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AGA Clinical Practice Update on Diagnosis and Management of Cyclic Vomiting Syndrome: Commentary

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DESCRIPTION: The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update (CPU) is to review the available evidence and provide expert advice regarding the diagnosis and management of cyclic vomiting syndrome. **METHODS:** This CPU was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of *Gastroenterology*. This expert commentary incorporates important as well as recently published studies in this field, and it reflects the experiences of the authors who are experts in treating patients with cyclic vomiting syndrome.

Keywords: Cyclic Vomiting; Neuromodulators; Prophylactic Treatment; Biopsychosocial Model.

Cyclic vomiting syndrome (CVS) is a chronic disorder of gut–brain interaction characterized by acute episodes of nausea, vomiting, and retching, separated in time by episode-free periods. Individuals with CVS can identify a stereotypic pattern of symptoms that present during both the prodromal and emetic phases. Although there are effective treatments for most patients, the condition remains underdiagnosed and thus undertreated.[1] Most patients experience years of diagnostic delays, extensive and futile investigations, and even unnecessary surgical procedures. Approximately one-half of people with CVS visit the emergency department (ED) at least annually, and 1 in 3 adults with CVS will become disabled.[2] Access to care, early recognition of CVS, and appropriate treatment can reduce CVS symptoms, reduce health care utilization, and improve patients' quality of life.[2–4]

The poor recognition of CVS stands in stark contrast to the high prevalence of CVS in the adult population. The prevalence of CVS is approximately 2% in the United States and is more common in women.[5] Yet, only a small fraction of all individuals with CVS are likely to have received a CVS diagnosis.[6] The purpose of this best practice expert commentary is to describe the diagnostic and management approaches to adults with CVS.

Diagnosis

The general awareness of CVS and prompt recognition of the condition is key to its effective management. In essence, a clinician should consider CVS as a potential diagnosis in any adult presenting with the core clinical feature of episodic bouts of repetitive vomiting. CVS has 4 distinct phases—inter-episodic, prodromal, emetic, and recovery—each of which is associated with a distinct treatment approach and management goal.[7] These phases are represented schematically in Figure 1. Like other disorders of gut–brain interaction, CVS is diagnosed on the basis of clinical criteria, as established by the Rome Foundation[8] and shown in Box 1 (*top panel*).

Clinical Features of CVS

The hallmark of CVS is recurrent, acute episodes of vomiting and retching. Although most patients meet Rome IV criteria, there is a wide range of presentations and clinical severity seen in clinical practice. There are diagnostic clues that support a CVS diagnosis and are important for clinicians to recognize. First, many patients (approximately 65%) with CVS experience prodromal symptoms, lasting a median of 1 hour, before the onset of vomiting.[9] Some patients may report an impending sense of doom before an episode. Most patients with CVS report panic[7] and many are often unable to communicate effectively during this phase. Second, although CVS is a disorder of nausea and vomiting, the prodromal and emetic phases can be associated with multiple constitutional; cognitive or affective; autonomic; and motor symptoms, including fatigue, feeling hot or cold, mental fog, restlessness, anxiety, headache, bowel urgency, acute diarrhea or constipation, abdominal pain, diaphoresis, flushing, or shakiness or tremulousness. Classically, each patient with CVS can identify an order of onset and specific cluster of these symptoms that are stereotypically associated with their prodromal and/or emetic phase. Third, abdominal pain is present in most patients during a CVS episode and thus, this symptom should not preclude a diagnosis of CVS.[10] Finally, although CVS episodes can present at any time of day, most episodes tend to occur in the early morning hours.[7,11]

Abbreviations used in this paper: **ANMS, American Neurogastroenterology and Motility Society; CHS, cannabinoid hyperemesis syndrome; CVS, cyclic vomiting syndrome; CVSA, Cyclic Vomiting Syndrome Association; ED, emergency department; IV, intravenous.**

