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REVIEW

Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment—a Systematic Review

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Abstract Cannabinoid hyperemesis syndrome (CHS) is a syndrome of cyclic vomiting associated with cannabis use. Our objective is to summarize the available evidence on CHS diagnosis, pathophysiology, and treatment. We performed a systematic review using MEDLINE, Ovid MEDLINE, Embase, Web of Science, and the Cochrane Library from January 2000 through September 24, 2015. Articles eligible for inclusion were evaluated using the Grading and Recommendations Assessment, Development, and Evaluation (GRADE) criteria. Data were abstracted from the articles and case reports and were combined in a cumulative synthesis. The frequency of identified diagnostic characteristics was calculated from the cumulative synthesis and evidence for pathophysiologic hypothesis as well as treatment options were evaluated using the GRADE criteria. The systematic search returned 2178 articles. After duplicates were

removed, 1253 abstracts were reviewed and 183 were included. Fourteen diagnostic characteristics were identified, and the frequency of major characteristics was as follows: history of regular cannabis for any duration of time (100%), cyclic nausea and vomiting (100%), resolution of symptoms after stopping cannabis (96.8%), compulsive hot baths with symptom relief (92.3%), male predominance (72.9%), abdominal pain (85.1%), and at least weekly cannabis use (97.4%). The pathophysiology of CHS remains unclear with a dearth of research dedicated to investigating its underlying mechanism. Supportive care with intravenous fluids, dopamine antagonists, topical capsaicin cream, and avoidance of narcotic medications has shown some benefit in the acute setting. Cannabis cessation appears to be the best treatment. CHS is a cyclic vomiting syndrome, preceded by daily to weekly cannabis use, usually accompanied by symptom improvement with hot bathing, and resolution with cessation of cannabis. The pathophysiology underlying CHS is unclear. Cannabis cessation appears to be the best treatment

Keywords Cannabinoid hyperemesis syndrome · Cyclic vomiting syndrome · Cannabis · Marijuana

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Introduction

The United Nations reported that 277 million people worldwide have used cannabis—roughly 4.9% of the total population [1]. In 2014, 22.2 million Americans aged 12 or older (8.4% of the population) were current cannabis users [2]. Cannabis policy in the USA is undergoing a transformation; following the 2016 elections, 26 states and Washington D.C. currently have laws legalizing cannabis in some form, and

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three other states are soon to adopt legislation. Seven states and Washington D.C. now allow some form of recreational use [3] . Cannabis has been approved for treatment of a range of medical conditions including nausea and vomiting due to chemotherapy, appetite stimulation in HIV/acquired immuno-deficiency syndrome (AIDS), chronic pain, spasticity due to multiple sclerosis, depression, and many more [4] depending upon state laws. Adverse effects from cannabis, from both recreational and medical use, have been reported for decades, though reports have increased with increased cannabis access [5]. Among the more common adverse effects is the cannabi-noid hyperemesis syndrome (CHS), first reported in 2004 [6]. CHS is a syndrome of cyclic vomiting in the setting of chron-ic, high-dose cannabis use that is frequently associated with compulsive hot baths/showers, used in attempt to control symptoms.

Patients with CHS present frequently to various health care settings with intractable nausea and vomiting. These patients often undergo expensive medical testing, may require hospital admission for symptom management, and often experience sig-nificant delays in diagnosis [7]. CHS is under-recognized due to a combination of factors including the paradoxical use for treat-ment of nausea and vomiting, the stigma associated with can-nabis use, and the illegal status of cannabis in many regions leading to under-reporting of use. The frequency of emergency department visits and high rates of hospital admission for CHS exemplify the difficulty in symptom management. The lack of knowledge and treatment recommendations regarding CHS compounds this issue. Subsequently, CHS is a costly illness to manage. In an observational study of CHS patients followed over 2 years, the median charge for ED visits and hospital admissions was $95,023 (IQR = $62,420–$268,110) [7].

Cannabis has presumably been used by humans for thousands of years, [8] yet CHS is only now being recog-nized. CHS has been reported numerous times in [9–11] large case series, small case series, and more than 80 individual case reports [6, 8, 11–82]. There are many sug-gested pathophysiologic mechanisms of CHS, though ev-idence for each is minimal (see Table 3). It is not clear why cannabis appears to suppress emesis under certain circumstances and induces it in others. It is also unknown why only some individuals develop CHS when the use of cannabis is so widespread.

Given the relatively new recognition of CHS as a clinical syndrome, diagnosis and treatment practices vary widely. Many authors have proposed diagnostic criteria (see Table 7), but it is unclear if these criteria consistently capture patients with the diagnosis. Additionally, criteria vary signif-icantly, which may contribute to diagnostic uncertainty among providers. Therefore, our objectives are to summarize and evaluate the available scientific evidence on CHS diagnosis, pathophysiology, and treatment utilizing systematic literature review methodology.

Materials and Methods

Search Strategy

The systematic review was performed utilizing the PRISMA guidelines [83]. Relevant publications were identified by searching the following databases: MEDLINE (via PubMed, Ovid MEDLINE (1946-current), Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Ovid MEDLINE Daily), Embase (via Embase.com), Web of Science, and the Cochrane Library (via Wiley Online Library). Publication date was limited from January 2000 through articles indexed in the databases as of September 24, 2015. English language limits were applied, and human and animal studies were included. Multiple subject headings (including Medical Subject Headings (MeSH) terms in MEDLINE and Emtree terms in Embase) and text words were used to identify each concept (cannabinoids and hyperemesis) and develop the search strat-egies (see Appendix for a list of all database search strategies). Additional records were identified through the following sources: ClinicalTrials.gov, ProQuest Dissertations & Theses (which includes COS Conference Papers Index; ProQuest Dissertations & Theses: UK & Ireland; ProQuest Dissertations & Theses A&I), and conference proceedings and meeting abstracts available online since 2000 from North American Congress of Clinical Toxicology, American Academy of Clinical Toxicology, American College of Medical Toxicology, and Society for Academic Emergency Medicine. The references of included studies were cross-ref-erenced, and additional studies not identified by the initial search strategy were added. The references of included studies were cross-referenced, and additional studies not identified by the initial search strategy were added.

