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TITLE PAGE

Title: Cyclic Vomiting Syndrome: A Case Series and Review of the Literature.

Short running head: Cyclic Vomiting Syndrome.

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Abbreviations:

5-HT	5-hydroxytryptamine
CRF	corticotrophin releasing factor
CVS	cyclic vomiting syndrome
GE	gastric emptying
GI	gastrointestinal
IBS	irritable bowel syndrome
TCAD	tricyclic antidepressants
THC	delta-9-tetrahydrocannabinol

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ABSTRACT

Objective: Cyclic vomiting syndrome (CVS) is under-recognised. Treatment is difficult as the pathophysiology is incompletely understood. We report our experience of treating patients with amitriptyline, and review the literature to summarise symptoms and associated features, epidemiology, potential pathophysiological mechanisms, differential diagnoses, and treatment.

Design: Consecutive adult patients with CVS were identified during a 5-year period from January 2010 until December 2015. Medical records were reviewed retrospectively, and age and sex of the patient, symptoms, associated features, and response to treatment with amitriptyline were recorded.

Setting: A luminal gastroenterology clinic at a teaching hospital.

Results: Seventeen patients were identified (mean age 29.8 years, 13 (76.5%) female). Five had a history of cannabis use. Duration of symptoms prior to diagnosis ranged from 5 months to 15 years. Fourteen patients commenced amitriptyline, and in eight (57.1%) symptoms either ceased entirely or improved. Review of the literature suggested the prevalence of CVS was 0.5%. Symptoms are stereotypical, with acute episodes of nausea and vomiting, interspersed by periods when the patient is symptom-free. Proposed pathophysiologies include neuroendocrine dysfunction, mutations in mitochondrial DNA, and re-intoxication effects from cannabis stored in fat tissues. Treatment during the acute phase is supportive, with rehydration, sedation, and anti-emetics. Prophylaxis to prevent future attacks with anti-histamines, anti-migraine drugs, anti-epileptics, and tricyclic antidepressants may be beneficial. Complete cessation of cannabis smoking should be advised.

Conclusions: Diagnosis of CVS is often delayed in adults. Once identified, patients respond well to amitriptyline.

INTRODUCTION

Up to 3% of the population will report symptoms of vomiting in cross-sectional surveys. (1) Cyclic vomiting syndrome (CVS) is an uncommon condition characterised by stereotypical acute episodes of severe nausea and vomiting, interspersed by periods of days to months during which the patient is symptom-free. The condition was first recognised and reported in the paediatric literature many years ago, (2) and the epidemiology of CVS in children is therefore well-described. (3, 4) However, it has only been in the last 20 to 30 years that there has been increasing recognition that this condition can also present in adulthood. (5) In addition, excessive nausea and vomiting with a very similar pattern to CVS has also been described in association with prolonged cannabis usage. (6)

Theories behind the potential pathophysiology behind CVS have been proposed. A well-recognised hypothesis is that CVS is caused by psychological or infectious triggers, which lead to alterations in autonomic brain-gut pathways. (7, 8) The association between CVS and migraine headache also supports an underlying stress-sensitive disorder, (9) with a common pathophysiological mechanism. Despite the improved awareness of the possibility of CVS occurring in adults, there can be a delay in the diagnosis for many years. Patients are often misdiagnosed, or dismissed, when presenting to emergency departments. A survey undertaken in the United States found that the median number of visits per patient to the emergency department with symptoms compatible with CVS was 15, (10) with a median of seven visits before the diagnosis was confirmed. Other investigators have reported that there can be a delay in diagnosis of up to 8 years in adults, (11) which compares with around 3 years in children. Management may also be inappropriate and, due to the abdominal pain some individuals report during attacks, which is often relieved by opiates, patients are often labelled as exhibiting narcotic-seeking behaviour. The condition can impact on the patient's quality of life, social functioning, and ability to maintain employment.

We present a case series of 17 patients with CVS, some of whom were using cannabis, treated with the tricyclic antidepressant (TCAD) amitriptyline, according to the senior author's first-line choice of prophylactic therapy, and review the epidemiology, clinical features, pathophysiology, and diagnostic work-up, as well as the published evidence behind the overall management of adults with CVS.

