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Novel Treatments for Cyclic Vomiting Syndrome: Beyond Ondansetron and Amitriptyline

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Opinion statement

Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder that is characterized by episodic nausea and vomiting. Initially thought to only affect children, CVS in adults was often misdiagnosed with significant delays in therapy. Over the last decade, there has been a considerable increase in recognition of CVS in adults but there continues to be a lack of knowledge about management of this disorder. This paper seeks to provide best practices in the treatment of CVS and also highlight some novel therapies that have the potential in better treating this disorder in the future. Due to the absence of randomized control trials, we provide recommendations based on review of the available literature and expert consensus on the therapy of CVS. This paper will discuss prophylactic and abortive therapy and general measures used to treat an episode of CVS and also discuss pathophysiology as it pertains to novel therapy. Recent recognition of the association of chronic marijuana use with cyclic vomiting has led to the possibility of a new diagnosis called "Cannabinoid Hyperemesis Syndrome," which is indistinguishable from CVS. The treatment for this purported condition is abstinence from marijuana despite scant evidence that marijuana use is causative. Hence, this review will also discuss emerging data on the role for the endocannabinoid system in CVS and therapeutic agents targeting the endocannabinoid system, which offer the potential of transforming the care of these patients.

Introduction

Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder that is characterized by sudden, recurrent episodes of intense nausea and vomiting. The prevalence of CVS is approximately 1–2 % in children and is thought to be as common in adults [1, 2]. CVS primarily affects Caucasians, usually in the second and third decade of life in adults. Both males and females are affected with conflicting data on gender preponderance. The pathophysiology is unknown but preliminary studies suggest that genetic factors, altered neurocircuitry involving the brain-gut axis, and possibly the endocannabinoid system play a role in the neurobiology of CVS. CVS is also related to migraines, with a personal and family history of migraine in 43 and 64 % of patients, respectively [3]. In fact, this is a supportive criterion for making a diagnosis of CVS [4••]. There are no specific laboratory markers and the diagnosis of CVS is usually made using the Rome IV criteria as shown in Table 1 [4••].

The Rome IV criteria are very similar to the Rome III criteria except that a provision was made to recognize the pattern of coalescence of symptoms in CVS. While patients usually return to normal health in between episodes, over time and especially if untreated, patients can develop inter-episodic nausea, dyspepsia, and less intense vomiting which is termed "coalescence" of symptoms. Additionally, the Rome foundation established criteria for "Cannabinoid hyperemesis syndrome" [4••], which is indistinguishable from CVS except for the use of chronic marijuana in these patients. Hot showers used for relief at the time of an episode or the compulsive hot-water bathing pattern is touted as being pathognomonic of cannabinoid hyperemesis syndrome but data shows that this phenomenon is also seen in CVS patients who denied marijuana use [5•]. This remains controversial, as there are limited data on the role of chronic marijuana in CVS. Whether cannabinoid hyperemesis syndrome is a subset of CVS or a distinct entity remains to be determined.

Episodes of CVS are often triggered by physiological and emotional stress [3, 6]. Triggers can include both positive stress such as holidays and birthdays or negative events such as job loss and the death of a loved one. Specific foods precipitate episodes of CVS only in a minority of patients. CVS typically has four phases, which include: (1) the prodromal phase, (2) emetic phase, (3) recovery phase, and (4) the inter-episodic or asymptomatic phase. These phases were first described by David Fleischer and have important therapeutic implications [6]. For instance, abortive therapy is most effective when administered during the prodromal phase of an episode as opposed to the emetic phase. It is important for physicians to recognize this and emphasize this management strategy.

CVS is associated with negligible mortality but exerts a significant impact on patients and families with work and school absenteeism, divorce, job loss, and disability [3, 6]. Patients with CVS suffer from high degrees of psychological stress, which can in turn trigger episodes. The current conventional model of care is disease-centered and does not address psychosocial factors, which are important drivers of disease

Table 1. Rome IV criteria for CVS

- Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)
  - Abrupt in onset
  - Occurring at least 1 week apart
- 3 or more discrete episodes in the prior year
  - Two episodes in the past 6 months
  - Absence of nausea and vomiting between episodes
  - But other milder symptoms can be present in between episodes
- No metabolic, gastrointestinal, central nervous system structural, or biochemical disorders
- Supportive criteria include a personal or family history of migraine headaches

Criteria must be fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis

severity in CVS. The current review aside from discussing pharmacologic therapy and newer medications emphasizes the use of a biopsychosocial model in the treatment of CVS.

