# Cyclic Vomiting Syndrome: A Disorder of All Ages

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**Abstract:** Initially described in children, cyclic vomiting syndrome (CVS) is an idiopathic disorder that affects patients of all ages and is characterized by recurrent episodes of vomiting separated by symptom-free intervals or baseline health. Frequent misdiagnoses and delays in diagnosis often lead to years of recurrent vomiting. Similarities in the clinical features and symptoms of children and adults with CVS are often linked to migraines. Association with mitochondrial disorders and neuroendocrine dysfunction have been described in the pediatric CVS literature, whereas migraines, anxiety, and panic are common in adults with CVS. Various psychological, infectious, and physical stressors commonly precipitate episodes of CVS. Treatment is mostly empiric, with few controlled therapeutic studies conducted thus far. Associations with migraines have aided in developing pharmacologic treatment strategies for prophylaxis as well as abortive therapy during episodes, including the use of triptans. Most children outgrow CVS with time, though some children transition to migraine headaches or continue to have CVS as adults. Improved recognition of CVS in adults, along with the emergence of data in the use of anticonvulsants and antiemetics, may help further delineate pathophysiologic connections and therapeutic options for this debilitating disorder.

Keywords
Cyclic vomiting syndrome, nausea, migraine, stress

Cyclic vomiting syndrome (CVS) is a disorder of unknown etiology and pathogenesis typically characterized by recurrent episodes of vomiting separated by baseline or symptom-free periods.[1] Classically perceived as a pediatric disorder, CVS is now receiving greater recognition in the adult population. Improved understanding of this idiopathic disorder in pediatrics has resulted from research in epidemiology and studies detailing the pathophysiologic associations with migraines, mitochondrial dysfunction, and neuroendocrine abnormalities. Recently, a task force of experts from the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) provided a consensus statement detailing guidelines in the diagnosis and management of CVS in children.[2] CVS is typically misdiagnosed as gastroenteritis, gastroesophageal reflux, food poisoning, recurrent

flu, or eating disorders.[3] Delays in diagnosis, however, appear less frequently in pediatric patients (1.9 years) than in adults (7.9 years).[4,5] Although the exact prevalence of CVS is unknown, estimates in two recent studies of white children aged 5–15 and Turkish children aged 6–17 reported a prevalence of 2%.[6,7] The incidence of new cases of CVS was reported to be 3.15 per 100,000 children per year in a recent series of 1,647 children in Ireland.[8] Similar to the gender profile in migraine headaches, there is a slight predominance of girls over boys (57:43), though, due to limited data, it is unknown whether this is also true in adults.[9] The natural history of CVS in children is variable. Although a small percentage of children traverse all three phases of periodic disease (progressing from CVS to abdominal migraine and finally to migraine headaches), the majority of children experience resolution at a median age of 9.9 years.[4,10] Approximately one third of children with CVS will transition to migraine headaches as adults.[4] Although unknown, the natural history in adults appears to be distinct, with an average age of onset of 21–35 years in limited case series (Table 1).[5]

First reported in 1806 in France by Heberden,[11] Samuel Gee is credited, in England in 1882, with the most accurate modern description of CVS.[12] An association with migraine headaches was noted as early as 1898 by Whitney[13] and 1904 by Rachford.[14] Current research in pediatrics involves pursuing mitochondrial associations in CVS and evaluating supplemental therapies, including L-carnitine and coenzyme Q10, as well as identifying neuroendocrine mechanisms mediating vomiting in these patients.

**Table 1.** Comparison of Children and Adults With Cyclic Vomiting Syndrome (CVS)

| Features | Children | Adults |
|---|---|---|
| Age of onset | 4.8 years | 21–35 years |
| Delay in diagnosis | 1.9 years | 7.9 years |
| Prevalence of CVS | 2% | Unknown |
| Female:male ratio | 57:43 | Unknown |
| Typical episode duration | 27 hours | 3–6 days |
| Median frequency of episodes | 4 weeks | 3 months |
| Interepisodic symptoms | Uncommon | 50–63% |
| Prodromal symptoms | 67% | 93% |
| Abdominal pain with episodes | 81% | 58% |
| Recurring triggers for episodes | 76% | 63–80% |
| Migraine association | 39–87% | 24–70% |