CASE SERIES

Our study included seventeen adults (4 men, 13 women) aged between 19 and 75 years of age (mean age 29.8 years (standard deviation 14.8 years)), who presented to a single gastroenterologist's clinic between 2010 and 2015 with symptoms felt to be compatible with a diagnosis of CVS (Table 1). The duration of symptoms at the time of consultation ranged from 5 months to 15 years (median 2 years) with 11 (64.7%) of the 17 patients having required in-patient admission for treatment of their symptoms at some point. The duration of each episode ranged between one and 14 days in 15 of the patients. However, two patients had experienced a coalescence of their attacks, and reported that these could last for between 21 and 35 days. Thirteen (76.5%) of the 17 patients described a uniform length of their attacks, whilst another three (17.6%) patients described episodes of varying length. Thirteen (76.5%) of 17 patients complained of abdominal pain during the emetic phase. Although only one patient in our series had a personal history of migraine headache, another five (29.4%) had a family history of migraine, and five patients (29.4%) had a history of regular and chronic cannabis smoking.

Of the 17 patients, 14 (82.4%) agreed to be commenced on amitriptyline. One patient declined treatment, and the remaining two patients had already experienced remission of their symptoms spontaneously, with no recent attacks, and therefore felt they did not require any

treatment. Of those who commenced amitriptyline, nine (64.3%) required dose titration up to a maximum tolerated dosage (median 45mg, range 10mg to 140mg). In total, six (42.9%) patients achieved full remission after commencing amitriptyline, with no further attacks of CVS during extended follow-up. Two (14.3%) noticed a substantial improvement in their symptoms, by physician's global assessment, with a reduction in the frequency of attacks of CVS, after commencing amitriptyline. Three (21.4%) patients reported no improvement in their symptoms, one of whom continued to use cannabis throughout treatment. The remaining three patients did not attend their follow-up appointments after commencing the medication.

A recent systematic review and meta-analysis of 25 separate cohorts of patients with CVS reported a higher proportion of patients with headaches or migraines (40%) than seen in our case series. (12) There was also a family history of headaches or migraines in 40% in this meta-analysis. The attacks lasted a mean of 5.9 days, and patients reported an average of 14 episodes per year. Similar to our study, the response to TCADs was high, with >75% of patients responding to therapy.

DIAGNOSTIC CRITERIA FOR CVS

The diagnosis of CVS is made using the Rome III criteria. (13) These consist of stereotypical episodes of vomiting lasting less than 1 week in duration, with three or more of these episodes per year, and the absence of nausea or vomiting between episodes. These criteria have to have been fulfilled for the last 3 months, with an onset of symptoms of at least 6 months before the diagnosis is made. Supportive criteria include either a personal or family history of migraine headaches.

EPIDEMIOLOGY

There is a relative paucity of epidemiological data available for CVS in the adult population. Two large cohort studies undertaken in the United States suggest that between 3% and 5% of adult patients referred to gastrointestinal (GI) motility centres fulfilled diagnostic criteria for CVS. (14, 15) Since these studies are focused on patients referred to tertiary GI centres, it is likely that the true prevalence of CVS is lower within the general population. This is supported by data from a population-based study, conducted among adolescents in Sri Lanka, which reported a prevalence of 0.5%. (16)

CLINICAL FEATURES AND ASSOCIATIONS

Attacks can last between 1 and 14 days, with the average length being 4 to 6 days. (15) The episodes are characterised by four phases. Firstly, the inter-episodic phase, occurring between attacks, and during which the patient is asymptomatic. This is followed by the prodromal phase, which occurs prior to the onset of vomiting. During this phase the patient may experience an ‘aura’, consisting of persistent nausea, anorexia, and/or sweating. Next is the hyperemesis phase, which is characterised by intense and repeated vomiting. This can last up to 7 days and is often accompanied by epigastric pain. (17) Finally, the recovery phase occurs, during which the vomiting gradually improves and the patient’s appetite returns. Common triggers that have been identified include emotional stress or arousal, menstruation, or fatigue. (15) However, often the attacks have no clear precipitant.

