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Cyclic Vomiting Syndrome and Cannabis Hyperemesis Syndrome

The State of the Science

ABSTRACT

This article provides a narrative review of the state of the science for both cyclic vomiting syndrome and cannabis hyperemesis syndrome along with a discussion of the relationship between these 2 conditions. The scope of this review includes the historical context of these conditions as well as the prevalence, diagnostic criteria, pathogenesis, and treatment strategies for both conditions. A synopsis of the endocannabinoid system provides a basis for the hypothesis that a lack of cannabidiol in modern high-potency Δ^9-tetrahydrocannabinol cannabis may be contributory to cannabis hyperemesis syndrome and possibly other cannabis use disorders. In concluding assessment, though the publications addressing both adult cyclic vomiting syndrome and cannabis hyperemesis syndrome are steadily increasing overall, the state of the science supporting the treatments, prognosis, etiology, and confounding factors (including cannabis use) is of moderate quality. Much of the literature portrays these conditions separately and as such sometimes fails to account for the confounding of adult cyclic vomiting syndrome with cannabis hyperemesis syndrome. The diagnostic and therapeutic approaches are, at present, based generally on case series publications and expert opinion, with a very limited number of randomized controlled trials and a complete absence of Level 1 evidence within the cyclic vomiting literature overall as well as for cannabis hyperemesis syndrome specifically.

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Despite a century and a half of clinical advancement in gastroenterological care since cyclic vomiting syndrome (CVS) was first identified within the literature, this rare yet debilitating condition remains an enigma in both etiology and cure (Hasler et al., 2019; Lombard, 1861). Cyclic vomiting syndrome is an uncommon condition with an onset either in childhood or in adulthood and, when children are affected, the syndrome classically resolves around puberty. With adult-onset CVS, the broad differential of nausea, vomiting, and abdominal pain is a complex presentation that contributes to a delay in diagnosis (often years). This diagnostic delay creates a significant healthcare burden for the patient and the society and may lead to unnecessary surgical referrals (Fleisher, Gornowicz, Adams, Burch, & Feldman, 2005; Venkatesan et al. 2014a).

Furthermore, this syndrome is commonly associated with anxiety and depression as well as opioid and cannabis use (Bhandari & Venkatesan, 2017). A high percentage of cyclic vomiting patients use cannabis for their symptoms regardless of its legality, and yet a nearly identical syndrome, termed cannabis

hyperemesis syndrome (CHS), is associated with long-term cannabis use (though the specific pathogenesis is unclear) (Venkatesan et al., 2019a). This article provides a narrative review of the state of the science for both CVS and CHS, including a discussion of the relationship between these two conditions. A brief overview of the endocannabinoid system is provided along with a hypothesis that the lack of cannabidiol (CBD) (one of the two primary cannabinoids of the cannabis plant) within modern high-potency cannabis may be contributory to CHS, as well as other cannabis use disorders.

Historical Context

Cyclic vomiting syndrome has a long history of etiological debate within the medical literature, with most observations occurring in pediatric patients. The earliest publication originated more than 150 years ago with Dr. H. C. Lombard's reading to the Medical Society of Geneva (Lombard, 1861). The primary author (J.R.L.) translated this French-language article into English, which is available as Supplemental Digital Content, available at: http://links.lww.com/GNJ/A89. Dr. Lombard described his then unidentified pediatric syndrome as "a neurosis of digestion" (as translated), which he admitted was a somewhat vague diagnostic description. His presentation was a call for additional study among colleagues with the hope of identifying both a cause and a cure, as well as perhaps a more appropriate name. At that time, he described several features now known to be pathognomonic of pediatric CVS including (1) a stereotypical yet recurrent cycle of symptoms, (2) the observance of well health between episodes, (3) the absence of organic pathology by autopsy, and (4) a tendency for resolution after puberty.

Many authors have referenced a later article by Dr. Samuel Gee as the earliest publication of CVS (Bhandari et al., 2018; CVSA, 2019; Fleisher et al., 2005; Hejazi & McCallum, 2011; Hejazi & McCallum, 2014; Issenman, 2017; Kovacic, Sood, & Venkatesan, 2018). In that 1882 publication, Dr. Gee described a case series of nine children with "fitful or recurrent vomiting." The publication of case studies over the more recent decades has established both an adult-onset variation of CVS (Abell, Kim, & Malagelada, 1988; Hermus et al., 2016; Keller, Desuki, Hobohm, Münzel, & Ostad, 2015; Prakash & Clouse, 1999; Shearer, Luthra, & Ford, 2018) and a probable toxicity-induced variant described as CHS (Allen, de Moore, Heddle, & Twartz, 2004; Schreck et al., 2018; Sontineni, Chaudhary, Sontineni, & Lanspa, 2009). The classic pediatric variety, with typical resolution in puberty and associations with migraine and anxiety, has been well characterized within the gastrointestinal (GI), neurological, and pediatric literature (Boronat, Ferreira-Maia, Matijasevich, & Wang, 2017; Irwin, Barmherzig, & Gelfand, 2017; Li et al., 2008; Li, Murray, Heitlinger, Robbins, & Hayes, 1998; Rashid et al., 2016; Romano, Dipasquale, Rybak, Comito, & Borrelli, 2018; Zeevenhooven, Koppen, & Benninga, 2017). Therefore, this article adds to the discussion by providing an evaluation of adult CVS and its potential relationship to CHS in the context of endocannabinoid dysregulation.

CVS, Adult-Onset

Prevalence

Similar to pediatric CVS, adult-onset CVS is a condition of stereotypical emetic episodes that tend to be predictable for the patient in duration and symptomatology over a long period of time (Aziz et al., 2019; Evans & Whyte, 2013; Kumar et al., 2012). Both adult and pediatric CVS are rare conditions (Bhandari et al., 2018; Issenman, 2017) and until recently, population-based epidemiological data for adult CVS were absent (Hasler et al., 2019; S. Rosen and A. Singhla, e-mail communication, 2019).

The Global Epidemiology Study of Functional Gastrointestinal Disorders (FGID) surveyed 73,076 adults from 33 countries to identify the prevalence of meeting criteria for at least one of 22 functional GI disorders, including CVS (Sperber et al., 2021). The study used an anonymous Internet survey in 26 countries (n = 54,127) and conducted face-to-face household surveys in nine additional countries that tended to be more rural and with less access to communication technology (n = 18,949). From the Internet-based portion of the survey, the overall prevalence of adult CVS was 1.2% with slightly higher rates in women versus men (1.2% vs. 1.1%) and decline in incidence with age. The interview method revealed a much smaller CVS prevalence at 0.3%, yet a consistent slightly higher prevalence in women than in men (0.5% vs. 0.2%) and conversely a small increase in the incidence of CVS with age (see Table 1). The authors conjectured that "cultural sensitivities around reporting of FGID symptoms may have led to the large differences in prevalence rates observed between the 2 survey methods" (Sperber et al., 2021, p. 111). Therefore, the true prevalence of CVS in adults remains unclear but appears to be low.

