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Cyclic Vomiting Syndrome in Pediatric Patients: A Review of Therapeutics

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Cyclic vomiting syndrome (CVS) is a functional gastrointestinal disorder that can present quite a challenge to clinicians caring for children with this complex disease. Different therapeutic interventions are recommended for prophylaxis and acute abortive therapy for a CVS attack. The aim of this review is to summarize therapeutic treatment recommendations from the 2008 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHN) Consensus Statement on the Diagnosis and Management of Cyclic Vomiting Syndrome and discuss studies contemporary to this expert recommendation. After an extensive search of medical databases, 8 studies that evaluated therapeutic treatments for CVS were identified. Amitriptyline and cyproheptadine remain the standard of care for prophylaxis. Nutritional supplements such as carnitine and coenzyme Q10 have shown efficacy in decreasing episodes and severity in small studies with high tolerability among patients. The combination of ondansetron and sumatriptan are recommended for abortion of an acute vomiting episode, but other agents such as aprepitant and sedative agents can be considered when vomiting is refractory to initial treatments.

ABBREVIATIONS CVS, cyclic vomiting syndrome; IBS, irritable bowel syndrome; NASPGHN, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; SQ, subcutaneous

KEYWORDS child; familial cyclic vomiting syndrome; vomiting

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Introduction

Functional gastrointestinal disorders are reported to affect 10% to 40% of children.[1] These disorders include, regurgitation, colic, dyschezia, cyclic vomiting syndrome (CVS), abdominal migraines, rumination, functional vomiting, functional constipation, functional diarrhea, functional dyspepsia, irritable bowel syndrome (IBS), aerophagia, chronic constipation, and rumination syndrome.[1] These diseases and disorders are challenging to diagnose, as few clear objective diagnostic tests are available and diagnosis is based on subjective symptoms and interpretation by a skilled clinician using the Rome Criteria.[1] Not only are these disorders a challenge to diagnose, but they also present a challenge for treatment. In this review, we will aim to focus on only pediatric functional vomiting, specifically, CVS.

Cyclic vomiting syndrome, sometimes referred to as functional vomiting or abdominal migraines, is characterized by cycles of intense relentless vomiting followed by periods of general wellness. According to the Rome Criteria, CVS should be considered if a child has had at least 5 vomiting attacks over any time interval or 3 attacks over a 6-month period.[1] These episodic attacks could last from 1 hour to 10 days occurring at least 1 week apart with a return to baseline between episodes.[1,2] In addition to vomiting, many patients also experience pallor listlessness, anorexia, nausea, abdominal pain, headache, and photophobia.[2,3] These episodes can have many triggering factors that vary between children, but include stress, excitement, change in routine, and sometimes menstrual cycle in older adolescences and adults.[2,3] Additionally, CVS can have a crossover with many other conditions such as migraines, mitochondrial disorders, autonomic dysfunction, and use of cannabinoids.[3] These comorbidities may actually be helpful to clinicians to tailor treatment to the etiology of a patient's CVS, but the diverse symptoms and other underlying disease may also make diagnosis and treatment challenging. There have been other recent reviews on CVS,[1,3–7] but in this review, we will focus solely on the pharmacologic treatment of CVS including abortive therapy, prophylaxis, management of comorbid conditions and sequelae, non-pharmacologic treatments, and novel areas of research for this challenging disease. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHN) Consensus Statement on the Diagnosis and Management of Cyclic Vomiting Syndrome was published in 2008[2] and the Guidelines on Management of Cyclic Vomiting Syndrome in Adults by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association was published in 2019.[8] For this review, we will summarize these expert guidelines and focus in detail on pediatric studies after 2008.

Methods

We searched PubMed (2008–2021) and MEDLINE (2008–2021), using the terms: "cyclic vomiting syndrome," "functional vomiting," "abdominal migraines," and synonyms or related terms. We reviewed the reference lists of all identified studies and reviews. We decided to only include studies published after 2008 because the NASPGHN Consensus Statement on the Diagnosis and Management of Cyclic Vomiting Syndrome was published in 2008.[2] We included controlled trials, cohort, and case-control studies in pediatric patients with CVS and excluded case reports. We identified 8 studies that met the inclusion criteria and are evaluated in this article (Table).