Although the stereotypical pattern of attacks, interspersed with symptom-free episodes, is part of the symptom-based diagnostic criteria for CVS, Fleisher et al. describe a phenomenon of ‘attack coalescence’, in which patients suffer more frequent episodes of

vomiting, with fewer and shorter symptom-free periods. (18) In such instances, patients can be symptomatic for prolonged periods of time, and suffer from intense anxiety and low mood. In fact, anxiety is common in patients with CVS, and panic attacks may occur during the prodromal phase of an episode in up to two-thirds of patients. (18)

Other associated conditions include depression, irritable bowel syndrome (IBS), gastro-oesophageal reflux, and diabetes mellitus. (15, 17, 19) Studies have shown that CVS has an association with migraine headaches. As a result, a personal or a family history of migraine headaches forms part of the supportive criterion for the diagnosis. (13) In a case series of 41 adult patients with CVS, 70% of the patients suffered from migraines, and 57% had a first- or second-degree relative with migraine headaches. (18)

Despite the well-described anti-emetic properties of cannabinoids, (20) numerous studies have now shown a paradoxical relationship between long-term cannabis use and recurrent vomiting episodes. A study performed by Allen et al. described nine patients with recognised long-term cannabis use and cyclic vomiting. (6) In seven of these patients cessation of cannabis led to complete termination of the vomiting attacks. However, this success has not been reproduced in other studies, notably in a series by Namin et al., in which 13 of 31 adults with CVS admitted to heavy cannabis use, but only two had complete resolution of their symptoms upon stopping the drug. (15)

The authors also reported that up to three-quarters of the patients in their case series found that having a hot shower alleviated their symptoms of nausea. (15) This pattern of compulsive bathing has been well-described in the literature, with patients reporting relief from nausea upon contact with water. (6, 21-24) In a large case series of 98 patients, 91% found relief following hot water bathing, (25) although this has also been reported in up to 50% of patients with CVS who do not use cannabis. (26)

AETIOLOGY AND PATHOPHYSIOLOGY

CVS is an idiopathic disorder, and as such its pathogenesis is largely unknown, although numerous theories have been proposed. Some investigators have suggested that CVS is linked to neuroendocrine dysfunction of the brain-gut axis. It is hypothesised that psychological or infectious stressors lead to activation of the corticotrophin-releasing factor (CRF) signalling system, and induce episodes of CVS through autonomic alterations that impact on gut motility. The activation of CRF has been shown to stimulate inhibitory motor nerves in the dorsal motor nucleus of the vagus, thereby triggering emesis and delayed gastric emptying (GE). (7, 8) Interestingly, studies have demonstrated that TCADs inhibit the promoter activity of the CRF gene, hence supporting their role as prophylactic agents for CVS. (27, 28) Autonomic abnormalities demonstrated in CVS patients include orthostatic tachycardia, abnormal response of heart rate to deep breathing, and absent sympathetic skin responses in the hands and feet, although the presence of these abnormalities did not appear to correlate with GE time. (29)

Abnormal GE has also been postulated as a pathophysiological mechanism for CVS. Whilst delayed GE due to CRF activation has been demonstrated during the hyperemesis phase of CVS, rapid GE has been observed in between CVS attacks in adult patients. (15, 30) In a study of 92 adults with CVS, rapid GE was evident in 59%, slow GE in 14%, and normal GE in 27%. (19) The subgroup with delayed GE was explained by concomitant use of narcotics or cannabis, and GE was either rapid or normal when repeated without their influence. (19) Hence, rapid or normal GE during the recovery phase of CVS is an important differentiating factor of the condition from gastroparesis. Other investigators have reported gastric motility abnormalities on electrogastrography, with findings of tachygastria (increased rates of electrical activity in the stomach), and blunting of wave amplitudes post-meal digestion. (15, 31)

The association between CVS and migraine headaches highlights possible common pathophysiological mechanisms between the two conditions. It has been suggested that CVS may be part of the migraine spectrum, or a diverse manifestation of a migraine diathesis, where headaches are not present. In the absence of defined diagnostic biomarkers for migraines and CVS, the association between the two conditions is supported by the efficacy of anti-migraine medications, in particular TCADs and sumatriptan, (32-35) in reducing the severity and duration of CVS episodes.

Genetic studies have suggested that mitochondrial DNA mutations may be involved. Persons with mitochondrial defects may be predisposed to the onset of vomiting during periods of increased energy demands, such as infection and stress. (36) Studies of mitochondrial DNA polymorphisms have described an association of 16519T and 3010A polymorphism with both paediatric CVS and adult migraines. (37, 38) However, no association was demonstrated in adult onset CVS, (37, 39) suggesting that the two are genetically distinct. More recently, next generation sequencing has implicated variants in the RYR2 gene, which is involved in stress-induced calcium channels in autonomic neurons, in the pathophysiology of CVS, (40) although the targeted approach used by the investigators means that other potential genetic markers of CVS were not analysed.