Diagnostic Criteria

The syndrome of adult CVS is without measurable biomarkers, and as such, the diagnostic criteria continue to be its unique symptom pattern; ultimately, CVS is a diagnosis of exclusion (Kovacic et al., 2018). A careful history along with a generally normal physical examination may eventually lead the astute clinician to the

TABLE 1. Prevalence Rates of CVS and CHS

		Gender		Age Group (Years)		
		Female	Male	18–39	40–64	65+
Internet survey (n = 54,127)						
CVS	1.2 (1.1–1.2)	1.2 (1.1–1.3)	2.01 (1.0–1.2)	1.6 (1.4–1.8)	0.9 (0.8–1.0)	0.6 (0.5–0.8)
CHS	0.05 (0.03–0.07)	0.02 (0.01–0.04)	0.08 (0.05–0.11)	0.11 (0.07–15)	0.01 (0.00–0.02)	0.01 (0.00–0.03)
Household interview (n = 18,949)						
CVS	0.3 (0.3–0.4)	0.5 (0.3–0.6)	0.2 (0.1–0.3)	0.3 (0.2–0.4)	0.4 (0.2–0.5)	0.5 (0.2–0.7)
CHS	2.01 (0.00–0.02)	0.00	2.01 (0.00–0.03)	2.01 (0.00–0.04)	0.00	0.00

Note. CHS = cannabis hyperemesis syndrome; CVS = cyclic vomiting syndrome.

Pooled prevalence rates by percentage (95% confidence interval) for CVS and CHS from a population-based internet survey sample in 26 countries and from a household interview survey sample involving nine countries (Sperber et al., 2021, pp. 103–104).

diagnosis. A hallmark of the disease is its repetitive and cyclical nature over time, so by definition the syndrome cannot be diagnosed with the initial onset of symptoms. Furthermore, nausea, vomiting, and abdominal pain are nonspecific symptoms with a broad differential. Indeed, the mean time to diagnosis from the onset of symptoms for an adult CVS patient is 7.3 ± 6.9 years (Venkatesan et al., 2014a). Patients may suffer an extended period without a clear diagnosis, and these episodes can lead to multiple emergency department (ED) visits, hospitalizations, and surgical referrals.

In a survey of 41 CVS patients, 16 of them underwent a combined total of 17 surgical attempts to cure their recurrent vomiting, yet none resulted in improvement (Fleisher et al., 2005). An Internet survey questionnaire of 437 patients reported 20% (n = 88) of responders as having a cholecystectomy for symptoms that were ultimately attributed to a diagnosis of CVS (Venkatesan et al., 2014a). In short, CVS often involves a high level of healthcare utilization along with unnecessary suffering, including surgery without benefit, and typically a long delay between symptom onset and diagnosis of the condition.

Key features of CVS include a rapid onset of intense nausea, vomiting, and crampy abdominal pain. The episodes will last from a few hours to a week or more, interspersed with wellness periods from weeks to months. Attacks may be without trigger, yet provoking factors are common and similar to persons with migraines: food sensitivities such as chocolate, alcohol, cheeses, and monosodium glutamate; health conditions such as motion sickness, sleep deprivation, and infection; and emotional stressors including both unpleasant events (e.g., examinations or the loss of a loved one) and pleasant, yet stressful events (e.g., weddings, parties, and vacations) (Abell et al., 2008; Kovacic et al., 2018). When the recurrence pattern is associated with a menstrual cycle, it is termed catamenial CVS.

The Rome Foundation (Rome IV) criteria are considered the standard for CVS diagnosis (Drossman & Hasler, 2016; Stanghellini et al., 2016; S. Rosen, personal communication, 2019); see Supplemental Digital Content Box 1, available at: http://links.lww.com/GNJ/A90. The *International Classification of Diseases, Tenth Revision* (*ICD-10*) billing codes for CVS are R11.15, *cyclical vomiting syndrome unrelated to migraine*, G43.A0, *cyclical vomiting, in migraine, not intractable*, and G43.A1, *cyclical vomiting in migraine, intractable*.

The cycle of illness for CVS is divided into four phases, and a careful history should focus on identifying not only a recurrent pattern for the patient but the relative consistency of each of these phases:

- The interepisodic *wellness period* during which time the patient is generally symptom free, typically for a span of weeks to months.
- A *prodromal phase* which lasts anywhere from a few hours to a day; this phase has similarities to the migraine prodrome with symptoms such as nausea, pallor, sensitivity to light, sound, smell, pressure, and temperature, as well as the possibility for fatigue, myalgias, and abdominal pain.
- The *emetic phase* of sudden onset with severe vomiting even continuing after an evacuated stomach; there is a significant intolerance to the consumption of any food or drink, and emesis may occur with or without nausea. This phase will last from a few hours to a few days, with retching multiple times an hour, and may be accompanied by pallor, dizziness, flushing, drooling, listlessness, diaphoresis, abdominal pain, and other symptoms such as diarrhea and core temperature variations including low-grade fever or hypothermia.
- Finally, the *recovery phase,* which is marked with the easing of nausea, retching, and other symptoms, until

the intake of food can be tolerated, which marks the beginning of the wellness phase once again.

Pathogenesis

Current theories of CVS pathogenesis include autonomic dysfunction (Hejazi et al., 2011; Venkatesan et al., 2010a), dysregulation of the brain–gut axis (Drossman & Hasler, 2016; Levinthal & Bielefeldt, 2014), stress-mediated activation of the corticotrophin-releasing factor signaling system (Adamiak & Jensen, 2015; Venkatesan et al., 2010a), dysfunction of the hypothalamic–pituitary–adrenal axis (Bhandari et al., 2018; Donnet & Redon, 2018; Richards, 2017), altered genetic factors in children such as mitochondrial DNA mutations (Boles et al., 2009; Gelfand & Gallagher, 2016; Zaki et al., 2009) or polymorphisms involving the cannabinoid receptor Type 1 and mu-opioid receptor genes (Wasilewski et al., 2017), and a dysfunction or dysregulation of the endocannabinoid system (Venkatesan, Zadvornova, Raff, & Hillard, 2016). No single etiological hypothesis is dominant at this point. Furthermore, a complicating factor for both adult and pediatric CVS is the common coexistence of psychiatric comorbidities such as depression and anxiety. Additional associations include migraine, syncope, chronic fatigue, irritable bowel syndrome, and alcohol, tobacco, and cannabis use (Koloski et al., 2012; Sagar et al., 2018).

