TITLE PAGE: Cyclic Vomiting Syndrome: Pathophysiology, Co-Morbidities, and Future Research Directions

William L. Hasler[1], David J. Levinthal[2], Sally E. Tarbell[3], Kathleen A. Adams[4], B U.K. Li[5], Robert M. Issenman[6], Irene Sarosiek[7], Safwan S. Jaradeh[8], Ravi N. Sharaf [9], Shahnaz Sultan[10], Thangam Venkatesan[11]

Division of Gastroenterology, University of Michigan Health System, Ann Arbor, MI[1], Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, PA[2],Department of Psychiatry and Behavioral Sciences, Northwestern Feinberg School of Medicine, Chicago, IL[3], Cyclic Vomiting Syndrome Association, Milwaukee, WI[4], Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI[5], Division of Pediatric Gastroenterology, McMaster University[6], Division of Gastroenterology, Texas Tech University Health Sciences Center, El Paso, TX[7], Stanford University Medical School, Stanford, CA[8], Division of Gastroenterology and Department of Healthcare Policy and Research, Department of Medicine, Weill Cornell Medical Center, New York, NY[9], Minneapolis VA Health Care System, Minneapolis, MN[10], Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, WI[11]

ADDRESS CORRESPONDENCE TO:

William L. Hasler, MD

University of Michigan Health System

3912 Taubman Center, SPC 5362

Ann Arbor, MI 48109

Telephone: (734) 936-4780

FAX: (734) 936-7392

E-mail: whasler@umich.edu

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ABSTRACT

Cyclic vomiting syndrome (CVS) is characterized by severe episodic emesis in adults and children. Cannabinoid hyperemesis syndrome (CHS) is an increasingly recognized CVS-like illness that has been associated with chronic cannabis use. There are significant gaps in our understanding of the pathophysiology, clinical features, comorbidities, and effective management options of CVS. Recommendations for treating CVS are based on limited clinical

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data, as no placebo-controlled, randomized trials have yet been conducted. Diseases associated with CVS, including migraine, mitochondrial disorders, autonomic dysfunction and psychiatric comorbidities, provide clues about pathophysiologic mechanisms and suggest potential therapies. We review our current understanding of CVS and propose future research directions with the aim of developing effective therapy. Establishing a multicenter, standardized registry of CVS patients could drive research on multiple fronts including developing CVS-specific outcome measures to broaden our understanding of clinical profiles, to serve as treatment endpoints in clinical trials, and to provide a platform for patient recruitment for randomized clinical trials. Such a robust database would also facilitate conduct of research that aims to determine the underlying pathophysiological mechanisms and genetic basis for CVS, as well as identifying potential biomarkers for the disorder. Soliciting government and industry support is crucial to establishing the necessary infrastructure and achieving these goals. Patient advocacy groups like the Cyclic Vomiting Syndrome Association (CVSA), which partner with clinicians and researchers to disseminate new information, promote ongoing interactions between patients, their families, clinicians, investigators, to support ongoing CVS research and education must be an integral part of this endeavour.

Key Words: cannabinoids, cyclic vomiting, migraine headaches, multicenter registry, psychosocial dysfunction

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INTRODUCTION

The preceding articles in this Supplement of Neurogastroenterology and Motility have detailed what is known about the clinical features, diagnosis, and management of cyclic vomiting syndrome (CVS) and a related disorder, cannabinoid hyperemesis syndrome (CHS), in adult patients. Formal diagnostic criteria for CVS in adults were not defined until publication of the Rome III consensus statements in 2006 (1). The CVS criteria were subsequently revised in 2016 by the Rome IV committee, based mostly on expert consensus, rather than rigorous investigation between successive versions (2). The Rome IV process also published new criteria for CHS which are discussed elsewhere in this supplement.

Our understanding of CVS in adults is derived largely from retrospective studies conducted at tertiary care centers. Needless to say, numerous critical knowledge gaps remain and pose significant barriers for developing effective management options for the treatment of CVS. Progress has been limited by the relatively recent recognition of CVS in adults, lack of widespread knowledge about CVS in the medical community resulting in misdiagnosis and

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delayed diagnosis, lack of standardized database information, and low-quality evidence on available treatment options. Even a clinical feature as rudimentary as the prevalence of CVS in adults is not well established. Most clinicians consider CVS in adults to be rare, but a recent report calculated a prevalence of 10.8% among outpatients in a specialty gastroenterology clinic, a rate that approaches that of gastroparesis, chronic constipation, and irritable bowel syndrome in tertiary outpatient cohorts (3-6). However, another recent population-based survey estimated a lower prevalence of 2% of CVS in adults (7). While these preliminary estimates are important, determining the actual prevalence of CVS in adults has fundamental implications for allocation of funding and future research. Treatment trials in CVS would be facilitated by recruitment into a national clinical registry of patients who are well-phenotyped using standardized criteria. By virtue of its size and robust data structure, such a resource would permit performance of randomized, controlled trials (RCTs) of novel CVS therapies—an area lacking in the current literature. Even in children with CVS, only one recent RCT was published reporting comparable effectiveness of amitriptyline and cyproheptadine (8).

PATHOPHYSIOLOGY AND COMORBID CONDITIONS

To better design mechanism-driven management approaches, it is essential that we elucidate the pathogenesis, clinical features, and disease associations in CVS. Acquisition of such information could provide answers to several intriguing questions such as: Why do CVS patients only periodically experience symptoms? How are CVS episodes triggered? What is the reason for the heterogeneity in severity of CVS symptoms? Why do some patients respond to certain medications such as amitriptyline while others do not? These are a few examples of research questions to be answered. A viable CVS model must consider the diversity of attack triggers and the breadth of prodromal symptoms experienced at the onset of CVS episodes. Ideally, any disease model should also provide an ability to predict an individual's disease course.