Despite the well-known anti-emetic effects of cannabis, its chronic use has been associated with recurrent vomiting episodes. Potential mechanisms for this paradoxical effect include the accumulation of delta-9-tetrahydrocannabinol (THC), the principal compound found in cannabis. (41) THC is a highly lipophilic compound, and long-term use causes it to accumulate within fat tissue, resulting in a prolonged elimination half-life. Increased lipolysis during times of increased stress, or food deprivation, may produce a “re-intoxication effect” of THC when released from fat stores. (42) Hence patients with chronic cannabis use, and large fat stores, are susceptible to increased plasma THC levels during times of stress.

THC is thought to act on a distinct cannabinoid receptor, CB1 in the central and enteric nervous system, and chronic stimulation may cause toxicity in sensitive patients. (43) Stimulation of CB1 receptors by cannabinoids reduces gastric motility, and slows gastric emptying. In patients with chronic cannabis use, this neuromodulatory effect on the gut is thought to override the brain CB1 antiemetic effect. (43-45) CB1 receptors are also located near the thermoregulatory centre of the hypothalamus, (46) possibly accounting for the relief of symptoms with compulsive hot water bathing. It has been suggested that hot water bathing may counteract the cannabis-induced disequilibrium at the thermoregulatory centre. (41, 43)

DIAGNOSTIC WORK-UP AND INVESTIGATIONS

The stereotypical pattern of CVS is distinct; therefore a careful and detailed history should eliminate the majority of other GI and extra-intestinal pathologies that may mimic some of the symptoms of CVS. Important differentials, which may need to be excluded prior to making a diagnosis of CVS, are shown in Table 2. Gastroparesis, in particular, can be excluded if rapid or normal GE is present on a GE study during the recovery phase of CVS. (30) Performing GE studies would be challenging during the hyperemesis phase and, as GE can be delayed at this point in the natural history of the disorder, they are probably best avoided in this situation.

If CVS is suspected, then a panel of screening laboratory tests including full blood count, urea and electrolytes, liver function testing, and amylase, urinalysis, and plain film radiography can be undertaken. (17) If performed during the emetic phase, these investigations will eliminate the potential complications of CVS such as electrolyte disturbance, dehydration, or haematemesis. (47) If an alternative diagnosis is suspected then appropriate diagnostic testing should be performed. Addison’s disease can present with upper

abdominal pain and recurrent vomiting, and therefore masquerade as CVS, (48) so a short tetracosactide test may be useful to exclude this. Once a diagnosis of CVS is secured, repeated investigation is unlikely to be fruitful, and in the acute setting this should be limited to the aforementioned panel of blood tests.

TREATMENT

The aim of treatment of CVS is the termination of symptoms during an acute episode, and the prevention of future attacks. Proposed prophylactic therapies include TCADs, anti-histamines, beta-blockers, selected anti-epileptic drugs, and some anti-migraine medications or anti-emetics. As CVS is a relatively uncommon condition there are no therapeutic randomised controlled trials reporting on the efficacy of any of these medications. Thus, clinical practice is based mainly upon data from retrospective and prospective cohort studies, often adapted from the paediatric population. A summary of the drugs used, along with suggested doses, derived from the literature is provided in Table 3.

Supportive Measures

Patients diagnosed with CVS should be given general lifestyle advice and education about the condition. This should include self-management of anxiety and avoidance of identified triggers, including cannabis, as well as appropriate supportive care during acute episodes. Some patients report sleep deprivation as a trigger, (47) although there are no studies of interventions to improve sleep hygiene in patients with CVS. Given the negative experiences these patients often encounter with healthcare professionals, particularly within the emergency department, a multidisciplinary approach is often helpful, with input from an experienced gastroenterologist, specialist nurse, and/or psychological support. This may help

facilitate individualized treatment plans, which can be used during acute episodes if the patient should need to attend the emergency department, and can also help avoid further unnecessary diagnostic testing. (47) Providing the patient with a letter from the specialist explaining the diagnosis, and the treatment required, may be beneficial.

