Cannabis hyperemesis syndrome: an update on the pathophysiology and management

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Abstract

Cannabis hyperemesis syndrome (CHS) is a form of functional gut-brain axis disorder characterized by bouts of episodic nausea and vomiting worsened by cannabis intake. It is considered as a variant of cyclical vomiting syndrome seen in cannabis users especially characterized by compulsive hot bathing/showers to relieve the symptoms. CHS was reported for the first time in 2004, and since then, an increasing number of cases have been reported. With cannabis use increasing throughout the world as the threshold for legalization becomes lower, its user numbers are expected to rise over time. Despite this trend, a strict criterion for the diagnosis of CHS is lacking. Early recognition of CHS is essential to prevent complications related to severe volume depletion. The recent body of research recognizes that patients with CHS impose a burden on the healthcare systems. Understanding the pathophysiology of the endocannabinoid system (ECS) remains central in explaining the clinical features and potential drug targets for the treatment of CHS. The frequency and prevalence of CHS change in accordance with the doses of tetrahydrocannabinol and other cannabinoids in various formulations of cannabis. CHS is unique in presentation, because of the cannabis's biphasic effect as anti-emetic at low doses and pro-emetic at higher doses, and the association with pathological hot water bathing. In this narrative review, we elaborate on the role of the ECS, its management, and the identification of gaps in our current knowledge of CHS to further enhance its understanding in the future.

Keywords Cannabis hyperemesis syndrome, cannabis, marijuana, endocannabinoid system

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Introduction

Cannabis is the most commonly abused drug in the United States (US). Its use dates back to 3900 BC. However, our understanding of its effects has unfolded significantly over the last 3 decades. The extract of the plant cannabis sativa has been reported to be used for decades in the control of pain and cramps, according to the Chinese literature [1]. Recognition of the function of the endocannabinoid system (ECS) was a breakthrough in explaining the effects of cannabis on different organs, at least in part [2]. The primary psychoactive component of cannabis is tetrahydrocannabinol (THC). These advances enhanced the understanding of cannabinoid (CB) receptors, which led to a better appreciation of the role of cannabis in inflammation, seizures, emesis, and as an appetite stimulant. There is a growing body of research showing the benefit of cannabis in the aforementioned disorders, and its legalization will further augment research on understanding its critical role in new drug developments [3,4]. However, these changes also come with substantial risks regarding its adverse effects, such as

paradoxical hyperemesis, intoxication and behavioral changes (anxiety, panic attacks, and psychoactive changes). Prolonged cannabis use can also result in dependency. Approximately 9% of individuals who use cannabis report dependence at some point in their use [5]. Cannabis can paradoxically act as an antiemetic during acute ingestion at low doses, whereas persistent high-dose ingestion could result in vomiting, a behavior similar to cyclical vomiting [6]. It appears from the current literature that the prevalence of cannabis hyperemesis syndrome (CHS) is higher in the US compared to Canada and the United Kingdom, although the prevalence of cannabis use is similar in these countries [7,8]. It is unclear whether the increased legalization of cannabis has also contributed to these findings, but this certainly could be a possibility. Hence, raising the awareness of CHS with an understanding of its pathophysiology and the potential role of therapeutic agents is paramount.

The term CHS was first used more than a decade ago in 2004 [9]. Since then, several CHS cases have been reported in the literature with clear recognition and association with cannabis [10]. However, given the degree of heterogeneity among these case reports and a need for strict criteria, the Rome IV diagnostic criteria were introduced in the category of functional gut disorders. The Rome IV committee defines functional gastrointestinal disorders as disturbances in the gut-brain axis without an organic pathology to explain those symptoms [7]. This functional nausea and vomiting symptom complex may be cyclical or chronic in nature. A strict definition of CHS is lacking; therefore, it is also sometimes considered as a variant of cyclical vomiting syndrome (CVS). Rome IV categorizes CHS as an extension of CVS, with symptom onset associated with heavy cannabis use. It defines CHS as episodic nausea and vomiting episodes resembling CVS, associated with prolonged and excessive use of cannabis and with the relief of symptoms after sustained cessation of its use. The symptoms may or may not improve with compulsive hot showers [11]. However, details about the chronicity of use and duration of sustained cessation remain unclear. It is challenging to estimate the exact prevalence of CHS because most of the case reports have not used these strict criteria. In this review, we discuss the pathophysiology and treatments, and identify the strict prevalence based on the Rome criteria.