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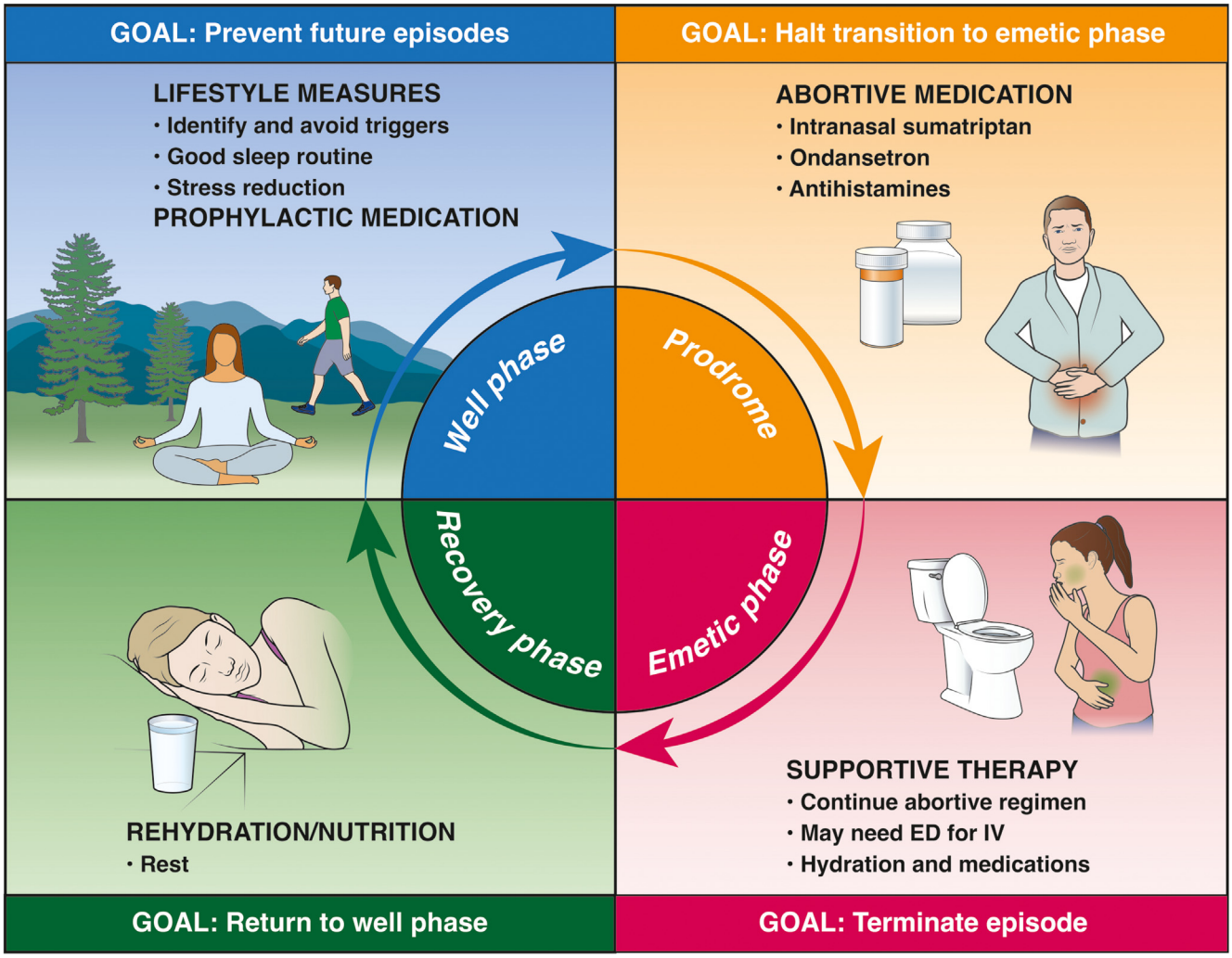

Figure 1. Phases and treatment goals for cyclic vomiting syndrome.

Recognition of the various CVS phases is essential. For example, the prodromal phase is the ideal time to deliver abortive therapies, and earlier intervention is associated with a higher probability of successfully aborting an episode. Patient education on this point is imperative to optimal care—essentially, "rehearsing" with patients the

Box 1. Diagnostic Criteria for Cyclic Vomiting Syndrome

Rome IV criteria for CVS in adults[a]

- Stereotypical episodes of acute-onset vomiting lasting <7 days
- At least 3 discrete episodes in a year, of which 2 have occurred in the prior 6 months; episodes should be separated by at least 1 week of baseline health
- Absence of vomiting between episodes, but presence of some milder symptoms, such as nausea, occasional vomiting, and dyspepsia may be present

[a]A personal history or family history of migraine headaches is regarded as a supportive criterion in the diagnosis of CVS.

ANMS-CVSA guideline criteria for mild vs moderate–severe CVS

- Mild CVS: <4 episodes/y each lasting <2 days, without ED visits or hospitalizations
- Moderate–severe CVS: ≥4 episodes/y, each lasting >2 days, and requiring at least 1 ED visit or hospitalization

actions they can take to best abort an episode. Abortive therapy will be discussed in more detail in the management section of this article. During the emetic phase, patients frequently find it hard to communicate and often may seem agitated. Providers, particularly in the ED, may need to rely on caregivers or an individualized plan of treatment provided by a CVS expert in such cases.