A United States (U.S.) nationwide analysis of 20,952 hospitalized CVS patients in comparison with a random sampling of 44,262 hospitalized non-CVS patients found significant correlations with younger age, White race, marijuana use, tobacco smoking, irritable bowel syndrome, gastroparesis, migraine, anxiety, and gastroesophageal reflux disease (Bhandari & Venkatesan, 2017, p. 6). Other studies highlight the psychiatric comorbidities as an important feature of CVS and patients should be screened for these as a routine component of CVS workup (Sagar & Ford, 2017; Thavamani, Umapathi, Velayuthan, & Sankararaman, 2022).

Treatment of CVS

Although the publication of CVS-related literature is steadily increasing, the state of the science supporting adult CVS incidence, symptoms, treatments, prognosis, etiology, and confounding factors (including cannabis use) are primarily based on case series publications and retrospective chart review studies.[1] Within the existent literature, there are very few randomized controlled trials (RCTs) and zero publications meeting Level 1 evidence criteria within the CVS literature for either children or adults (Hasler et al., 2019; Issenman, 2017; Lee, Abbott, Mahlangu, Moodie, & Anderson, 2012; Levinthal, 2016; Shearer et al., 2018). For this review, we identified only two small RCTs evaluating CVS pharmacological treatments and both were pediatric studies.

The first was a single-blind RCT aimed to investigate the difference between amitriptyline* (tricyclic antidepressant) or cyproheptadine* (antihistamine) in the prevention of future attacks and involved 64 children between the ages of 3 and 15 years (Badihian, Saneian, Badihian, & Yaghini, 2018); no statistical significance in effect was found between the two groups. The second RCT compared amitriptyline* (n = 34) with topiramate* (anticonvulsant) (n = 36) in prophylactic treatment of pediatric CVS patients 4–13 years of age (Bagherian, Yaghini, Saneian, & Badihian, 2019). After 3 months of therapy, 79.4% (n = 27) of the amitriptyline* group achieved a 50% reduction and greater in either frequency or duration of attacks over baseline compared with 44.4% (n = 16) of the topiramate* group (p = .003).

Current guidelines for the management of CVS are published as a collaborative effort between the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association (Venkatesan et al., 2019b). For prevention and treatment considerations, one therapeutic approach is to consider CVS a migraine variant (Hayes, VanGilder, Berendse, Lemon, & Kappes, 2018; Irwin et al., 2017; LenglarT et al., 2021; Yu, Priyadharsini, & Venkatesan, 2018). The CVS guidelines recommend that mild cases with quick recovery periods can be treated with abortive medications only (defined as less than four episodes per year and episodes lasting for less than 2 days). Moderate to severe cases of CVS (defined as 4 episodes and greater per year, episodes of 2 days and greater, prolonged recovery, or ED visits and/or hospitalizations) may need prophylactic treatment in addition to abortive therapy (Venkatesan et al., 2019b).

Symptomatic and Supportive Treatment During the Acute Phase and Recovery

During the acute phase (prodrome to emetic), evidence indicates that some medications used for acute migraine may be abortive in CVS. The basic abortive treatments include intranasal or subcutaneous sumatriptan* (selective serotonin receptor agonist) along with ondansetron sublingually and/or oral aprepitant (antiemetic). Once the emetic phase has started, intravenous (IV) treatments, usually given in the ED setting, are often necessitated, with an emphasis on the use of IV benzodiazepines plus fluid hydration.

[1]This article discusses the off-label use of Food and Drug Administration (FDA)-approved drugs as the only drugs approved for CVS specifically are the symptomatic agents, such as antiemetics for nausea and vomiting. Off-label use of FDA-approved drugs is designated with a superscript*.

Because of the complexity in treating these patients, and the surprising failure of standard antiemetics in this population, having a written treatment plan can be facilitative for both the patient and ED clinician (Issenman, 2017; Venkatesan et al., 2019b). Other IV agents that may be helpful include promethazine (antiemetic) diphenhydramine* (antihistamine) and proton pump inhibitors (Bhandari & Venkatesan, 2016; Calhoun & Pruitt, 2014; Mooers, Srivastava, Garacci, & Venkatesan, 2021). Clinicians assessing for cannabis use in CVS patients (in attempts to differentiate CHS) should note that proton pump inhibitors (IV pantoprazole* in particular) may result in a false-positive cannabis toxicology screen during the ED or inpatient workup (Felton, Zitomersky, Manzi, & Lightdale, 2015; Gomila et al., 2017).

Fosaprepitant*, an IV antiemetic approved for chemotherapy-induced nausea and vomiting, should be considered if available (Bhandari & Venkatesan, 2016; Hermus et al., 2016; Venkatesan et al., 2019b). Limited amounts of narcotics may be provided as needed for moderate to severe abdominal pain (Venkatesan et al., 2010b).

As the patient moves into the recovery phase, one key element is to limit the oral intake of fluids. Rapid oral fluid replacement can send a recovery phase patient back to the emetic phase; offer ice chips initially, continue IV fluids if available, and progress with small volume clear liquids until the patient begins to feel well once again.

Preventive Treatment During the Wellness Phase

A daily tricyclic antidepressant (amitriptyline* or nortriptyline*) is the first-line choice for decreasing CVS frequency and severity over time, with alternate agents to include topiramate* (anticonvulsant), aprepitant* (antiemetic), and zonisamide* or levetiracetam* (anticonvulsants) (Venkatesan et al., 2019b). Mitochondrial dysfunction has also been implicated in both CVS and migraine, and the use of mitochondrial supplements[2] such as coenzyme Q10 and riboflavin may reduce the incidence of CVS episodes in some patients (Kovacic et al., 2018; Venkatesan et al., 2014b).

Lifestyle modifications including stress-reducing measures, the practice of good sleep hygiene, the identification and avoidance of triggers (a lifestyle diary can be helpful in the identification of triggers), and the implementation of an exercise program may all be helpful in decreasing CVS episodes (Bhandari et al., 2018). And as a final consideration, although use of opioids for abdominal pain is often indicated during the acute emetic phase, outpatient narcotics should be minimized in this group overall.

[2]Supplements are not FDA-approved to treat any medical condition.

