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REVIEW ARTICLE

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Role of chronic cannabis use: Cyclic vomiting syndrome vs cannabinoid hyperemesis syndrome

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Abstract

Cannabis is commonly used in cyclic vomiting syndrome (CVS) due to its antiemetic and anxiolytic properties. Paradoxically, chronic cannabis use in the context of cyclic vomiting has led to the recognition of a putative new disorder called cannabinoid hyperemesis syndrome (CHS). Since its first description in 2004, numerous case series and case reports have emerged describing this phenomenon. Although not pathognomonic, a patient behavior called "compulsive hot water bathing" has been associated with CHS. There is considerable controversy about how CHS is defined. Most of the data remain heterogenous with limited follow-up, making it difficult to ascertain whether chronic cannabis use is causal, merely a clinical association with CVS, or unmasks or triggers symptoms in patients inherently predisposed to develop CVS. This article will discuss the role of cannabis in the regulation of nausea and vomiting, specifically focusing on both CVS and CHS, in order to address controversies in this context. To this objective, we have collated and analyzed published case series and case reports on CHS in order to determine the number of reported cases that meet current Rome IV criteria for CHS. We have also identified limitations in the existing diagnostic framework and propose revised criteria to diagnose CHS. Future research in this area should improve our understanding of the role of cannabis use in cyclic vomiting and help us better understand and manage this disorder.

KEYWORDS

cannabis, cyclic vomiting, endocannabinoids, hot water bathing, hyperemesis, systematic review

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1 | INTRODUCTION

Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder that is characterized by recurrent episodes of severe nausea and vomiting and is currently defined by Rome IV criteria.[1] Cannabinoid hyperemesis syndrome (CHS) shares many clinical features with CVS except for its association with chronic, heavy cannabis use. CHS was first described in 2004 by Allen et al[2] in nine patients. This report was followed by several case series and individual case reports describing a similar pattern of episodic nausea and severe vomiting referred to as "hyperemesis."[3,4] Heavy cannabis use preceded the onset of symptoms in these patients, suggesting that chronic cannabis use leads to hyperemesis. A diagnostic framework for CHS was proposed, although there has been considerable variation in the diagnostic criteria used in the literature to define cases. This heterogeneity has led to significant controversy and uncertainty about CHS as a distinct entity.

The diagnosis of CHS is now made using Rome IV criteria which include stereotypical episodic vomiting resembling CVS occurring after prolonged, excessive cannabis use (Table 1). Notably, the criteria included cessation of vomiting episodes following sustained abstinence from cannabis to make this diagnosis, although it lacked more specific details about the duration required for symptom resolution. The pathological phenomenon of "hot water bathing" was a supporting criterion even though this behavior can also be seen in ~50% of patients with CVS who do not use cannabis. We discuss the strengths and limitations of the Rome IV framework for diagnosis and propose revised criteria for CHS in this article.

The prevalence of CHS in adults remains uncertain and is in large part due to the lack of consistent diagnostic criteria. A recent population-based study identified only seven cases of CHS when the newer Rome IV diagnostic criteria were applied.[5] In stark contrast, another study reported that nearly a third of daily or near-daily cannabis users presenting to the emergency department were identified as having CHS.[6] A major flaw in this particular study was that the authors defined CHS primarily on the reported use of hot showers/baths to relieve symptoms of nausea and vomiting. There were no data on the frequency of hot showers, frequency of vomiting, or even whether the vomiting was episodic in nature, which is a defining characteristic for both CVS and CHS. Previous studies clearly demonstrate that the "compulsive hot water bathing" pattern that frequently accompanies CHS is also commonly seen in adult patients with CVS who do not have cannabis use, as well as in those with chronic nausea and vomiting.[7,8] Thus, it is unlikely that all patients described in the study by Habboushe et al had CHS, and more rigorous criteria are needed to determine the true prevalence of CHS.

Gaps in knowledge about the basic features of CHS and the relationship of chronic cannabis use with cyclic vomiting require attention especially in light of the varied perceptions and beliefs of the risks and benefits of cannabis use. In addition, the concerted medical and recreational movements for cannabis liberalization and legalization will likely increase cannabis use in the future.[9,10] In this article, we will discuss the role of cannabis and the endocannabinoid system (ECS) in the regulation of nausea and vomiting, as it pertains to both CVS and CHS. We will then present an overview of the published

TABLE 1 Rome IV criteria for cannabinoid hyperemesis syndrome

Stereotypical episodic vomiting resembling (CVS) in terms of onset, duration, and frequency
Presentation after prolonged, excessive cannabis use
Relief of vomiting episodes by sustained cessation of cannabis use
Supportive remarks:
May be associated with pathologic bathing behavior (prolonged hot baths or showers).

Note: Criteria fulfilled for the last 3 months, symptom onset at least 6 months before diagnosis.