CVS is, by definition, a syndrome with episodic bouts of uncontrollable vomiting, separated by periods of relative wellness. These attacks are often accompanied by other symptoms including intense nausea, abdominal pain, headaches, photo- and phonophobia, and several autonomic symptoms similar to those observed in migraine headache. As with most disorders defined by characteristic symptom profiles, CVS is probably not driven by a single pathogenic mechanism. Rather, it is useful to conceptualize its pathogenesis as resulting from from the cumulative interaction of unique combinations of a number of distinct phenotypic

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processes and comorbid conditions leading to cyclical emesis (Figure 1). Viewed in this way, the similarity of CVS to other periodic disorders such as migraine and epilepsy offers clues about potential phenotypes that may lead to the development of CVS in adults. Other periodic disorders such as migraines, seizures, or panic attacks appear to have a "threshold" above which triggers can elicit attacks. Similarly, CVS may have an "attack threshold" that when breached by different mechanisms is capable of eliciting repetitive vomiting in susceptible patients (9). These thresholds may differ widely among patients. Hence the key to developing effective, personalized treatments for CVS hinges on recognizing disease triggers and mechanisms and rasing the individual threshold for developing symptoms. The diversity of pathways may either reflect the presence of specific subtypes of CVS (e.g. catamenial, hypothalamic surge, CHS), distinct genetic predispositions (e.g. RYR2 gene encoding a stress-induced neuronal calcium channel polymorphisms), and/or a sensitivity to distinct symptom triggers (e.g. psychological stressors, hypoglycemia) (10-14). In order to develop targeted CVS therapies, future research needs to define CVS subtypes based on mechanistic definitions, rather than solely on symptom criteria.

CVS as a putative neurogenic disorder

CVS shares clinical features with central nervous system (CNS) disorders such as migraine, in which episodic symptoms are triggered by various stimuli, and is followed by quiescent, largely asymptomatic intervals. Both CVS and migraine attacks can be triggered by acute psychological or physiological stress, sleep deprivation, and menses (9, 14, 15). A personal or family history of migraine disorder is the most prominent CNS comorbidity in CVS, with 24-70% of adults reporting this association (16, 17). It is important to recognize that many migraine sufferers report prominent nausea and vomiting with their headaches. CVS also shares some clinical features with epilepsy and even panic disorder (14, 18). The compelling clinical connection between migraine, panic and CVS suggests that CVS is a neurogenic disorder.

Neuronal hyperexcitability may represent a common link between CVS and other episodic CNS disorders (19-21). Hyperexcitability may be a consequence of genetic variants in ion channel and/or neurotransmitter receptor structure and function, or may result from aberrant development of neural circuits. The specific neural circuits for nausea and vomiting within higher centers of the brain are beginning to be elucidated using functional imaging methods in human subjects. Studies delineating alterations in brain network functional connectivity,

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particularly within networks involving the amygdala and the insular cortex, may further explain the role of brain abnormalities in CVS(22). It is possible that neuronal hyperexcitability and a lowered threshold to trigger specific patterns of neural activity within these cortical and subcortical circuits are pathogenic features of CVS. These concepts may partly explain the clinical benefits of anticonvulsant and antimigraine therapeutics in CVS (9). Improving our understanding of these pathophysiologic factors in well-defined CVS populations may translate into development of novel and/or personalized CVS therapies.

Genetic factors in CVS

CVS, migraines, and epilepsy all share links to some form of mitochondrial dysfunction. This dysfunction could be subclinical at baseline but exacerbated by physiological stressors such as an acute systemic illness. Some genetic links to mitochondrial dysfunction have been demonstrated in pediatric CVS, such as mitochondrial DNA polymorphisms (16519T, 3010A) or other mitochondrial DNA deletions (23-25). The functional significance of these single nucleotide polymorphisms (SNPs) remains unknown. Further, these mitochondrial associations have not been replicated in adults with CVS suggesting the role of other non-mitochondrial factors in adult CVS patients. Inborn errors of metabolism, including fatty acid oxidation disorders and urea cycle defects, have been associated with pediatric CVS (26). Recent studies found that ion channel polymorphisms (RYR2, SCN4A) that impact cellular stress responses may be associated with CVS (13). The synergic roles of nuclear DNA mutations (identified by NextGen sequencing) that impact the function of ion channels, axonal transport (KIF1B), or energy production (TRAP1) have been investigated in children with CVS (13, 23, 25). Larger genetic and functional studies of CVS in both adults and children will be needed to better establish the heritable basis of this disorder. It is critical that these studies involve well-characterized patient subsets in order to better delineate genotype-phenotype relationships. As an example, a patient with hypoglycemia-triggered CVS attacks might be more likely to have genetically-determined mitochondrial dysfunction than an individual with CVS attacks provoked primarily by psychological stressors.

Cannabinoids in CVS and CHS

It remains to be determined if CHS is a disorder truly distinct from CVS or is a subtype of CVS. Both CVS and CHS have common clinical presentations except for a history of chronic, regular cannabis use preceding the onset of CVS-like episodes in CHS. There is considerable

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variation in the application of diagnostic criteria for CHS, and the diagnosis remains inconsistent between centers. However, creating a precise definition of CHS is difficult for a few reasons. First, the duration, potency, and amount of cannabis use needed to elicit CHS is not well established. Furthermore, various cannabis products contain wide ranging concentrations of cannabinoid mixtures, and it is not known which compound(s) drive the development of CHS. Thus, given the general lack of regulation and heterogeneity of cannabis products that are available, it is difficult to quantify the true exposure to any one cannabinoid compound in a given CHS patient. The relatively high potency of modern cannabis products [with generally higher Δ^9- tetrahydrocannabinol (THC) to cannabidiol (CBD) ratios] may result in cannabinoid (CB_1) receptor downregulation resulting paradoxically in emesis. Again as with CVS, it is plausible that a certain threshold needs to be breached by a multiude of factors that may explain the periodic nature of symptoms.

Preliminary data in CVS indicate that the endocannabinoid system (ECS) is involved in the pathophysiology of CVS. Serum levels of endocannabinoid related lipids (N-oleoylethanolamine and N-palmitoylethanolamide) are higher during the emetic phase of CVS than during the inter-episodic phase (27). Recently, the AG and GG genotypes of CB_1 receptor rs806380 were associated with an increased risk of CVS while the CC genotype of CB_1 receptor rs806368, and AG and GG genotypes of mu-opioid receptor rs1799971 were associated with a decreased risk of CVS (28). This highlights a potential genetic basis for ECS dysregulation at the receptor level rather than an absolute deficiency of endocannabinoids in CVS and may indicate that some individuals may be genetically predisposed to develop cyclical emesis when chronically exposed to cannabis. Taken together, these observations suggest a role for the ECS in CVS and CHS with both genetic (i.e. CB_1 receptor SNPs) and environmental (i.e. exposure to high potency cannabis products) factors altering stress responses that may contribute to the development of core CVS/CHS symptoms.