Study Selection

Two reviewers (CS and AM) independently reviewed all titles generated by the search to identify potentially relevant articles. Duplicates were removed. Articles that were clearly not rele-vant based on title and abstract were excluded. The full text of all relevant articles were obtained and reviewed. The articles were then segregated into diagnosis, pathophysiology, or treatment categories. The articles were eligible for inclusion under the category of "diagnosis" if they (1) directly studied the criteria used to diagnose CHS from a population or case-based perspective or (2) presented a specific set of diagnostic criteria to define CHS as part of a larger research question or (3) presented a case or cases of CHS and explained the diag-nostic criteria used to identify these patients. Articles eligible for inclusion under the category of "pathophysiology" were those that (1) used animal, human, or in vitro models to ex-plore the pathophysiology of CHS or cyclic vomiting or (2) animal or human studies that investigated the role of the

endocannabinoid system in vomiting. Articles eligible for inclusion under the category of "treatment" were those that (1) presented results of treatment outcomes using specific interventions, both behavioral and pharmacologic, to manage CHS or (2) used animal studies to evaluate treatments for CHS or cyclic vomiting. When the two reviewers disagreed on article eligibility, a consensus was reached through discussion.

Data Collection

The reviewers assigned each included article to nonexclusive groups of diagnosis, pathophysiology, or treatment. Relevant study characteristics were abstracted including study design and primary findings.

The following data, when available, were extracted from each case report or case series: sample size, gender, age at presentation, age of first cannabis use, age at CHS symptom onset, duration and frequency of cannabis use, presence of cyclic vomiting, presence of abdominal pain, weight loss, presence of compulsive hot baths/showers, response to trial of abstinence, time to improvement of symptoms with abstinence, and amount of weight loss, if present.

Reviewers identified hypotheses to explain the pathophysiology of CHS. For each mechanism proposed, reviewers explored the supportive evidence and the study design.

Similarly, reviewers identified treatment modalities proposed for CHS. For each treatment modality, reviewers explored the evidence and the study design.

Assessment of Study Quality

The strength and quality of each study were evaluated using the GRADE working group metrics [83]. Grading and Recommendations Assessment, Development, and Evaluation (GRADE) defines high-quality studies as randomized trials or double-upgraded observational studies. Moderate-quality studies are defined as downgraded randomized trials or upgraded observational studies. Low-quality studies are defined as double-downgraded randomized trials or observational studies. Very low-quality studies are defined as triple-downgraded randomized trials or downgraded observational studies or case series/case reports.

The quality of evidence for each main outcome of this systematic review was evaluated using the GRADE working group metrics [83]. High-quality outcomes are defined as those for which further research is very unlikely to change our confidence in the estimate of effect. Moderate-quality outcomes are defined as those for which further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low-quality outcomes are those for which further research is very likely to have an important impact on our confidence in the estimate of effect

and is likely to change the estimate. Very low-quality outcomes are those for which any estimate of effect is very uncertain.

Data Analysis

Data were extracted from individual case reports and summarized as a single large cohort (individual case report synthesis). Next, after exclusion of duplicate cases, the individual case reports were combined with data from the case series and summarized as a single larger cohort (cumulative synthesis). Median values (plus interquartile range) were calculated for age at diagnosis, cannabis use age of onset, and age at symptom onset. The duration of cannabis use prior to symptom onset was categorized as either less than or equal to 1, 2 to 5, 6 to 10, and greater than 11 years. The amount of cannabis consumed was categorized as either less than daily, daily, weekly, less than weekly, or dose not specified. Cannabis use reported as "heavy" was interpreted to mean "daily." Cannabis use reported as "frequent" was interpreted to mean "weekly." The presence of cyclic vomiting, abdominal pain, relief with compulsive hot baths/showers, relief with abstinence, and ongoing symptoms with ongoing cannabis use was determined from each article and summarized as percentages of the total number of patients where the specific symptom category was documented.

The frequency of each individual proposed diagnostic characteristic was calculated by dividing the total number of CHS patients manifesting that characteristic (from the cumulative synthesis) by the total number of patients for which that diagnostic characteristic was reported.

Results

The systematic search returned 2154 articles. Twenty-four additional articles were identified through the bibliographies of articles returned in the primary search. After removal of duplicates, 1253 abstracts were independently screened by reviewers, of which 170 satisfied criteria for inclusion. The low quality of the articles precluded meta-analysis.

There was a significant overlap in the sorting of articles into the categories of diagnosis, pathophysiology, and treatment. Thus, some articles were classified in more than one category. We identified 116 articles related to diagnosis, 61 to pathophysiology, and 13 to treatment. There were 24 animal studies related to pathophysiology [84–107]. No animal studies were identified that addressed diagnosis or treatment. There were 88 case reports and 8 case series of four or more patients. Of the 88 case reports, 8 were excluded secondary to inability to access the original text, the report being published in a non-English language or if the case did not ultimately yield a clinical diagnosis of CHS as reported by the authors

Table 1 Overview of case series, individual case report synthesis, and cumulative synthesis