Opioids decrease gastric motility and are known to cause GI side effects including nausea and vomiting (Farmer et al., 2018; Smith & Laufer, 2014). Chronic narcotic exposure may set the patient up for narcotic bowel syndrome, which can mimic a coalescence of CVS symptoms (a shortening of the wellness phase) (Camilleri, Lembo, & Katzka, 2017; Drossman, 2016). Finally, the CVS guidelines recommend screening and treatment for comorbid conditions, which are common in this population (especially, anxiety, depression, migraines, sleep disorders, and substance use) with referral to the appropriate allied health services.

Considerations for Ketamine in Refractory CVS

Many CVS patients are slow to break the emetic phase and often will have prolonged hospitalizations despite appropriate management. Evolving evidence supports the potential use of IV ketamine* (general anesthetic) for treatment of resistant depression and intractable pain. Recently two small pilot studies have evaluated ketamine* for CVS abortive therapy (Ahuja, Kingsley, Diable, Binion, & DJ, 2018; Valdovinos, Frazee, Hailozian, Haro, & Herring, 2020).

A retrospective chart review of ED patients with intractable nausea and vomiting examined discharge to home or hospital admission by ketamine* dose in patients who received the drug at least once. The sample experienced a total of 108 ketamine* exposures, with 40 hospital admissions (a 37% admission rate), and the mean index ketamine* dose was 24.4 mg. Response to ketamine* was dose dependent with less than 15 mg resulting in 100% hospital admissions while more than 15 mg resulted in a 31.2% admission rate (Ahuja et al., 2018).

The second study was a nonblinded open-label design in which a convenience sample of ED patients (n = 28) with nausea and vomiting and a history of CVS were given 15 mg of ketamine* by slow IV push plus 12.5 mg of chlorpromazine IV drip (phenothiazine antiemetic). After 120 minutes postmedication, the median number of observed episodes of emesis was 0 (interquartile range: 0–1) as compared with a median of seven episodes reported by subjects in the 2 hours prior to treatment. Subject-rated nausea and pain scores decreased by a mean of 4.9 (95% confidence interval [CI]: 3.2–5.0) and 4.1 (95% CI: 4.0–5.8) points, respectively, on a 0–10 numeric rating scale at 120 minutes post-treatment. Patient satisfaction was high with 100% of the study subjects reporting that they would like this therapy in the future.

Finally, the team performed an electronic query of the ED visits in the 24 months before the index visit for each patient and determined that "opioids were used less frequently [during the study visit] than

during prior visits for the same complaint" though no specific analysis or numbers were provided (Valdovinos et al., 2020, p. 330). These two pilot studies provide direction for further study, including the consideration for using ketamine* plus chlorpromazine in acute CVS (or CHS) not otherwise responding to guideline-recommended agents.

Cannabis Hyperemesis Syndrome

The clinical picture of CVS is complicated by a prevalence of cannabis use in this population, coupled with the potential for cannabis to cause a cycling emesis very similar to idiopathic CVS. In 2004, a group from Australia proposed the new syndrome of CHS with the presentation of a case series of 10 individuals with new adult-onset cyclic vomiting (Allen et al., 2004). The pattern described in these cases was cyclic vomiting associated with a history of daily cannabis use, and the resolution of symptoms in all patients who were able to abstain from cannabis (seven out of 10), as well as a return of symptoms rapidly with a reintroduction of cannabis even after an extended period of abstinence.

The team described CHS as having a near-typical CVS presentation, but with a prodromal phase of early morning nausea and occasional vomiting for months or years prior to the first hyperemetic phase. The emesis would then come on suddenly, last 24–48 hours, and then resolve back into a baseline morning nausea prodrome. The key to these cases was that the initial cannabis use was not for the self-treatment of symptomatic nausea and vomiting, but rather that the cannabis use predated the onset of cyclic vomiting symptoms.

The possibility that some CVS cases may have been CHS is concerning, given reports that large proportions of CVS patients use cannabis, presumably for the long-recognized antiemetic effects of the substance.[3] In a large anonymous Internet survey, 81% of CVS patients reported the use of cannabis to assist with their symptoms including nausea and pain (Venkatesan et al., 2014a). A hospital-based survey in Milwaukee, Wisconsin, found that 14% of their CVS patients reported the use of cannabis to alleviate symptoms, versus 3% of non-CVS patients (Bhandari & Venkatesan, 2017). A retrospective chart review from the Mayo Clinic in Rochester, NY, from 1993 to 2006, found cannabis to be more significantly associated with CVS than with functional vomiting (odds ratio: 2.9, 95% CI: 1.2–7.2), and that 79% of their adult CVS patients reported cannabis use (Choung et al., 2012).

More recently, a population of CVS patients from a specialized CVS clinic in Milwaukee, Wisconsin was administered a cannabis use survey, with 140 patients completing the questionnaire (23% of those invited to participate). Within the sample, 41% (n = 57) reported using cannabis in the prior 6 months. Among the cannabis users, 53% (n = 30) were regular cannabis users of more than four times per week and 50% of that group (n = 15 of 30) reported using cannabis on a regular basis before they developed CVS (Venkatesan, Hillard, Rein, Banerjee, & Lisdahl, 2020).

The consideration of cannabis as a potential causative agent is often not mentioned in published cases of adult-onset CVS, and it is likely that the syndrome of CHS continues to be underrecognized and underdiagnosed (Attout et al., 2020; Lua, Olney, & Isles, 2019; Sagar et al., 2018). A large global market survey of 6,300 individuals in 2015 identified the overall prevalence of CHS at 0.1% (Aziz et al., 2019) whereas the more recent Global Epidemiology Survey of FGID noted an even smaller prevalence at 0.01%–0.05% (Table 1) (Sperber et al., 2021). However, each of these global surveys needs to be considered with local increases in cannabis use (and cannabis potency) in the newly legalized areas as well as traditionally heavy use areas such as Western Europe, Canada, the U.S., Latin America, and the Caribbean Islands. Furthermore, many CVS case studies either do not mention cannabis use at all or list it as a recreational or therapeutic measure without specific consideration as a possible cause of the symptomology (Al-Mahrouqi, Al Busaidi, & Al Alawi, 2020; Hejazi & McCallum, 2011; Sagar et al., 2018).

Another intermixing point between the conditions of CVS and CHS is compulsive hot water bathing, often to the point of using near scalding hot water, which provides the patient with transient relief from nausea and vomiting. Hot water bathing is associated with both conditions, though it is more strongly associated with CHS in particular. For nine of the 10 patients in the Australian case series (Allen et al., 2004), relief from the acute emetic phase and abdominal pain was gained through hot showers.