Autonomic and neuroendocrine dysfunction in CVS

Autonomic or neuroendocrine disturbances appear to be important phenotypes that are associated with CVS. An upregulated hypothalamic-pituitary-adrenal (HPA) axis has been observed during CVS episodes in a subset of children described by Sato *et al.* and one adult (11). HPA hyperresponsiveness may drive the release of corticotropin-releasing factor (CRF)

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which has potent actions on proximal gut motility (29). However, most studies measured CRF in the periphery, and it remains unclear how central CRF plays a role in CVS.

Many adults with CVS exhibit sympathetic nervous system dysregulation (30-32). Postural orthostatic tachycardia, abnormal thermoregulatory sweat studies, and aberrant heart rate variability measurements have all been associated with CVS, but it is uncertain if CVS treatment alters these parameters (30). Patients with CVS also have varied gastric motility patterns which include accelerated (59%), normal (27%) and delayed gastric emptying (14%) during inter-episodic intervals of the illness (33). Accelerated gastric emptying may in fact be a surrogate marker for underlying autonomic dysfunction in CVS. Further, delayed gastric emptying should not be interpreted as gastroparesis particularly in the setting of typical episodic vomiting and could be explained by the use of chronic cannabis and opioids. For example, a previously described cohort of patients with cyclic gastroparesis may have simply had undiagnosed CVS . It is particularly important to perform gastric emptying studies during the inter-episodic phase to allow for any meaningful intrerpretation.

Impact of stress on manifestations of CVS

Patterns of neuroendocrine and autonomic dysfunction in CVS may reflect aberrant CNS regulation of “allostasis”, the process by which the body responds to stressors to regain homeostasis. Impaired allostatic regulation is observed with mood disorders, chronic stress, drug abuse, and other CNS illnesses (34). The cumulative impact of chronic stress, or “allostatic load”, can be measured over time using physiological and serum biomarkers including neuroendocrine (e.g. stress hormones), metabolic (e.g. serum lipids), immunologic (e.g. autoimmune), cardiovascular (e.g. vital signs), and anthropometric (e.g. body mass) factors (35). It is logistically difficult to characterize physiological changes during the prodromal or active emetic phases of CVS, but longitudinal studies of allostatic regulation in CVS can still be informative when performed during the inter-episodic phase. Future studies employing wearable sensor technologies will define if changing patterns of stress, cognitive/emotional events, physical activity, sleep patterns and autonomic reactivity measured during inter-episodic (and potentially prodromal) phases can serve as predictive biomarkers for CVS episodes.

High levels of perceived stress can trigger episodes of CVS, migraines, seizures, and panic attacks, which share one or more phenotypic factors, raising the possibility that these conditions have a common CNS pathway (9, 14, 17). Negative life experiences are known to shape the development of neural circuits for cognitive and emotional processing, and such

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neural plasticity may in turn lead to CVS attacks that are more easily triggered. Thus, a cognitive vulnerability to stressors may be an important phenotype shared between CVS and other stress-sensitive disorders. Future research should characterize the psychological traits and cognitive biases that contribute to the stress-sensitivity of CVS attacks. The role of lifestyle factors including stress management, consistent sleep routines, regularly scheduled meals, maintenance of hydration, regular exercise, and identification of episode triggers, factors that have been implemented in migraine prevention, may provide additional insight into CVS episode prevention (36, 37). Understanding these relationships may provide a rational basis for using psychological or mind-body interventions to influence the disease course in CVS.

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PSYCHIATRIC COMORBIDITY IN CVS

Psychiatric disorders are considered separately from other comorbidities given their prominence in CVS. Anxiety, panic, and depression are commonly reported in adults with CVS (10, 38). However, few studies in adult CVS have used standardized diagnostic interviews to ascertain psychiatric disorders, which is the gold standard for psychiatric research. Rather, most studies that report the presence of psychiatric conditions in CVS have employed either patient report, chart review, or other screening instruments. The lack of standardized evaluation of psychiatric comorbidities, the low numbers of CVS patients in individual studies, as well as the potential bias from tertiary care patient samples makes it difficult to accurately calculate the true prevalence of psychiatric conditions in the adult CVS population. It will be important in future studies to systematically evaluate patients for the presence of psychiatric disorders, as such conditions likely influence the disease course. As an example, one case report found that persistent nausea provoked anxiety, leading to conditioned, anticipatory nausea and vomiting that in turn aggravated the patient's CVS course (39). The relevance of psychiatric factors to clinical presentations in different CVS subsets warrants further characterization.

Population studies have found anxiety and depressive disorders to be independently associated with many physical conditions such as hypertension, arthritis, thyroid disease, migraine, fibromyalgia, respiratory, cardiovascular and gastrointestinal disorders, and this comorbidity is significantly associated with poor quality of life and disability in affected adults (40). In similar fashion, it is likely that the presence of such psychiatric comorbidities would impact the functional status and quality of life of adults with CVS independent of their primary CVS symptoms.

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FUTURE RESEARCH DIRECTIONS IN CVS

In addition to providing details about clinical and pathophysiologic features, future investigation in CVS should include high quality trials to confirm the benefits of existing and future CVS therapies. These efforts will have a greater likelihood of success with collaboration of clinical investigators across multiple medical centers that also include engagement with community providers.

Data acquisition

Further investigation into characterizing CVS epidemiology and subphenotypes will require the conduct of clinical trials that validate the development of a CVS-specific symptom score, quality of life assessment, and resource utilization questionnaires. Creation of a large national database of well-characterized CVS patients using these instruments should be linked to a standardized electronic medical record platform to support these research objectives. Instruments such as the Patient Assessment of Upper Gastrointestinal Disorders Symptoms (PAGI-SYM) survey, Gastroparesis Cardinal Symptom Index (GCSI), Leeds Dyspepsia Survey, and Daily Diary of Gastroparesis Symptoms (GSDD) have been employed to quantify symptom severity in database analyses of other disorders of chronic nausea and vomiting (41). However, such instruments include recall time frames of up to several weeks and assume relatively stable, continuous symptoms and likely are inappropriate for CVS trials, which would require instruments that are responsive to brief, discrete episodes lasting hours to days separated by prolonged, asymptomatic inter-episodic intervals. Recently developed questionnaires such as the Patient-Reported Outcomes Measures Information System (PROMIS) in gastroenterology may also not have recall periods that are long enough to be meaningful for CVS studies (42, 43). Similarly, quality of life instruments for CVS should address unique features of CVS including periodicity, variable intervals between episodes and impact on activities of daily living. Additionally, use of standardized psychological surveys in large CVS populations will enhance understanding of the impact of psychosocial dysfunction on CVS severity as has been done for other conditions with chronic nausea and vomiting such as gastroparesis (44).