Akin to migraines, episodes of CVS are often triggered by psychological and physiological factors. One of the most common CVS triggers is stress, which studies have confirmed in approximately 70%–80% of patients.[12,13] Although negative stress, such as death or work and family conflicts, can certainly lead to episodes, even positive events, such as birthdays, family reunions, and vacations, can trigger episodes. Other triggers include sleep deprivation; hormonal fluctuations linked with phases of the menstrual cycle; travel; motion sickness; or physiological stressors, such as acute infections or surgery. Less common triggers include prolonged fasting or intense periods of exercise. Providers should help patients recognize triggers and develop strategies to eliminate or mitigate them.

The emetic phase is characterized by uncontrollable bouts of retching and vomiting that can last for hours to days. Most clinicians ask about vomiting but tend to ignore retching and/or unremitting nausea, which are equally disabling. Patients may also drink large amounts of water or even stick their fingers in their throat to vomit, which provides some temporary relief. Providers should not misconstrue these behaviors as malingering, as it is a self-soothing pattern that appears to be specific to CVS.[9]

Hot water bathing or showering—targeting exposure of the trunk or back—is common in the prodromal and emetic phases of an episode and provides temporary relief. In fact, approximately 48% of patients with CVS who do not use cannabis find relief from hot bathing or showering.[14] Thus, such behavior is not pathognomonic for a related condition—cannabinoid hyperemesis syndrome (CHS)—and it may also be observed in a subset of patients with chronic nausea vomiting syndrome.[5] Patients engaging in hot water bathing will often stay in a hot bath or take multiple showers,[7] sometimes leading to burns from prolonged exposure to hot water.[15] The pathophysiology underlying this behavior remains unclear but, in clinical experience, it seems to be more closely associated with CVS or CHS than chronic nausea vomiting syndrome.

Comorbid Conditions in CVS

Several conditions are associated with adult CVS, the most common of which are mood disorders, including anxiety, depression, and panic disorder (collectively present in 50%–60% of patients). A quite notable proportion of adult patients with CVS experience migraine (present in 20%–30%)[2] or even seizure disorders (approximately 3%),[3] which suggests some common pathophysiological mechanism that operates across episodic conditions. There is emerging appreciation that autonomic imbalances, including postural orthostatic tachycardia syndrome, are observed in a substantial subgroup of patients with CVS and may relate to its underlying pathophysiologic mechanisms.[13,16] The presence of these typical comorbid conditions helps to make a CVS diagnosis and to guide management, leading to improved clinical outcomes. For example, improving anxiety may decrease the frequency of CVS episodes and improve inter-episodic nausea, and treating postural orthostatic tachycardia syndrome may improve patients' overall functional status.[2]

Temporal Patterns of CVS Episodes

The Rome IV criteria lay out cutoffs for typical length of episodes (<7 days) and amount of time between them (≥1 week). Yet, there is considerable heterogeneity in the duration of CVS episodes, with nearly 15% of patients with CVS experiencing episodes that last longer than 7 days.[17] Similarly, episode frequency varies widely, with more severe forms of CVS characterized by a greater number of episodes. To account for the variability in CVS severity, the ANMS-CVSA clinical guideline proposed making the clinical distinction between mild and moderate–severe forms of CVS, and this distinction was based on strong expert consensus of the guideline committee.[2,18,19] For example, patients with <4 episodes/y each lasting <2 days without ED visits or hospitalizations would be regarded as having mild CVS. Patients with ≥4 episodes/y, each lasting >2 days, and requiring ED visits or hospitalizations, would be regarded as having moderate–severe CVS (see Box 1, *bottom panel*).[2] Both prophylactic and abortive treatment should be offered to patients with moderate–severe CVS, whereas only abortive treatment should be offered to patients with mild CVS.