## Clinical Features and Symptoms

CVS is distinguished by discrete, recurrent, and severe episodes of vomiting. Stereotypy of episodes in regard to time of onset, duration, and symptomatology is a consistent finding in both children and adults with CVS. In children, an on-off pattern with intervals of returning to complete normalcy or baseline health between episodes is most common.[3] Interepisodic symptoms of nausea and vomiting have been reported in 50–63% of adult patients.[5,15] Low-grade, baseline abdominal pain and nausea indistinguishable from functional dyspepsia is also a common feature in adults, often precipitated by stress and anxiety.[16] The duration of the episode generally ranges from hours to days, with a median duration of 27 hours in children and 3–6 days in adults.[4,17] The median frequency of episodes is 4 weeks in children and 3 months in adults.[4,17,18] The most common time of onset in all age groups is nighttime or early morning, with most patients experiencing onset from 1 AM to 7 AM.[19] Among children with CVS, 67% have a well-described prodrome, with a median duration of 0.5–1.5 hours that precedes the vomiting episodes compared to 93% in one adult series of 41 patients.[4,15] Despite the similarities to migraines, these prodromes rarely include visual disturbances and are characterized by prevomiting autonomic symptoms of pallor, nausea, abdominal pain, sweating, and lethargy. The typical recovery phase is variable, ranging from minutes to 10 days, in all ages, with a median of 8 hours in children.

CVS episodes are characterized by intense persistent nausea and repeated vomiting occurring at least 4 times per hour for at least 1 hour.[2] The vomiting is typically projectile and contains bile, mucus, and, occasionally, blood. The latter can occur at any time during the episode as a result of prolapse gastropathy, peptic esophagitis, and, less commonly, Mallory-Weiss tears from forceful, repetitive vomiting.[20] These patients can appear remarkably debilitated during episodes. There are many symptoms that typically accompany vomiting during CVS episodes. Abdominal pain, retching, anorexia, and nausea are the most common gastrointestinal symptoms. Abdominal pain during episodes (which occurs in 81% of children and 58% of adults) can be excruciating on occasion and may prompt unnecessary exploratory laparotomy. In a series of 41 adults prior to their diagnosis of CVS, 39% underwent various surgical procedures, 10 of which were cholecystectomies,[15] in futile attempts to cure recurrent vomiting episodes.

Nausea is reported by patients as the most persistent and distressing symptom. It is minimally relieved by vomiting, often receding only while sleeping or with sedation.

Behaviors such as assuming a fetal position, withdrawing socially, drinking compulsively, taking prolonged hot or cold baths, and avoiding lights and sounds are common attempts to alleviate nausea.[19] The nausea is accompanied by autonomic dysfunction in CVS. The most common autonomic symptoms are lethargy and pallor. Other autonomic symptoms include fever, flushing, drooling, diarrhea, hypothermia, and hypertension. Fewer than half of the patients have migraine features, including headache, photophobia, and phonophobia. Other symptoms during episodes include sensory hypersensitivity, vertigo, and sweating, which has been reported as a common feature in adults.

Even though children return to baseline health between episodes and are well approximately 90% of the time, CVS can have a significant impact on the quality of life of affected children.[19] Over half (58%) of all affected patients require intravenous hydration during episodes, and 19% require this with every episode.[4] School-age children miss an average of 24 days of school per year, owing to episodes of vomiting. High medical morbidity is reflected by the average annualized cost of management of $17,000, including doctor visits, emergency department visits, in-patient hospitalizations, missed work by parents, and biochemical, radiographic, and endoscopic testing.[21] Interepisodic nausea, abdominal pain, anxiety, and disability are frequent symptoms in adults. Often, patients with increasing frequency of episodes can deteriorate to a form of coalescent CVS, with continuous nausea, emesis, and disability that can continue for weeks to months.[15] These patients are commonly sick more days than they are well. This coalescent pattern can exacerbate underlying stress and anxiety and is commonly associated with lower attendance at school or work, marital discord, and the need for financial assistance. Many of these patients with continuous symptoms have profound weight loss requiring nutritional support. The progression to coalescence of episodes is most often observed in patients with untreated CVS. It is unclear whether the pathophysiology of this pattern differs from typical CVS; however, most of these patients do improve with conventional CVS therapy.[5]