Given these constraints, novel symptom, quality of life, psychosocial, and disease-related disability instruments could be adapted from existing instruments from episodic disorders related to CVS, such as migraine. One example is the Migraine Disability Assessment (MIDAS) which assesses functional impairment associated with migraine (45). Likewise, development of resource utilization measures including emergency department visits,

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hospitalizations, medication usage, and health care costs should consider variable attack frequencies between patients and include longer observation periods extending up to 12 months. Defining healthcare utilization patterns of CVS patients and their resource costs will be critical to help secure research funding from foundation and governmental organizations. In addition, research directed at improving patient management protocols and emergency department protocols hold promise of low cost, high impact changes to the patient experience.

In addition to acquiring new information from validated survey instruments, it will be useful to adopt a standardized panel of biomarkers from patient specimens to gain insight into CVS pathophysiology. Studies in small cohorts employing blood, urine, and saliva samples to quantify neurohumoral and metabolic functions and genetic profiles of mitochondrial DNA and ion channel distributions, and functional MRI imaging methodologies to discern altered CNS signaling have identified factors which may be of importance in some CVS subsets (11, 13, 20, 22-26). Broad-based application of biomarker panels including these and other testing across multiple centers in diverse CVS patient populations will delineate the relevance of these and other parameters in modifying the clinical presentation of this disorder.

Expanded understanding of pathophysiology

A critical component to better understanding CVS and CHS is the acquisition of more definitive data on the pathophysiology of these conditions (Table 1).Definition of underlying mechanisms for symptoms and its triggers will allow clinicians and patients to better predict and avoid triggers of CVS episodes. The role of genetic factors such as mitochondrial DNA, ion channels, neurohumoral function (endocannabinoid system and the hypothalamic-pituitary-adrenal axis) , and neurogenic contributors in CVS development need to be studied systematically. This will be crucial for the deveopement of targeted therapies in CVS ,which are now solely symptom-based. This comprehensive information base relating to CVS and CHS pathophysiology may identify new directions to pursue in treating these challenging conditions.

Detailed profiling of clinical features

Acquisition of comprehensive assessments of clinical features of CVS and CHS patients across centers in prospective fashion will provide essential new details about manifestations of these conditions (Table 1). Defining the prevalence of disorders associated with CVS and CHS in relation to other conditions similarly characterized by unexplained chronic vomiting should

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help clinicians who are initially evaluating an undiagnosed patient. Characterizing demographic and comorbid features of CVS will permit greater distinction from other functional disorders including chronic nausea and vomiting syndrome (CNVS)(2). Furthermore, such information may help to determine if unusual cases of coalescent CVS are distinct from CNVS and should be managed differently or if they represent a merging of the two functional gastroduodenal disorders which would then be offered common management approaches. Adoption of standardized psychological questionnaires will permit better understating of psychiatric comorbidities in CVS. An exhaustive clinical database providing greater clarity on different CVS subtypes (e.g. catamenial, migraine-associated, stress-related, CHS, etc.) will offer a foundation for further investigation to determine if any subtype warrants consideration of dedicated therapies. In particular, improved data collection on suspected CHS patients will determine if CHS truly mimics CVS in the quantitative aspects of its cyclical emetic profile, if there are undefined risk factors relating to its development, and if only cannabis cessation is effective for controlling the condition. The data provided by these efforts will provide support for future revision of diagnostic criteria for CVS and CHS in evidence-based fashion by the Rome Foundation and other organizations. Finally, comprehensive delineation of inpatient and outpatient resource utilization across centers will emphasize the impact of CVS on both affected patients and families and the healthcare infrastructure to support efforts to obtain external funding for CVS treatment protocols.

Treatment trial priorities

There is a great need to identify and validate therapies to develop better prophylaxis measures and to abort acute emetic episodes in CVS. (Table 2). The health care costs due to hospitalizations from CVS are high amounting to $200 million annually based on a nationwide inpatient sample (46). This number does not include the additional staggering costs associated with medication therapies, emergency department care, outpatient visits and procedures, and lost time at work or in schooling due to CVS. These observations underscore the need for developing effective and safe therapies in CVS and reducing health care utilization. Deficiencies of existing small, single-center case series include poor patient characterization, a lack of validated instruments to quantify symptoms and health care utilization, and a failure to conduct trials in a controlled fashion. Several issues must be considered when designing CVS treatment trials and barriers to conducting such trials should be acknowledged. Such treatment

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trials should consider both outpatient preventative protocols in addition to abortive therapies to be taken at home and parenteral treatments provided in an outpatient setting such as an infusion clinic or urgent care center, the emergency department , and in an inpatient setting. Furthermore, these trials should look at the organization and processes of care as well as the comparative efficacy of multi-drug protocols for well defined subsets of patients.

The experience of performing controlled trials of tricyclic agents for other functional gastrointestinal disorders has been illuminating. More than 5 years were required to enroll 216 patients with severe functional bowel disorders into a controlled trial of the tricyclic drug desipramine (47). Despite this prolonged recruitment, the trial did not show statistically significant benefits on intention-to-treat analyses (P=0.16). Likewise, recruitment spanned more than 6 years in a trial to compare the effects of amitriptyline to escitalopram or placebo in 292 patients with functional dyspepsia (48). In a clinical setting most closely mimicking CVS, subject recruitment proceeded for more than 3 years to enroll 130 patients into a negative placebo-controlled trial of nortriptyline in idiopathic gastroparesis (49). The only published RCT of amitriptyline in CVS employed cyproheptadine as the comparator in a total of 64 children (8). The main observation of this study was the non-superiority of one therapy over the other over 12 weeks, but the actual efficacy of either treatment above placebo (or no therapy at all) was not proven. Given these observations and the fact that TCAs appear to be among the most effective agents used for CVS prophylaxis, such trials in CVS may require a longer duration of time for adequate recruitment. Also, if such TCA trials in CVS are considered, extended observation periods up to for 6-12 months may be required.