The first case of CHS was published in the U.S. several years later (Chang & Windish, 2009). That same year, Sontineni et al. released a case report along with an initial listing of diagnostic criteria that included compulsive hot bathing for symptom relief as supportive, but not essential, for CHS diagnosis (Sontineni et al., 2009); see Supplemental Digital Content Box 2, available at: http://links.lww.com/GNJ/A91. Yet other authors have noted a pattern of hot water bathing for relief of symptoms in CVS patients who deny cannabis use (Aziz et al., 2019).

An Internet survey of marijuana and hot shower use in adults reported that 72.2% of CVS patients with a history of marijuana use describe relief with hot showers or baths, whereas 47.5% of CVS patients with no history of marijuana use also report relief with hot showers or

[3]The FDA has not approved the marketing of cannabis for the treatment of any disease or condition.

baths (Venkatesan et al., 2014a). Ultimately, the key diagnostic element of CHS is a history of cannabis use that predates the onset of symptoms and the resolution of symptoms with cessation of cannabis use (Schreck et al., 2018; Venkatesan et al., 2020). So, although the unique behavior of symptom relief with hot bathing is strongly associated with CHS, it is not specific enough to CHS alone as it occurs in up to 50% of non–marijuana-consuming CVS patients as well (Rosen et al., 2021).

The CHS variant of CVS likely has been present among all cohorts of adult CVS patients (Venkatesan et al., 2020). For example, an earlier case report of recurrent vomiting marked by the "use of marijuana and the taking of several showers and baths each day" (de Moore, Baker, & Bui, 1996, p. 291) did not consider the patient's cannabis use as a potential causative agent. Indeed, the syndrome of CHS was somewhat difficult for the clinical GI community to recognize because (1) cannabis became an illegal substance in most parts of the world during the last century, so patients tended to deny or minimize reporting of its use; (2) the antinausea and antiemetic properties of Δ^9-tetrahydrocannabinol (THC) have been well recognized by both patients and clinicians, and as such a cannabis-related CVS is counterintuitive; (3) CVS patients do use cannabis for symptom alleviation without having CHS; and (4) the continued U.S. Drug Enforcement Administration (DEA) Schedule I classification of marijuana is a formidable barrier to research through common funding mechanisms.

This final point creates an atmosphere of illegitimacy hovering over most discussions of cannabis and has a dampening effect on research design, even unintentionally. For example, in 2017, a group from St. James's University Hospital in Leeds, UK (where cannabis continues to be illegal in all forms), published original research from a survey study involving 920 patients who were recruited over a 2-year period from six medical GI outpatient clinics, where 10.8% of respondents met diagnostic criteria for CVS ($n = 99$). Although in their survey they found CVS to be associated with younger age, never married social status, psychiatric diagnoses, and cigarette smoking ($p \leq .01$), the researchers did not collect any data on cannabis use (Sagar & Ford, 2017).

Still, there has been a marked increase in the number of published cases of CHS since it was first identified in 2004, including fatal cases (Nourbakhsh, Miller, Gofton, Jones, & Adeagbo, 2019; Sorensen, DeSanto, Borgelt, Phillips, & Monte, 2017; von Both & Santos, 2021) and associations with synthetic cannabis use (Argamany, Reveles, & Duhon, 2016; Hopkins & Gilchrist, 2013; Liu, Villamagna, & Yoo, 2017). Many authors attribute the rise in cases directly to the increase of cannabis availability by U.S. state-level legalization and/or to the increased percentage of THC (the main intoxicating component in cannabis) within the cannabis products (Al-Shammari, Maklad, Yoo, & Makar, 2017; Bhandari, Jha, Lisdahl, Hillard, & Venkatesan, 2019; Gubatan, Staller, Barshop, & Kuo, 2016). However, increased recognition of CHS cases may correlate with cannabis use and disclosure of such in the age of legalization, in combination with an increased provider recognition of the syndrome and a publication bias for a newly recognized syndrome (Hermus et al., 2016; Sontineni et al., 2009; Soriano-Co, Batke, & Cappell, 2010).

Whatever the cause for the increase of this syndrome within the case literature, the Rome IV standards designate CHS as a unique nausea and vomiting disorder with a diagnosis separate from, but in the same category as, CVS (Schmulson & Drossman, 2017). Yet other authors continue to describe CHS as a CVS variant (Aziz et al., 2019). Taking this latter approach, CHS may be considered an induced or toxin-related CVS variant in which the symptoms are attributed to chronic (most often daily) long-term cannabis consumption (often 2 years or more), which resolve with abstinence and tend to reoccur quickly with relapse of use (Aziz et al., 2019). The level of evidence for this designation is low, however, relying entirely on case reports, retrospective chart review studies, and expert opinion. Further study is needed, including longitudinal studies of cannabis users, combined with the continued advancement of our understanding on how the consumption of exogenous cannabinoids interacts with human physiology in both acute and chronic exposure.

Treatment of CHS

The only RCTs for CHS treatment identified in the literature with this review are the haloperidol versus ondansetron for CHS (HaVOC) trial (Ruberto et al., 2021) and a small pilot trial of topical capsaicin cream for CHS (Dean et al., 2020). The HaVOC trial was a randomized triple-blind clinical trial comparing the effect of IV haloperidol* ($n = 13$) to IV ondansetron ($n = 17$). Inclusion criteria were age more than 18 years, a working diagnosis of CHS, and a presentation to one of two academic EDs in Ontario, Canada. The primary outcome measure was the average of abdominal pain and nausea scores as measured on a 10-cm visual analog scale (VAS) at 2 hours versus baseline; the mean difference between the ondansetron and haloperidol* groups was 2.3 cm favoring haloperidol* 95% CI: 0.6–4.0; $p = .01$. Secondary measures including overall treatment success, reduced use of rescue antiemetics, and shorter time to discharge were also favorable to haloperidol* (2.5-hour difference [95% CI: 0.1–5.0], $p = .03$). In the discussion, the authors concluded that "this randomized controlled trial demonstrates the

superiority of intravenous haloperidol over ondansetron, especially at a low, one-time dose of 0.05 mg/kg, for the common symptoms of nausea, vomiting, and abdominal pain" in the treatment of acute-phase CHS (Ruberto et al., 2021, p. 618).