## Psychological Associations With Cyclic Vomiting Syndrome

Various stressors have been noted to precipitate episodes of CVS. In 76% of children and 63–80% of adults with CVS, a recurring trigger preceding the vomiting episodes has been identified.[4,22] These triggers consist of psychological, infectious, and physical stressors. Stress and infections are the most common triggers (44% and 31%, respectively). Interestingly, two thirds of the stress in children is positive rather than negative. Various infections can trigger episodes, particularly chronic sinusitis. Other triggers include dietary factors (23%), physical exhaustion (24%), atopic symptoms (6%), motion sickness (12%), and menses (catamenial CVS).[4] The largest fraction of children (32%) have a seasonal clustering of episodes, with more episodes during the winter and fewer during the summer. Although this pattern correlates with the school year, we can only speculate that less school-related stress and less exposure to infections trigger fewer episodes. Winter holidays, including Thanksgiving, Christmas, and New Year, can serve as excitatory triggers for some children.

Clinically significant anxiety is common in adults with CVS and includes anticipatory anxiety for fear of upcoming episodes and the burden of symptoms during episodes that cause physical suffering and diminished quality of life.[22] One series found a history of physical, emotional, or sexual abuse during childhood in 44% of adults with CVS.[15] A more recent evaluation of 31 adult patients revealed that 84% had an anxiety disorder.[23] A study of adolescents with CVS found them to be at an increased risk for internalizing psychiatric disorders, with 47% of subjects meeting diagnostic criteria for an anxiety disorder.[24] Panic attack symptoms have been reported in adults with CVS during episodes as well as during the interepisodic period.[15] Panic attacks have also been reported as a common trigger for CVS in adults.

Depression can be a common finding in CVS patients. One study noted that 78% of adults with CVS suffered from mild-to-severe depression.[23] Whether this comorbidity acts as a contributing factor for CVS or is a result of debilitating episodes is unknown. Pediatric series have shown an unusually high percentage of CVS patients with a family history of depression (40%) compared to the general population.[4] Whether depression plays a role in possible susceptibility to CVS is currently unknown.

## Differential Diagnosis

Differentiating a cyclic versus a chronic pattern of vomiting is the first step in narrowing the differential diagnosis. Although the majority of patients with a cyclical pattern are ultimately diagnosed with CVS, the remaining patients have specific causes for vomiting found on diagnostic testing.[4] The majority of disorders mimicking CVS by presenting with a cyclic pattern of vomiting are extraintestinal in origin. Among gastrointestinal disorders, the most serious involve anatomic anomalies of the gastrointestinal tract, including malrotation with intermittent volvulus, which can cause ischemic necrosis. Other gastrointestinal causes include disorders of gut motor function and hepatopancreatobiliary disorders. The most common extraintestinal cause is acute hydronephrosis resulting

from proximal or distal ureteral obstruction. Metabolic causes include mitochondrial disorders (disorders of fatty acid oxidation, mitochondrial encephalopathy, lactic acid, and stroke-like syndrome), urea cycle defects (partial ornithine transcarbamylase deficiency), organic acidurias (propionic acidemia), aminoacidurias, and porphyrin degradation disorders (acute intermittent porphyria).[25,26] Neurosurgical causes include various lesions of the infratentorial region, including cerebellar medulloblastoma, brain stem glioma, and Chiari malformation.[3] Psychiatric disorders include Münchausen-by-proxy, anorexia nervosa, and bulimia nervosa.

## Pathophysiology

CVS is considered an idiopathic disorder, as no etiopathogenesis has been documented. Several tenable hypotheses and associations have been raised to explain this unique disorder mainly based upon clinical observations of CVS and related conditions. Recent scientific investigations and proposed etiologies include mitochondrial gene mutations, gastrointestinal dysrhythmias, autonomic dysfunction, and migraine associations. The current theory is that CVS is a functional brain-gut disorder involving central neuroendocrine mediation and peripheral gastrointestinal manifestations.[4,27,28]

### *Migraines*

An association with migraines was identified over one century ago.[13,14] Documented associations of CVS with migraine headaches include a more prevalent family history of migraines than that of the general population.[9] Although migraine headaches are common in adults with CVS, progression of clinical CVS episodes to migraine headaches with advancing age is more common in children.[9,29] In the absence of definitive diagnostic tests for migraines and CVS, a putative causal relationship is further supported by similar symptomatology (eg, pallor, lethargy, nausea, photophobia, phonophobia) and positive responses in both groups to antimigraine therapy.