Hyperemesis induced by cannabis

Cannabis has traditionally been used as an appetite stimulant and antiemetic drug and is FDA approved for chemotherapy-related nausea and vomiting when traditional therapy fails. It has multiple effects on the gastrointestinal system, including secretions, appetite stimulation, modulation of inflammation, and motility [12-14]. However, its use is also associated with CHS, signifying its biphasic effect. Disorders involving the gut-brain axis, such as irritable bowel syndrome, functional dyspepsia, functional nausea, and vomiting disorders, have been shown to be related to abnormalities in psychological status, visceral hypersensitivity, dysfunction

of autonomic activity and gastric emptying [15,8]. Cannabis consists of more than 100 types of cannabinoidal agents, and its potency is determined by the ratio of THC and other cannabinoidal agents [16]. Therefore, this ratio also determines the toxicity during its use. The role of cannabis's antiemetic activity is demonstrated in both species capable of vomiting (ferrets, least shrews, musk shrews) and those that are not, such as rodents [17-19]. In shrews and ferrets, anandamide (AEA) and arachidonolyglycerol (2-AG) reduce emesis in a dose-dependent fashion. CB agonists (both natural and synthetic) and transient receptor potential cation channel subfamily V member 1 (TRPV1) agonists have demonstrated antiemetic effects [17,20]. In animals such as rodents, which lack a vomiting reflex, indirect markers of vomiting are used (taste avoidance, conditioned gaping, change in the facial expression). Cannabinoids reduced these behaviors in rodents suggestive of their anti-emetic effect [18].

Understanding the ECS and its effects on the vomiting center of the brain are fundamental to explain the effect of cannabis for this biphasic response [21]. The ECS is composed of ligands, receptors, signaling, and enzymes (its regulators and inhibitors) [22].

1. **Ligands**: Ligands in the ECS are produced during the stress response and bind to their receptors (Table 1). These ligands can be classified into either endogenous or exogenous types. Exogenous ligands include N-acyl ethanolamines and mono-acyl-glycerols. Several hundreds of CB agonists and antagonists exist that can potentially act on receptors. Some of the most commonly known exogenous ligands include THC (made of a dibenzopyran ring), cannabidiol, cannabigerol, and cannabinol [23]. They bind to receptors such as G protein-coupled receptors (GPR) GPR18 and GPR55, peroxisome proliferator-activated receptors (PPARs), and TRPV1 [24]. Endogenous ligands are AEA and 2-AG, derived from arachidonic acid; 2-AG has significantly high concentrations in the brain and is mainly involved in signaling. Both of these endogenous ligands are produced

Table 1 Ligands and receptors of the endocannabinoid system

Major ligands	Minor ligands
2- arachidonolyglycerol	N-arachidonoyl-dopamine
N-arachidonoyl ethanolamine anandamide	Noladin ether Virodhamine
CB1 Receptors	**CB2 Receptors**
Location: Predominately in the brain	Predominantly in splenic macrophages. Minor location in the brain.
Type: GPCR. Located in the plasma membrane. Other areas of the cell (mitochondria, intracellular space, lysosome, and endosome)	GPCR. Located in the plasma membrane
Function: Anxiety, depression and appetite control, secretions from gastrointestinal tract, hepatic metabolism, cardiac dysfunction	Nociception, inflammation, and addiction

CB, cannabinoid; GPCR, G-protein coupled receptor

on demand from cell membrane lipids [25]. AEA and 2-AG are transported from intracellular to extracellular space by diffusion, endocytosis, carrier transport, translocation and possible heat shock proteins [26]. They are involved in the stimulation of CB receptors in the pre- and post-synaptic areas in the brain (multiple areas including the temporal lobe, orbitofrontal cortex, insula, and parahippocampal) to produce their effects [27].

2. **Receptors**: The 2 primary CB receptors are type 1 (CB1) and type 2 (CB2). CB1 is present predominately in the brain, where it affects appetite, food control and cognition, along with addiction [25]. CB2 is mainly involved in pain and inflammation control. Additional receptors on which CBs can act include TRPV1, PPARα, GRP55, and GRP119. Vagal control of gut motor functions such as nausea and vomiting is regulated by the endocannabinoids acting on the brainstem via CB1, CB2 and TRPV1 receptors.

3. **Signaling**: 2-AG exerts its action by retrograde signaling (Fig. 1). Calcium signaling and TRPV1 channel are also involved, especially with AEA. TRPV1 channels (also known as the capsaicin receptor and vanilloid receptor 1) are affected by capsaicin, used as a possible therapeutic modality for CHS [24].