Management of CVS

General measures

Patients can prevent CVS episodes by avoiding known triggers such as sleep deprivation, fasting, and physical exhaustion. Patients with CVS have significantly poorer quality of sleep with increased sleep disturbance, increased latency to onset of sleep, daytime dysfunction, and need medications to sleep more often when compared to normal subjects [37•]. In some cases, obtaining a sleep study and consultation with a sleep medicine specialist may be indicated. Several patients with CVS have multiple comorbid conditions such as anxiety and depression and appropriate referral to a psychologist for cognitive behavioral therapy should be considered. A small subset of patients identifies specific foods as triggers and avoiding these is also helpful. Chronic marijuana use has been associated with non-response to therapy and paradoxically with increased vomiting episodes. Patient should be counseled about reducing and ultimately abstaining from marijuana in addition to other measures. Education of patients and families about CVS and providing information along with an emergency (ED) protocol for management of CVS episodes helps alleviate anxiety and can improve overall patient outcomes.

Prophylactic therapy

CVS is treated with medications such as tricyclic antidepressants (TCAs), which are effective as prophylactic agents for migraines. Prophylactic therapy should be considered in patients who have moderate or severe CVS. While there is no clear consensus on the definition of severity in CVS, patients with >2 episodes per month, prolonged or very severe symptoms and/or symptoms that interfere with daily living can be considered to have moderate-to-severe CVS and are suitable candidates for prophylactic therapy. Prophylactic therapy should also be considered in patients who fail abortive therapy or need to use abortive agents excessively. This should be initiated after discussing the risks and benefits of treatment with the patient. The goal of prophylactic therapy is to reduce the severity and frequency of CVS episodes, avert (ED) visits and hospitalizations, and improve quality of life.

Use of tricyclic antidepressants in CVS

TCAs are considered first-line treatment for prophylaxis of CVS: amitriptyline has been the most effective agent reported in both children and adults with CVS [7, 8]. An open-label trial in patients with CVS treated with TCAs for up to 2 years reported a significant reduction in frequency and duration of CVS episodes and ED visits: 80 % of patients noted global improvement in symptoms with a reduction in the duration of CVS episodes [9]. Side effects were reported in 34 % of patients but did not result in discontinuation of therapy. A retrospective study showed similar results with 86 % of patients responding to

prophylactic therapy with tricyclic antidepressants, antiepileptic medications such as topiramate, and/or mitochondrial supplements [3]. Twenty-six percent of patients had side effects including behavioral changes, nightmares, and increased somnolence, and discontinued TCAs.

A step-up approach is typically advocated while using TCAs beginning with low initial doses (e.g., amitriptyline 25 mg at night) with incremental dose increases to a target of 75–100 mg at night. This approach is recommended to limit side effects that can occur with higher doses [10]. Of note, the effective dose used in CVS is much higher than the conventional dose of 25 mg used in other functional gastrointestinal diseases. Other TCAs with fewer side effects like nortriptyline, imipramine, or desipramine may be tried if amitriptyline cannot be tolerated due to side effects [10].

Common side effects of TCAs include dryness of mouth, blurring of vision, drowsiness, constipation, and sometimes, behavioral changes. Patients should be counseled that they will get acclimatized to the drowsiness over 2–3 months. Amitriptyline can cause QT prolongation and we recommend checking an EKG at baseline and interval EKGs while titrating the dose of amitriptyline. Nonresponse to TCAs occurs in approximately 13 % of patients; factors for nonresponse include coexisting migraine headaches, psychiatric disorders, and chronic narcotic and marijuana use [11]. Unfortunately, concerns with toxicity and unfamiliarity with using higher doses than what is used in other functional gastrointestinal disorders have led to underutilization of TCAs. Of note, newer antidepressive agents such as selective serotonin reuptake inhibitors (SSRIs), which have replaced TCA use in psychiatry, are not effective in the treatment of CVS.