Lastly, a notable subset of patients with severe CVS experience a worsening disease trajectory that unfolds over years, characterized by increased episodic length and frequency, with progressively few, if any, asymptomatic days. In some patients, this pattern culminates in daily nausea and vomiting. Although these patients may lose the prototypical "well periods" between episodes, they often continue to have intermittent episodes with more severe nausea and vomiting. Other patients with coalescent CVS still retain an episodic pattern of retching and vomiting, but often experience chronic nausea.[2,7] Coalescent CVS poses a major diagnostic challenge due to the lack of asymptomatic periods and/or episodic vomiting patterns, and a patient at this stage of illness would meet Rome IV symptom criteria for chronic nausea vomiting syndrome. However, patients with true coalescent CVS universally endorse a pattern of episodic nausea and vomiting that occurred for years before their coalescent phase, and a careful history should be able to identify this feature. The subset of patients with coalescent CVS should be offered prophylactic therapy akin to patients with moderate–severe CVS, although management remains challenging.

Diagnostic Workup

Clinical recognition of CVS remains the anchor of the diagnostic approach. However, the ANMS-CVSA guideline endorses some limited testing to rule out similar or

Table 1. Prophylactic and Abortive Medication Therapies in Adults With Cyclic Vomiting Syndrome

Variable	Medication	Mechanism of action	Dosage	Common adverse effects	Clinical considerations
Prophylactic therapy (for moderate–severe CVS)					
TCA	Amitriptyline Nortriptyline Doxepin	5-HT and NE reuptake inhibition	Starting dosage: 25 mg qhs Goal dosage (any TCA): 75–150 mg or 1–1.5 mg/kg qhs	Somnolence, dry mouth, blurred vision, constipation, weight gain and prolonged QTc on ECG	Slow titration (10–25 mg increments, every 2 wk, up to goal dosage) is generally better tolerated Amitriptyline may have more anticholinergic/ antihistaminergic activity than nortriptyline Dosed at night
Anticonvulsants	Topiramate	Unclear May increase GABA receptor activity and inhibit glutamate receptor activity	Starting dosage: 25 mg daily Goal dosage: 100–150 mg daily in divided doses	Cognitive dysfunction, paresthesia, headache, fatigue, nausea, dizziness, or mood problems	Titrate up by 25 mg each week until target dose Monitor serum electrolytes and renal function twice annually Increased risk of kidney stones; do not use in patients with history of kidney stones Must not be used during pregnancy Associated with some weight loss (may be advantageous in patients with higher body mass index)
	Zonisamide	Sodium and calcium channel blockade channel; modulation of GABA receptors	Starting dosage: 100 mg daily Goal dosage: 200–400 mg daily	Irritability, confusion, depression	Titrate up by 100 mg daily every 2 wk to goal dose Monitor electrolytes and renal function twice annually Increased risk of kidney stones Associated with weight loss
	Levetiracetem	Binding to SV2 influence on SV2-dependent neurotransmitter release	Starting dosage: 500 mg bid Goal dosage: 1000–2000 mg daily in divided doses	CNS depression Hypertension Anemia	Titrate up by 500 mg daily every 2 wk to goal dosage No need for therapeutic drug monitoring Monitor complete blood count
Neurokinin-1 system	Aprepitant	Neurokinin-1 receptor antagonist	125 mg 2–3 times weekly (adults >60 kg) 80 mg 2–3 times weekly (smaller adults 40–60 kg)	Neutropenia Fatigue	Potential interference with oral contraceptive pills Safer in pregnancy Challenging to obtain insurance coverage for "off-label" use in CVS Expensive
Nutritional supplements	Coenzyme Q10 Riboflavin	Supports mitochondrial function Unclear mechanism in CVS	300–400 mg daily 200 mg twice daily	Elevated liver enzymes Diarrhea	Monitor liver enzymes

Table 1. Continued

Variable	Medication	Mechanism of action	Dosage	Common adverse effects	Clinical considerations
Abortive therapy (for either mild or moderate–severe CVS)					
Triptans	Sumatriptan	$5HT_{1B/1D/1F}$ receptor agonist	Single dose (20 mg intranasally or 6 mg subcutaneously), repeated once after 2 h if needed, not to exceed 2 doses in a 24-h period	Chest discomfort Fatigue Dizziness Paresthesia Unpleasant taste	Should not be used during pregnancy Contraindicated in patients with ischemic heart disease, stroke, peripheral vascular disease, or uncontrolled hypertension
Antiemetics	Ondansetron	5-HT_3 receptor antagonist	8 mg (sublingual) every 4–6 h during episode	Headache Malaise Drowsiness Constipation with frequent doses	Baseline ECG is advised; associated with prolonged QTc
	Promethazine	Dopamine receptor antagonist with antihistaminergic and anticholinergic effects	12.5–25 mg by mouth/per rectal every 4–6 h during episode	CNS depression, anticholinergic effects, extrapyramidal symptoms	Peripheral IV administration can cause tissue injury, including gangrene or thrombophlebitis
	Prochlorperazine	Dopamine receptor antagonist	5–10 mg every 6–8 h 25 mg suppository every 12 h	CNS depression, anticholinergic effects, extrapyramidal symptoms, drug-induced leukopenia or neutropenia, rare cause of neuroleptic malignant syndrome	Caution in patients with history of leukopenia or neutropenia, dementia, glaucoma, or seizure disorder
Sedatives	Alprazolam Lorazepam	GABA receptor agonist	0.5–2 mg every 4–6 h	CNS depression, anterograde amnesia, paradoxical aggression in older adults	Caution in pregnancy and those with history of substance abuse
	Diphenhydramine	Histamine type 1 receptor antagonist with anticholinergic effects	12.5–25 mg every 4–6 h during episode	Anticholinergic effects, oversedation, confusion	Caution in older adult patients, those with glaucoma, benign prostatic hypertrophy, ischemic heart disease, or hypertension