Key Points

- Cannabinoid hyperemesis syndrome (CHS) presents with cyclical emetic episodes mimicking cyclic vomiting syndrome after long-standing cannabis use, often with associated pathologic bathing behaviors and is currently diagnosed with Rome IV criteria.
- A systematic review of the literature on CHS shows significant limitations due to incompletely characterized case series and individual cases, especially with regard to follow-up, and variable diagnostic criteria which preceded development of Rome IV criteria.
- The limitations of the Rome IV criteria are discussed with proposed revisions to optimize future diagnosis of CHS.
- Future research in CHS focused on pathophysiology, clinical presentation and natural history is needed to ascertain whether CHS is a distinct entity or a subset of CVS.

literature on CHS and use this data to challenge the current concept that CHS is distinct from CVS. We also propose new strategies to enhance our understanding of CHS, and address controversies and knowledge gaps that exist.

2 | EFFECTS OF CANNABINOIDS IN THE REGULATION OF NAUSEA AND VOMITING

Cannabis has been used as medicine dating back to the Neolithic period. It has been recently used to alleviate multiple symptoms including nausea, vomiting, and pain, as well as for treating refractory seizures.[11-13] The mechanism of action of cannabis was not well understood until the early 1990s when the ECS was discovered.[14] The ECS consists of two primary endogenous ligands, N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), their receptors, and degrading enzymes. The cannabinoid receptors consist of the cannabinoid receptor type 1 (CB1R) and cannabinoid receptor type 2 (CB2R).[15] These receptors are distributed in both the central and the peripheral nervous systems and are present on presynaptic nerve terminals of both inhibitory and excitatory neurons.[16] Endogenous ligands are synthesized on demand during periods of stress and are important in the regulation and attenuation of nausea, vomiting, and stress. AEA is degraded by fatty acid amide hydrolase (FAAH), and 2-AG is degraded by monoacylglycerol lipase (MAG-lipase).[17]9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, exerts its effects primarily by acting on CB1R. [14,16]

Several preclinical and human studies indicate that cannabinoid receptor agonists (phytocannabinoids [ie, cannabis] and endocannabinoids [ECs]) inhibit peripherally and centrally initiated emesis through their actions on CB1R.[18,19] CB1Rs are densely distributed in areas of the brain such as the dorsal vagal complex, which is a critical part of the neurocircuitry that generates emesis.[20] Further, CB1R antagonists can initiate or worsen emesis.[21] The role of CB2R in nausea and vomiting is less clear. Studies of emesis in animals are particularly challenging as commonly used laboratory species such as rats and mice do not vomit. Thus, other species which do vomit, such as ferrets and shrews, are often used. However, most rodents exhibit "gaping" behaviors that appear to be induced by nauseogenic stimuli, and these behaviors are accepted surrogate markers for nausea.[22]9-tetrahydrocannabinolic acid (THCA), a precursor of THC, reduced lithium chloride-induced emesis in the musk shrew and also reduced "conditioned gaping" in rats.[23] This effect was reversed by administration of rimonabant, a CB1R antagonist. In contrast to humans, there were no psychoactive effects in rhesus monkeys with administration of THC up to 5 mg/kg, demonstrating different dose responses that produce anti-emetic effects vs psychomotor impairment among different species.[19]

Human studies also indicate that the ECS is involved in mediating nausea and vomiting. A study by Chouker et al[24] showed that subjects who were prone to motion sickness had lower endocannabinoid levels and reduced CB1R mRNA expression during simulated parabolic flight compared to those who did not have motion sickness. This suggests that a relative EC deficiency may be associated with disorders of nausea and vomiting and thus, conversely, augmenting ECs may be useful in relief of vomiting.[24] Following this, a study of the ECS and the hypothalamic-pituitary-adrenal (HPA) axis in CVS revealed an increase in EC levels during the emetic phase of the illness compared to the interepisodic phase.[25] However, how this increase in ECs compares to the response in normal subjects exposed to emetic stimuli remains to be determined; also, the same study showed an increase in salivary cortisol in CVS patients who used cannabis compared to non-users.[25] Whether this increase in salivary cortisol in cannabis users represents an adaptive or maladaptive response is unclear.

Taken together, these and other findings indicate that cannabinoid receptor agonists inhibit vomiting and that CB1 receptor antagonists initiate or potentiate vomiting. Thus, the ECS is well positioned to play a major role in both CVS and CHS. We speculate that the paradoxical effects of chronic cannabis may be caused by differential degrees of CB1R downregulation in genetically predisposed individuals. This potential mechanism is supported by studies in rats which show that CB1R downregulation occurs after prolonged and repeated exposure to cannabis inducing tolerance to its effects.[26] Postmortem studies in humans also demonstrate CB1R downregulation in the human brain with chronic cannabis use compared to non-users.[27] Other reasons for the paradoxical emetic effects of chronic cannabis use could be the result of increasing potency of cannabis (with higher ratios of THC to cannabidiol) and prolonged duration of use. It is likely that cannabis has a biphasic mechanism of action, where it has anti-emetic effects at lower or less frequent dosing but is pro-emetic at higher or more sustained doses. Additionally, cannabis also has peripheral effects and affects gastric motility in both animal and clinical models. Δ^9-tetrahydrocannabinol reduced rates of gastric emptying in mice and rats and caused a significant delay in gastric motility when administered to healthy volunteers, which may contribute to episodes of hyperemesis.[28,29] These findings are of clinical importance and must be considered if gastric emptying studies are performed in patients with disorders of cyclic vomiting who use cannabis.