4. **Enzymes**: AEA and 2-AG are synthesized from membrane lipids on demand [28]. Diacylglycerol (DAG) is split by DAG lipase, resulting in the production of 2-AG. N-acyl-phosphatidylethanolamine is split by phospholipase-D, resulting in the synthesis of AEA. Both these conversions are mediated by a calcium-sensitive rate-limiting step [29]. Inactivation of both AEA and 2-AG occurs intracellularly. For example, 2-AG is hydrolyzed predominantly by monoacylglycerol lipase (MAG), while AEA is predominately degraded by the fatty acid amide hydrolase (FAAH) pathway. MAG is localized in the mucosa and muscle layers of duodenum, ileum, proximal and distal colon. FAAH is located in myenteric plexus in the whole gut [30,31]. AEA levels drop during stress, and increasing the levels of AEA (by inhibiting its degradation) could be a potential therapeutic target.

ECS and CHS

The ECS is actively involved in motility, secretions, emesis, satiety and inflammation [32]. The underlying mechanism of the cannabis-induced biphasic effect related to emesis is not clearly understood, but the literature supports the role of the brainstem and hypothalamic–pituitary–adrenal (HPA) axis. The possible mechanisms described include changes in the density of the receptors, interaction with active cannabis metabolites, the potency of agents, disequilibrium with the hypothalamic–gut axis, and interactions with active agents
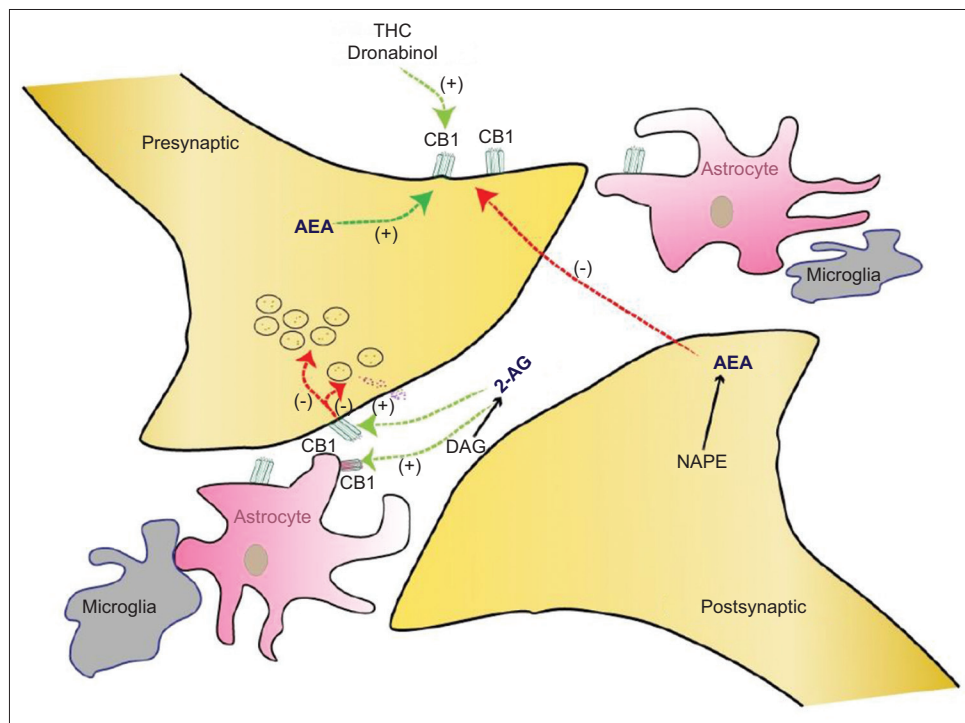

Figure 1 Endocannabinoid system (ECS) with cannabinoid receptors (CB-1, CB-2) and enzymes involved in synthesis and degradation. Anandamide (AEA) & 2-AG (arachidonolyglycerol) both derived from arachidonic acid. 2-AG is significantly higher concentraion in the brain. It inhibits neurotransmitter release (by binding to CB-1 and by affecting Ca+ metabolism in neurons). CB-1 (brain predominately; also in smalll amounts in GI-enteric NS, NEC, enterocytes [affects permeability and motility], heart [myocytes], skeletal muscle, liver, reproductive system, and afferrant pain nerve fibers). CB-2 predominately in macrophages in the spleen and small amounts in CNS peripheral tissues, Both are G-coupled receptors (GPCR)

(explained below) [33]. It could be a combination of these that produces the various clinical effects of cannabis. ECS affects nausea and vomiting pathways in multiple ways, as noted in Fig. 2.