Literature Review

Pharmacologic Treatment. Pharmacologic treatments for CVS can be divided into several different groups. Abortive therapy is used in an acute CVS episode and prophylaxis is used to prevent future CVS episodes. In addition to abortive and prophylaxis, if CVS is related to an underlying illness, there may be treatments for these conditions that could improve CVS and many supportive care therapies can be used to treat some of the symptoms of CVS. In this section, we will review these treatment modalities for CVS.

Abortive Therapy. When a child presents to a clinic or emergency department with a CVS episode, it is imperative to abort the cycle as soon as possible to avoid dehydration and electrolyte abnormalities. When the NASPGHN Consensus Statement was published in 2008, there were no controlled or open trials evaluating abortive therapies for CVS, but the task force recommended the off-label use of antimigraine $5HT_{1B/1D}$ agonists (triptans) and the antiemetic 5HT3 receptor antagonists such as ondansetron and granisetron for abortive therapy. Other antiemetics such as promethazine (H_1 antagonist) and prochlorperazine (D_2 antagonists) have been used clinically, but these have been shown to be ineffective when compared with ondansetron.[9] Adult CVS guidelines recommend $5HT_3$ receptor antagonists, triptans, and/or aprepitant to abort an acute episode.[8]

In a 2010 study, 12 hospitalized patients (11 children and 1 adult) with CVS were treated with sumatriptan administered either subcutaneously or by nasal spray in 35 separate attacks.[10] Four of these 11 patients treated with SQ sumatriptan had complete resolution of vomiting.[10] Five patients had a response characterized as effective and during 10 episodes, sumatriptan was non-effective.[10] Overall, 54% of attacks were aborted with sumatriptan.[10] In this population, 33% of patients reported a family history of migraine in a first-degree relative.[10] The authors noted that the efficacy of sumatriptan was higher in patients with a family history of migraine, yet this was not statistically significant.[10]

The neurokinin-1 antagonist, aprepitant, was retrospectively studied for acute abortion of CVS episodes and prophylaxis of CVS episodes in 41 children who met the NASPGHAN criteria.[11] Sixteen patients were treated prophylactically and 25 received aprepitant for acute treatment.[11] When given aprepitant for an acute episode, 76% of patients had a response (3/25 complete response and 16/25 partial response).[11] Results of the prophylaxis arm are discussed below, but the authors concluded that aprepitant appears to improve both acute and prophylactic CVS in pediatric patients.[11] Although this study shows promise, aprepitant has not been directly compared with the standard of care (ondansetron and/or sumatriptan); therefore, its exact role in a CVS treatment algorithm cannot be determined. Yet, if a patient fails first-line abortive therapy with ondansetron and/or sumatriptan, aprepitant is an alternative agent that should be considered.

When antiemetics and triptans fail to abort the cycle the expert task force recommends, sedatives such as the benzodiazepine lorazepam. Sedating antihistamines such as chlorpromazine and diphenhydramine could also be beneficial for refractory episodes due to their sedative effects and some antiemetic effects.[2]

Prophylaxis. At the time the NASPGHN Consensus Statement was published, the task force was not able to provide evidence-based recommendations for prophylaxis due to a limited number of clinical studies; therefore, expert recommendations were not given. The NASPGHN consensus statement reports that cyproheptadine, propranolol, amitriptyline, phenobarbital, and pizotifen were associated with the highest response rates in children with CVS.[2] In contrast, the Adult CVS guidelines recommend the use of amitriptyline prophylaxis for any adult patient with moderate to severe CVS.[8]

The NASPGHN expert task force recommended that cyproheptadine, an antihistamine and serotonin receptor antagonist, be used as the first-line therapy in children 5 years old and younger.[2] Cyproheptadine can cause weight gain due to increased appetite and may not be the best choice for overweight children, but can also be dosed at bedtime to lessen the appetite stimulation and overeating.[2] The NASPGHN Consensus Statement noted that pizotifen, which is similar to cyproheptadine, has shown to be highly efficacious, yet it is currently not available in the United States.[2]