Antiepileptic agents and mitochondrial supplements in CVS

Other medications shown to be effective in patients with CVS are anticonvulsants such as zonisamide and levetiracetam. In an uncontrolled study of 20 patients who were unresponsive or intolerant to TCAs started on zonisamide (median dose of 400 mg/day) or levetiracetam (median dose of 1000 mg/day), at least a moderate clinical response was seen in 75 % of patients, of which 20 % reported symptomatic remissions [12]. Side effects occurred in many of these patients and included headache, dizziness, confusion, and fatigue and were managed clinically by adjusting the dosage or switching to another antiepileptic drug. Antiepileptic drugs were discontinued only in one patient due to side effects.

One other anticonvulsant that is frequently used in prophylaxis is topiramate despite the lack of controlled clinical trials in CVS. The justification for its use has been its efficacy in migraine headaches. Topiramate has been found to be effective either alone or in conjunction with TCAs in retrospective studies [3, 13]. Side effects of topiramate may include confusion, cognitive impairment, and renal stones. The authors recommend checking serum bicarbonate levels every 6 months as topiramate can cause acidosis. Supplementation with sodium bicarbonate is recommended when bicarbonate levels are <20 mmol/L to prevent long-term complications of acidosis such as osteoporosis.

Mitochondrial supplements, coenzyme Q10 and L-carnitine are also used in patients with CVS. This is based on the hypothesis that children with CVS may have underlying mitochondrial dysfunction leading to an energy imbalance. Children with CVS have been shown to have two mitochondrial

polymorphisms 3010A and 16519T but these have not been found in adults with CVS [14, 15•]. Coenzyme Q10 has been found to have therapeutic efficacy in migraine prophylaxis as demonstrated in a randomized control trial in adults aged 18–65 years of age [16]. One study based on an Internet survey found that 68 % of those receiving coenzyme Q10 reported at least a 50 % reduction in the frequency, duration, or severity of episodes [17]. Patients receiving coenzyme Q10 did not report any side effects, whereas half of the patients receiving amitriptyline had side effects [17]. However, this study was limited to mostly children and there is limited data for its use in adults.

Carnitine, a cofactor for long-chain fatty acid transport into mitochondria, is also used in CVS [7]. One case series documented an increase in average time between CVS episodes from 1.7 to 1.1 years with carnitine (average dose of 50 mg/kg) [18]. Another case series showed that a protocol consisting of mitochondrial-targeted cofactors (coenzyme Q10 and L-carnitine) along with amitriptyline was highly effective in preventing vomiting episodes [19]. This study has not been replicated and remains to be validated in other cohorts.

Abortive therapy

Abortive therapy refers to medications that the patient can self-administer at home during the prodromal phase of a CVS episode to prevent progression to a full-blown CVS episode. This typically consists of either a single medication or a combination of medications that can be administered at home. The goal of such therapy is to restore the patient's ability to function, enable the patient to control his/her symptoms, and avoid ED visits and hospitalizations. Abortive therapy is most effective when administered during the prodromal phase of an episode. The oral route is typically avoided and medications are either given in a sublingual, intranasal form or parenteral form (subcutaneous route). Antimigraine medications, such as triptans (usually sumatriptan), have been found to be effective in aborting attacks [20, 21]. Sumatriptan is a 5-hydroxytryptamine receptor 1B/1D agonist and can be administered intranasally or subcutaneously. Experts also use other triptans such as zolmitriptan and frovatriptan though there is a lack of clinical trials supporting their use in CVS. Ondansetron, a 5-HT_3 antagonist, is a potent antiemetic that is also used in conjunction with triptans as an abortive agent. Its effect can be enhanced with the combination of a benzodiazepine and/or diphenhydramine. Ondansetron can cause QT prolongation and an EKG should be obtained before its use. Patients must be cautioned against excessive use of these medications and if there is evidence of excessive use, prophylactic therapy should be initiated or altered.

Supportive treatment

During an acute episode of CVS, patients have unrelenting nausea and vomiting, severe abdominal pain, symptoms of panic and autonomic symptoms such as hot flashes, sweating, and drooling. The main goal of supportive treatment is to treat symptoms expeditiously to alleviate much of the anxiety that can further exacerbate symptoms. Treatment of an acute episode can be done in an ED and/or hospital setting. However, patients with CVS are often not given a high priority in the ED and alternative arrangements such as an infusion clinic should be considered. In general, treatment consists of adequate hydration and administration of antiemetics, sedatives, and analgesic medications.