Terminating the Acute Episode

The aim of treatment during the prodromal phase is to abort symptoms before they progress to the acute vomiting phase. Treatment should be initiated at the earliest signs of nausea. Sumatriptan (a 5-hydroxytryptamine (HT)-$_1$ receptor antagonist) has been shown to have some efficacy in aborting the attacks during the prodromal phase, (12) when administered, intranasally, subcutaneously, or even orally, particularly in patients with a family history of migraine. (34, 35, 49)

If symptoms progress to persistent emesis, prompt intravenous rehydration and electrolyte replacement is often required, in combination with anti-emetics and anxiolytics. Some clinicians advocate the use of a sedating benzodiazepine to induce sleep, such as lorazepam, in combination with a 5-HT$_3$ antagonist, such as ondansetron, and dexamethasone in order to terminate the episode. (50) Children with CVS appear to respond well to prochlorperazine when used in conjunction with an anti-histamine such as diphenhydramine. (47) Symptomatic relief with this combination has not been analysed in adults. Opioid analgesia may also be required during the acute phase if abdominal pain is a key feature although, as with any functional GI disorder, these drugs should be used only in the acute setting, and doses minimised, in order to avoid dependence. Indeed, continued use is thought to be a poor prognostic marker of CVS, and is associated with coalescence of acute attacks, although the direction of this association is unclear. (51)

Prolonging the Inter-episodic Phase with Prophylactic Therapy

Regular prophylactic treatment is often warranted in patients with CVS due to the deleterious effects the condition can have on their activities of daily living and quality of life, which can be greater than that of other functional GI disorders, such as IBS. (52) TCADs, mainly amitriptyline, have been used as prophylaxis in adults with CVS for more than 15 years, with an initial case series of 17 adult patients showing a partial response in 58.8%. (33) The aim is to titrate the dosage of TCAD upwards in increments of 10mg to 25mg every few weeks, to the maximum tolerated dose, with the minimum number of side effects. In a study of 41 patients conducted by Hejazi et al., the frequency and duration of acute episodes was significantly reduced with prophylactic TCADs, and clinical well-being was also improved. (32) In a larger study containing 132 adult patients, factors influencing non-response to TCADs included chronic cannabis use, concomitant psychological illness, reliance on narcotic drugs in between episodes, or a history of migraine. (53)

There is some evidence from a small case series of 20 adults with CVS to support the use of the anti-epileptic medications zonisamide and levetiracetam in those who do not respond to conventional TCADs alone. (54) A moderate response was reported by 15 of the patients, of whom four reported complete remission of their symptoms. However, the side effect profile of these medications, most notably dizziness and fatigue, may make them a less appealing treatment option.

The supplementary agents co-enzyme Q10, a mitochondrial electron carrier, and L-carnitine, an amino acid compound involved in fat oxidation, have gained popularity in recent years as adjuncts to conventional TCAD therapy. A case series performed by Boles et al., which combined these co-factors with high dose amitriptyline in patients aged between 3 and 26 years, saw an improvement in symptoms in 26 out of 29 subjects, (55) and symptom resolution in 23 of these individuals. In an internet survey of patients with CVS or their

parents, conducted by the same author, (56) efficacy of co-enzyme Q10 appeared comparable to that of amitriptyline, but side effects were higher with amitriptyline.

Due to its possible relationship with migraine diathesis, many of the medications used for migraine prevention have been considered in the management of CVS. The use of propranolol in the prophylactic treatment of CVS in children was first reported in 1982, (57) either alone or in combination with prokinetic agents such as erythromycin. (58) When the histamine-$_1$ receptor antagonist cyproheptadine was used in six children aged between 2 and 16 years, four had a complete response, and one a partial response. (59) Aprepitant, which is a neurokinin-1 receptor antagonist used in the prophylaxis of post-operative and chemotherapy-induced nausea and vomiting, has also been reported to be efficacious in children, with a response in 13 of 16 patients treated with this drug. (60) However, there is no evidence in the literature to support the efficacy of any of these drugs in adults with CVS. There have also been case reports in single patients of the successful use of botulimum toxin type A injections, (61) which are often used for migraine prophylaxis, meloxicam, (62) a non-steroidal anti-inflammatory drug, and valproate, (63) an anti-epileptic drug, in the prophylaxis of CVS.

CONCLUSIONS

CVS has evolved as a unique clinical entity, with increased recognition and acceptance as a well-defined clinical disorder. Current knowledge of the condition is based on anecdotal case reports and case series that have been vital in establishing diagnostic criteria. The diagnosis can be made through careful history taking, with the classical presentation of multiple vomiting episodes, interspersed with symptom-free phases. Chronic cannabis use should be considered, and patients with unexplained vomiting should therefore always be asked about any use of the drug during the clinical history, as well as about relief

of their symptoms with hot water bathing. Misdiagnosis, and confusion with conditions such as gastroparesis, is common.