Considerations for Capsaicin

The common behavior of using very hot water for self-management of CHS led some clinicians to try the application of over-the-counter capsaicin cream[4] (0.025%, 0.075%, or 0.1%) to the abdomen (or other regions such as the back and the arms) in an attempt to abort acute cyclic vomiting in patients with emetic-phase CHS (Lee & Coralic, 2022; Richards, Lapoint, & Burillo-Putze, 2018). These creams were initially developed for arthritic pain syndromes and the mechanism of action is hypothesized to be both a downregulation of cutaneous nociceptor fibers and, separately, a depressed expression of the capsaicin receptor, transient receptor potential vanilloid-1 ($TRPV_1$), a receptor responsible for the sensation of heat (Anand & Bley, 2011; Lo Vecchio, Andersen, Elberling, & Arendt-Nielsen, 2021). When applied to the skin, capsaicin, a neuropeptide-active agent derived from *Capsicum* sp. (hot chili peppers), strongly engages with $TRPV_1$ and, through activation and subsequent desensitization, decreases its activity (Geraghty, Mazzone, Carter, & Kunde, 2011; Sharkey et al., 2007). Similarly, noxious heat (~43° C) decreases $TRPV_1$ activity (Joseph, Wang, Lee, Ro, & Chung, 2013; Richards et al., 2018). The overall evidence for using topical capsaicin in acute CHS as a clinical recommendation is low, relying generally on a small number of published case reports (McConachie, Caputo, Wilhelm, & Kale-Pradhan, 2019).

There are, however, three retrospective studies and a singular small RCT to be considered. The first is a retrospective cohort series ($n = 22$) that reported no significant effects of capsaicin on CHS symptoms (McCloskey, Goldberger, Rajasimhan, McKeever, & Vearrier, 2017). Second, a retrospective cohort analysis of 43 patients demonstrated support for lower antiemetic doses needed to achieve symptomatic relief when capsaicin was used concurrently (four vs. two doses, $p = .015$) (Wagner, Hoppe, Zuckerman, Schwarz, & McLaughlin, 2020). Third, a retrospective cohort study (capsaicin: $n = 149$; no capsaicin: $n = 52$) showed a greater effect in total symptomatic relief (55% of the capsaicin group vs. 21% of the no capsaicin group, $p < .001$) as well as a shorter average time to discharge from the ED in the capsaicin group (2.72 vs. 6.11 hours, $p = .001$) (Kum, Bell, Fang, & VanWert, 2021). However, the imbalance between the treatment group and the control, combined with the unblinded treatment and retrospective design, leaves the study's conclusions as highly speculative.

Finally, the singular published RCT is a pilot-level trial that enrolled 30 convivence-sample ED patients with CHS who presented to a large-volume urban academic trauma center between December 2017 and July 2019 (treatment: $n = 17$; placebo: $n = 13$). Patients were treated with either 5 g of topical 0.1% capsaicin cream or an identical-appearing moisturizing cream (blinded placebo control). An ED nurse applied the cream once to the abdomen in a uniform manner; otherwise, patients received conventional therapy per the ED physician independent of study enrollment. A VAS was used to measure the subjective intensity of the patient's nausea at 30 and 60 minutes after application of the cream.

The study did not meet its primary endpoint of nausea reduction by VAS at 30 minutes (4.1 cm [95% CI: 2.8–5.4] vs. 6.1 cm [95% CI: 4.1–8.1] $p = .075$), and one patient in the treatment group experienced an adverse event consisting of skin irritation requiring immediate removal of the cream. However, the study did meet its secondary endpoint of decreased nausea by VAS at 60 minutes (3.2 cm [95% CI: 1.6–4.8] vs. 6.4 cm [95% CI: 4.7–8.1] $p = .007$), and a higher proportion of the capsaicin group patients also reported a complete resolution of nausea at discharge (29.4% vs. 0%, relative risk = 3.4, 95% CI: 1.6–7.1). These results are weakened, however, by the capsaicin group randomly having a lower mean nausea VAS at baseline compared with the placebo control group (6 ± 2.9 cm vs. 8.5 ± 2.0 cm) (Dean et al., 2020).

Taken together, these small capsaicin studies describe a potential effect with probable CHS cases; yet as previously noted, around 50% of noncannabis using CVS patients may also gain relief from hot water bathing and therefore, classical CVS patients could be considered for capsaicin therapy studies as well. For example, in the Dean et al. (2020) RCT described previously, 17.6% of the capsaicin group ($n = 3$) reported less than weekly cannabis use, and one patient (5.9%) denied any cannabis use, so up to one-fourth of the treatment group may have been those with CVS versus those with CHS. Furthermore, an additional research consideration is the availability of a high-potency 8.0% capsaicin patch* approved for the management of neuropathic pain (Abrams, Pedowitz, & Simpson, 2021; Anand & Bley, 2011; Bonezzi et al., 2020), and yet there are no published reports of it being trialed in any acute CHS or CVS case.

The improvement described in some of these capsaicin studies, combined with the mechanistically related behavior of gaining relief from hot water, suggests the need for more RCT's evaluating the efficacy of topical capsaicin for acute cyclic vomiting episodes

[4]Over-the-counter capsaicin cream has not been found by the FDA to be safe and effective for any condition.

TABLE 2. The Natural Cannabinoids

Compound Name	Variations	First Reported
Cannabin-type cannabinoids (65)		
Cannabinol (CBN)	11	Wood, Spivey, and Easterfield (1899)
Cannabidiol (CBD)	8	Adams, Hunt, and Clark (1940)
Cannabidiolic acid (CBD-A)	1	Krejci and Santavy (1955)
Cannabigerol (CBG)	16	Gaoni and Mechoulam (1964a)
Cannabichromene (CBC)	9	Gaoni and Mechoulam (1966)
Cannabitriol (CBT)	9	Obata and Ishikawa (1966)
Cannabicyclol (CBL)	3	Mechoulam and Gaoni (1967)
Cannabinodiol (CBND)	2	Van Ginneken, Vree, Breimer, Thijssen, and Van Rossum (1972)
Cannabielsoin (CBE)	5	Bercht et al. (1973)
Cannabidivarin (CBDV)	1	Shoyama, Hirano, Makino, Umekita, and Nishioka (1977)
THC-type cannabinoids (30)		
Δ^9-tetrahydrocannabinol (Δ^9-THC)	23	Gaoni and Mechoulam (1964b)
Tetrahydrocannabinolic acid (THC-A)	1	Yamauchi, Shoyama, Aramaki, Azuma, and Nishioka (1967)
Tetrahydrocannabivarin (THCV)	1	Gill (1971) and Merkus (1971)
Δ^8tetrahydrocannabinol (Δ^8-THC)	5	Krejcí and Šantavý (1975)
Miscellaneous-type cannabinoids (30)		
CBCN, CBF, CBR, DCBF, OTHC, others...	30	Various authors, 1974–2015
Total known cannabinoids = 125		

Note. CBCN = Cannabichromanone; CBF = Cannabifuran; CBR = Cannabiripsol; DCBF = Dehydrocannabifuran; OTHC = 10-oxo-$\Delta^{6a(10a)}$-tetrahydrocannabinol.