It would be prudent to pursue trials of more recently approved agents with fewer side effects as potential prophylactic therapies. Newer agents such as NK1 receptor antagonists have been found to be effective in CVS in children and adolescents based on a single retrospective study and clinical experience, but there are no RCTs examing the efficay in CVS in adults.(50) Such trials would expand the treatment options available and enable us to better tailor therapy for individual patients. For instance a patient who is obese may prefer not to use an agent that can cause weight gain like a TCA vs. a patient with profound weight loss who may benefit from such therapy. A single-center case series reported reductions in CVS episode severity and frequency with the antiepileptic drugs zonisamide and levetiracetam in patients failing tricyclic medications (51). Others have reported a beneficial impact of the antiepileptic medication topiramate when used as CVS prophylaxis (52). Data supporting these specific

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prophylactic measures are described in the preceding articles in this supplement of Neurogastroenterology and Motility. Newer therapies that target CGRP receptors have shown efficacy in migraine prophylaxis in Phase IIb and III trials, and erenumab and fremanezumab have recently been approved by the FDA for this indication (53, 54). These medications have not been studied in CVS, but may be effective in those with or without migraine headaches given the strong link between CVS and migraine (55). Goals of future prospective investigations would be to confirm utility of any of these proposed therapies in reducing the frequency, duration, or severity of CVS attacks and to better define which patient subsets are likely to respond to different treatment options.

Likewise, better options are needed for aborting CVS attacks once started. The NK_1 receptor antagonist aprepitant appears to have beneficial effects in pediatric CVS patients, with mounting clinical experience suggesting a major benefit in adult CVS patients as well (50). Also, aprepitant was found to improve several outcome endpoints relating to nausea, vomiting, and other symptoms to greater degrees than placebo in 126 patients with gastroparesis symptoms (56). Furthermore, given the association of migraines with CVS, efforts should be made to assess benefits of antimigraine therapies to abort attacks in adult CVS patients. In particular, controlled trials of 5-$HT_{1B,1D}$ receptor agonists including intranasal sumatriptan should be considered for controlling acute emetic episodes in CVS. Coupled with controlled trials for CVS prophylaxis, defining a broader set of abortive therapies for CVS flares will permit confident definition of a data-driven management approach to this disorder.

Research infrastructure

The existing research infrastructure is not adequate to address these research needs in CVS. To further our understanding of the clinical features, pathophysiology, and management of CVS, it will be necessary to construct collaborative relationships between clinicians and investigators across a diverse and large number of academic and community institutions and patient support groups such as the CVSA. Generating a multicenter registry of large numbers of CVS patients from broad backgrounds and managed in heterogeneous practices could provide details on the longitudinal course of CVS and function as a source of recruitment for controlled medication trials. Data entered into such a CVS registry would need to be standardized across centers to guarantee its quality using validated symptom, quality of life, and resource usage instruments as described above. A model for such a structure is the National Institutes of Health (NIH)-funded Gastroparesis Clinical Research Consortium, which has been

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functioning for more than a decade. Prior to construction of this Consortium, research in gastroparesis exhibited many features similar to those which plague current CVS investigations. Since the consortium began recruitment, more than 1000 gastroparesis patients have been enrolled in longitudinal databases and three major prospective studies enrolling more than 100 patients each have been conducted (49, 55, 56). Longitudinal demographic and clinical data relating to age, sex, symptom duration (48, 56, 57), traumatic events preceding symptom onset such as early adverse life events, both physiological and psychological, comorbid illnesses, associated psychological dysfunction, disease-specific quality of life, healthcare resource utilization (including hospitalizations and emergency department visits), and prior and ongoing treatments have been systematically collected in all enrolled patients. In addition to organizing clinical data, establishing a biobank with collection of specimens in a central repository will greatly facilitate translational research that will contribute to our understanding of the underlying pathophysiology. This will enable us to identify novel biomarkers to make an accurate diagnosis and predict response to therapies. Examples of such models which have been highly successful include both organic disorders like inflammatory bowel disease (58), and functional GI dsorders like gastroparesis. Novel factors relating to islet cell autoantibodies and hemoxygenase-1 gene polymorphisms were identified in gastroparesis (59, 60). Constructing databases of similar structure for CVS would be pivotal in changing the current paradigm of diagnosis and treatment of CVS.

A single-center foundation for such activities in CVS already has been generated. It should be recognized that, collectively, two of the authors of this article from one institution (BL, TV) have entered approximately 2000 adult and pediatric CVS patients in clinical databases, parts of which are stored in REDCap (Research Electronic Database Capture) (61). REDCap is a secure online platform for building and managing databases in which data from electronic medical records can be imported and shared across institutions. Funding from public and private sources are needed to organize a national registry and provide the necessary infrastructure to foster collaborative, multicenter research. These efforts will be crucial to understanding the pathophysiology, conducting robust clinical trials, and determining longitudinal outcomes all of which will serve to improve patient outcomes. This will facilitated by patient support organizations such as the CVSA and participation by community providers.

Although industry support would be unlikely for established therapies using generic drugs such as tricyclic antidepressants or older antiemetic classes, corporate funding could be sought for RCTs of newer antiepileptic agents, NK_1 receptor antagonists, $5\text{-}HT_{1B,1D}$ receptor agonists, or newer antimigraine therapies. Support from governmental agencies such as the

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NIH will also be critical for future CVS research. The Food and Drug Administration (FDA) could provide direction to conduct of clinical trials in CVS with publication of appropriate advisory guidelines. As an example, a document was released to describe FDA recommendations regarding trial design in gastroparesis including definition of primary and secondary outcome measures, trial duration, and subject recruitment protocols (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM455645.pdf).