bid, twice per day; CNS, central nervous system; ECG, electrocardiogram; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine (serotonin); NE, norepinephrine; qhs, every night or at bedtime; QTc, corrected QT interval; SV2, synaptic vesicle protein 2; TCA, tricyclic antidepressant.

overlapping conditions.[2] A basic workup for uninvestigated, episodic vomiting should include blood work (ie, complete blood count, serum electrolytes and glucose, liver function testing, and lipase) and urinalysis. One-time esophagogastroduodenoscopy or mode of upper gastrointestinal imaging could effectively exclude obstructive lesions that may account for episodic nausea and vomiting. If an esophagogastroduodenoscopy is performed soon after a recent CVS episode, it is important to recognize epiphenomena of recent retching and vomiting (ie, mild gastritis or erythematous streaking, Mallory-Weiss tear, or esophagitis) as not being causal. Repeated esophagogastroduodenoscopy or upper gastrointestinal imaging studies should be avoided. Gastric emptying scans should not be ordered routinely, as few patients with CVS have delayed emptying and results obtained during a CVS episode are uninterpretable.[2] Furthermore, use of cannabis or opiates complicates interpretation of a gastric emptying study. Other diagnostic testing should be dictated on the basis of individual patient history and only when indicated. These might include workup for Addison's disease, hypothyroidism, and hepatic porphyria, which can mimic CVS.[9,20] Patients with any localizing neurologic symptoms should undergo brain imaging and referral to a neurologist.[2]

Cannabis Use Patterns in CVS

Many patients with CVS use cannabis either recreationally or to alleviate CVS episodes. Cannabis use in a patient with CVS often raises concerns for CHS.[21] A full discussion of CVS vs CHS is beyond the scope of this article, but a few details about these disorders should be highlighted . First, experts have proposed that CHS is a subset of CVS when prolonged (>1 year) and heavy cannabis use (ie, >4 times weekly, but often daily) precedes the onset of symptoms.[22,23] Cannabis use in patients with CVS is more occasional and often postdates the onset of the episodic vomiting (cannabis cannot be causal in such patients). Second, there is expert consensus that the length of time for cannabis cessation required to retrospectively diagnose CHS should be 6 months or at least 3 typical cycle lengths for the patient.[22,23] If a patient continues to experience vomiting after this cessation period, then CHS can be ruled out. Lastly, patients using cannabis are often stigmatized by the health care system and face challenges in accessing treatment. It is imperative that all patients, including those with ongoing cannabis use and uncertainty about the diagnosis of CVS vs CHS, be offered abortive and/or prophylactic therapy. These treatments can still be effective for many patients, even with ongoing cannabis use.

Management

Lifestyle Modification

Involvement of referral (eg, neurologist, psychiatrist, and sleep specialist) and allied health services (eg, psychologist or counselor and substance use specialist) can help patients tackle many of the comorbid conditions associated with CVS, such as anxiety or depression, migraines, sleep disorders, and substance use.[2] Addressing these underlying conditions by means of pharmacologic and/or nonpharmacologic therapies, such as cognitive behavioral therapy or mindfulness meditation, can substantially improve CVS symptoms and overall quality of life.[24] Patients should attempt to identify and mitigate or avoid CVS triggers during the inter-episodic phase. Advising patients to get regular sleep, avoid prolonged fasting, and pursue stress management techniques are general approaches that all patients with CVS should follow.