Although there are a lack of controlled therapeutic trials, effective empirical treatments have been reported. TCADs, such as amitriptyline, have been shown to be effective in inducing remission in CVS. In our small case series, six of 14 patients achieved full remission with amitriptyline, and a further two showed a substantial improvement in symptoms. The findings are in keeping with a meta-analysis of previous studies, (12) and thus support the use of TCADs as an efficacious prophylactic treatment option for CVS.

Two of the five patients who smoked cannabis treated with amitriptyline in our case series achieved full remission, and one reported only a single attack, after initiating amitriptyline. It should be noted that one of the patients who did not respond to amitriptyline had both a history of cannabis use and a family history of migraine. Prior studies have suggested that TCADs may be less effective in patients with a personal or family history of migraine use, or cannabis use.

Whilst understanding of CVS has vastly improved in the last decade, the long-term natural history and outcomes of the condition remains unknown. Further research into tapering TCADs once remission is achieved, and the likelihood of spontaneous resolution of the symptoms of CVS, as is often seen with other functional GI disorders, (64, 65) would be of great benefit in guiding ongoing treatment.

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TABLES

Table 1. Case Series of Patients with Symptoms Compatible with Cyclic Vomiting Syndrome.

Sex	Age at diagnosis	History of migraine	Family history of migraine	Cannabis Use	Dose of amitriptyline	Dose titrated	Remission	Duration of follow-up (years)
Female	22	Yes	No	No	10mg	No	DNA	DNA
Female	22	No	No	No	25mg	No	Yes	3
Male	24	No	No	No	10mg	Up to 35mg	Yes	2
Female	19	No	No	Yes	10mg	Up to 25mg	Yes	1
Male	25	No	No	Yes	10mg	Up to 45mg	Improved, one further episode	4
Male	44	No	No	Yes	10mg	Up to 140mg	Yes	5
Female	22	No	Yes	Yes	25mg	Up to 50mg	No, continued cannabis use	1
Male	22	No	Yes	No	25mg	No	Yes	1
Female	30	No	No	No	25mg	Up to 50mg	Improved, five further episodes	1
Female	26	No	Yes	No	25mg	No	DNA	DNA
Female	22	No	No	No	10mg	Up to 20mg, but reduced due to lethargy	No	2
Female	28	No	No	No	10mg	Up to 25mg	No	1
Female	22	No	No	Yes	N/A	N/A	DNA	DNA
Female	75	No	No	No	25mg	No	Yes	3

Female	55	No	No	No	N/A	N/A	Yes, without treatment	DNA
Female	26	No	Yes	No	N/A	N/A	Yes, without treatment	1
Female	22	No	Yes	No	25mg	Up to 75mg	DNA	1

DNA; did not attend

N/A; not applicable

Table 2. Disorders That May Form Part of the Differential Diagnosis for Cyclic Vomiting Syndrome.

Gastric disorders	Peptic ulcer disease with gastric outlet obstruction Gastroparesis
Intestinal disorders	Intermittent small bowel obstruction Chronic intestinal pseudo-obstruction Volvulus
Pancreatico-biliary disorders	Cholecystitis Pancreatitis Sphincter of Oddi dysfunction
Extra-intestinal disorders	Addison's disease Acute intermittent porphyria Cerebral mass leading to raised intracranial pressure or hydrocephalus Vestibular disturbances Renal colic

Table 3. Drugs Used in the Treatment of Cyclic Vomiting Syndrome, and their Suggested Dosages.

Setting	Drug	Suggested Dosage
Terminating the acute episode	Sumatriptan	Intranasally: 20mg as a single dose, maximum dose of 40mg per day Subcutaneous: 6mg as a single dose, maximum dose of 12mg per day
	Lorazepam	0.5 – 2mg up to four times daily
	Ondasetron	8mg three times daily
Prolonging the inter-episodic phase with prophylactic therapy	Tricyclic antidepressants (e.g. amitriptyline)	10 – 150mg per day
	Zonisamide	100 – 700mg per day
	Levetiracetam	500mg – 3g per day
	Co-enzyme Q10	300 – 500mg per day
	L-carnitine	990mg three times daily
	Propranolol	80mg per day
	Erythromycin	250mg three times daily
	Cyproheptadine	4 – 8mg three times daily
	Aprepitant	40 – 125 mg per day twice weekly