The NASPGHN expert task force recommend the tricyclic antidepressant amitriptyline as the preferred first-line agent for children older than 5 years old. They recommend starting doses of 0.25 to 0.5 mg/kg/dose as a single bedtime dose followed by an increase to a goal of 1 mg/kg/day and titrating up to a maximum of 2 mg/kg/day if necessary, for at least 4 weeks.[2] In a single-blinded randomized trial, 64 children (3–15 years old) were randomly assigned to receive either amitriptyline 0.5 mg/kg/day and titrated to 1 mg/kg/day after 1 week or cyproheptadine 0.1 mg/kg/day and titrated to

Table. Pediatric Cyclic Vomiting Syndrome Studies

Reference	Study Design (Population)	Intervention/Medication	Findings
Badihian[12]	Single blind, randomized clinical trial Valproate (64 children age 3–15 yr)	CVS prophylaxis Amitriptyline: 0.5–1 mg/kg/day Cyproheptadine: 0.1–0.2 mg/kg/day Duration: 6 mo	Mean monthly attacks (p = 0.197): amitriptyline: 0.38 ± 0.55 vs cyproheptadine 0.59 ± 0.71 Mean duration of attacks (hr) (p = 0.212): amitriptyline: 1.14 ± 2.86 vs cyproheptadine: 1.81 ± 2.22 Full remission (p = 0.206): amitriptyline: 65.6% vs cyproheptadine: 50% Conclusions: No difference in amitriptyline vs cyproheptadine for CVS prophylaxis
Bagherian[15]	Prospective, randomized clinical trial (36 children age 3–15 yr, with no comorbidities; 2 patients in the amitriptyline group withdrew)	CVS prophylaxis Amitriptyline: 1 mg/kg/day Topiramate: 1–2 mg/kg/day Duration: 3 mo	Frequency of attacks per month (p = 0.368): amitriptyline: 0.91 ± 0.4 vs topiramate: 1.07 ± 0.55 Duration of attacks in hr (p = 0.017): amitriptyline: 3.43 ± 2.46 vs topiramate: 4.9 ± 3.03 Cessation of attacks (p = 0.016): amitriptyline: 23 of 34 (68%) vs topiramate: 14 of 36 (39%)
Boles[18]	Retrospective, internet based direct to patient survey ([N = 385]; 18 were excluded due to no formal diagnosis of CVS or not meeting criteria; amitriptyline [n = 277]; Co-Q10 [n = 82])	CVS prophylaxis Amitriptyline vs Co-Q10	Efficacy: Patients or parents reported similar levels of efficacy. Patients evaluated episode parameters (frequency, duration, number of emesis, nausea severity) Reduction in at least 1 of the 4 symptom parameters: Amitriptyline: 72% of patients; Co-Q10: 68% of patients Adverse events (p < 0.001): amitriptyline: 50% of patients; Co-Q10: none Subjects consider benefits outweigh risk (p = 0.008): amitriptyline: 47% of patients; Co-Q10: 77% of patients Conclusion: Prospective studies needed, but Co-Q10 could be considered as a low-risk alternative or additional therapy
Boles[17]	Retrospective (42 patients with CVS; 30 cases included)	CVS prophylaxis Avoidance of fasting, amitriptyline, cyproheptadine, Co-Q10, L-carnitine	Post-intervention outcome (n = 30): Complete resolution: 23 (76%) Improved by 75%: 3 (10%) Improved by 50%: 1 (3%) Treatment failure: 3 (10%) Other: intolerant to amitriptyline: n = 2; Multiple comorbidities: n = 1 Conclusion: mitochondrial-targeted cofactors with the addition of amitriptyline or cyproheptadine are highly effective for CVS prophylaxis

(Table cont. on page 4)

0.2 mg/kg/day for 6 months.[12] Symptoms and episodes were evaluated for 2 months prior to the start of drug therapy. The mean monthly frequency of attacks in the amitriptyline group was 0.38 ± 0.55 and 0.59 ± 0.71 in the cyproheptadine group.[12] Complete remission was reported in 65% of patients in the amitriptyline group compared with 50% of patients in the cyproheptadine group.[12] Although there were fewer monthly attacks and a higher percentage of patients with remission in the amitriptyline group compared with the cyproheptadine group, these outcomes were not statistically significant.[12] In this study, the age range was 3 to 15 years and the NASPGHN expert task force recommends cyproheptadine in children 5 years old and younger; therefore, it would be interesting to see a subanalysis of children 5 years old and younger and children older than 5 years old with these 2 drugs.