Finally, patient advocacy groups must remain active to keep the spotlight on CVS care and research. The diagnosis of CVS is often delayed for an inordinate period of time. Consequently, patients and their families are caught in a downward spiral of misunderstanding and endless, repetitive diagnostic testing. The value of a robust clinical care structure to accurately identify CVS in patients with characteristic clinical presentations and to initiate treatment in a consistent, evidence-based fashion cannot be overemphasized. However, organized participation by patients is also critical to advance research and education in CVS. The Cyclic Vomiting Syndrome Association (CVSA) is a non-profit, self-help organization that was co-founded by Kathleen Adams in 1993. The CVSA plays a critical role to exchange, support and disseminate knowledge about CVS and promote research in this area. Continued leadership and collaboration from the CVSA will be essential to achieve the goals laid out in this article.

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References

1. Tack J, Talley NJ, Camilleri M*, et al.* Functional gastroduodenal disorders. *Gastroenterology* 2006; **130**: 1466-1479.
2. Stanghellini V, Talley NJ, Chan F*, et al.* Rome IV - Gastroduodenal Disorders. *Gastroenterology* 2016; **150**: 1380-1392.
3. Sagar RC, Sood R, Gracie DJ*, et al.* Cyclic vomiting syndrome is a prevalent and under-recognized condition in the gastroenterology outpatient clinic. *Neurogastroenterol Motil* 2018; **30**.
4. Jung HK, Choung RS, Locke GR, 3rd*, et al.* The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology* 2009; **136**: 1225-1233.
5. Basilisco G, Coletta M. Chronic constipation: a critical review. *Dig Liver Dis* 2013; **45**: 886-893.
6. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol* 2014; **6**: 71-80.
7. Aziz I, Palsson OS, Whitehead WE, Sperber AD, Simren M, Tornblom H. Epidemiology, Clinical Characteristics, and Associations for Rome IV Functional Nausea and Vomiting Disorders in Adults. *Clin Gastroenterol Hepatol* 2018.
8. 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**: 135-140.
9. Levinthal DJ. The Cyclic Vomiting Syndrome Threshold: A Framework for Understanding Pathogenesis and Predicting Successful Treatments. *Clin Transl Gastroenterol* 2016; **7**: e198.
10. Li BUK. Managing cyclic vomiting syndrome in children: beyond the guidelines. *Eur J Pediatr* 2018; **177**: 1435-1442.
11. Sato T, Igarashi N, Minami S*, et al.* Recurrent attacks of vomiting, hypertension and psychotic depression: a syndrome of periodic catecholamine and prostaglandin discharge. *Acta Endocrinol (Copenh)* 1988; **117**: 189-197.
12. Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA. Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment-a Systematic Review. *J Med Toxicol* 2017; **13**: 71-87.
13. Lee J, Wong SA, Li BU, Boles RG. NextGen nuclear DNA sequencing in cyclic vomiting syndrome reveals a significant association with the stress-induced calcium channel (RYR2). *Neurogastroenterol Motil* 2015; **27**: 990-996.

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Author Manuscript

14. Fleisher DR, Gornowicz B, Adams K, Burch R, Feldman EJ. Cyclic Vomiting Syndrome in 41 adults: the illness, the patients, and problems of management. *BMC Med* 2005; **3**: 20.

15. Cutrer FM, Charles A. The neurogenic basis of migraine. *Headache* 2008; **48**: 1411-1414.

16. Abell TL, Adams KA, Boles RG*, et al.* Cyclic vomiting syndrome in adults. *Neurogastroenterol Motil* 2008; **20**: 269-284.

17. Li BU, Murray RD, Heitlinger LA, Robbins JL, Hayes JR. Is cyclic vomiting syndrome related to migraine? *J Pediatr* 1999; **134**: 567-572.

18. Scaramelli A, Braga P, Avellanal A*, et al.* Prodromal symptoms in epileptic patients: clinical characterization of the pre-ictal phase. *Seizure* 2009; **18**: 246-250.

19. Bagal SK, Marron BE, Owen RM, Storer RI, Swain NA. Voltage gated sodium channels as drug discovery targets. *Channels (Austin)* 2015; **9**: 360-366.

20. Zamponi GW. Targeting voltage-gated calcium channels in neurological and psychiatric diseases. *Nat Rev Drug Discov* 2016; **15**: 19-34.

21. Yuan H, Low CM, Moody OA, Jenkins A, Traynelis SF. Ionotropic GABA and Glutamate Receptor Mutations and Human Neurologic Diseases. *Mol Pharmacol* 2015; **88**: 203-217.

22. Ellingsen DM, Garcia RG, Lee J*, et al.* Cyclic Vomiting Syndrome is characterized by altered functional brain connectivity of the insular cortex: A cross-comparison with migraine and healthy adults. *Neurogastroenterol Motil* 2017; **29**.

23. Boles RG, Zaki EA, Lavenbarg T*, et al.* Are pediatric and adult-onset cyclic vomiting syndrome (CVS) biologically different conditions? Relationship of adult-onset CVS with the migraine and pediatric CVS-associated common mtDNA polymorphisms 16519T and 3010A. *Neurogastroenterol Motil* 2009; **21**: 936-e972.

24. Zaki EA, Freilinger T, Klopstock T*, et al.* Two common mitochondrial DNA polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome. *Cephalalgia* 2009; **29**: 719-728.

25. Venkatesan T, Zaki EA, Kumar N*, et al.* Quantitative pedigree analysis and mitochondrial DNA sequence variants in adults with cyclic vomiting syndrome. *BMC Gastroenterol* 2014; **14**: 181.

26. Gelfand AA, Gallagher RC. Cyclic vomiting syndrome versus inborn errors of metabolism: A review with clinical recommendations. *Headache* 2016; **56**: 215-221.

27. Venkatesan T, Zadvornova Y, Raff H, Hillard CJ. Endocannabinoid-related lipids are increased during an episode of cyclic vomiting syndrome. *Neurogastroenterol Motil* 2016; **28**: 1409-1418.

Author Manuscript

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28. Wasilewski A, Lewandowska U, Mosinska P*, et al.* Cannabinoid Receptor Type 1 and mu-Opioid Receptor Polymorphisms Are Associated With Cyclic Vomiting Syndrome. *Am J Gastroenterol* 2017; **112**: 933-939.

29. Tache Y. Cyclic vomiting syndrome: the corticotropin-releasing-factor hypothesis. *Dig Dis Sci* 1999; **44**: 79S-86S.

30. Venkatesan T, Prieto T, Barboi A*, et al.* Autonomic nerve function in adults with cyclic vomiting syndrome: a prospective study. *Neurogastroenterol Motil* 2010; **22**: 1303-1307, e1339.