Prophylactic Therapies

Prophylactic therapy is indicated for those with moderate–severe CVS (ie, those with >4 episodes per year, each of which last >2 days, and is associated with some ED utilization or hospitalizations). The goal of prophylactic medications is to extend the length of the inter-episodic phase and/or reduce the length and severity of the emetic phase. The ANMS-CVSA guideline recommends several prophylactic and abortive treatments for CVS in adults (Table 1),[e1,2] although these recommendations were necessarily based on case series and expert opinion, given the lack of randomized, placebo-controlled clinical trials in CVS. The choice of prophylactic medication should be individualized and clinical considerations for prophylaxis are provided in Table 1. Tricyclic antidepressants are strongly recommended as first-line prophylactic medications, whereas topiramate, aprepitant, zonisamide, and levetiracetam are effective second-line agents.

Abortive Therapy

The goal of abortive therapy is to completely avoid the emetic phase, or at least drastically reduce its severity. As noted previously, the probability of aborting an episode is highest when medications are taken as early into the prodromal phase as possible. However, using abortive therapy is particularly challenging for patients who transition quickly from the inter-episodic to the emetic phase without a prodrome. Several evidence-based abortive treatments for CVS in adults are provided in Table 1.[2,e1] Although some patients respond to monotherapy, nearly all patients with CVS require combinations of ≥2 agents to reliably abort CVS attacks. Most common abortive treatment regimens include the use of sumatriptan and an antiemetic agent, such as ondansetron. Even if actively retching and vomiting, sumatriptan can be administered via nasal spray, which can be delivered in a head-forward position that optimizes medication contact with anterior nasal receptors, or potentially via subcutaneous injection in some patients.[e2,2] Ondansetron is available in a sublingual tablet form that may improve drug absorption compared with tablets, and other antiemetics, such as promethazine and prochlorperazine, are available in rectal suppository form. Inducing sedation is often an effective abortive strategy in CVS, and promethazine may be useful in this regard. Other sedating agents, such as diphenhydramine or benzodiazepines, may also be needed in an "abortive cocktail" of medications. Alprazolam is available in both a sublingual tablet form and a rectally administered form,

which may be particularly advantageous. Although typically reserved for use in the ED, patients with CVS also respond to sedating antipsychotic medications (eg, droperidol and haloperidol).[e3] If a patient cannot abort an episode at home, then presentation to an ED for intravenous (IV) fluids and IV abortive therapy is reasonable. However, many patients with shorter-duration attacks (ie, <24 hours) tend to stay home and not seek or require ED-based care.

In the recovery phase, the priority is to consume electrolyte-rich fluids (ie, sports drinks) or nutrient drinks. Patients in the recovery phase may feel nauseated or have dyspeptic symptoms, but generally can tolerate moderate volumes of liquid intake. Most patients' recovery phase lasts approximately 1–2 days.

Emergency Department Management of CVS

A full discussion of the ED management of a patient with CVS is beyond the scope of this update, but several points are worth noting. First, all patients presenting with an episode of uncontrolled retching and vomiting should be treated regardless of suspicion for potential CHS. Second, many patients with CVS episodes experience severe abdominal pain, which, only in the most severe refractory forms, may require a dose of narcotic pain medication as a component of an abortive regimen.[2] Non-narcotic approaches are preferable, and we suggest IV ketorolac as a first-line, non-narcotic analgesic in this setting. Third, sedation is an important treatment goal in and of itself, and patients may do best in a quiet, darker room in the ED, along with IV benzodiazepines, to best induce sedation. Finally, all patients with CVS should receive IV dextrose-containing fluids and most patients with CVS benefit from IV administration of antiemetic medication.

Future Directions

There are major gaps in understanding of the pathophysiology and natural history of CVS, which limits the development of more effective treatments.[e4] Similarly, an incomplete understanding of the clinical features and comorbidities that predict clinical responses is a barrier to developing personalized therapeutic approaches.[e5] Recent data revealed substantial racial disparities in clinical outcomes for patients with CVS for reasons that are not well understood and warrant future research.[e6,e7] Clinical research leveraging multicenter, standardized registries of patients with CVS and directed investments by both industry and governmental sources are needed. Fortunately, the increasing recognition of CVS and its profound impact on patients and the health care system are likely to motivate progress in the years to come.

Conclusions

CVS is a common and disabling condition in adults, but need not be so, as it is a treatable condition. Prompt recognition remains the key factor in avoiding unnecessary investigations and providing patients with effective treatments.

Supplementary Material

Note: To access the supplementary references e1–e7 accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.05.031.

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All authors wrote the paper and critically reviewed the manuscript.

Conflicts of interest
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