Adapted from Andre, Hausman, and Guerriero (2016); Appendino (2020); Elsohly and Slade (2005); Radwan et al. (2021); and Rock and Parker (2021).

in known CHS patients and also in CVS patients, possibly focusing on those who report a positive response to hot bathing. Yet, the low cost, ready availability, and benign safety profile for topical capsaicin use in this population overall has led some authors to support the routine consideration of this therapy even prior to the completion of more rigorous studies (Lapoint et al., 2018; Lee & Coralic, 2022; Stumpf & Williams, 2021).

Considerations for CBD

Cannabis (*C. sativa* sp.) represents a highly variable, primarily dioecious (having male and female forms), singular plant species that produces cannabinoid molecules (the phytocannabinoids) primarily within the flower of the female plant. Phytocannabinoids are a class of closely related molecules (the natural cannabinoids) that are isolated from the various strains of the cannabis plant (Radwan, Chandra, Gul, & ElSohly, 2021). The 125 known phytocannabinoids can be grouped into three broad categories: The CBD-type, the THC-type, and a miscellaneous class (see Table 2).

When cannabinoid molecules are consumed, some of them modulate the activity of the mammalian endocannabinoid system, first described in the early 1990s (Devane et al., 1992). Despite its relatively recent addition to human physiology studies, the endocannabinoid system is evolutionarily ancient originating from a common bilaterian ancestor around 500 million years ago and receptors are found within the entire animal kingdom (though with a secondary evolutionary loss of cannabinoid receptors in insects and some nematodes) (McPartland, Agraval, Gleeson, Heasman, & Glass, 2006).

In mammals, the primary endocannabinoid receptors are the G-protein coupled receptors cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2) along with six transient receptor potential (TRP) ion channel receptors (specifically $TRPV_{1\text{-}4}$, $TRPA_4$, and $TRPM_8$) (Muller, Morales, & Reggio, 2018). Two primary activating ligands, the endocannabinoids, engage with these receptors: *N*-arachidonoyl ethanolamine (anandamide or AEA) and 2-arachidonyl glycerol (2-AG). For nervous tissue, the activating ligands are produced on

demand at the postsynaptic terminal and undergo retrograde travel to activate CB_1 at the presynaptic terminal. This typically results in an inhibition of neurotransmitter release at that neuron. AEA and 2-AG also activate the postsynaptic receptor $TRPV_1$ leading to an increase in the postsynaptic ion current (Yin, Wang, & Zhang, 2019).

CB_1 is concentrated in the basal ganglia, hippocampus, and cerebellum, but with a notable absence in the lower brain stem sparing cardiac and respiratory depression effects (Hanus, 2009; Katona, 2009). In addition, skeletal and cardiac muscle tissue express CB_1 along with adipose tissue and cells of the hepatic, pancreatic, and reproductive systems (Peng et al., 2022).

The second primary cannabinoid receptor, CB_2, is located on the brain microglial cells and other cells of the immune system including the spleen, tonsils, thymus, T-cells, B-cells, natural killer cells, and macrophages (Cabral & Griffin-Thomas, 2009). Exogenous CB_2 activation primarily has anti-inflammatory effects including the downregulation of cytokine release, decreased nitric oxide and reactive oxygen production, and decreased cellular migration (Turcotte, Blanchet, Laviolette, & Flamand, 2016).

The cannabinoid receptors have a complex molecular structure, which allows for a single receptor to recognize multiple classes of compounds producing a variety outcome effects. The phytocannabinoids are chemically quite distinct from the endocannabinoids AEA and 2-AG (which are eicosanoids) and yet they engage with CB_1 and CB_2, as well as several of the TRP channels (Console-Bram, Marcu, & Abood, 2012).

The phytocannabinoid THC operates as a CB1 receptor agonist when consumed, yet THC does not have any known action on $TRPV_1$ (Darmani et al., 2014; Muller et al., 2018). Conversely, the second most common cannabinoid of the cannabis plant, CBD, is a negative allosteric modulator of CB_1 and as such CBD consumption can attenuate THC-related agonist effects including euphoria, tachycardia, anxiety, paranoia, hunger, and sedation (Boggs, Nguyen, Morgenson, Taffe, & Ranganathan, 2018; Chung, Fierro, & Pessoa-Mahana, 2019; Laprairie, Bagher, Kelly, & Denovan-Wright, 2015; Morgan, Freeman, Schafer, & Curran, 2010). At the CB_2 receptor, CBD operates as an inverse agonist leading to muted immune cell migration and anti-inflammatory effects (Pertwee, 2008).

Finally, CBD is a capsaicin–analog with direct agonist activity on $TRPV_1$ (Izzo & Sharkey, 2010; Pisanti et al., 2017). Because of its lack of agonism of CB_1 in particular, CBD is nonpsychoactive when consumed, and originally the molecule was considered an inert cannabinoid (Mechoulam & Shvo, 1963). Yet, subsequent studies have demonstrated CBD consumption to correlate with neuroprotective, antiemetic, anti-inflammatory, and antianxiety effects (Pisanti et al., 2017). Further evidence suggests that CBD has a potential therapeutic role in the treatment of cannabis use disorders by decreasing THC cravings and dependence use patterns (Babalonis et al., 2017; Crippa et al., 2013; Freeman et al., 2020; Russo & Guy, 2006; Shannon & Opila-Lehman, 2015; Zuardi et al., 2012).

Because of biological limitations within the cannabis plant, very high THC plant strains are unable to simultaneously produce significant amounts of CBD or any of the other minor cannabinoids to a measurable amount (Clarke & Watson, 2002). This is because both THC and CBD are produced through enzymatic synthase from a single precursor, cannabigerolic acid. Therefore, as the ratio of THC goes up, the percentages of CBD-type cannabinoids are pushed downward (de Meijer et al., 2003).