The NASPGHN expert task force recommended that

Table. Pediatric Cyclic Vomiting Syndrome Studies *(cont.)*

Reference	Study Design (Population)	Intervention/Medication	Findings
Cristofori[11]	Retrospective (41 children with median age of 8 yr)	Prophylactic or acute treatment of CVS Aprepitant Prophylaxis dose: <40 kg = 40 mg twice per wk >40 kg – <60 kg = 80 mg twice per wk >60 kg = 125 mg twice per wk Acute dose: <15 kg = 80 mg day 1, 40 mg day 2 and 3 if needed 15–20 kg = 80 mg day 1, 80 mg day 2 and 3 if needed >20 kg = 125 mg day 1, 80 mg on day 2 and 3 if needed	Prophylactic treatment (n = 16) Complete resolution: 18.75% (n = 3) Partial response: 52.5% (n = 10) Acute treatment (n = 25) Complete resolution: 12% (n = 3) Partial response: 64% (n = 16) Adverse events: Side-effects reported in 5 of 16 patients on prophylactic therapy (i.e., hiccough, fatigue, increased appetite, headache). One child stopped therapy due to severe migraines
Haghighat[13]	Retrospective (221 children with a median age of 5.7 yr)	CVS prophylaxis Propranolol: 1 mg/kg/day	Responded: 93.2% (n = 206); propranolol discontinued at 6-mo follow-up Therapy restarted: 7.8% (n = 16); no need for long-term prophylaxis in most patients Adverse events: 21 patients were excluded due to side-effects, loss to follow-up, or change in diagnosis
Hikita[14]	Prospective, open-label (13 children with severe CVS)	CVS prophylaxis Valproate: 10–40 mg/kg/day	Failed standard treatment: 9 of 13 patients Complete resolution: 2 patients Improvement of symptoms: 9 patients, No response: 2 patients Other: 4 patients relapsed when valproate dose was decreased Adverse events: none
Hikita[10]	Open-label (12 patients; 11 children and 1 adult)	CVS abortive therapy Sumatriptan: SQ: ([age ×4 + 20]/100 × 3 mg] Nasal spray: 20 mg	SQ: 11 patients with 35 CVS attacks; 54% of attacks responded (19 attacks) Nasal spray: 5 patients with 6 attacks; 33.3% of attacks responded (2 attacks) Adverse events: None Other: Efficacy of sumatriptan was higher in patients with a family history of migraine compared with those without (p = 0.0482)

Co-Q10, coenzyme Q10; CVS, cyclic vomiting syndrome; SQ, subcutaneous

propranolol, a ß-blocker has moderate efficacy and is recommended for second-line CVS prophylaxis for children of any age.[2] Caution should be used in children with low resting heart rate. Other ß-blockers may be considered, and although they may have fewer side effects, those that do not cross the blood brain barrier such as atenolol and nadolol may have decreased efficacy.[2] In a 2017 study of 221 pediatric patients with CVS treated with propranolol 1 mg/kg/day titrated to a maximum of 3 mg/kg/day and had regular follow-up to complete the study, 206 patients had a response of at least a 50% decrease in CVS episode frequency or severity.[13] Propranolol was discontinued after 6 months of therapy and recurrence of symptoms only occurred in 16 (7.8%) patients.[13] The authors concluded that there is no need for long-term prophylaxis for children treated for 6 months with propranolol.[13] Although this study did show a prolonged symptom free period, it is not uncommon for well time between CVS episodes to extend beyond 6 months, which was the duration of follow-up that was studied.

The anticonvulsant medications have been used to treat CVS. Specifically, the anticonvulsant phenobarbital at a dose of a single bedtime dose of 2 mg/kg/day was recommended by the NASPGHN expert task force as an alternative second-line agent.[2] The anticonvulsant valproate was given as prophylaxis in 13 children with refractory CVS after failing propranolol, amitriptyline, cyproheptadine, phenobarbital, phenytoin, and carbamazepine.[14] After treatment with valproate 10 to