Studies have shown that 39–87% of children with CVS and 24–70% of adults with CVS have a migraine association based upon either a positive family history or concomitant or subsequent development of migraines in the patient.[4,17] The progression of cyclic vomiting in childhood to abdominal migraines and eventually migraine headaches in adulthood has been labeled by Barlow as the periodic syndrome.[30] Many studies have confirmed this observation, including reports of adults with migraines whose headaches started with recurrent vomiting.[31,32] Migraine headaches, abdominal migraine, and CVS differ in their primary symptoms, but all have similar rates of secondary symptoms of pallor, lethargy, anorexia, and nausea.[4] Although all three diagnoses appear to be manifestations of a migraine diathesis, their nosological distinction is based upon their predominant symptoms. Compared to patients without a migraine association, these migraine-associated CVS patients generally experience milder episodes with significantly fewer emeses per episode, more symptoms of abdominal pain, headache, photophobia, and social withdrawal, a greater association with psychological stress, and significantly higher response rates to antimigraine therapy (79% vs 36%).[9,15,29]

Among the antimigraine drugs that achieve such a positive response is sumatriptan, a selective 1B/1D serotonin agonist. This action on serotonin receptors, which has similar rates of response to patients with migraine headaches, suggests a central role of action presumably by decreasing cerebrovascular dilatation. Neuroimaging studies have identified a locus of migraine activation in the brainstem with variable responses to sumatriptan.[33] Recent studies on migraine headaches have identified the periaqueductal gray (PAG) matter as a site of dysfunction in migraine attacks. PAG dysfunction may fail to attenuate afferent signals for vomiting and other autonomic symptoms during attacks.[34] Until we have a better understanding of the mechanisms involved in migraines and CVS, we cannot be certain whether CVS patients with no personal or family history of migraine have distinct or similar pathophysiologic cascades.

### *Mitochondrial Dysfunction*

Gastrointestinal symptoms are common in mitochondrial disease, particularly when patients are subject to heightened demands for energy. Mitochondrial dysfunction can be a product of cellular energy deficits during periods of stress, anxiety, infection, and fasting, which are some of the most common triggers for CVS. An association with mitochondrial DNA (mtDNA) mutations has been noted in children with CVS, with mtDNA rearrangements found in the hypervariable region of the D-loop.[26] Some migraines and cyclic vomiting appear to result from disordered energy metabolism in mitochondrial encephalopathy lactic acidosis and stroke-like syndrome.[35] Because mtDNA is maternally derived, the finding of a matrilineal predominance of migraines with CVS further suggests an association.[19] Elevated urinary organic acids, nonspecific lactate elevations, and organic acid abnormalities are found during some CVS episodes similar to those seen in patients with known mitochondrial disorders.[26,36] Treatment with intravenous dextrose during attacks, daily administration of L-carnitine, and avoidance of fasting alleviate symptoms in many patients with CVS, suggesting that there could be subtle underlying mitochondrial dysfunction evident during CVS episodes even in patients without identified mutations.

### *Autonomic Dysfunction*

Symptoms of fever, lethargy, pallor, flushing, drooling, diarrhea, and gut dysmotility commonly occur during episodes of CVS and are mediated by the autonomic nervous system. There are several lines of evidence that support the role of autonomic dysfunction in CVS, including clinical parallels in familial dysautonomia, documented alterations in autonomic tone, and evidence of abnormalities in gastrointestinal motility and myoelectric activity.