3 | CANNABIS USE IN CVS AND CHS

Although cannabis is the most commonly used illicit drug in the United States,[30] the growing movement in support of cannabis use has led its legalization for medical purposes in 30 states and for recreational use in 10 states and the District of Columbia. Therefore, an increasing number of adolescents and adults are routinely exposed to cannabis in the United States. Though cannabis has >200 constituents, its psychotropic effects are primarily due to THC. Another compound found in cannabis, cannabidiol (CBD), also has acute antiemetic effects but does not share the psychotropic effects of THC.[31-34] Cannabis preparations commonly used for recreational use contain increasing amounts of THC (relative to CBD content), and these changes in THC:CBD ratio are thought to account for

the increasing toxicity associated with its use.[35,36] While cannabis preparations have been used for purported medical benefits as antiemetics, recent reports have linked its use with CHS.[3,10,37,38] CHS is now defined by Rome IV criteria shown in Table 1.[1]

There are ample data showing that many CVS patients resort to alternative therapies like cannabis to treat their symptoms. A study of 82 patients with CVS and functional vomiting showed that the use of cannabis was significantly higher in CVS (OR = 2.9 [1.2, 7.2], P = 0.02), compared to those with functional vomiting.[8] An Internet-based study of 514 patients with CVS showed that 81% used cannabis for its therapeutic potential.[7] A more recent study (unpublished data) used validated tools in a large cohort of CVS patients to characterize cannabis-use patterns and to ascertain the proportion of CVS patients who could be reclassified as having CHS based on recent Rome IV criteria.[39] Of 140 respondents, 41% were current cannabis users and 21% were regular users (defined as those using cannabis ≥ 24 times a week over the prior 6 months). Among all cannabis users, 88% reported abstaining from cannabis for at least one month, but only one user in this study reported subsequent resolution of CVS episodes. However, this particular patient subsequently resumed using cannabis and remains symptom-free.[39] Among this cohort, none of the patients met Rome IV criteria for CHS. This could be because the duration of abstinence from cannabis required for resolution of symptoms is greater than a month, and long-term studies will be needed to clarify this question. The absence of potential CHS cases in a well-characterized CVS cohort, when combined with the described case reports of CHS, raises important questions that warrant further investigation. For example: Why does cannabis relieve vomiting in some patients but exacerbate it in others? Is this phenomenon dose-related, due to a specific genetic predisposition or both? Does cannabis use drive a distinct emetic disorder, or does it trigger CVS attacks, thus representing a subset of CVS? It is possible that previously diagnosed cases of CHS are overestimates, and more systematic study will reveal the true prevalence of CHS.

4 | HEALTHCARE UTILIZATION FOR CYCLIC VOMITING FOLLOWING CANNABIS LEGALIZATION

With a growing interest in the use of cannabis for medical purposes, several studies have focused on healthcare utilization associated with cannabis use. In a retrospective cross-sectional study of ED visits in Colorado, there was nearly a doubling of the reported rate of cyclic vomiting cases in the year following marijuana legalization compared to the year prior.[40] However, the absolute number of cases in the postlegalization period was fairly low with a reported cyclic vomiting rate of ~0.07% of all ED visits. Using different methodology, a retrospective single-center study found that the presence of cannabis abuse was associated with a ~1.5-fold increase in median ED visits per year for vomiting, compared to those without cannabis abuse.[41] Finally, another study using the National Emergency Department Sample found that the rate of ED visits for vomiting among those with cannabis-use disorder increased more than ~5.5-fold between 2006 and 2013, reaching an absolute prevalence of ~13 per 100 000 ED visits. During this period, the individual ED visit costs were found to have increased 70% and the total aggregate costs for ED visits with vomiting in those with cannabis-use disorder in 2013 was about $83 million.[42] Clearly, there is some indication that the more widespread use of cannabis in the population has increased the number of cannabis-related cyclic vomiting episodes over time, even though the overall prevalence of cyclic vomiting among those regular cannabis users is fairly low. There also remains a possibility that the initial reports of CHS instigated more directed queries about cannabis use in adults who present to EDs with vomiting, leading to an apparent increase in related cases due to an ascertainment bias.

5 | CHS: SYSTEMATIC REVIEW

5.1 | Methods

We conducted a review of all cases diagnosed with CHS from January 2000 to March 2018. The objective of our study was to identify all articles relevant to the diagnosis of CHS and to determine what proportion of previously reported CHS patients would meet current Rome IV criteria for CHS. We obtained articles used in the original literature search by Monte et al using MEDLINE, Ovid MEDLINE, Embase, Web of Science, and the Cochrane Library from January 2000 through September 24, 2015.[43] Search terms included cannabinoids, cannabis, marijuana abuse, medical marijuana, tetrahydrocannabinol, hyperemesis, emesis, vomiting, cannabis addiction, medical cannabis and hyperemesis. This search had identified a total of 2178 articles, of which 183 articles were available for inclusion.