40 mg/kg/day, 2 patients had complete resolution of symptoms, 9 patients had improvement in symptoms, and 2 patients failed to respond.[14] Four patients did experience a relapse in CVS symptoms, but overall prophylaxis with valproate was associated with 11 (85%) patients having reduction in the frequency of attacks.[14] Thirty-six children age 3 to 15 years old with CVS were randomly assigned to receive amitriptyline (1 mg/kg/day) or topiramate (1–2 mg/kg/day) and followed for 3 months.[15] Two patients in the amitriptyline group did not complete the trial.[15] At baseline the frequency and duration of attacks were not different between the 2 groups, but after the intervention the duration of attacks in the topiramate group was significantly lower compared with the amitriptyline group. However, 68% of patients in the amitriptyline group and only 39% of patients in the topiramate group had cessation of CVS attacks after the intervention.[15] Similar to other cited CVS studies, this study also had a rather short follow-up period of 3 months and it is not abnormal for the typical nadir of the disease process to result in a lack of symptoms for 3 months. A longer follow-up is needed to determine if amitriptyline is more efficacious compared with topiramate.

In patients who do not show improvement or experience adverse events that prohibit the continued use of amitriptyline, a pharmacist may consider pharmacogenomic testing for *CYP2D6* and CYP2C19 genetic variations. When pharmacogenomic results are available, the Clinical Pharmacogenetics Implementation Consortium guidelines should be used to guide dosing of tricyclic antidepressants.[16]

As discussed above in the abortive section, aprepitant has also shown benefit for prophylaxis. After a 1-year intention to treat follow-up, 81% of patients prescribed aprepitant for prophylaxis had a response (3/16 complete response and 10/16 partial response).[11] This resulted in a significant decrease in CVS episodes per year, hospital admissions per year, length of CVS episodes, number of vomits per hour, and an increase in well days and school attendance compared with previous years for each patient.[11] Although these results show promise, the cost of aprepitant may be prohibitive for prophylactic therapy for patients with CVS.

Management of Comorbid Conditions and Sequelae. Both the NASPGHN expert task force and the Adult CVS guidelines discuss the importance of treating underlying comorbid conditions that could be contributing to the etiology of CVS.[2,8] These could include anxiety, depression, migraine headache, mitochondrial disease, sleep disorders, autonomic dysfunction, and/or substance abuse.[2,8] For example, carnitine 50 to 100 mg/kg/day and coenzyme Q 5 to 10 mg/kg/day may be beneficial in children with CVS related to mitochondrial disease.[2,8] Additionally, the NASPGHN expert task force advise that low dose estrogen oral contraceptives may be useful in treating adolescent girls with CVS that is triggered by menstrual cycles.[2] A retrospective review evaluated 30 patients with CVS treated with a CVS protocol including: avoidance of dietary fasting, coenzyme Q10 10 mg/kg/day (maximum 200 mg per day) divided twice a day, L-carnitine 100 mg/kg/day (maximum 4 grams per day) divided twice a day, and amitriptyline 0.25 mg/kg/day divided twice a day in patients older than 5 years old or cyproheptadine 0.25 mg/kg/day divided twice a day in patients 5 years old or younger.[17] Additionally, 2 patients who were refractory to the above protocol received topiramate 25 mg twice per day. Vomiting episodes resolved in 23 cases and improved by >75% in 3 patients and >50% in 1 patient.[17] Three patients were deemed treatment failures, 2 of which had intolerance to amitriptyline and 1 patient had multiple congenital gastrointestinal anomalies.[17] The authors concluded that the addition of mitochondrial-targeted cofactors to the standard therapeutics of amitriptyline or cyproheptadine is highly effective in preventing vomiting.[17] In an internet-based survey, 22 patients taking coenzyme Q10 and 162 patients taking the standard of care amitriptyline for prophylaxis for CVS were asked to rate symptom parameters including frequency, duration, number of emesis, nausea severity, and tolerability of treatment.[18] Patients considered the benefit of treatment outweighed the risk in 47% of the amitriptyline group and 77% of the coenzyme Q10 group, leading the authors to conclude that coenzyme Q10 should be considered as a potentially efficacious and tolerable treatment that should be considered for CVS prophylaxis.[18]

Even with new evidence published since the publication of the NASPGHN expert recommendations, amitriptyline and cyproheptadine still have the most evidence for first-line prophylaxis. In patients with underlying etiologies for CVS such as mitochondrial disease or migraines, other agents may also be considered either first-line or if the standard first-line therapies fail.