Article	Sample (n)	Male n (%)	Female n (%)	Age (years) at diagnosis median (IQR)	Cannabis use age (years) of onset median (IQR)	Age (years) at symptom onset median (IQR)	Duration of cannabis use (years) prior to symptom onset median (IQR)	Cannabis use n (frequency of use)	Cyclic vomiting n (%)	Abdominal pain n (%)	Relief with hot bathing % (n/total queried)	Relief with abstinence or reduction % (n/total queried)
Simonetto* [12]	98	66(67)	32(33)	Mean = 32.3 (±9.9)	na	Mean = 25.3 ±8.9 (n = 98)	32 (≤1), 42 (2–5), 11 (6–10), 13 (≥11) (n = 98)	58 (daily), 35 (weekly), 5 (<weekly) (n = 98)	98 (100)	84 (86)	91 (52/57)	100 (6/6)
Allen [6]	9	6(66)	3(33)	29 (21–37) (n = 9)	17 (15.5–18.5) (n = 9)	22 (15.8–28.3) (n = 9)	0 (≤1), 5 (2–5), 1 (6–10), 3 (≥11) (n = 9)	9 (>daily) (n = 9)	9 (100)	na	88 (8/9)	100 (7/7)
Soriano-Co [12]	8	5(63)	3(37)	34 (31.9–36.2) (n = 8)	13 (11.3–14.8) (n = 8)	30.5 (32.4–32.4) (n = 8)	0 (≤1), 0 (2–5), 1 (6–10), 7 (≥11) (n = 8)	8 (>daily) (n = 8)	8 (100)	8 (100)	100 (8/8)	80 (4/5)
Wallace [b] [10]	31	24(78)	7(22)	34 (27.8–40.3) (n = 32)	16 (14–18) (n = 27)	24 (18.3–29.8) (n = 27)	2 (≤1), 9 (2–5), 3 (6–10), 12 (≥11) (n = 26)	28(>daily), 3 (quantity not specified) (n = 31)	31 (100)	na	96 (29/30)	96 (24/25)
Sofka [13]	4	3(75)	1(25)	25.5 (22.3–28.6) (n = 4)	16 (14.5–17.5) (n = 4)	14 (11.5–16.5) (n = 4)	0 (≤1), 0 (2–5), 3 (6–10), 1 (≥11) (n = 4)	4 (>daily) (n = −4)	4 (100)	4 (100)	100 (4/4)	100 (1/1)
Patterson [10]	4	4(100)	0(0)	29 (24.6–33.4) (n = 4)	15.5 (14.9–16.1) (n = 4)	27.5 (18.5–36.5) (n = 4)	1 (≤1), 1 (2–5), 0 (6–10), 2 (≥11) (n = 4)	1 (>daily) 3 (daily) (n = 4)	4 (100)	3 (75)	100 (4/4)	100 (4/4)
Nicolson [15]	4	2(50)	2(50)	23 (21.3–24.6) (n = 4)	16.5 (15.6–17.4) (n = 4)	20 (17.5–22.5) (n = 4)	1 (≤1), 1 (2–5), 2 (6–10), 0 (≥11) (n = 4)	1 (>daily) 3 (daily) (n = 4)	4 (100)	3 (75)	100 (4/4)	100 (2/2)
Masri [14]	4	4(100)	0(0)	25 (22.6–27.4) (n = 4)	16 (14–18) (n = 2)	22 (19.4–24.6) (n = 4)	0 (≤1), 0 (2–5), 1 (6–10), 0 (≥11) (n = 1)	1 (>daily), 1 (daily), 0 (weekly), 2 (quantity not specified) (n = 4)	4 (100)	4 (100)	100 (4/4)	100 (1/1)
Individual case report synthesis	80	64(80)	16(20)	28.5 (22.6–34.4) (n = 78)	16 (12–18) (n = 53)	24 (19.5–28.5) (n = 68)	11 (≤1), 16 (2–5), 11 (6–10), 13 (≥11) (n = 51)	26 (>daily), 36 (daily), 6 (weekly), 12 (quantity not specified) (n = 80)	80 (100)	66 (82)	91 (73/80)	97 (37/38)
Cumulative synthesis	211	154 (72.9)	57 (27.1)	28 (12) (n = 111)	16 (4) (n = 84)	24 (10) (n = 101)	45 (≤1) 65 (2–5) 30 (6–10) 39 (≥11) (n = 179)	50 (>daily), 101 (daily), 41 (weekly), 5 (<weekly), 14 (quantity not specified) (n = 211)	100 (211)	172 (85.1) (n = 202)	92.3 (157/170)	96.8 (62/64)

a Raw data not available, statistics represented as reported by study authors

b Not included in cumulative synthesis as raw data not available

[108–118]. Our search did not yield any randomized trials assessing the diagnosis, pathophysiology, or treatment of CHS. Given that evidence statements are based primarily on case reports and case series, the vast majority of evidence is considered limited. Therefore, limited evidence ratings should not be misconstrued as negative clinical findings but, rather, that there are no higher-level studies to qualify the statement as higher-level evidence. The primary findings for each category are summarized in the following sections.

Diagnosis of CHS

Seven unique diagnostic frameworks were identified [6, 9, 30, 51, 119–121]. There was a significant overlap among major diagnostic characteristics between the authors. The major diagnostic characteristics and frequency of each are as follows: history of regular cannabis use for over 1 year (74.8%), severe nausea and vomiting (100%), vomiting that recurs in a cyclic pattern over months (100%), resolution of symptoms after stopping cannabis (96.8%), compulsive hot baths/showers with symptom relief (92.3%), male predominance (72.9%), abdominal pain (85.1%), at least weekly cannabis use (97.4%), history of daily cannabis use (76.6%), and age less than 50 at time of evaluation (100%) (see Table 2). The following symptoms were inconsistently captured, and thus, their frequency could not be determined: reliable return of symptoms within weeks of resuming use, normal bowel habits, negative medical workup, and weight loss >5 kg (see table 2).

Cumulative Synthesis

The cumulative synthesis represents data from the individual case report synthesis as well as the case series, excluding duplicate cases (Table 1) [6, 8, 11–82]. In the cumulative synthesis, 211 individual patients are represented. Secondary to heterogeneity across studies and incomplete reporting, not all diagnostic characteristics were reported for each patient. There were 154 males (72.9%) and 57 females (27.1%). The median age at diagnosis was 28 years (IQR = 22–34) (n = 111). The median age of onset of cannabis use was 16 (IQR = 14–18) (n = 84). The median age at symptom onset was 24 (IQR = 19–29) (n = 101). In all cases, the use of cannabis predated the onset of CHS symptoms. The duration of cannabis use prior to onset of symptoms for the 179 patients in which it was captured was as follows: 45 patients (25.1%) used it for ≤1 year, 65 patients (36.3%) used it for 2–5 years, 30 patients (16.8%) used it for 6–10 years, and 39 patients (21.8%) it used for ≥11 years. The frequency of cannabis use was reported in 211 patients as follows: 50 (23.7%) used greater than daily, 101 (47.9%) used daily, 41 (19.4%) used weekly, 5 (2.4%) used less than once per week, and in 14 (6.6%), the quantity was not specified (see Fig. 1). Cyclic nausea and vomiting was reported in 100% of patients. Abdominal pain was reported in 85.1% of cases. Relief of symptoms with compulsive hot baths/showers was reported in 92.3% of cases (n = 170).

