included in phase 3 clinical trials.[92] Given its similar mechanism of action to triptans, it is plausible that lasmitidan would be effective in the treatment of CVS, though its practical use may be limited by lack of a non-oral formulation. In addition, lasmitidan has centrally-mediated common side effects (e.g., dizziness, vertigo) and there is an 8-hour driving restriction with lasmitidan.[93]

4 | NEUROMODULATORY DEVICES

While increased understanding of migraine pathophysiology has improved our pharmacological therapeutic options for migraine treatment, it has also given way to treatment via neuromodulation for the treatment of migraine disease. Indeed, we have seen the lines blur between acute versus preventive treatment. Similar to CGRP therapy, neuromodulation is another therapeutic option that has efficacy in the dual role of acute and preventive treatment of migraine. It is increasingly recognized that neuromodulation can play an important role in modulating the frequency and/or duration of migraine attacks. While medications target neurochemical pathways involved in the pathophysiology of migraine, neuromodulatory devices interrupt the neurophysiologic mechanisms of the migraine attack.

There are five neuromodulation devices now FDA-cleared for treatment of migraine. These include single-pulse transcranial magnetic stimulation (sTMS), remote electrical nerve stimulation (REN), external trigeminal nerve stimulation (eTNS), external vagal nerve stimulation (nVNS), and combined occipital and trigeminal nerve stimulation (eCOT-NS); all are approved for acute treatment of migraine, and all but eCOT-NS are approved for preventive treatment. Of these, three (REN, nVNS, and sTMS) have been studied in adolescents ages 12–17 and have been FDA-cleared in this population.[94–96] The eTNS device is now available without a prescription.

The proposed mechanisms of neuromodulation devices are variable and likely involve multiple pain circuits. Communication between the anterior cingulate cortex, first branch of the trigeminal nerve and the trigeminal nucleus caudalis has been implicated in the mechanism of action of the eTNS device[97] and may also be involved in the efficacy of eCOT-NS based on its stimulation of the trigeminal nerve, while disruption of cortical spreading depression (CSD) and inhibition of thalamocortical pathways are thought to contribute to the efficacy of sTMS.[98] In contrast, REN exerts effects through stimulation of peripheral nerve endings in the upper arm, which is thought to modulate pain signaling centrally through A-delta and C-fiber pathways (the same pathways implicated in efficacy of anti-CGRP therapies and

TABLE 2 FDA Cleared non-invasive neuromodulation devices for migraine treatment.

Device	Current trade name and manufacturer	Adult acute treatment	Adolescent[a] acute treatment	Adult preventive treatment	Adolescent[a] preventive treatment	Side effects
Single Pulse Transcranial Magnetic Stimulator (sTMS)	SAVI Dual™; eNeura®[96,111]	Yes	Yes	Yes	Yes	Light-headedness, paresthesia, tinnitus, dizziness[94,111,112]
Non-Invasive External Vagal Nerve Stimulator (nVNS)	GammaCore™; ElectroCore Inc[113]	Yes	Yes	Yes	Yes	Application site irritation, muscle twitching, pain, dizziness, paresthesia[96,113]
Remote Electrical Neuromodulator (REN)	Nerivio®; Theranica Inc.[114]	Yes	Yes	Yes	Yes	Local warmth, paresethsiea, pain, skin irritation, hand numbness or muscle twitching[114–116]
External Trigeminal Nerve Stimulator (eTNS)[b]	Cefaly®; Cefaly Technologies Inc.[117]	Yes		Yes		Sleepiness, headache, skin irriation, nausea[116–118]
Combined Occipital and Supraorbital Transcutaneous Nerve Stimulation (eCOT-NS)	Relivion®; Neurolief Inc.[119]	Yes		No		Paresthesia during and after treatment, pain, nausea, skin reaction or irritation, sleepiness, dizziness, headache[119–121]

[a]FDA cleared for ages 12–17.

[b]Available over the counter.

onabotulinumtoxinA, respectively).[99–101] Further research is needed for the better understanding of the mechanisms of effectiveness of these devices, which likely each involve complex interactions of neurophysiological and neurochemical pain pathways.

Perhaps most interesting to the field of CVS and other disorders with prominent GI symptoms that may be associated with migraine is the non-invasive vagal nerve stimulation device (nVNS). While the nVNS mechanism of action is not fully understood, it is thought to modulate central descending pathways for pain control through stimulation of the vagus nerve resulting in altered gamma-amino-butyric acid (GABA) and serotonin signaling; like sTMS, it has also been proposed to disrupt CSD and inhibit thalamocortical pathways.[102] The authors are currently unaware of nVNS use or efficacy in the treatment of CVS or other GI disorders associated with migraine disease; however, this may be an important area for future research given the proposed role of the vagus nerve in mediating autonomic function and health of the brain-gut axis[102,103] Of note, percutaneous electrical nerve field stimulation (PEFNS), which will be covered in depth elsewhere in this special supplement, has been found to be effective in pediatric disorders of gut-brain interaction and CVS, including improvements in abdominal pain and anxiety.[104–110] However, is not currently cleared or used for migraine disease and studies did not include validated patient-reported outcome measures for migraine. This treatment may provide an opportunity for research in the management of migraine disease. Current FDA cleared non-invasive neuromodulation devices for the treatment of migraine disease are listed in Table 2.

5 | CONCLUSIONS

There is a paucity of known effective acute and preventive treatments for CVS. CVS pathophysiology may overlap with migraine pathophysiology, at least for some patients. Some treatments used in migraine have historically also been useful for CVS treatment. Novel therapies for migraine that target the CGRP pathway, 5-HT receptor subsets, or neuromodulation, may be helpful for treating CVS as well and should be studied for the acute and preventive treatment of CVS.

AUTHOR CONTRIBUTIONS

All authors contributed to the concept, original drafting, and revisions of the manuscript.

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No specific funding for this manuscript, though the authors received travel expenses to attend the *Third International* Symposium on *Cyclic Vomiting* Syndrome (CVS) and *Cannabinoid Hyperemesis* Syndrome (CHS).

CONFLICT OF INTEREST STATEMENT

KAG: Dr. Greene has received personal compensation as a speaker for education programs for the American Headache Society. She has previously received personal compensation as a consultant for

Theranica. She is the site PI for clinical trials for Amgen, Upsher-Smith and Eli-Lilly for which her institution receives financial support, but Dr. Greene does not receive personal compensation.

LCIV: Dr. Charleston has received personal compensation for serving as a consultant for Allergan/AbbVie, Amneal, Aurene Corporation/eNeura, Biohaven, Haleon, LinPharma, Mi-Helper (stock options), Pfizer, and Satsuma; received grant/research support from the Disparities in Headache Advisory Council and Amgen. He has received CME honoraria from American Headache Society, American Academy of Neurology, BrainWeekend, Migraine360 CME Program, NeurologyWeek, and the Primary Care Education Consortium. He receives a salary as faculty from Michigan State University College of Human Medicine and Thomas Jefferson University. He is a non-compensated associate editor for *Headache: The Journal of Head and Face Pain* and serves as a non-compensated Board Member-at-Large for the Clinical Neurological Society of America.

AAG: In the last 24 months, Dr. Gelfand has received honoraria from UpToDate (for authorship), the American Academy of Neurology (for editing) the Taiwan Headache Society (for speaking) and the Weill Cornell Neurology Department (for speaking). She receives a stipend from the American Headache Society for her role as Editor of *Headache*. She receives grant support from PCORI as a member of the Steering Committee for the REACH study.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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