To and associates observed heightened sympathetic cardiovascular tone and diminished parasympathetic vagal modulation via spectral analysis of R-R interval variability in CVS patients compared to controls.[37] Rashed and colleagues revealed similar adrenergic autonomic abnormalities between CVS and migraine patients by showing lowered postural adjustment ratios.[38] Chelminsky and Chelminsky recently demonstrated sympathetic autonomic dysfunction in CVS patients via abnormal tilt table testing showing postural tachycardia syndrome and abnormal sudomotor testing compatible with autonomic neuropathy.[39] Rapid gastric emptying at baseline, which may be related to autonomic dysfunction, and delayed gastric emptying during episodes have been demonstrated in adults with CVS.[23] Although the significance remains controversial, there is some electrogastrographic evidence of baseline gastric dysmotility in children with CVS that may respond to erythromycin[40-42] and prominent postprandial tachygastria and blunting of the amplitude of waves in adults with CVS.[23,40]

### *Neuroendocrine Dysfunction*

The primary function of corticotropin-releasing factor (CRF) is stimulation of the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which activates the hypophyseal-pituitary-adrenal axis (HPA). Activation of the HPA axis was first described in CVS by Wolfe and Adler[43] and Sato and coworkers.[43,44] Sato and associates described elevated levels of ACTH, antidiuretic hormone, cortisol, prostaglandin E2, and serum and urinary catecholamines during episodes of CVS.[45] Blunting of this accentuated HPA axis response with coincident reduction of CVS symptoms has been shown through the use of the α-adrenoceptor agonist clonidine by Sato and coworkers[45] and the use of high-dose dexamethasone by Wolfe and Adler.[43]

The role of CRF as a brain-gut mediator in foregut function has been extensively described in animals by Lenz and associates,[46] Taché and colleagues,[27] and others. It is hypothesized that CRF is released from the hypothalamus in response to stress. This CRF release can stimulate the inhibitory motor nerves in the dorsal motor nucleus of the vagus, causing delayed gastric emptying and nausea.[27,28] Clinical CVS in humans is precipitated by parallel stimuli that augment CRF release in animals. In addition, the same hormones in a subset of Sato's group reflected a stimulated HPA axis, presumably initiated by CRF release, that appeared to give rise to the prominent symptoms of hypertension, anorexia, and delayed gastric emptying. Current studies examining the role of CRF in CVS may not only elucidate the pathophysiologic cascade but could also open potential therapeutic avenues involving CRF antagonists. Tricyclic antidepressants, which inhibit the promoter activity of the CRF gene, are some of the most successful prophylactic agents in treating CVS.[47,48]

### *Miscellaneous Associations*

Coexisting neurologic findings of developmental delay, generalized seizures, and hypotonia, as well as neuromuscular disease manifestations, which include cognitive disorders, skeletal myopathy, and cranial nerve dysfunction, have been found in up to 25% of CVS patients.[49] CVS patients with these findings have been labeled as CVS+. A comparison of CVS+ patients to CVS patients with no neurologic findings revealed that CVS+ patients have an earlier age of onset. They also have a 3- to 8-fold greater prevalence of dysautonomic-related disorders (eg, migraine, chronic fatigue, neurovascular dystrophy) and constitutional abnormalities (eg, growth retardation, birth defects).[49]

Recent case reports of adult and child CVS patients with epileptiform activity on electroencephalography have shown response to antiepileptic drugs, including carbamazepine and topiramate.[50,51]

The use of marijuana by CVS patients to alleviate nausea and vomiting has been suggested as a contributing factor for worsening CVS symptoms. One series of 9 patients noted the termination of cyclic emesis after cessation of chronic use of marijuana.[52,53] Another case report noted that 7 of 13 marijuana users in a series of 31 CVS patients experienced improvement of nausea and anxiety with marijuana use.[23] Therefore, it is possible that, although marijuana may be a trigger for some people, it can alleviate symptoms in others with CVS.

## Diagnostic Evaluation

At present, there are no specific tests for diagnosing CVS, and the diagnosis rests upon fulfilling clinical criteria. In a recent consensus statement on the diagnosis of CVS in children, NASPGHAN proposed criteria that included the following: at least 5 episodes overall or a minimum of 3 episodes noted in a 6-month period; recurrent attacks of vomiting and nausea lasting 1 hour to 10 days and occurring at least 1 week apart; stereotypy of symptoms and episodes; vomiting during episodes occurring at least

4 times per hour for at least 1 hour; returning to baseline health between episodes; and not being attributable to another disorder.[2] Approximately 90% of children who fulfill these criteria are found to have CVS.[54] Most of the testing with recurrent vomiting is directed toward identifying underlying gastrointestinal, neurologic, renal, metabolic, and endocrine causes in the remaining 10% of children. The challenge is to determine which and how much testing should be performed, as a shotgun approach can be costly, time-consuming, and invasive. Cost-decision analysis suggests that, in order to rule out pathology such as intestinal malrotation predisposing to intermittent volvulus, an upper gastrointestinal tract radiograph with a small bowel follow-through, followed by 2 months of empiric antimigraine therapy, is the most cost-effective initial treatment strategy for CVS.[21] If no therapeutic response occurs, more systematic testing should be performed.