The cumulative synthesis identified two potentially novel diagnostic characteristics for CHS. The median age of onset of cannabis use was 16 (IQR = 14–18) (age of onset reported in 84/211 cases), suggesting that many patients who develop CHS begin their cannabis use early in life. Additionally, the median age of symptom onset was found to be 24 (IQR = 19–29) (age of symptom onset reported in 101/211 cases). Underreporting of this clinical characteristic limits its generalizability and should be considered as supporting the diagnosis if present, although should not preclude the diagnosis.

The synthesis also highlights the difficulty of diagnosis, as the mean delay of symptom onset to diagnosis of CHS was 4.1 years (SD = 4.6).

Our results suggest that the following individual diagnostic characteristics have the highest sensitivity for identifying patients with CHS: at least weekly cannabis use for greater than

Fig. 1 Reported frequency of cannabis use from cumulative synthesis

Reported frequency of cannabis use among 211 CHS patients
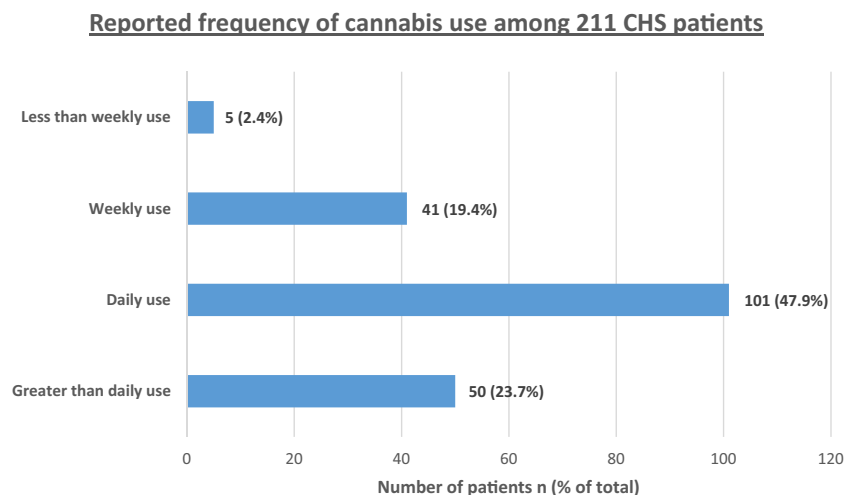
1 year, severe nausea and vomiting that recurs in a cyclic pattern over months and that is usually accompanied by abdominal pain, resolution of symptoms after stopping cannabis, and compulsive hot baths/showers with symptom relief (Table 2).

Pathophysiology of CHS

Many hypotheses have been proposed to explain the pathophysiology of CHS (Table 3); however, the GRADE quality of evidence to support any of the proposed mechanisms was very low. Some data suggest that CHS is caused by dysregulation of the endocannabinoid system, a group of endogenous cannabinoid receptors (CB-1 and CB-2) located in the brain, gastrointestinal tract, peripheral nervous system, and immune system of mammals [122]. The endocannabinoid system is thought to play a role in gastrointestinal motility [123, 124] appetite [125], nausea/vomiting [126], inflammation [127], mood [128], sleep [129], pain [130], and more. There was very limited evidence that the emetogenic and anti-emetic effects of Δ9-tetrahydrocannabinol (THC) and its analogs are mediated through CB-1 receptors (CB1r) and thus underlie the syndrome of CHS, though this mechanism is the most parsimonious and is supported by both animal and in vitro studies [88, 106]. We found very limited evidence to support the theory that a genetic variation in metabolic enzymes accounts for the appearance of CHS symptomatology; however, this theory is attractive in that it may explain why some, but not all, chronic cannabis users develop CHS [131]. There is also some evidence to suggest that cannabinoids interact directly with CB-1 receptors in the gastrointestinal tract and alter gastrointestinal motility [16, 92, 95, 132–134]. Animal studies lend some credibility to this theory; however, results are not consistently reproducible in human studies. Additionally, many inferential hypotheses were identified that attribute different aspects of CHS to a myriad of dysregulatory issues at CB-1 receptors throughout the body (brain, gastrointestinal tract, and vasculature) [97, 98, 102, 105, 133, 135–137]. The experimental evidence behind these inferences illustrates the complexity of the pathophysiology of CHS and raises many additional questions. Other hypotheses were identified, but the data to support them were so limited as to not warrant discussion in this review [57, 84–87, 89, 91, 99–105, 107, 122, 126, 138–165].

The pathophysiology of CHS is unclear secondary to a dearth of research dedicated to explicitly investigating its underlying mechanism. Nevertheless, some limited evidence suggests a dynamic interplay between cannabinoid metabolism and complex pharmacodynamics at the CB-1 receptor. Limited evidence also suggests that an individual's genetics, as well as variability in the cannabinoid components of individual plants [131], may play a role in the manifestation of CHS.