Anecdotal experience in children suggests that intravenous administration of 10 % dextrose solution is an effective means to maintain hydration as this may potentially address the energy imbalance thought to be responsible for these episodes [22]. Antiemetics may include ondansetron or promethazine. Electrolytes should be closely monitored and replenished if needed though electrolyte imbalances are seldom encountered. Sedatives such as diphenhydramine, lorazepam, and chlorpromazine can be administered to promote sleep and to provide temporary relief from the nausea and vomiting [23]. Intravenous analgesic agents like opioids (e.g., morphine and hydromorphone) may be initially necessary to control abdominal pain. Given the lack of objective markers to measure pain, pain management should be based on patient report. Physicians should also be aware of the possibility of physical and psychological dependence, and administration of opiates should be monitored closely in the inpatient but more so in the outpatient setting. A suggested algorithm for management of CVS is shown in Fig. 1.

Novel agents in CVS

NK1–receptor antagonists

Other novel pharmaceutical agents under consideration for treatment of CVS include aprepitant, a promising new tachykinin (NK1) receptor antagonist [24, 25]. Tachykinin receptors are divided into tachykinin1, 2, and 3 based on their affinity for specific ligands and are referred to as neurokinin 1 (NK1), neurokinin 2 (NK2), and neurokinin 3 (NK3) receptors, respectively. NK1 receptors have preferential affinity for substance P. The NK1 receptor is expressed in the central and peripheral nervous system, cardiovascular, genitourinary, and immune systems and also the gastrointestinal tract. Of note, NK1 receptors are present in the nucleus tractus solitarius and the area postrema, which are involved in the vomiting reflex. Substance P exerts its effects through binding with the NK1 receptor. The substance P/NK1 receptor pathway plays an important role in pain, inflammation, salivation, depression, affective states, stress responses, emotion, vigilance, and emesis.

Aprepitant (Emend®) is the first NK1 receptor antagonist that was approved for prevention of chemotherapy-induced nausea and vomiting (CINV). Since then, its prodrug, fosaprepitant in an intravenous form has also been approved for use. The NK1 receptor antagonists also have antidepressant and anxiolytic effects. Evidence for this comes from preclinical data where NK1 receptor knockout mice exhibit significantly attenuated responses to stressful stimuli [26]. These offer exciting opportunities for trials in CVS not only to prevent emesis but also to treat coexistent anxiety and depression that is seen in the majority of patients. In a recent study involving 41 children refractory to conventional therapies, 76–81 % of subjects were able to achieve partial to complete remission with aprepitant used as a prophylactic agent [27•]. Further studies of NK1 receptor antagonists in adults with CVS are warranted.

Endogenous cannabinoid agonists (CB1R agonists) and the role of marijuana in CVS

There is considerable interest in the role of cannabis in CVS given an increase in its use with ongoing legalization efforts in the USA. The active principal in marijuana is ^{9}-tetrahydrocannabinol (THC) [28]. THC binds to at least two G