A second literature search was then repeated using the same search terms in the time frame of September 25, 2015-March 2018 in order to capture additional articles that were published after the original search by Monte et al. A total of 864 abstracts were reviewed, and articles relevant to the diagnosis of CHS were included. Those that primarily addressed treatment with capsaicin, duplicate articles, studies published in non-English journals, and those that were not relevant to CHS were excluded from analysis. Many patients in both the case series and individual reports had comorbid diagnoses that may have contributed to refractory nausea and vomiting, such as hyperemesis gravidarum, and these cases were also excluded. Patients presenting with only a single emetic episode or with attacks which could have been explained by other pathogenic factors were also excluded. The quality of the data was heterogenous with variations in diagnostic criteria, the reporting of cannabis use, and a specific follow-up period.

We (author TV assisted by YP) performed data abstraction on all these CHS cases including demographic data, cannabis-use patterns (duration and frequency of use), hot shower bathing patterns, and duration of follow-up. We then applied Rome IV criteria to both case series and individual cases to determine the number of patients who actually met the current Rome IV criteria for CHS. Rome IV criteria

require "*sustained* cessation of cannabis use resulting in resolution of symptoms" to make a diagnosis of CHS. However, since the Rome IV criteria do not specify the minimum required duration for abstinence from cannabis, we chose a minimum duration of at least a month (4 weeks) of abstinence from cannabis prior to the resolution of symptoms to make a diagnosis of CHS. This particular duration of time was chosen due to the prolonged 2- to 3-month elimination period that results from the lipophilic storage of cannabis in the setting of chronic use. Although this represented a reasonable minimum length of time to demonstrate improvement or resolution of symptoms following abstinence, this duration of time may still be insufficient as even after THC is cleared, restoration of CB receptor function may take even longer. Thus, patients may need to be followed for a length of time that equals at minimum three typical cycles or a period of 6-12 months to determine whether cannabis cessation truly results in durable resolution of symptoms.

6 | RESULTS

Our review of the literature identified a total of 25 case series (n = 271) and 105 individual case reports of patients identified with CHS (Table 2).[2,4,44-171] Most of the reported case series and case studies predated the publication of Rome IV criteria for CHS. Not surprisingly, these earlier reports had significant heterogeneity in the criteria used to define CHS cases. Some authors diagnosed CHS when patients presented with cyclic vomiting in the context of chronic cannabis use. Others used cyclic vomiting with hot shower bathing patterns as pathognomonic features of CHS.

In the case series totaling 271 patients ("case series"), the mean age was 30.5 ± 7.6 years and the majority of patients were male (186; 68.6%). The mean duration of cannabis use preceding onset of symptoms was 6.6 ± 4.3 years. Daily cannabis use was found in two-thirds (68%), and weekly cannabis use in about one-sixth (~16%) of patients. The frequency of cannabis use was not documented in 16% of the sample. The compulsive hot water bathing pattern was noted in 71.5% (194) of patients, with data not available in four patients. The mean age of patients in individual case reports ("case reports") was 29.4 ± 9 years, and these individuals were similarly composed mostly of males (72.3%). Duration of cannabis use among the case report group was 8.0 ± 8.4 years, and daily cannabis use was reported in 69.5%, very similar to the case series group. The hot water bathing pattern in the case report group was noted to be ~ 86%.

Among the case series and individual case reports, only 44/271 (16.2%) and 27/105 (25.7%) respectively had a follow-up period of at least ≥4 weeks. This precluded making a definite diagnosis of CHS (using Rome IV criteria) in the vast majority of cases series and case reports due to such inadequate follow-up. However, among those in both groups who were followed for at least 4 weeks, 86% of case series patients (38/44) and 78% of case report patients (21/27) with a total of 59/71(83%) met Rome IV criteria for CHS. Among all 376 cases, only 59 (15.7%) or approximately 1/6 of the cases of "CHS" reported in the literature met the Rome IV criteria for CHS.

In summary, the case series provided fewer clinical details on the patients with proposed CHS than did the individual patient reports. This was particularly evident in the larger series by Simonetto et al (98 patients) and Schreck et al (29 patients), in which details regarding cannabis cessation were difficult to extract.[4,164] Follow-up of patients following abstinence from cannabis was also missing in most of the case series and case reports, a major limitation that questions the validity of the diagnosis of CHS in many of these cases. Future reports describing CHS should include greater rigor in characterizing symptom improvement or resolution with prolonged and documented (eg, toxicology screening for THC) cannabis abstinence to better understand the disorder and to avoid inappropriately invoking this diagnosis when other conditions may be causative of symptoms.

In general, the low numbers of patients who fulfilled Rome IV criteria for CHS in the reported case series and reports resulted largely from inadequate outcome data and length of follow-up. These long-term outcomes data were not systematically captured in previous studies due to the lack of overall diagnostic framework and were admittedly difficult to capture in acute care settings. This likely led to an overestimate of CHS. Transitioning to a more nuanced and defined diagnostic framework will enable a better understanding of the association between cannabis and CHS.