Treatment of CHS

The only definitive treatment identified for CHS was abstinence (low GRADE quality of evidence). Several studies demonstrated this effect. Wallace et al. reported that among 25 patients with CHS who abstained, 24 had complete

Table 2 Major commonly cited diagnostic characteristics

Diagnostic characteristic	Frequency (%) (total *n* with criterion reported)	GRADE rating
History of regular cannabis use for years (over 1 year) [6, 16, 30, 51, 119, 120]	74.8 (179)	Low
Severe nausea and vomiting [16, 119, 120]	100 (211)	Low
Vomiting that recurs in a cyclic pattern over months [6, 30, 119, 121]	100 (211)	Low
Resolution of symptoms after stopping cannabis [6, 16, 30, 119–121]	96.8 (64)	Low
Reliable return of symptoms within weeks of resuming use [30]	[a]	Low
Compulsive hot baths with symptom relief [6, 16, 30, 51, 119–121]	92.3 (170)	Low
Male predominance [121]	72.9 (227)	Low
Abdominal pain [30, 119–121]	85.1 (202)	Low
At least weekly cannabis use [16, 120]	97.4 (197)	Low
History of daily cannabis use [121]	76.6 (197)	Low
Age less than 50 at onset of illness [16, 120, 121]	100 (227)	Low
Normal bowel habits [16]	[a]	Very low
Negative medical workup [16, 30, 119, 121]	[a]	Very low
Weight loss >5 kg [16, 120]	[a]	Very low

[a] Criterion inconsistently documented in case reports, thus limiting frequency analysis

Table 3 Proposed pathophysiologic mechanisms for CHS	Mechanism	GRADE rating
	The emetogenic and anti-emetic effects of Δ9-THC and its analogs are mediated through CB-1 receptors (CB1r) and thus underlie the syndrome of CHS [106, 135]	Very low
	Cannabinoids may bind to CB-1 receptors in the gastrointestinal tract and decrease GI motility and gastric emptying, which may override brainstem-mediated antiemetic effects and precipitate hyperemesis [9, 92, 95, 132]	Very low
	Chronic cannabis use may lead to paradoxical and plastic changes in expression and downstream effects of cannabinoid receptors [133]	Very low
	Chronic cannabis use leads to desensitization and downregulation of CB1 receptors that ordinarily have peripheral antiemetic effects, causing rebound vomiting and spasmodic pain that abates with abstinence and corresponding recovery of CB-1 receptor activity [98, 136, 185]	Very low
	In chronic cannabis users, cannabinoid metabolites may accumulate in the brain and fatty tissues inducing a toxic effect [90, 94]	Very low
	CHS may be caused by a non-THC, cannabinoid-like structure within *Cannabis sativa*, such as cannabidiol [96, 186]	Very low
	Patients susceptible to developing CHS may have genetic variation in their metabolic enzymes resulting in toxic levels of cannabinoid metabolites [131]	Very low
	Δ9-THC may act as a partial agonist on CB1 receptors and thus relatively antagonize the effects of full endogenous agonists on these receptors, thus precipitating sudden withdrawal and hyperemesis in sensitive patients [97, 105]	Very low
	THC causes dilation of splanchnic vasculature, resulting in CHS. Hot bathing leads to peripheral venodilation and shunts blood away from the splanchnic bed, resulting in symptom improvement [102, 137]	Very low

symptom resolution [10]. Similarly, Allen et al., Simonetto et al., Patterson et al., and Soriano-Co et al. reported symptom resolution in seven out of seven [6], six out of six [9], four out of four [11], and four out of five [12] patients, respectively. The cumulative synthesis (see Table 1) demonstrated that among 64 patients with documented cannabis cessation, 62 (96.8%) had complete resolution of symptoms. The two patients who reported no resolution of symptoms did not have urine testing performed to confirm abstinence [8, 56]. Among 21 patients who did not abstain, all had ongoing symptoms.

There has been limited research into the supportive and symptomatic care of CHS patients. Secondary to intractable vomiting and high-temperature baths/showers, patients may present with moderate to severe dehydration and acute renal failure requiring aggressive fluid resuscitation [20, 30, 38, 166]. In regard to symptomatic care, there is very limited evidence to support the use of dopamine antagonists [40, 167]. For example, Hickey et al. reported complete resolution of emesis 1 h after administration of 5 mg haloperidol to a CHS patient with intractable vomiting [40]. Δ9-THC has been shown to increase dopamine synthesis, turnover, efflux, and dopamine cell firing [103], which may explain clinical improvement with haloperidol treatment. There is also some limited evidence to support the use of capsaicin cream to treat the symptoms of CHS. In a case series of five patients, LaPoint et al. reported complete resolution of nausea and emesis in all patients after application of topical capsaicin cream to the abdomen [168]. Similar positive responses are documented elsewhere [169]. The authors suggest that capsaicin may exert its effects via the TRVP-1 receptor, capsaicin's only known receptor, which is known to interact with the endocannabinoid system [169]. Some authors recommend the avoidance of narcotic pain medication in the treatment of CHS as opioid analgesic use is associated with bowel dysfunction and could theoretically worsen CHS symptoms and additionally create opioid dependence [170] (see Table 5 for a summary of treatments and associated data to support each modality).

Cannabis cessation appears to be the best treatment. Supportive care in the form of intravenous hydration and anti-emetics may be necessary secondary to profound dehydration and acute renal failure. Very limited evidence suggests that dopamine antagonist medications and the application of capsaicin cream to the abdomen may be helpful strategies to manage acute symptoms. Though there is not any direct evidence, avoidance of narcotic pain medication may be useful due to the possibility of worsening symptoms and creating dependence.

Limitations

This study is limited by the heterogeneity of the case series and case reports and the lack of controlled studies examining this syndrome. While case reports and case series demonstrate a consistent syndrome characterized by heavy cannabis use and relief of symptoms with hot showers, there is inherent publication bias; clinicians are more likely to report cases consistent with the initially reported index case. The internal

validity of our findings is limited by the possibility of missing articles from our search strategy. We limited the search to English-language articles, so any relevant articles published in foreign languages were not included, and articles not indexed in MEDLINE, Embase, Web of Science, or the Cochrane Library would be missed. Second, due to lack of diagnostic criteria, there was significant heterogeneity in the reporting of patient characteristics for the case series and case reports, resulting in limited data for several of the diagnostic characteristics analyzed. Therefore, the presented diagnostic frequency is reflective only of reported criteria and low frequency may simply be a reflection of failure to report the item. Therefore, the proposed criteria need validation in a prospective cohort. Third, reporting of cannabis use patterns was subjective with variable metrics (cones, bongs, joints, cigarettes, grams/day etc.) resulting in possible lack of accuracy for this statistic. Fourth, there was limited reporting of effective treatment modalities for CHS, and publication bias favors reporting of successful treatments rather than ineffective therapies. For instance, one Colorado cannabis prescriber anecdotally reports two cases in which patients developed symptoms consistent with CHS after the patients switched to a different cannabis product. Their symptoms subsequently resolved when they switched back to their original brand. This information is not published but raises questions regarding the role of an unidentified molecule, whether cannabinoid or non-cannabinoid (e.g., a pesticide) may precipitate of the syndrome. In practice, clinicians may have evolved treatment algorithms for managing CHS patients, but our search did not identify any studies reporting this.