Distinguishing a cyclic pattern of vomiting from chronic vomiting is a key first step in the diagnosis of CVS.[54] However, care must be taken in evaluating adults with chronic baseline nausea and vomiting. Symptoms that may be mistaken for chronic gastrointestinal disorders (peptic, allergic, inflammatory) may actually be anxiety-driven symptoms or coalescent CVS common in adult CVS sufferers.[15] This population may benefit from gastrointestinal endoscopic evaluation, which is not routinely recommended in evaluating cyclical vomiting in children. The most potentially devastating causes of recurrent vomiting (including anatomic anomalies of the gastrointestinal tract and renal hydronephrosis) should be sought by upper gastrointestinal series with small bowel follow-through and renal ultrasound examination, respectively. Metabolic and endocrine testing has the highest diagnostic yield during an episode of CVS and must be performed before intravenous glucose and fluids are administered, as these agents can alter respective findings on metabolic screening and evaluation of the HPA axis metabolites.[4] If vomiting is associated with progressive or focal neurologic findings, magnetic resonance imaging of the head is warranted.

## Treatment

Current treatment for CVS can be divided into supportive therapy (during episodes), prophylactic therapy (to prevent episodes), and abortive therapy (to prevent progression from prodromal symptoms to the vomiting phase). Strategies for management of CVS during the interepisodic period include avoidance of identified triggers, lifestyle changes, and psychological interventions. Although limited data exist on treatment outcomes in children and adults with CVS, a recent NASPGHAN consensus statement has outlined guidelines for management of CVS in children based mainly upon pediatric case series.[2]

**Table 2.** Prophylactic Pharmacotherapy (Dosing Based on Off-Label Pediatric Experience)

| |
|---|
| **Antimigraines** |
| • **Amitriptyline:** start at 0.5 mg/kg and advance to 1–2 mg/kg per day QHS (adults 10–100 mg QHS). Monitor electrocardiogram QTc interval prior to starting. 1st choice >5 yrs old. SE: sedation, anticholinergic. |
| • **Propranolol:** 0.25–1 mg/kg per day BID or TID (adults 40 mg BID). Monitor resting heart rate. SE: hypotension, bradycardia, fatigue. |
| • **Cyproheptadine:** 0.25–0.5 mg/kg per day BID or TID. 1st choice <5 yrs old. SE: sedation, weight gain, anticholinergic. |
| • **Alternatives:** nortriptyline, imipramine. |
| **Anticonvulsants** |
| • **Phenobarbital:** 2 mg/kg per day QHS. SE: sedation, cognitive impairment. |
| • **Valproate:** 500–1,000 mg ER QHS. SE: somnolence, hepatotoxicity. |
| • **Carbamazepine:** 5–10 mg/kg per day BID. SE: sedation, anticholinergic. |
| • **Alternatives:** gabapentin, topiramate, levetiracetam, zonisamide. |
| **Supplements** |
| • **L-carnitine:** 50–100 mg/kg per day BID or TID (adults 660 mg–1 g BID or TID). SE: diarrhea, fishy body odor. |
| • **Coenzyme Q10:** 10 mg/kg per day BID or TID. |

Data from Li et al,[2] Sunku, Li,[4] Abell et al,[5] Chelminsky, Chelminsky,[39] Stout et al,[47] Boles et al,[49] Gokhale et al,[56] and Clouse et al.[57]

ER=extended release; SE=side effects.