7 | DIAGNOSIS OF CHS

The diagnostic criteria used for CHS have been heterogenous leading to significant confusion about what constitutes CHS and even whether it a separate entity. While *the Rome IV criteria lay a framework for making a diagnosis of CHS, it has limitations and thus warrants iterative revision. The CVS Guidelines Committee proposes a revised set of criteria to optimize the diagnostic accuracy of CHS*. Our proposed revised criteria are shown below in Table 3. There was consensus among the majority of committee members regarding the proposed revised criteria. These criteria provide more specific details regarding patterns of cannabis use and in particular the duration of follow-up required for establishing the diagnosis, which are not adequately specified in the Rome IV criteria. Our proposed criteria were developed following a review of the available literature, properties of cannabis and our cumulative knowledge of purported CHS. Both the case series and individual case reports support our proposed revised criteria.

Cyclic vomiting episodes following chronic cannabis use are required for a diagnosis of CHS. In contrast to Rome IV, we have specified that at minimum, cannabis use of >4 times/week for at least a year preceding the onset of cyclic vomiting is necessary for the development of CHS. This is supported by current literature showing that prolonged, high-dose cannabis use precedes development of CHS in the majority of described cases. Most patients in both the case series and case reports reported daily cannabis use for more than a year. Patients using <4 times/week are "occasional cannabis users" and should not be considered to have CHS. Data describing amounts, potency, and routes of cannabis used were less complete,

TABLE 2 Review of case series and individual case reports of cannabinoid hyperemesis syndrome

	Article	n	Age (mean ± SD)	Gender/male n (%)	Years of cannabis use prior to onset of CVS symptoms (mean ± SD)	Cannabis-use patterns	Hot water bathing	No. of patients with follow-up of at least 1 month n (%)	Duration of follow-up (in months)	No. who met Rome IV criteria n (%)
1.	Allen (2004)	9	NA	7 (77.8)	8.9 ± 8.6	Daily = 100%	8 (88.%)	7 (77.8%)	20.6 ± 4.7	7 (77.8)
2.	Swanson (2005)	2	37.5 ± 17.7	2 (100)	NA	NA	NA	1 (50%)	3.0[a]	1 (50)
3.	Chang and Windish (2009)	2	24 ± 1.4	1 (50)	4.5 ± 3.5	Daily: 100%	100%	NA	NA	0 (0)
4.	Soriano (2010)	8	32.4 ± 4.1	5 (62.5)	16.4 ± 4.0	Daily: 100%	100%	4 (50%)	3.3 ± 2.6	4 (50)
5.	Patterson (2010)	4	30.3 ± 9.6	4 (100)	9.8 ± 10.4	Daily: 100%	100%	2 (50%)	7.0 ± 7.0	1 (25)
6.	Miller (2010)	2	17.5 ± 0.7	1 (50)	1.0 ± 1.4	Daily = 100%	100%	2 (100%)	1.5 ± 0.7	2 (100)
7.	Oruganti (2010)	20	19-65	14 (70)	NA	NA	17/20 (85%)	NA	NA	0 (0)
8.	Donnino (2011)	3	32 ± 1 6.5	3 (100)	1.5 ± 0.7 One patient: data NA	Daily: 100% One patient: data NA	100%	2 (66.7%)	7.0 ± 2.8	2 (66.7)
9.	Manuballa (2011)	4	46 ± 3.4	3 (75)	NA	Daily: 100%	100%	NA	NA	0 (0)
10..	Simonetto (2012)	98	32.3 ± 9.9	66 (67)	≤1:32% 2-5:44% 6-10:11% ≥11:13%	≤ 1 time/week: 5%, 1-3 times/week: 20%, 4-6 times/week: 16%, Daily: 59%	57 (58%)	10 (10.2%)	1-3 (range)	6 (6.1)
11.	Nicolson (2012)	4	23.3 ± 3.0	2 (50)	4.3 ± 3.9	Daily: 100%	100%	1 (25%)	3[a]	1 (25)
12.	Martinez (2012)	9	30	8 (88)	NA	Daily: 88%	56%	No follow-up	NA	0 (0)
13.	Masri (2012)	4	26.2 ± 5.6	4 (100)	6.0 ± 4.2 (2 patients: data NA)	Daily = 50%	100%	No follow-up	NA	0 (0)
14.	Torka (2012)	2	34.5 ± 20.5	2 (100)	1.1 ± 1.2	Weekly = 100%	100%	No follow-up	NA	0 (0)
15.	Perrotta (2012)	20	30 ± 10	10 (50)	NA	Daily: 100%	70%	No follow-up	NA	0 (0)
16.	Sofka (2013)	4	26.2 ± 3.5	3 (75)	8.4 ± 1.9	Daily: 100%	100%	NA	NA	0 (0)
17.	Williamson (2014)	2	29 ± 14.1	2 (100)	8.0 ± 8.5	Daily = 100%	100%	No follow-up	NA	0 (0)
18.	Braver (2015)	2	39 ± 7.1	2 (100)	NA	Daily: 100%	100%	NA	NA	0 (0)
19.	Sawni (2015)	2	15.5 ± 0.7	0 (0)	NA	One patient : 2 to 3 times/week other patient: data NA	100%	NA	NA	0 (0)
20.	Bertolino (2015)	6	35.2 ± 6.2	3 (50)	8.6 ± 6.2 One patient: data NA	Daily = 100%	100%	5 (83.3%)	4.2 ± 2.3	4 (66.7)
21.	Ruffle (2015)	10	27 (median)	5 (50)	3.5 (median)	NA	80%	10 (100%)	9.5 (median)	10 (100)
22.	Soota K. Lee (2016)	2	44.5 ± 4.9	2 (100)	Patient 1: 10; Patient 2: data NA	NA	NA	Not applicable	Not applicable	0 (0)
23.	Marillier (2017)	19	29.8	16 (84.2)	8.5 ± 6.8	Daily = 100%	89.5%	NA	NA	0 (0)