Discussion

There is a large body of literature describing the diagnosis, pathophysiology, and treatment of CHS. However, most of the evidence is considered low quality because it is in the form of case reports and case series. When these reports are combined, a larger and more robust set of diagnostic characteristics, evaluation of pathophysiology, and determination of effective treatments can be generated. Based on our knowledge of 211 unique CHS patients, the following characteristics are associated with the syndrome: (1) severe cyclic vomiting that is usually accompanied with abdominal pain, (2) symptom onset preceded by at least weekly cannabis use, (3) temporary relief of symptoms with compulsive hot baths/showers, (4) resolution of symptoms with cessation of cannabis use, (5) onset of cannabis use in the teenage years, and (6) symptom onset in the third decade of life. While not all these criteria must be met to make the diagnosis, of 133 cases for which raw data were available, 85 met at least four criteria (75.2%) and 104 (92%) met at least three criteria. Secondary to incomplete and inconsistent reporting of the proposed diagnostic

characteristics in the case report literature, the aforementioned data may be an underestimate of the actual occurrence of these symptoms in CHS patients.

CHS shares many clinical similarities with cyclic vomiting syndrome (CVS), a functional gastrointestinal disorder. A diagnostic dilemma arises when CVS patients concurrently use cannabis, as it can be difficult to discern if the true underlying disorder is CHS or CVS that is being symptomatically managed with cannabis. Several studies were identified in our search that attempted to isolate and diagnose CHS patients among cohorts of CVS patients and deserve special mention [171–173]. The Rome criteria were developed by an international committee of experts in order to delineate and standardize the diagnosis of functional gastrointestinal disorders [174]. The Rome III diagnostic criteria for CVS are as follows: stereotypical episodes of acute onset of vomiting lasting less than 1 week, three or more discrete episodes in the prior year, and absence of nausea and vomiting between episodes in the absence of organic disease. Kim et al. demonstrated a near doubling of the prevalence of CVS following legalization of cannabis in Colorado (prevalence ratio 1.92, 95% confidence interval [CI] = 1.33 to 2.79), and these patients were more likely to have cannabis use documented (OR = 3.59, 95% CI = 1.44–9.00) [5]. Additionally, five observational studies were identified which reported a significant prevalence of cannabis use and compulsive hot baths/showers among CVS patients (see Table 4) [175–179]. For example, Venkatesan et al. found that among 437 CVS patients, 81% were cannabis users and 67% reported using hot showers for symptom relief [179]. Bathing behavior was associated with cannabis use (OR 2.54, 95% CI = 1.2–4.3, P = 0.0006). Additionally, Fajardo et al. found that among 48 CVS patients, 22% of cases and 12% of controls were active or previous cannabis users (OR = 2.1, 95% CI = 0.7–6.1) [175]. Cannabis use, when present, preceded symptom onset in CVS patients. These studies suggest that there is a cohort of CHS patients who may be misdiagnosed with CVS. In situations where the diagnosis is in question, cannabis use that precedes the onset of the vomiting syndrome as well as compulsive hot baths/showers should alert the clinician to consider recommending a trial of cannabis abstinence.

CHS shares many clinical features with other CVSs. We identified four case reports of patients initially diagnosed as hyperemesis gravidarium but were ultimately diagnosed as CHS, with a history of chronic cannabis use, compulsive hot baths/showers, and a history of cyclic vomiting predating the pregnancy [18, 64, 180, 181]. These studies exemplify the diagnostic difficulty in the identification of CHS and suggest that CHS may be more common than is reported.

The pathophysiologic processes underlying CHS are unclear at this time. Many hypotheses exist, yet there is very limited evidence to support any one unifying mechanism. The best evidence suggests a dynamic interplay between

Table 4 Cyclic vomiting syndrome and cannabinoid hyperemesis syndrome diagnostic dilemmas

Author	Study design	Primary findings	GRADE rating
Kim [5]	Observational, retrospective	Following legalization of cannabis in Colorado, the prevalence of cyclic vomiting nearly doubled (prevalence ratio 1.92, 95% confidence interval [CI] = 1.33 to 2.79) and patients were more likely to have cannabis use documented (OR = 3.59, 95% CI = 1.44–9.00)	Low
Fajardo [175]	Observational, retrospective, case-control	Among 48 CVS patients, 22% of cases and 12% of controls were active or previous cannabis users (OR = 2.1, 95% CI = 0.7–6.1). Cannabis use, when present, preceded symptom onset in CVS patients.	Very low
Hejazi [187]	Observational, case-control	Among 132 CVS patients, 53% of patients deemed "non-responders" to standard therapy were chronic cannabis users	Very low
Namin [177]	Observational, cross-sectional survey	Of 31 patients diagnosed with cyclic vomiting syndrome, 72% reported hot showers as a self-therapy. Forty-two percent used cannabis daily to weekly and 2 experienced resolution of symptoms with cessation.	Very low
Oruganti [178]	Observational, cross-sectional survey	Of 20 patients diagnosed with CVS, 12 used cannabis chronically and all took hot baths/showers to alleviate symptoms.	Very low
Venkates [179]	Observational, cross-sectional survey	Among 437 CVS patients, 81% were cannabis users and 67% reported using hot showers for symptom relief. Bathing behavior was associated with cannabis use (OR 2.54, 95% confidence interval [CI] = 1.2–4.3, $P = 0.0006$)	Low