A. **Antiemetic activity:** ECS plays an important neuromodulator of nausea and vomiting, especially during stress response [34]. Nausea and vomiting during a stress phenomenon (chemotherapy, migraine, motion sickness) are predominately mediated by brainstem nuclei, HPA and the vagus nerve [35,36] (Fig. 2). The ECS provides negative feedback for the HPA axis, and decreased effects of ECS during stress are known to increase HPA activity [37]. This increased activity of HPA via the vagus nerve produces emesis. The mechanism by which ECS inhibition occurs is unknown, although activation of CB1 receptors in the central nervous system (CNS) is the most likely pathway. As CB1 receptors are predominately present in the CNS, their levels also drop during stress [17]. Individuals with acute motion sickness showed significantly higher stress scores with lower endocannabinoid levels. Serum levels of AEA have been shown to drop during motion sickness. Thus, increasing the blood levels of AEA by inhibition of its degradation by FAAH can improve nausea and vomiting [34]. As endocannabinoid activity is lowered in stress response, enhancing ECS signaling could be used as a potential anti-emetic strategy. This mechanism has been shown to improve nausea and vomiting induced by cisplatin and nicotine [36].

B. **Pro-emesis activity:** THC in higher amounts can cause intoxication, resulting in paradoxical pro-emetic characteristics. THC is stored in fat cells in the body. Stress and food-deprivation stimulate the sympathetic nervous system, which increases lipolysis to meet body demands mediated by the action of adrenocorticotrophic hormone

(ACTH) on adipocyte receptors [38]. Increased ACTH enhances the release of THC stored in adipocytes, leading to emesis. Therefore, higher THC levels (after heavy ingestion of cannabis with highly potent THC) can explain its pro-emetic activity. Furthermore, the presence of stress or food deprivation can raise THC levels (reintoxication) [39].

C. **Combined activity:** The potency of cannabis is directly related to the ratio of THC and cannabidiol in the preparation. As ingestion cannabis includes a variety of compounds, its potency directs the type of activity (anti-emetic or pro-emetic). In addition to THC metabolites, cannabis has multiple other CBs (cannabidiol, cannabigerol), which play a role in the initiation of emesis. The high potency of some cannabis preparations explains the biphasic effect of cannabis, i.e., anti-emetic at low doses and pro-emetic at higher ones [40]. However, there are still considerable gaps in our knowledge as regards the in healthy vs. diseased state, genetic predisposition, downregulation of CB receptors among chronic cannabis users, and what role they play in the emesis and inter-emesis period.

Diagnosis

CHS is traditionally diagnosed as the presence of hyperemesis in the setting of chronic cannabis use associated with pathological hot bathing behaviors. However, there has been considerable heterogeneity in previous literature with respect to categorizing patients with this diagnosis. CHS involves 3 phases: prodromal, hyperemetic and recovery. The prodromal phase is characterized by nausea, abdominal discomfort and fear of vomiting. The hyperemetic phase
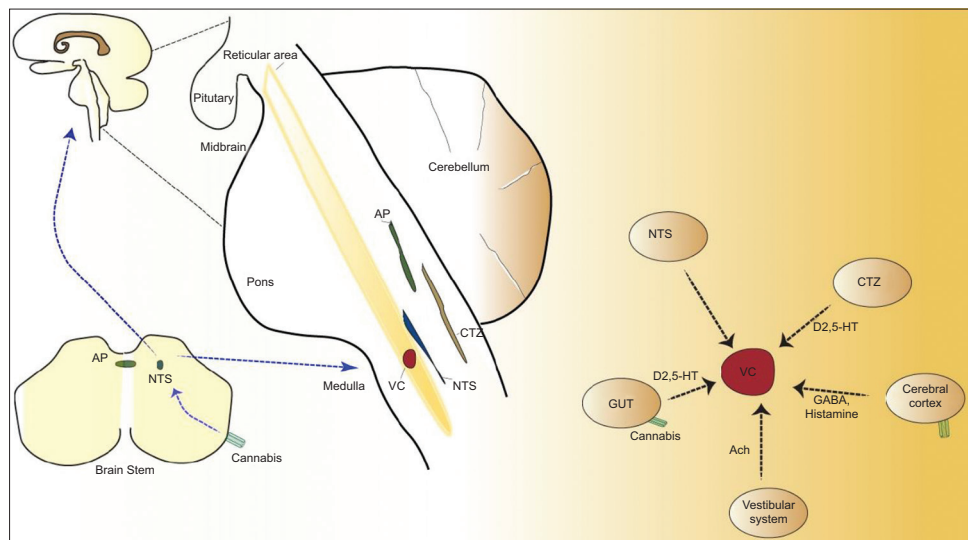