(Continued)

TABLE 2 (Continued)

	Article	n	Age (mean ± SD)	Gender/male n (%)	Years of cannabis use prior to onset of CVS symptoms (mean ± SD)	Cannabis-use patterns	Hot water bathing	No. of patients with follow-up of at least 1 month n (%)	Duration of follow-up (in months)	No. who met Rome IV criteria n (%)
24.	Pelisser (2017)	4	23.5 (median)	3 (75)	NA	NA	75%	NA	NA	0 (0)
25.	Schreck (2018)	29	25.8	18 (62)	2	Daily = 100%	55.2%	NA	NA	0 (0)
	Case reports[b]	105	29.4 ± 9.09; 4 patients, data NA	76 (72.3)	63 patients = 8.02 ± 8.42; 42 patients = data NA	73/105 patients had daily cannabis use = 69.5%; 3 patients had weekly cannabis use; 29 patients, data NA	90/105 patient = 86%; 9 patients: data NA	27 (25.7%) 73 patients: data NA 5 patients: < 4 weeks of follow-up	8.2 ± 18.9 73 patients: data NA	Total number of patients who met Rome IV criteria = 21/105; 20%

Notes: [a]STD is not reported in cases where data is available for only a single patient in this case series.
[b]Represents the cumulative synthesis of individual case reports, NA—not available.

and we propose that future data collection be standardized and comprehensive with details regarding cannabis use (Table 4). This will be important as there may exist thresholds for cannabis use (ie, by duration, route, frequency of use, and/or dosing), which can lead to hyperemesis in individual patients.

Other important considerations included length of follow-up after abstinence from cannabis. Ongoing evaluation in an outpatient setting to assess response to abstinence from cannabis, prior to making a diagnosis of CHS is critical given the episodic nature of the illness. For example, a patient who experienced 3 cycles/year while regularly using cannabis would need to be followed for at least one year after abstinence from cannabis to establish a diagnosis of CHS. Similarly, a patient with an episode every 6 weeks would need to be followed for ~4-5 months after cannabis cessation. Because CHS and CVS both consist of self-limiting episodes of emesis, it is crucial that the clinician who encounters a patient with possible CHS recognizes the need to establish causality prior to ascribing this diagnosis. The exact length of time that one would need to abstain from cannabis before resolution/reduction of CVS episodes occurs is not known as this will likely depend on the duration, quantity, and potency of cannabis use and genetic factors that could influence the response to cannabis use in individual patients.[172,173]

We acknowledge that maintaining complete abstinence from cannabis can be a challenge given patient perceptions and beliefs about cannabis use and its potential therapeutic benefits. A limitation of both the Rome IV criteria and our proposed criteria is the challenge with patients who cannot or are reluctant to stop cannabis due to perceived benefits. In this instance, careful consideration of the quantity of cannabis used (daily vs occasional use) and screening for cannabis-use disorder should be undertaken. A presumptive diagnosis of CHS may be considered when chronic (>1 year), daily use is encountered in the context of cyclic vomiting, and a failure to respond to standard prophylactic agents. Treatment for CVS with TCAs and ongoing care by an experienced team with counseling to reduce and ultimately stop cannabis use is recommended. Avoiding a confrontational and judgmental approach and establishing a rapport with the care team is crucial to achieving good patient care outcomes.

Future systematic studies on cannabis and its role in vomiting disorders like CVS and CHS should guide and inform recommendations regarding its medicinal and recreational use. Several important questions about the exact duration and amount of cannabis and genetic factors that predispose to hyperemesis are not known. Future studies involving patterns of cannabis use and genetic variants which potentially cause or exacerbate vomiting should help us better understand this disorder. Such human studies are particularly important as animals such as rats and mice used in preclinical studies do not vomit, which makes research in this area challenging.