cannabinoid metabolism and complex pharmacodynamics at the CB-1 receptor. In addition, our study identified three unique cases of CHS caused by synthetic cannabinoids [23, 41, 182]. These agents are potent agonists of the cannabinoid CB1 receptors, similar to THC, suggesting that agonism at the CB1 receptor may be responsible for CHS. Supportive care with IV fluids and anti-emetics is the mainstay of treatment in the acute phase of illness. There is very limited evidence to suggest that agents such as dopamine antagonists and capsaicin cream and avoidance of opiate pain medications may be of benefit. While many providers utilize these agents in practice and find them effective, prospective case-control studies are needed before recommendations can be made based upon effectiveness. The authors of this study acknowledge the potential difficulties of such studies, owing to the fact that CHS is a heterogeneous clinical entity, and thus, selecting a comparable group of patients may prove difficult. Additionally, agents such as topical capsaicin cream are not commonly stocked in hospitals and emergency departments but could be made available in the outpatient setting. There is moderate evidence to support that the definitive treatment for CHS is cannabis cessation. In this study, 96.8% of patients who ceased cannabis use experienced complete resolution of symptoms.

This systematic review is the first and most comprehensive characterization of the CHS literature. We believe that these evidence-based recommendations will improve diagnosis, highlight the limitations of pathophysiology understanding, and provide guidelines for treatment of this difficult condition.

Our proposed diagnostic characteristics are listed in Table 6 with corresponding GRADE quality recommendations.

A careful social history is needed in all cyclic vomiting patients. Cannabis has various therapeutic properties including anti-emesis, appetite stimulation, and analgesia [4]. These properties have led to cannabis use in patients with cachexia associated with AIDS, chemotherapy-induced nausea and vomiting, peripheral neuropathy, chronic pain, and CVSs [4]. Cyclic vomiting patients and those using cannabis for its myriad of health benefits may perceive that cannabis is helping their condition instead of exacerbating it. This systematic review suggests that there may be a demographic of cyclic vomiting patients who have been mislabeled. This may also be true for hyperemesis gravidarum and gastroparesis patients. Simonetto et al. reported that among 61 CHS patients who underwent gastric emptying studies, 18 (30%) demonstrated delayed emptying [9]. Since cannabis use has been shown to delay gastric emptying [92, 132], this finding should not preclude the diagnosis of CHS. When diagnosis is in doubt, a trial of cannabis cessation may support the diagnosis [183].

It is difficult to quantify the precise amount of cannabis consumed by patients who manifest CHS. Reporting is often subjective and qualitative, and there is no metric for how much physiologically active compounds are contained in one joint, cone, bong, etc. In addition, higher THC content through selective breeding of plants and more selective use of female buds that contain more concentrated THC levels may cause CHS to appear in patients who report lower amounts of cannabis use [170].

Table 5 Proposed treatments for CHS

Proposed treatment	Supportive evidence	Author	Study design	GRADE rating
Cessation of cannabis	Cessation of cannabis led to resolution of symptoms in 30 of 31 patients	Wallace [10]	Case series	Very low
	Among 10 CHS patients with follow-up, 30% did not abstain and continued to have symptoms and 60% stopped using and had complete resolution of symptoms. One patient experienced no symptomatic improvement with self-reported abstinence.	Simonetto [16]	Case series	Very low
	Among 10 patients, 7 of 10 abstained and had resolution of symptoms. Three patients did not and illness continued. Three patients rechallenged themselves after a period of abstinence, and all suffered a return to illness	Allen [6]	Case series	Very low
Application of capsaicin cream to the abdomen	Five CHS patients experienced near complete resolution of symptoms after application of topical capsaicin cream to the abdomen	LaPoint [168]	Case series	Very low
	Case report of dramatic relief of symptoms in CHS patient with topical application of capsaicin	Biary [169]	Case report	Very low
Dopamine antagonists	Δ9-THC increases dopamine synthesis, turnover, and efflux and dopamine cell firing. Δ9-THC withdrawal, induced by abrupt discontinuation of chronic Δ9-THC treatment or administration of rimonabant, results in decreased dopamine efflux and neurotransmission	Schulze [103]	Experimental model	Very low
	CHS patient received 5 mg haloperidol and experienced complete resolution of symptoms within 1 h	Hickey [40]	Case report	Very low
Avoidance of opiate-based medications	Opioid analgesic use is associated with bowel dysfunction, and GI side effects have been reported in up to 47% of opioid-treated patients	Argoff [188]	Review	Very low
	Opiates should be used with caution as they have the potential to cause emesis	Galli [170]	Case report	Very low

Initial reports describe an average of 7.1 emergency department visits, 3.1 hospitalizations, and 5.0 clinic visits prior to diagnosis [12], but as the syndrome is recognized more and cannabis availability increases, more rapid diagnosis is likely. Exclusion of a major medical etiology is mandatory prior to the consideration of CHS. Other medical conditions that may present similarly to CHS include, but are not limited to, bowel perforation, cholangitis, pancreatitis, and ruptured aortic aneurysm [184]. Martinez et al. suggest that a minimum workup should include basic laboratories, abdominal ultrasound (US) and/or computerized tomography (CT) scan, and esophagogastroduodenoscopy (EGD) with initial admission. However, the literature suggests that patients often undergo multiple CT scans, EGDs, and even exploratory surgeries prior to diagnosis. In one multicenter cohort study, the mean numbers of abdominal CT studies and abdominal/pelvic US

and abdominal radiographs were 5.3 ± 4.1, 3.8 ± 3.6, and 5.5 ± 6, respectively [7]. For one participating ED with seven patients enrolled in the study, the median charge for ED visits and hospital admissions over the course of a patient's illness was $95,023 (range $62,420 to 268,110).