Supportive Care for Symptomatic Management. Aside from aborting the acute CVS cycle, it is important to manage the symptoms and consequences of chronic vomiting. Many patients will need intravenous fluid for dehydration. If the patient is already dehydrated at the time of presentation, an intravenous bolus of normal saline may be necessary. If vomiting continues, continuous intravenous fluid should be administered to maintain hydration until vomiting stops. In children with an underlying mitochondrial disease, intravenous fluids with higher dextrose percentage such as 10% should be considered. This should also be considered for those patients that hypoglycemia is a trigger for CVS episodes. Patients should have blood chemistries evaluated and electrolytes should be supplemented and corrected accordingly.

As previously discussed, many patients may have pain such as abdominal pain or headache, photophobia, list fullness, or other withdrawn behaviors. A patient's

pain should be addressed and treated accordingly. If photophobia is a complaint, the room should be kept dark with minimal stimulation. Additionally, patients should not be pestered to talk, answer questions, or respond. In acute attacks, it is common for a patient to seem minimally responsive, and care should be clustered as to not disrupt the patient any more than necessary.

Non-pharmacologic Treatments. The expert panel sited that anxiolytic medications and relaxation techniques have anecdotal evidence for usefulness in aborting a cycle.[2] When CVS is triggered due to stress, relaxation and coping techniques such as biofeedback, neurocognitive therapy, and psychological counseling that have been used for other stress-related illness triggers may have some utility in CVS.[8,19,20] The Adult CVS guidelines discuss the importance of having an individualized treatment plan for aborting an acute CVS episode.[8] Having a plan that can be shared with emergency room staff may help to ease anxiety from both patients and caregivers and expedite treatment of CVS with new providers or providers that are not accustom to treating CVS attacks.

In some patients for whom CVS is refractory to all pharmacologic treatments, placement of a gastric electrical stimulator could be considered. A small study of 11 patients with refractory CVS had a decrease in severity of symptoms after placement of either a temporary or permanent gastric electrical stimulator.[21]

Potential Future Treatments. Unfortunately, research and clinical trials for therapeutics to treat CVS are limited. At the time of this review, there are no clinical trials currently enrolling with children with CVS according to clinicaltrials.gov. There is 1 study enrolling patients age 18 to 60 years old with CVS: A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Safety and Efficacy of Staccato Granisetron (AZ-010) for the Acute Treatment of Moderate to Severe CVS.[22] Although this study is only enrolling adults at this time, it is promising that there are medications in the pipeline that may provide future benefit to children with CVS.

Conclusion

Treatment of CVS remains challenging with minimal high-level evidence to support therapeutic treatments. Despite the limited evidence, both pediatric and adult guidelines support the use of amitriptyline and cyproheptadine (for children younger than 5 years old) for prophylaxis in any patient with moderate to severe CVS.[2,8] It is important to critically evaluate patients with CVS for underlying comorbidities that could be treated and lessen the episodes of CVS. Nutritional supplements such as carnitine and coenzyme Q10 have shown some efficacy in small studies with high tolerability by patients; therefore, it should have a low threshold of initiation for patients who do not have disease control with first-line prophylaxis. The combination of ondansetron and sumatriptan are recommended for abortion of an acute vomiting episode, but other agents such as aprepitant and sedative agents should be considered when vomiting is refractory to initial treatments. It is important for clinicians to assist pediatric patients and their caregivers in the development of a treatment plan with both pharmacologic and non-pharmacologic therapies that can be used to guide abortive therapy for an acute CVS attack. This care plan should be constructed based on therapies that worked well for aborting previous CVS attacks in the past and have a step-wise approach of therapies to initiate at home, when to seek medical attention, and therapies that should be given when arriving in an emergency department. Pharmacists can play an important role in understanding the underlying etiology and triggers of CVS, and helping to develop a personalized care plan for each individual patient may help to guide therapy and quickly abort CVS episodes.