Figure 2 Pathways involving cannabis on the central nervous system. After the ingestion of cannabis, the active componenet binds to CB1 receptors in the spinal cord and brain stem. It affects signaling at Nucleus Tractus Solitarius (NTS), which affects the vomiting center (VC, located in the medulla oblongata of the brain stem) and thalamus. Various brain stem nuclei depicted with interaction with the vomiting center. Dorsal vagal complex (composed of area postrema and NTS) is affected by cannabis. Right panel showing vomiting center with different affecters (and neurotransmitters) of the VC. CTZ (Chemoreceptor trigger zone); AP-Area Postrema; VC-Vomiting center

includes intense and multiple episodes of vomiting, which bring the patient to medical attention. After symptoms improve, the recovery phase starts with the establishment of normal eating behaviors [41,42]. Episodic nausea and vomiting occur with a history of chronic use of cannabis [43]. Under-recognition of this disorder can lead to multiple investigations with increased healthcare expenses [44,45]. Sometimes, patients may also report a recent increase in cannabis use or a change in their source of cannabis purchase, which could indicate a change in the potency of cannabis. Some patients report relief of their symptoms with compulsive use of hot showers. Other disorders, such as Addison's disease, migraine headaches, hyperemesis of pregnancy, bulimia, and psychogenic vomiting [46], can also mimic these symptoms. However, these diagnoses can also coexist with CHS [47].

A thorough history, physical examination and directed testing of differential diagnoses may assist in ruling out these diagnoses. The Rome IV criteria provide some objectivity to

help with the diagnosis by placing CHS under the heading of functional gut-brain disorders, and consider it as a variant of CVS (Table 2). Venkatesan *et al* have proposed a new criterion for CHS with the use of clinical features, cannabis use patterns including duration and frequency, and symptoms resolution after at least 6 months of cessation [48]. However, questions remain about the dosage of cannabis, individual and genetic susceptibility, abstinence period and the inclusion of abdominal pain as a criterion. The clinical effects of volume depletion dominate complications related to CHS. Reports of severe volume depletion resulting in acute kidney injury and severe electrolyte disturbances with rhabdomyolysis have been reported in the literature [49]. Severe and persistent vomiting can also lead to Mallory-Weiss tear [47].

Pathological bathing behavior

Multiple studies report pathological frequent and prolonged hot shower behaviors with CHS. It is a learned trait by the patients to obtain relief from some of the symptoms of CHS and a few reports even describe CHS as "cannabis shower syndrome." Some other reports have considered this behavior as a firm requirement and potentially pathognomonic for CHS [50]. Hot showers have been reported to assist in stabilizing the hypothalamic thermostat, frequently altered by chronic cannabis use [51]. Accordingly, they have been reported as one of the therapeutic modalities for the management of the CHS. However, this mechanism has never been tested nor challenged. Further, these behaviors could also be noted in CVS, preadolescents, and adolescents with no prior exposure to cannabis [8]. These changes from

Table 2 Rome IV criteria for cannabis hyperemesis syndrome

Required criteria [8]	Comments
1. Symptoms present for past 3 months (with onset at least 6 months prior) 2. Stereotypical episodes lasting <1 week 3. At least 3 episodes in last 1 year and 2 episodes in last 6 months (occurring at least 1 week apart) 4. No vomiting between episodes. Milder symptoms can be present during this. All these criteria should be associated with chronic use of cannabis and stop after its cessation	Definition of chronic use needs more elaboration Cessation of cannabis use needs to be defined for an exact period