31. Chelimsky TC, Chelimsky GG. Autonomic abnormalities in cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr* 2007; **44**: 326-330.

32. To J, Issenman RM, Kamath MV. Evaluation of neurocardiac signals in pediatric patients with cyclic vomiting syndrome through power spectral analysis of heart rate variability. *J Pediatr* 1999; **135**: 363-366.

33. Hejazi RA, Lavenbarg TH, McCallum RW. Spectrum of gastric emptying patterns in adult patients with cyclic vomiting syndrome. *Neurogastroenterol Motil* 2010; **22**: 1298-1302, e1338.

34. Levinthal DJ, Bielefeldt K. Adult cyclical vomiting syndrome: a disorder of allostatic regulation? *Exp Brain Res* 2014; **232**: 2541-2547.

35. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev* 2010; **35**: 2-16.

36. Wells RE, Baute V, Wahbeh H. Complementary and Integrative Medicine for Neurologic Conditions. *Med Clin North Am* 2017; **101**: 881-893.

37. Kroon Van Diest AM, Ernst MM, Slater S, Powers SW. Similarities and Differences Between Migraine in Children and Adults: Presentation, Disability, and Response to Treatment. *Curr Pain Headache Rep* 2017; **21**: 48.

38. Namin F, Patel J, Lin Z*, et al.* Clinical, psychiatric and manometric profile of cyclic vomiting syndrome in adults and response to tricyclic therapy. *Neurogastroenterol Motil* 2007; **19**: 196-202.

39. McRonald FE, Fleisher DR. Anticipatory nausea in cyclical vomiting. *BMC Pediatr* 2005; **5**: 3.

40. Sareen J, Jacobi F, Cox BJ, Belik SL, Clara I, Stein MB. Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions. *Arch Intern Med* 2006; **166**: 2109-2116.

41. Hasler WL, Li BU, Koch KL, Parkman HP, Kovacic K, McCallum RW. Methodologic considerations for studies of chronic nausea and vomiting in adults and children. *Auton Neurosci* 2017; **202**: 28-39.

Author Manuscript

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42. Spiegel BM, Hays RD, Bolus R*, et al.* Development of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) gastrointestinal symptom scales. *Am J Gastroenterol* 2014; **109**: 1804-1814.

43. Khanna D, Hays RD, Shreiner AB*, et al.* Responsiveness to Change and Minimally Important Differences of the Patient-Reported Outcomes Measurement Information System Gastrointestinal Symptoms Scales. *Dig Dis Sci* 2017; **62**: 1186-1192.

44. Hasler WL, Parkman HP, Wilson LA*, et al.* Psychological dysfunction is associated with symptom severity but not disease etiology or degree of gastric retention in patients with gastroparesis. *Am J Gastroenterol* 2010; **105**: 2357-2367.

45. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. *Neurology* 2001; **56**: S20-28.

46. Bhandari S, Venkatesan T. Clinical Characteristics, Comorbidities and Hospital Outcomes in Hospitalizations with Cyclic Vomiting Syndrome: A Nationwide Analysis. *Dig Dis Sci* 2017; **62**: 2035-2044.

47. Drossman DA, Toner BB, Whitehead WE*, et al.* Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. *Gastroenterology* 2003; **125**: 19-31.

48. Talley NJ, Locke GR, Saito YA*, et al.* Effect of Amitriptyline and Escitalopram on Functional Dyspepsia: A Multicenter, Randomized Controlled Study. *Gastroenterology* 2015; **149**: 340-349 e342.

49. Parkman HP, Van Natta ML, Abell TL*, et al.* Effect of nortriptyline on symptoms of idiopathic gastroparesis: the NORIG randomized clinical trial. *JAMA* 2013; **310**: 2640-2649.

50. 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**: 309-317.

51. Clouse RE, Sayuk GS, Lustman PJ, Prakash C. Zonisamide or levetiracetam for adults with cyclic vomiting syndrome: a case series. *Clin Gastroenterol Hepatol* 2007; **5**: 44-48.

52. Sezer OB, Sezer T. A New Approach to the Prophylaxis of Cyclic Vomiting: Topiramate. *J Neurogastroenterol Motil* 2016; **22**: 656-660.

53. Goadsby PJ, Reuter U, Hallstrom Y*, et al.* A Controlled Trial of Erenumab for Episodic Migraine. *N Engl J Med* 2017; **377**: 2123-2132.

54. Silberstein SD, Dodick DW, Bigal ME*, et al.* Fremanezumab for the Preventive Treatment of Chronic Migraine. *N Engl J Med* 2017; **377**: 2113-2122.

55. Yu ES, Priyadharsini SSY, Venkatesan T. Migraine, Cyclic Vomiting Syndrome, and Other Gastrointestinal Disorders. *Curr Treat Options Gastroenterol* 2018; **16**: 511-527.

This article is protected by copyright. All rights reserved

Author Manuscript

56. Pasricha PJ, Yates KP, Sarosiek I*, et al.* Aprepitant Has Mixed Effects on Nausea and Reduces Other Symptoms in Patients With Gastroparesis and Related Disorders. *Gastroenterology* 2018; **154**: 65-76 e11.

57. Calles-Escandon J, Koch KL, Hasler WL*, et al.* Glucose sensor-augmented continuous subcutaneous insulin infusion in patients with diabetic gastroparesis: An open-label pilot prospective study. *PLoS One* 2018; **13**: e0194759.

58. Kugathasan S, Denson LA, Walters TD*, et al.* Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet* 2017; **389**: 1710-1718.

59. Siraj ES, Homko C, Wilson LA*, et al.* Islet Cell Associated Autoantibodies and C-Peptide Levels in Patients with Diabetes and Symptoms of Gastroparesis. *Front Endocrinol (Lausanne)* 2018; **9**: 32.

60. Gibbons SJ, Grover M, Choi KM*, et al.* Repeat polymorphisms in the Homo sapiens heme oxygenase-1 gene in diabetic and idiopathic gastroparesis. *PLoS One* 2017; **12**: e0187772.

61. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**: 377-381.