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References

1. Robin SG, Keller C, Zwiener R, et al. Prevalence of pediatric functional gastrointestinal disorders utilizing the Rome IV criteria. *J Pediatr*. 2018;195:134–139.
2. Li BU, Lefevre F, Chelimsky GG, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr*. 2008;47(3):379–393.
3. Hasler WL, Levinthal DJ, Tarbell SE, et al. Cyclic vomiting syndrome: pathophysiology, comorbidities, and future research directions. *Neurogastroenterol Motil*. 2019;31(suppl 2):e13607.
4. Gui S, Patel N, Issenman R, Kam AJ. Acute management of pediatric cyclic vomiting syndrome: a systematic review. *J Pediatr*. 2019;214:158–164.e4.

5. Bhandari S, Jha P, Lisdahl KM, et al. Recent trends in cyclic vomiting syndrome-associated hospitalisations with liberalisation of cannabis use in the state of Colorado. *Intern Med J*. 2019;49(5):649–655.
6. Bhandari S, Jha P, Thakur A, et al. Cyclic vomiting syndrome: epidemiology, diagnosis, and treatment. *Clin Auton Res*. 2018;28(2):203–209.
7. Bhandari S, Venkatesan T. Novel treatments for cyclic vomiting syndrome: beyond ondansetron and amitriptyline. *Curr Treat Options Gastroenterol*. 2016;14(4):495–506.
8. Venkatesan T, Levinthal DJ, Tarbell SE, et al. Guidelines on management of cyclic vomiting syndrome in adults by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association. *Neurogastroenterol Motil*. 2019;31(suppl 2):e13604.
9. Li BU, Balint JP. Cyclic vomiting syndrome: evolution in our understanding of a brain-gut disorder. *Adv Pediatr*. 2000;47:117–160.
10. Hikita T, Kodama H, Kaneko S, et al. Sumatriptan as a treatment for cyclic vomiting syndrome: a clinical trial. *Cephalalgia*. 2011;31(4):504–507.
11. Cristofori F, Thapar N, Saliakellis E, et al. Efficacy of the neurokinin-1 receptor antagonist aprepitant in children with cyclical vomiting syndrome. *Aliment Pharmacol Ther*. 2014;40(3):309–317.
12. Badihian N, Saneian H, Badihian S, Yaghini O. Prophylactic therapy of cyclic vomiting syndrome in children: comparison of amitriptyline and cyproheptadine: a randomized clinical trial. *Am J Gastroenterol*. 2018;113(1):135–140.
13. Haghighat M, Memari H, Honar N, et al. The efficacy and duration of treatment with propranolol in children with cyclic vomiting syndrome in southern Iran. *Prz Gastroenterol*. 2017;12(4):291–295.
14. Hikita T, Kodama H, Nakamoto N, et al. Effective prophylactic therapy for cyclic vomiting syndrome in children using valproate. *Brain Dev*. 2009;31(6):411–413.
15. Bagherian Z, Yaghini O, Saneian H, Badihian S. Comparison of the efficacy of amitriptyline and topiramate in prophylaxis of cyclic vomiting syndrome. *Iran J Child Neurol*. 2019;13(1):37–44.
16. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther*. 2017;102(1):37–44.
17. Boles RG. High degree of efficacy in the treatment of cyclic vomiting syndrome with combined co-enzyme Q10, L-carnitine and amitriptyline, a case series. *BMC Neurol*. 2011;11:102.
18. Boles RG, Lovett-Barr MR, Preston A, et al. Treatment of cyclic vomiting syndrome with co-enzyme Q10 and amitriptyline, a retrospective study. *BMC Neurol*. 2010;10:10.
19. Santucci NR, Chogle A, Mascarenhas M, et al. Non-pharmacologic approach to pediatric constipation. *Complement Ther Med*. 2021:59:102711.
20. Sikand M, Sharma P. Psychological intervention in cyclic vomiting syndrome in adolescents: a case series. *J Child Adolesc Ment Health*. 2019;31(3):182–188.
21. Grover I, Kim R, Spree DC, et al. Gastric electrical stimulation is an option for patients with refractory cyclic vomiting syndrome. *J Neurogastroenterol Motil*. 2016;22(4):643–649.
22. A randomized, double-blind, placebo controlled study to evaluate the safety and efficacy of Staccato Granisetron (AZ-010) for the acute treatment of moderate to severe cyclic vomiting syndrome. Accessed April 26, 2021. https://clinicaltrials.gov/ct2/show/NCT04645953?recrs=abdf&cond=cyclic+vomiting+ssyndrom&draw=2&rank=1