Avoidance of known triggers, particularly dietary triggers (eg, chocolate, cheese, monosodium glutamate, nitrites, caffeine), can reduce the frequency of episodes. Lifestyle changes include avoidance of anxiety and excitement triggers as well as energy-depleted states that can be induced by sleep deprivation, fasting, illness, and physical overexertion. Those with high-energy demand or a history of fasting-induced episodes can benefit from high-carbohydrate snacks between meals, before physical exertion, and at bedtime.[2] In some cases, stress management strategies with the aid of a psychologist can attenuate the effects of excitatory or negative stressors as well as reduce the fear and anticipation of future episodes.[55]

Daily use of prophylactic medications is based upon empiric therapy that is traditionally employed to treat

other disorders, including migraines, epilepsy, gastrointestinal dysmotility, and birth control (Table 2). Prophylaxis should be considered in patients who have episodes that are frequent (more than 1 episode per month), severe (prolonged for more than 3–5 days), debilitating (associated with hospitalization), or disabling (causing absence from school or work).[3] Prophylaxis is also recommended for those who fail a trial of abortive therapy or supportive measures. The ultimate goal of prophylaxis is to prevent attacks altogether but, at the very least, to reduce the frequency, duration, or intensity of episodes.

A family history of migraines is a strong indicator (79%) of a positive response to antimigraine therapy.[9] In addition, associated symptoms of headache, photophobia, and phonophobia should make one consider starting antimigraine prophylaxis with cyproheptadine, propranolol, or amitriptyline. In a limited pediatric case series, efficacy was 39–61% for cyproheptadine, 52–65% for propranolol, and 67–81% for amitriptyline. The criterion for efficacy was a greater-than-50% reduction in the frequency or severity of episodes. Cyproheptadine is the recommended choice for patients under 5 years of age. The side effect of daytime sedation may be reduced by single nighttime dosing instead of the usual twice- or thrice-daily dosing schedule. The side effects of increased appetite and excessive weight gain may make this a less favorable choice for overweight patients.[2] Propranolol is the second choice in children of all ages based upon consensus guidelines.[2] It is contraindicated in asthmatics, has the side effect of tiredness, and should be accompanied by monitoring of the resting heart rate for potential bradycardia. Amitriptyline has been the most effective prophylactic agent reported in pediatric and adult case series.[2,4,23] Higher response rates have been observed with higher dosing (1 mg/kg/day or greater) in both pediatric and adult studies. A step-up approach in dosing with incremental increases by 5–10 mg weekly is suggested for all ages to achieve the desired response while limiting side effects.[2,5] Nortriptyline and imipramine may be options for those who experience side effects from amitriptyline.

Other prophylactic agents that have been used for CVS include phenobarbital, valproate, gabapentin, and carbamazepine (Table 2).[56] Although they are specifically indicated when spike and wave patterns are noted on electroencephalogram, they are increasingly used in both migraine and CVS prophylaxis. Zonisamide and levetiracetam have shown moderate (75%) response in adults with CVS refractory to tricyclic antidepressant prophylaxis. However, moderate-to-severe side effects in 45% of patients in this series limit their use in adults who fail conventional prophylaxis.[57] Erythromycin has been useful as a prokinetic agent,[41] and low-dose estrogen birth control can be useful in teenage girls who have catamenial CVS. One case series documented a decreased frequency of CVS episodes with daily carnitine use.[58] Carnitine, a cofactor for long-chain fatty acid transport into mitochondria, may help CVS patients with metabolic or mitochondrial dysfunction.[2] Although no published data exist for its use, coenzyme Q10 has also been used as adjunctive therapy in CVS sufferers with suspected mitochondrial dysfunction.

Abortive therapy is intervention taken at the onset of an episode or even earlier during the prodromal phase, ideally to abort the vomiting phase altogether or reduce the duration or severity of the episode. Abortive therapy should be considered for those who have sporadic episodes that occur less than once per month and who prefer not taking prophylaxis or those who have breakthrough episodes while on prophylaxis.[3,59] As patients with intractable emesis are unable to tolerate oral medication, these medications usually must be administered parenterally or via rectal preparations.

The primary CVS abortive agents include 5-HT 1B/1D agonists commonly used for migraine headaches. Success rates are higher in those children with migraine-associated CVS, when used early in the episode, and in those with episodes less than 24 hours long.[4] Sumatriptan administered via oral, subcutaneous, or intranasal routes has a 51% efficacy rate compared to a 65% efficacy rate in headaches (Table 3).[4] The sensation of substernal and neck burning rarely occurs with intranasal administration. Use of zolmitriptan and frovatriptan in CVS is anecdotal.