TABLES

Table 1: Research Directions to Define Clinical Features and Pathophysiology of Cyclic Vomiting Syndrome

Clinical Features	Pathophysiology
• **Define CVS and CHS prevalence** • **Distinguish CVS and CHS from other functional GI disorders with chronic vomiting** • **Determine relationship of CHS to CVS** • **Clarify features of other CVS subsets (e.g. catamenial, migraine-associated, stress-related,cannabis-related etc.)**	• Elucidate mechanisms of CVS episodes • Idenitfy biomarkers in CVS : mitochondrial DNA, ion channelopathy, and neurohumoral and neurogenic factors • Clinical testing to assess importance of altered CNS processing, autonomic nervous system dysfunction, and gastric myoelectric

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• **Characterize psychosocial impact of CVS and CHS** • **Quantify healthcare resource utilitization**	and motor disturbances

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Table 2: Potential Future Therapeutic Targets for Treating Cyclic Vomiting Syndrome

Type of Therapy	Category	Specific Therapy	Proposed Mechanisms of Action
Prophylactic therapies	Anticonvulsants	Topiramate	Sodium and calcium channel blockade, GABA-A receptor interaction
		Zonisamide	Sodium and T-type calcium channel blockade
		Levetiracetam	Presynaptic calcium channel inhibition
		Lamotrigine	Sodium channel blockade, suppress glutamate/aspartate release
		Gabapentin	Calcium channel interaction
		Pregabalin	Calcium channel interaction, GABA analog
	Prophylactic antimigraine agents	Telcagepant	CGRP receptor antagonist
		Erenumab	CGRP receptor antagonist
		Ubrogepant	CGRP receptor antagonist
		Fremanezumab	Monoclonal antibody against calcitonin-related polypeptides
		Galcanezumab	Monoclonal antibody against calcitonin-related polypeptides
		Tonabersat	Gap junction modifier
		Perampanel	Ionotropic glutamate receptor antagonist
	Antidepressant/atypical neuroleptic	Amitriptyline	Tricyclic antidepressant,inhibits reuptake of serotonin and norepinephrine

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		Mirtazapine	CNS 5-HT_{1A} agonism, 5-HT_2 antagonism, 5-HT_{2C} inverse agonism, 5-HT_3 antagonism, a_2 antagonism, H_1 inverse agonism
		Olanzapine	5-HT_2 inverse agonism, 5-HT_3 antagonism, M_1 antagonism, M_3 antagonism, D_2 antagonism, H_1 inverse agonism
	Behavioral	Cognitive behavioral therapy	Reduced cognitive distortions (including catastrophizing)
		Meditation	Unknown
Abortive therapies	Antiemetics	Aprepitant	NK_1 receptor antagonist
		Rolapitant	NK_1 receptor antagonist
		Investigational NK_1 antagonists	NK_1 receptor antagonists
	Abortive antimigraine agents	Nasal/injectable sumatriptan	5-$HT_{1B/1D}$ receptor agonist
		Other triptans	5-$HT_{1B/1D}$ receptor agonists
	Miscellaneous medications	Topical capsaicin	TRPV1 receptor interaction
		Ketamine	NMDA receptor antagonist
		Candesartan	Angiotensin II receptor antagonist

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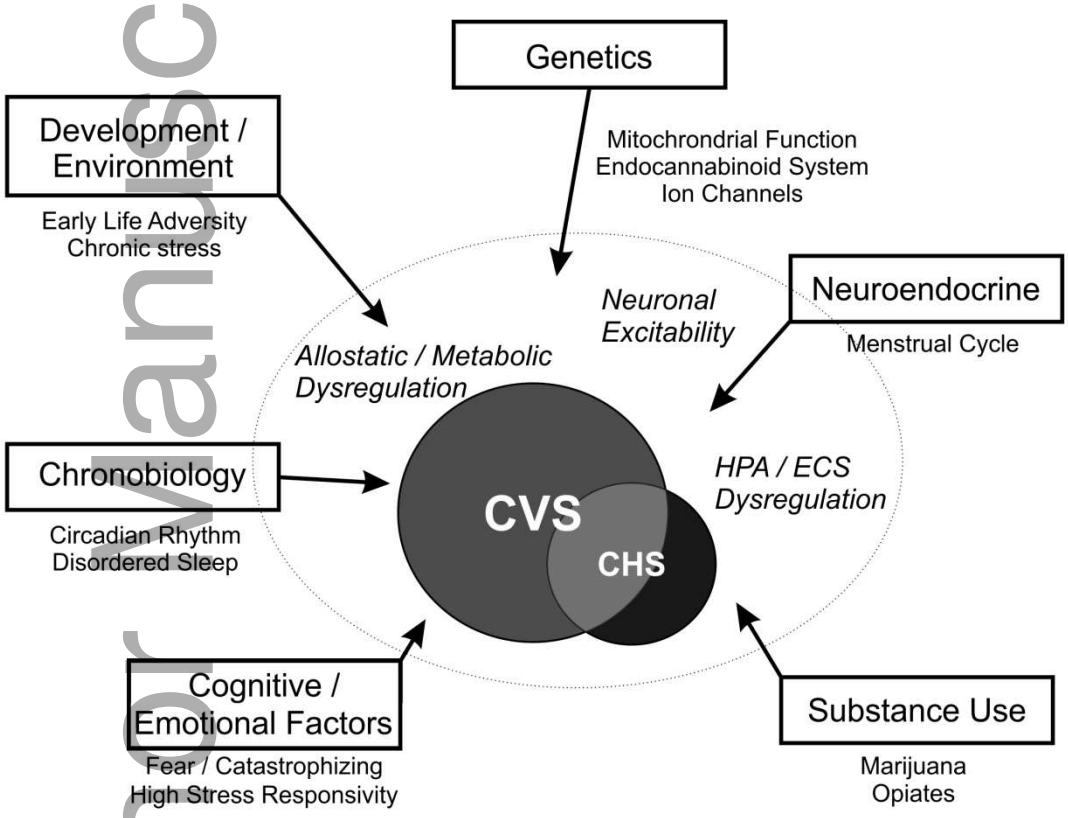
FIGURE LEGENDS

Figure 1: This model of adult CVS development envisions contributions from multiple phenotypic factors that collectively lead to a final common clinical presentation of episodic emesis and other comorbid conditions seen in CVS. Genetically predetermined and other factors may be modified by life experiences, chronic stress, or drug abuse.

Figure 1 : Proposed pathophysiologic model of CVS



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