We would suggest a pragmatic approach to diagnosis that starts with a complete history of cannabis use including age of initial onset, amount used per week, and behavioral factors associated with symptom relief (such as hot showers). Following this, underlying medical etiology of the symptoms should be ruled out using laboratory evaluation and imaging. However, this workup should only be performed initially and repeated only if there is a change in the patient's clinical status that suggests a new emergent condition. Greater education is needed among clinicians in order to limit repeated "exclusionary" workups and iatrogenesis. In addition, as the

Table 6 Diagnostic characteristics for cannabinoid hyperemesis syndrome

Diagnostic characteristic	GRADE rating
Severe cyclic vomiting usually accompanied by abdominal pain	Low
Symptom onset preceded by at least weekly cannabis use	Low
Temporary relief of symptoms with hot bathing	Low
Resolution of symptoms with cannabis cessation	Low
Supportive features: male gender, cannabis use onset in teenage years, symptom onset in third decade of life	Low

Table 7 Proposed diagnostic frameworks for cannabinoid hyperemesis syndrome

Author	Year
Allen [6]	2004
Sontineni [119]	2009
Simonetto [9]	2012
Pattathan [121]	2012
Sun [120]	2013
Cheung [30]	2014
Morris [51]	2014

trend toward cannabis legalization spreads, states need to create public health messages to warn cannabis users of the possibility of developing this syndrome.

Cessation of cannabis appears to be the best treatment for CHS. Our review revealed that CHS patients may often have poor follow-up. Follow-up was documented in only 85 of 211 patients (40.2%). Multidisciplinary care may be necessary for management and diagnosis. Patients may deny cannabis use as a cause of their symptoms and fail to follow-up or seek medical care at other facilities resulting in repeated testing and resource utilization [8]. Therefore, substance abuse experts should be involved when the diagnosis is made.

Further targeted basic science research is needed to elucidate the pathophysiology underlying CHS. Strong prospective epidemiologic studies are needed to determine the prevalence of the disorder and the rate of disease development among cannabis users. In addition, randomized studies are needed to establish effective treatments to terminate acute exacerbations. As demonstrated by Kim et al., with liberalization of cannabis laws, growing prevalence of CHS is likely. In addition, results from the 2014 National Survey on Drug Use and Health (NSDUH) indicate that 7.4% of adolescents aged 12–17 were current users [2]. Our results show the average age of cannabis use onset among CHS patients to be 16 (IQR = 14–18). Given a large, young aged demographic of chronic cannabis users, a prospective, case-control study would increase our understanding as to who is at risk for the development of CHS.

Conclusion

CHS is characterized by severe cyclic vomiting, usually accompanied by abdominal pain associated with early age of cannabis use with symptoms that most commonly develop in the third decade of life. Symptom onset is preceded by daily to weekly cannabis use. Patients usually report temporary relief of symptoms with compulsive hot baths/showers and experience resolution of symptoms with cessation of cannabis use. The pathophysiology underlying CHS is unclear. Cannabis cessation appears to be the best treatment.

Appendix: Search strategies

Cochrane Library (via Wiley Online Library)

1. MeSH descriptor: [Cannabinoids] explode all trees
2. MeSH descriptor: [Cannabis] explode all trees
3. MeSH descriptor: [Marijuana Abuse] explode all trees
4. MeSH descriptor: [Marijuana Smoking] explode all trees
5. MeSH descriptor: [Medical Marijuana] explode all trees
6. cannab*:ti,ab,kw (Word variations have been searched)
7. marijuana:ti,ab,kw (Word variations have been searched)
8. phytocannab*:ti,ab,kw (Word variations have been searched)
9. tetrahydrocannab*:ti,ab,kw (Word variations have been searched)
10. THC:ti,ab,kw (Word variations have been searched)
11. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12. MeSH descriptor: [Vomiting] explode all trees
13. emes*:ti,ab,kw (Word variations have been searched)
14. hypereme*:ti,ab,kw (Word variations have been searched)
15. vomit*:ti,ab,kw (Word variations have been searched)
16. #12 or #13 or #14 or #15
17. #11 and #16

Results: 34
Embase (via Embase.com)

1. 'cannabinoid'/exp
2. 'cannabis'/exp
3. 'cannabis addiction'/exp
4. 'cannabis use'/exp
5. 'medical cannabis'/exp
6. cannab*:ab,ti
7. marijuana:ab,ti
8. phytocannab*:ab,ti
9. tetrahydrocannab*:ab,ti

10. thc:ab,ti
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. 'vomiting'/exp
13. emes*:ab,ti
14. hypereme*:ab,ti
15. vomit*:ab,ti
16. #12 OR #13 OR #14 OR #15
17. #11 AND #16
18. #11 AND #16 AND [english]/lim AND [2000-2015]/py AND [embase]/lim

Results: 1099

Ovid Medline (Ovid MEDLINE (1946-current), Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Ovid MEDLINE Daily)

1. exp Cannabinoids/
2. exp Cannabis/
3. exp Marijuana Abuse/
4. exp Marijuana Smoking/
5. exp Medical Marijuana/
6. cannab$.mp.
7. marijuana.mp.
8. phytocannab$.mp.
9. tetrahydrocannab$.mp.
10. THC.mp.
11. or/1-10
12. exp Vomiting/
13. emes$.mp.
14. hypereme$.mp.
15. vomit$.mp.
16. or/12-15
17. 11 and 16
18. limit 17 to (english language and yr="2000 - 2015")

Results: 341

PubMed

1. "Cannabinoids"[Mesh]
2. "Cannabis"[Mesh]
3. "Marijuana Abuse"[Mesh]
4. "Marijuana Smoking"[Mesh]
5. "Medical Marijuana"[Mesh]
6. cannab*
7. marijuana
8. phytocannab*
9. tetrahydrocannab*
10. THC
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. "Vomiting"[Mesh]
13. emes*

14. hypereme*
15. vomit*
16. #12 OR #13 OR #14 OR #15
17. #11 AND #16
18. (#11 AND #16) AND "english"[Language] AND ("2000"[Date - Publication]: "2015"[Date - Publication])

Results: 357

Web of Science

1. TS=cannab*
2. TS=marijuana
3. TS=phytocannab*
4. TS=tetrahydrocannab*
5. TS=THC
6. #1 OR #2 OR #3 OR #4 OR #5
7. TS=emes*
8. TS=hypereme*
9. TS=vomit*
10. #7 OR #8 OR #9
11. (#6 AND #10) AND LANGUAGE: (English) Timespan=2000-2015

Results: 323

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