The diagnosis of CHS can not only be stigmatizing (akin to migraine sufferers mislabeled as acute opioid seekers) but has resulted in some providers withholding symptomatic care and potentially effective therapies.[174] The significant impact that this stigma has on individual patients, their families, and the entire healthcare system

TABLE 3 Proposed new diagnostic criteria for cannabinoid hyperemesis syndrome (CHS)

Clinical features	Stereotypical episodic vomiting resembling CVS in terms of onset, and frequency ≥3 episodes a year
Cannabis-use patterns	Duration of use >1 y preceding onset of symptoms Frequency of use >4 times a week on average
Cannabis cessation	[a]Resolution of symptoms should follow a period of cessation from cannabis for a minimum of 6 mo or at least equal to a duration that spans three typical cycles in an individual patient

Note: [a]Patients unwilling or unable to abstain from heavy cannabis use pose a diagnostic challenge and may be considered to have presumed CHS.

TABLE 4 Proposed data collection sheet for cannabinoid hyperemesis syndrome

1	Demographics
2	Vomiting episodes: a date of onset b frequency of vomiting episodes over the previous 12 mo and since onset of symptoms c duration of typical episode, presence of symptoms including headache abdominal pain d hot water bathing patterns and symptomatic response e duration of coexistent inter-episodic quiescent intervals
3	Cannabis use: a duration of cannabis use preceding onset of symptoms b frequency of cannabis use c type and potency (when available) of cannabis products d routes of use (smoked, oral, vaping etc.)
4	Comorbid conditions – a anxiety b depression c panic d migraine
5	Prior treatment and efficacy
6	Follow-up periods defined by absolute time (ie, at least 6 mo) or by a duration of time defined by patient cycle length (ie, at least three successive cycles in an individual patient).
7	Periods of abstinence measured by number of weeks and monitoring with urine toxicology screens when feasible

cannot be overemphasized. As with other drugs of abuse such as nicotine, research and efforts on a national scale are needed to educate and inform the public to achieve better outcomes. This also underscores the need for a multidisciplinary approach with incorporation of experts in mental health and substance abuse in the care team for this challenging group of patients.

8 | IS CHS A SEPARATE ENTITY?

8.1 | Epidemiology and clinical features

The striking similarities between CVS and CHS suggest that CHS may in fact represent a subset of CVS rather than being a distinct disease. To be considered separate conditions, CHS and CVS must affect different patient populations or exhibit differentiating clinical features, longitudinal courses, and/or responses to disease-specific therapies which would benefit one but not the other condition. The pathogenic importance of cannabis as a cause or trigger of nausea and vomiting syndromes is supported by recent epidemiologic findings showing 8% yearly increases in hospital discharges for persistent vomiting after cannabis legalization compared to the prelegalization era.[175] However, this may be due to a recognition bias, as the pattern of cyclic vomiting was not recognized by >80% of the time by (ED) physicians.[176] Of note, the same study indicated that a treatment protocol for CVS was available to ED physicians only in a minority of cases. This underscores the importance of having a specific protocol for management of CVS in an acute care setting, which can aid ED physicians streamline management of CVS in the future. It is possible that the liberalization and legalization of cannabis, with the concomitant media exposure, has inadvertently highlighted this previously unrecognized pattern of cyclic vomiting, leading to increased recognition of this pattern diagnosed as CHS over the last decade.

Are there clinical features that reliably distinguish CHS from CVS? Both disorders commonly affect young people. Overall, there is a male predominance to CHS, which reflects greater use of cannabis products among men. Some studies have shown that CVS is more common in women, but there have been mixed results regarding gender predilection.[177-180] Abdominal pain is considered by some to be essential for CHS diagnosis, but pain is also reported by a substantial proportion of patients with CVS.[181] More significantly, CHS has been prominently linked to a pattern of hot bathing or showering to relieve symptoms. This unusual behavior has been included by some as a mandatory criterion for CHS diagnosis.[4] One retrospective study commented that "the ability of hot water bathing and showering to

mitigate symptoms" is the most defining characteristic of CHS while a second small series commented that these behaviors are "pathognomonic" for CHS.[6,182] However, nearly 10% of CHS patients do not report this behavior even in articles which claim hot bathing to be essential for diagnosis.[4,43,174] The specificity of this behavior was rejected in a recent comparison study in which 48% of CVS patients with no cannabis use reported symptom relief with hot baths or showers compared to 72% who used cannabis.[7] This hot water bathing behavior has been observed in preadolescent children and adolescents with no exposure to cannabis (BUK Li and D Fleisher, personal communication). Thus, although the majority of studies show that chronic cannabis use is significantly associated with hot water bathing, this association is not pathognomonic of cannabis use.[5]

Both CHS and CVS are characterized by episodes of severe nausea, vomiting, and often abdominal pain that are relentless and can often be debilitating. They are typically self-limited in nature with or without supportive therapy. These and other similar clinical features support our hypothesis that CHS is a subset of CVS where chronic cannabis use either unmasks or propagates symptoms in individuals who are predisposed to develop CVS. However, many reports of CHS include patients presenting for the first time with vomiting (often associated with other potential causes of emesis like pregnancy).[45,170] Given the limited details provided, these observations reflect primarily the inadequacies of the published reports. However, they also raise the possibility that chronic cannabis use can cause symptoms of nausea and vomiting that are not episodic in pattern, and thus would clearly be distinct from CVS. This possibility would need to be confirmed or refuted in future series, perhaps best addressed in a matched cohort study.