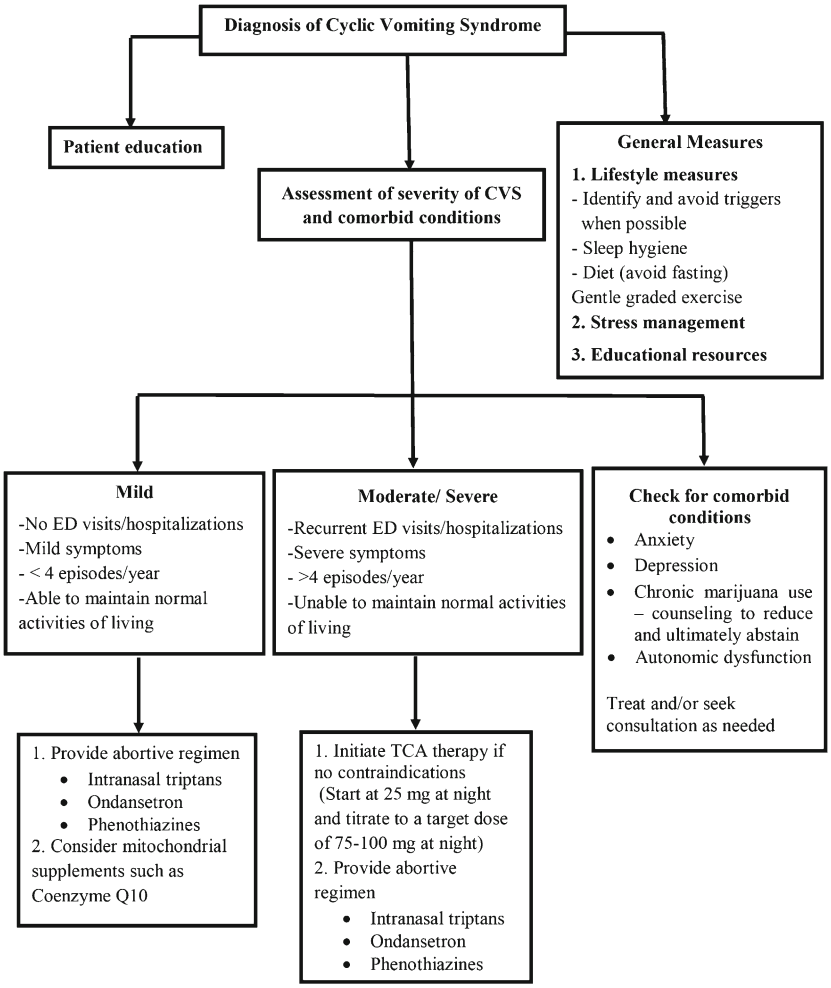

Fig. 1. Suggested algorithm for management of cyclic vomiting syndrome.

protein-coupled receptors named CB1 [29] and CB2 [30]. These receptors are activated endogenously by two ligands called endocannabinoids (N-arachidonylethanolamine (anandamide) [31] and 2-arachidonoylglycerol (2-AG) [32]). These ligands and the CB receptors comprise the endocannabinoid signaling system (ECS). The ECS plays an important role in the modulation of nausea and vomiting and also serves as a stress buffer. In animal models, CB1 receptor activation in the dorsal vagal complex of the brainstem mediates the antiemetic effect of cannabinoids [33, 34]. Nabilone, a commercially available CB1 receptor agonist is used for the treatment of CINV. Conversely, nausea and vomiting were frequent adverse effects reported with the CB1 receptor antagonist, Rimonabant, which was used in Europe for the treatment of obesity and metabolic disorders. [35] Paradoxically, chronic marijuana use has been associated with a pattern of episodic vomiting that is very similar to CVS [36] and a new term "cannabinoid hyperemesis syndrome" has been used to describe this syndrome. The Rome foundation recently established criteria for the diagnosis of cannabinoid hyperemesis syndrome [4••]. These findings of chronic

marijuana use with vomiting are yet to be reconciled with both preclinical and clinical data demonstrating the antiemetic effects of CB1 receptor agonists. It is possible that chronic cannabis use causes downregulation of CB1R and paradoxically causes emesis.

A recent study by Venkatesan et al. revealed that patients with CVS who used marijuana had significantly higher salivary cortisol and salivary alpha amylase concentrations during an episode of CVS compared to non-users [37•]. These findings may be due to an exaggerated response of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous (SNS) to stress in marijuana users. However, it is also possible that the stress response was attenuated by marijuana use in these patients. Future studies to elucidate the effects of marijuana on the stress response in CVS would be able to further elaborate on these findings. This is especially important given that a significant number of patients with CVS use marijuana for relief of symptoms: a recent internet survey found that 81 % of patients with CVS used marijuana [5•]. Allen et al. described 10 patients who had a pattern of cyclic vomiting and a compulsive hot water bathing pattern associated with chronic marijuana use [38]. The largest series of cyclic vomiting associated with marijuana included 98 patients but follow-up was available only in 10 patients [39]. Three (30 %) of these patients did not abstain from cannabis use and continued to have symptoms, while 6 patients (60 %) stopped using cannabis and noted complete resolution of their symptoms. The longest duration of follow-up was 1–3 months. Lack of long-term follow-up is a major limitation of these studies on marijuana use in CVS. While chronic marijuana use is strongly associated with cyclic vomiting and the compulsive hot-water bathing pattern, there are no data that prove causation. Several patients without marijuana use also have the compulsive hot-water bathing pattern and many patients who abstain from marijuana use continue to have CVS episodes [5•]. Of historical interest, even Charles Darwin appears to have had CVS and was prescribed hydrotherapy though there is no indication that he used marijuana [40]. Additionally, marijuana contains different metabolites such as cannabidiol and cannabidiolic acid, both of which have antiemetic properties but not psychotropic effects [41]. The role of marijuana in CVS remains obscure and merits further research.