Supportive care, which is used whenever intractable symptoms continue during an episode that fails to respond to abortive therapy, includes intravenous fluids, nonstimulating environment, antiemetics, sedation, and analgesia.[3,59] Also helpful can be intravenous fluids with high dextrose concentration (10%) and electrolytes, a quiet, nonstimulating environment in a dark room, and induction of sleep via sedatives. If a combination of antiemetics and benzodiazepines, in an attempt to alleviate nausea and help the patient sleep through the worst part of their cycle, is unsuccessful, analgesia is occasionally used first with nonsteroidal anti-inflammatory drugs and eventually with opioids, if needed. Interepisodic nausea, anxiety, and abdominal pain, common in adult CVS, can also benefit from supportive care, including antiemetics, antianxiety agents, and analgesics.

Ondansetron, a 5-HT3 antagonist, is primarily used as an antiemetic, with efficacy rates around 62%.[9] More effective at the higher dosing of 0.3–0.4 mg/kg per dose, the side-effect profile has been excellent, with few reports of drowsiness, dry mouth, and headache (Table 3).[19] Ondansetron generally reduces both nausea and vomiting but rarely aborts an episode. The addition of lorazepam provides sedation that may lessen intractable nausea. Sound

**Table 3.** Abortive Pharmacotherapy (Dosing Based on Off-Label Pediatric Experience)

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| **Antimigraines** |
| • **Sumatriptan:** 20 mg intranasally at episode onset and can repeat once or 25 mg orally once. SE: chest and neck burning, coronary vasospasm, headache.<br>• **Alternatives:** frovatriptan, rizatriptan, zolmitriptan. |
| **Antiemetics** |
| • **Ondansetron:** 0.3–0.4 mg/kg per dose every 4–6 hours intravenously/orally. SE: headache, drowsiness, dry mouth.<br>• **Alternatives:** granisetron, aprepitant. |
| **Sedatives** |
| • **Lorazepam:** 0.05–0.1 mg/kg per dose every 6 hours intravenously/orally. Useful adjunct to ondansetron. SE: sedation, respiratory depression.<br>• **Chlorpromazine:** 0.5–1 mg/kg per dose every 6 hours intravenously/orally. SE: drowsiness, hypotension, seizures.<br>• **Diphenhydramine:** 1.25 mg/kg per dose every 6 hours intravenously/orally. Useful adjunct to chlorpromazine. SE: hypotension, sedation, dizziness. |
| **Analgesics** |
| • **Ketorolac:** 0.5–1 mg/kg per dose every 6 hours intravenously/orally. SE: gastrointestinal bleeding, dyspepsia.<br>• **Alternatives:** opioids. |

Data from Li et al,[2] Sunku, Li,[4] Abell et al,[5] Van Calcar et al,[58] and Li.[59]

SE=side effects.

sleep prevents vomiting during CVS episodes. When all else fails, intravenous administration of a combination of chlorpromazine plus diphenhydramine can cause effective sedation.[60] Previous experience suggests that phenothiazine antiemetics (D2 antagonists) have poor efficacy in this disorder, even less than placebo responses, suggesting that dopaminergic pathways are not involved.[4]

A placebo effect (70%) has been described from consultation alone prior to instituting therapy.[61] Knowledge of the diagnosis and effective therapies, reductions in stress and known triggers, along with a limited diagnostic evaluation eliminating fears of organic pathology may contribute to this large placebo effect. A limited trial of lifestyle changes through the time period of 1–2 typical cycles may be considered an option for some.

## Summary

CVS is an idiopathic functional vomiting disorder initially described in children that is increasingly recognized in adults. Although documented pathophysiologic associations with migraine, mitochondrial disorders, and neuroendocrine abnormalities have been described in pediatric CVS, migraines, anxiety, and panic appear to be common associations in adults that require further study. The natural history of CVS in children suggests that most will outgrow this debilitating disorder with time, though some will transition to migraine headaches and even continue to suffer CVS as adults.

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