In the past four decades, through specialized cultivation intent on meeting market demands for increasing potency, the THC percentages of cannabis have doubled in both the U.S. and Europe with plant THC concentrations increasing by an average of 0.29% each year between 1970 and 2017 (Cascini, Aiello, & Di Tanna, 2012; ElSohly et al., 2016; Freeman et al., 2021). Retail cannabis stores commonly display flower THC percentages between 8% and 24% THC, with 28%–35% THC by dry weight representing the upper biological limit of the cannabis flower (Roberts, 2020; Weiblen et al., 2015). In further illustration of this trend, a recent Canadian study looked at hair samples from suspected CHS patients presenting to the ED and found high levels of THC and cannabinol (CBN—which is a degradation product of THC) but only trace to undetectable amounts of CBD, further confirming a paucity of CBD within the popular products of the recreational cannabis industry (Albert et al., 2019).

The notable absence of CBD in popular recreational cannabis products may explain, at least in speculation, an increased frequency of cannabis use disorders such as CHS. The specific mechanism of action for potential protective effects of CBD against the development of cannabis use disorders, including CHS, is unclear as the consumption of exogenous cannabinoids involves multiple receptor/ligand systems. These include the dopamine system, the opioid system, the endocannabinoid system, as well as serotonergic pathways, the TRP receptors of the neuro and somatosensory systems, and the process of hippocampal neurogenesis (Černe, 2020; Navarrete, García-Gutiérrez, Gasparyan, Austrich-Olivares, & Manzanares, 2021; Straiker, Dvorakova, Zimmowitch, & Mackie, 2018).

In contradiction to the hypothesis that the absence of protective effects from CBD may be significant to

the development of CHS, several authors have proposed that high-dose CBD may actually cause CHS citing a study by Parker, Kwiatkowska, Burton, and Mechoulam (2004) (Allen et al., 2004; Darmani, 2010; Galli, Sawaya, & Friedenberg, 2011; Rajaram Manoharan, Aggarwal, & Taneli, 2018; Venkatesan et al., 2020). These claims primarily stem from a partial misinterpretation of the animal study by Parker et al. (2004) that tested the effects of THC or CBD on lithium chloride (LiCl)-induced vomiting in the house musk shrew (*Suncus murinus*).

In the CBD arm of the study, 45 subjects were separated into five groups evaluating a range of CBD pretreatment doses on LiCl-induced vomiting. The CBD solution (dose range: 2.5 mg/kg to 40 mg/kg) was provided by intraperitoneal injection 10 minutes prior to the injection of LiCl toxin, plus there was one group to determine the emetic effects of high-dose CBD alone at 40 mg/kg ($n = 7$).

Cannabidiol had a biphasic therapeutic effect on induced vomiting in which it suppressed vomiting at low doses and enhanced vomiting at high doses, but when the maximal dose of 40 mg/kg CBD was injected alone, they concluded that "this dose of CBD does not produce vomiting in the shrew" (Parker et al., 2004, p. 158). So, in that study, high-dose CBD was less effective than THC in preventing lithium-induced vomiting and may have contributed to lithium-induced vomiting in a dose-dependent manner, but high-dose CBD did not cause vomiting by itself.

Finally, in 2018, the FDA approved Epidiolex (CBD) oral solution for the treatment of Lennox–Gastaut syndrome and Dravet syndrome, the first FDA-approved drug containing purified CBD from cannabis. The most common CBD adverse effects as listed in the Epidiolex prescription information include somnolence, decreased appetite, diarrhea, liver transaminase elevations, fatigue, malaise, asthenia, rash, insomnia, sleep disorders, and infections (Epidiolex, Full Prescribing Information, 2018), but not nausea and vomiting.

The treatment protocols for cannabis use disorders, such as cannabis dependency, are without effective pharmacological agents, and relapses after attempts at abstinence are high (Budney, Sofis, & Borodovsky, 2019). Therefore, in cannabis-dependent individuals who have developed cyclic vomiting and are unwilling to or fail in efforts to abstain from cannabis (which may be termed "intractable CHS"), transitioning from a THC-dominant to a CBD-dominant strain has theoretical promise, as does a consideration for the off-label administration of cannabidiol* solution. This is supported by (1) reports of CHS caused from the use of synthetic cannabis that mimics THC but not CBD, (2) increased incidence of CHS corresponding to increased market availability of very high THC strains that are generally lacking in CBD, (3) mounting research that demonstrates CBD to be antiemetic, antianxiety, anti-inflammatory, and neuroprotective, and (4) evidence that CBD exhibits an action on $TRPV_1$ similar to capsaicin both in vitro and in animal models (Pisanti et al., 2017).

Presently, no clinical studies have examined switching CHS patients to CBD-dominant strains of cannabis in those individuals unwilling or unable to cease their cannabis use (recognizing abstinence as gold standard treatment) (Rong et al., 2017). However, a recent survey evaluating a cohort of CVS patients from a specialty GI clinic did identify one patient with complete resolution of CVS symptoms after an abstinence from cannabis and a prior history of heavy cannabis use. The authors report, "This was the only cannabis-using patient in our study who could be reclassified as having CHS based on Rome IV criteria. This patient subsequently resumed using cannabis with a higher proportion of cannabidiol vs THC and reportedly remains episode-free" (Venkatesan et al., 2020, pp. 1087–1089).

Conclusion

Cyclic vomiting syndrome is a rare yet disabling syndrome with a long history within the GI literature. This syndrome afflicts both children and adults and may present either as an idiopathic (as in CVS) or an induced variation (with CHS), yet our understanding of the physiology for these two conditions and the levels of evidence supporting present treatment considerations are based primarily on case studies, retrospective review studies, and expert opinion collaborations. Future treatment RCTs as well as additional population-based epidemiological, longitudinal, and cohort studies are needed to advance our understanding of these two enigmatic and often severely disabling disorders. Further pathophysiologic and mechanistic studies involving the endocannabinoid system and its relationship to the capsaicin-receptor $TRPV_1$ are also needed, as well as evidence-based clinician understanding of the short-term and long-term effects of consuming phytocannabinoids, both positive and negative.

Although the present-day U.S. state-level legalization of cannabis has brought the discussion of cannabis and the endocannabinoid system into serious medical discussion, as well as public health consideration, healthcare providers still cannot make true evidence-based recommendations for, or against, cannabis use for their patients in many instances (such as using cannabis for CVS vs. cannabidiol* for CHS, for example). Significant regulatory barriers continue to preclude high-quality research involving cannabis, and healthcare organizations are hesitant, and often prohibited (because of receiving Medicare funding), from stepping beyond the U.S. federal stance of strict prohibition.

Changes to the present regulatory status of cannabis would provide opportunities for high-quality adequately funded research. These studies are needed for providers and patients to arrive at well-informed decisions concerning cannabis as a therapeutic, as well as to further develop best practice recommendations for treating GI classical conditions such as CVS and its affiliated cannabis use disorder, CHS. ✪

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