Drugs that can more selectively target cannabinoid receptors or inhibit enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), which degrade endocannabinoids without causing psychotropic side effects hold promise in the treatment of this disorder [42•]. Recently, the FAAH inhibitor, URB597, was found to attenuate cisplatin and nicotine-induced emesis in the house musk shrew [43].

It is our practice to advise patients to reduce and ultimately abstain from marijuana use while initiating therapy for CVS. It is especially important not to withhold therapy in these patients as episodes can continue despite abstinence from marijuana in a subset of patients.

Other therapies in CVS

Alternative therapy: acupressure and acupuncture

P6 acustimulation has been found to be effective in preventing post-operative nausea and vomiting [44] and also in alleviating nausea and vomiting in pregnancy [45]. It involves stimulating the P6 or Nei guan acupuncture point,

which is located on the anterior aspect of the forearm above the wrist crease. A case report on the use of acupuncture in two cases of "hysterical mutism" and two of functional vomiting showed that the treatment with acupuncture resulted in dramatic improvement in all four patients [46]. Its efficacy in CVS is yet to be ascertained but can be considered in conjunction with other therapies especially given its lack of side effects. One limitation may be cost, as insurance companies do not routinely cover alternative therapies. However, with the changing landscape of medical care, alternative medicine may soon become integrated into standard clinical practice allowing for adequate financial reimbursement.

Role of devices in CVS

Controlled studies on the role of gastric electrical stimulation in CVS are lacking. Further, most patients with CVS have rapid rather than delayed gastric emptying [47]. A recent open-label study involving 11 patients with CVS showed a reduction in nausea and vomiting and frequency of hospital admissions with gastric electrical stimulation at the end of 1 year [48]. However, these patients were not tried on standard therapies such as TCAs prior to the use of electrical stimulation. Randomized controlled trials are needed to validate these findings before this device can be recommended for use in CVS.

Biopsychosocial model of care

CVS is associated with several comorbid conditions such as anxiety, depression, and dysautonomia. In addition to pharmacotherapy, a biopsychosocial approach to address non-gastrointestinal issues in these patients is vital to achieve better patient outcomes. As with other functional GI disorders, preliminary data indicate that psychosocial factors are important determinants of quality of life in these patients. A biopsychosocial model of care to meet the psychosocial needs of these patients should improve overall health and quality of life. This will require a multidisciplinary team with integration of pharmacotherapy, cognitive behavioral therapy as well as other alternative and complementary therapies such as relaxation, hypnotherapy, and meditation into the routine model of care. Future studies to determine the effects of such an integrated health care model approach on patient outcomes are needed.

Conclusions

CVS is being increasingly recognized in adults. The exact pathogenesis is unknown and treatment is largely based on open-label trials, retrospective studies, and expert consensus. TCAs remain first-line of therapy in the prophylaxis of CVS though the incidence of side effects, and lack of familiarity with its use have limited its widespread use. Abortive treatment can be helpful in averting episodes and also enables patients to control their symptoms. Marijuana is used as an anxiolytic and also to improve nausea and appetite by patients but heavy chronic use is associated with cyclic vomiting despite preclinical and clinical data demonstrating its antiemetic properties. Patients should be advised to reduce and abstain from marijuana while undergoing treatment for CVS. The endocannabinoid system appears to plays a role in symptoms of CVS and opens up possibilities for novel therapeutic agents such as CB1-receptor

agonists and FAAH inhibitors that target this system. Other drugs such as NK1-receptor antagonists should be studied in CVS given their antiemetic, anxiolytic, and antidepressant properties.

In conclusion, CVS is a complex disorder with several comorbid conditions and should be managed with a biopsychosocial model of care. Emerging data on the role of the ECS and other neuromodulators of vomiting and stress offer the possibility of novel therapeutic agents for use in CVS in the future.

Resources for patients and families

1. Cyclic Vomiting Syndrome Association (CVSA)
   PO Box 270341
   Milwaukee, WI 53227
   Phone 414342–7880
   Email: cvsa@cvsaonline.org
   Website: cvsaonline.org
2. International Foundation for Functional Gastrointestinal Disorders (IFFGD)
   2819 West Highland Blvd.,
   Milwaukee, WI 53208
   Website: www.iffgd.org

Compliance with Ethical Standards

Conflict of Interest
Sanjay Bhandari and Thangam Venkatesan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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