8.2 | Treatment options for CHS

It has been contended that patients with CHS do not respond to standard therapies used for CVS.[183] One report determined that chronic cannabis users with CVS respond less often to prophylactic treatment with tricyclic antidepressants compared to those not on cannabis.[184] However, no multivariate comparisons were performed, and other known confounding factors (use of opioids and associated psychiatric comorbidities) that are associated with poor responses to TCAs were not considered. Conversely, another case series of patients with CVS with high proportions of cannabis users reported >80% response rates to tricyclic medications.[185] Moreover, Venkatesan et al in another series which applied multivariate regression analysis did not observe differences in response rates to standard prophylactic agents like TCAs in patients with CVS based on cannabis use.[181] Very little rigorous study has been devoted to use of prophylactic treatment of CHS, with no definitive indication that CHS requires a specific pharmacological approach distinct from that used for CVS prophylaxis. Based on these observations, we recommend that patients with moderate-to-severe cyclic vomiting that use cannabis be offered the same prophylactic medical therapies offered to patients with CVS.

Limited responses to abortive antiemetic medications are often mentioned in articles on CHS, while others report excellent responses to parenteral benzodiazepines ($GABA_A$ agonists) such as lorazepam, the neuromodulator olanzapine, or the potent D_2 antagonist haloperidol—an agent with overlapping pharmacology to many commonly used antiemetic including prochlorperazine and metoclopramide.[164,183,186] Prior studies have proposed selective benefits of topical capsaicin treatments for acute CHS attacks, potentially acting in similar fashion as hot baths.[162,187 182,187,188] However, similar treatments have not been employed for patients with CVS without cannabis exposure, so the specificity of these benefits for CHS is uncertain. Because of the paucity of investigations supporting or refuting the use of other CHS therapies, it is imperative that patients with possible CHS are not denied prescription of prophylactic or abortive treatments which benefit patients with CVS.

The treatment of CHS has focused on cannabis cessation leading to resolution of symptoms. The most comprehensive series to date by Allen et al followed patients for more than 2 years and given that duration we surmise that cannabis cessation did indeed result in resolution of vomiting episodes. However, many articles describe brief periods of abstinence from cannabis as short as a few days of hospitalization, which are not meaningful and challenge their validity in support of a diagnosis of CHS. When more stringent criteria have been applied, very few patients with purported CHS report symptom reduction lasting more than 3 months and almost no publications describe improvements for at least two typical cycles of episodic emesis. This highlights the limitation of the current CHS literature as there is an ascertainment bias and potential overattribution which could call into question the CHS diagnosis in some who have been told they have the condition. On the other hand, application of the Rome IV criteria could lead to an underestimate if follow-up is inadequate or if patients are unwilling to stop cannabis. Furthermore, symptom resolution following cessation of cannabis could be confounded by unrelated spontaneous resolution of symptoms which would muddy the apparent causal interpretation. In children with CVS, after 4 years of illness, spontaneous resolution (ie, off medication) occurs in 50%.[189] Although continued remission off medications has been described in adults, how often this occurs remains unknown due to the limited long-term follow-up data and persistent use of medication in adults with CVS.[190] Future reports describing CHS should include greater rigor in characterizing symptom improvement with prolonged cannabis abstinence to avoid inappropriately making this diagnosis.

9 | CONCLUSIONS

In summary, when the literature is taken as an aggregate, while there are some differences in the demographic profile (males vs female predominance) there is considerable overlap in the acute presentations of CHS and CVS. Our review of the literature reinforces our proposal that CHS is a subset of CVS in which chronic cannabis use triggers symptoms in patients who are genetically predisposed to develop CVS. Future studies should focus on standardized collection of data including cannabis-use patterns and accurate phenotyping and genotyping

of patients with CVS and CHS. Specifically, the potency of cannabis used, and antecedent duration and frequency of use should be characterized to assess its impact. Patients with presumed CHS should be advised to abstain from cannabis and should receive ongoing care from a multidisciplinary team including mental-health and substance-use experts. These patients should concomitantly be offered standard care with prophylactic and abortive therapy similar to patients with CVS. This is critical given the gaps in our knowledge about the pathophysiology, diagnosis and management of CHS and the stigma that is associated with such a disorder. Future studies should also focus on elucidating the underlying pathophysiology such as the role of the ECS and the HPA axis in both CVS and CHS. This should advance our knowledge in this area and help in the development of novel and targeted therapies. Government and industry-sponsored funding along with participation from patient advocacy groups such as the Cyclic Vomiting Syndrome Association (CVSA) are vital to achieve our goals of better understanding and treating this debilitating disorder.

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AUTHOR CONTRIBUTIONS

TV, BL, DL, WH, SJ, ST, KA, IS, RI, ST, RS, and AM analyzed data; CS collated and performed the literature search; TV, BL, WH, DL wrote the paper. All authors critically reviewed the manuscript.

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