Table 3 Treatment options for cannabis hyperemesis syndrome

Therapy	Mechanism and advantages	Adverse effects
Benzodiazepines [67,68]	Useful for their anti-anxiety, anti-emetic and inhibition of vestibular system	Sedation, altered consciousness
TCA [69]	Used prophylactically. Mixed results noted.	Arrhythmias
Anti-dopaminergic: Haloperidol [53,70] Droperidol [59]	Haloperidol is a broad spectrum antiemetic. May interfere with CB1 signaling [54]. Blockage of dopamine at the chemoreceptor trigger zone.	Arrhythmias, central nervous system side effects Dysrhythmias (QT prolongation), oversedation
Dopaminergic agents: Promethazine and prochlorperazine [71]	Effect CTZ area in the brain stem. Variable success noted	Arrhythmias, extrapyramidal effects, hypotension, and sedation related effects
Serotonergic antagonists: Ondansetron [54]	First-line agents used for emesis. Variable response noted [54,72]	Arrhythmias
Corticosteroids [73]	Rarely used with limited response [55,74]	Hyperglycemia and psychosis
Capsaicin [74,75]	Bind to TRPV1 receptors in proximity to CB1 [62]	Minimal. Skin irritation
Volume repletion	Prevents dehydration related symptoms	Minimal
Cannabis cessation [64]	Required for long-term management	Patient compliance

TRPV1, transient receptor potential cation channel subfamily V member 1; TCA, tricyclic antidepressant; CB, cannabinoid; CTZ, chemoreceptor trigger zone

Table 4 Gaps in our understanding of CHS

Component	Elements which need attention
Definition	Need further research and optimization of classification criteria
Pathophysiology	More elaboration of biphasic effect. Role of minor cannabinoid ligands and receptors. Further feedback mechanism of HPA and ECS systems with their precise role in CHS
Dosing	Precise dosing measurements need to elicit CHS response and intoxication by THC
Potency	Identifying the thresholds for the potency of THC to cannabinoid ratio to evaluate its role in CHS pathogenesis
Treatment	Standardizing primary first and second-line agents

CHS, cannabis hyperemesis syndrome; HPA, hypothalamic–pituitary–adrenal; ECS, endocannabinoid system; THC, tetrahydrocannabinol

hot bathing are probably not specific to CHS but can be seen across all functional nausea and vomiting disorders, including CVS, and are probably aggravated by cannabis use [9]. Thus, hot shower bathing may be more closely related to CHS, but is neither specific nor sensitive in its diagnosis. This is probably the reason for its non-inclusion in the Rome IV diagnostic criteria for CHS.

Management

CHS management primarily depends on the severity of the symptoms, the development of complications, and the prevention of further recurrence. Previous reports showed that the usual antiemetic agents, such as ondansetron, prochlorperazine, and promethazine, are not as effective [52]. Various treatment options have been tried in CHS, outlined in Table 3. In light of the unresponsiveness to the usual antiemetic agents, benzodiazepines, tricyclic antidepressants (TCA), capsaicin and corticosteroids have been tried with variable results [53-56]. Given the promising results from intravenous haloperidol, a double-blind, randomized controlled trial comparing it to ondansetron is currently underway [57]. Droperidol use has been reported rarely in CHS, probably because its use in the US has been restricted since the 2001 Food and Drug Administration black box warning about potential QT prolongation [58]. Nevertheless, droperidol is associated with less use of antiemetics and shorter total hospital stays [59]. Various mechanisms are involved in the cessation of symptoms via dopaminergic, serotoninergic, substance P and TRPV1 signaling. The prophylactic use of TCA for CVS has shown mixed response for the treatment of symptoms, with or without the use of cannabis [60].

Capsaicin is a topical agent that exerts its action via TRPV1 and has shown efficacy in the treatment of CHS [61]. Capsaicin has high specificity to these receptors and inhibits the release of substance P in the *nucleus tractus solitarius* and

the area postrema of the brain stem [62]. The use of capsaicin was associated with a reduction in opioids and total medical requirement in the treatment of CHS [63]. Minimal side effects, including skin irritation, have been noted. TPRV1 receptors can be activated at temperatures above 43°C, which could partly explain why pathological hot bathing can provide temporary relief in CHS [52].

The long-term treatment of CHS involves complete cessation of cannabis use and potentially a rehabilitation program. However, this requires significant effort on the patient's part [64]. The precise duration of cessation of cannabis is unknown, but has been reported to be from at least 3 months to 4 years [65,66]. This is in part due to the long half-life of THC, owing to its storage in the adipose tissue. As we acquire more data, the exact duration of cessation might be worth exploring (Table 4). It might help to refine the Rome IV criteria for the improvement of symptoms related to cannabis cessation. Furthermore, patients should be educated about the paradoxical effects of hyperemesis associated with cannabis, which could assist in the early identification of symptoms and prompt medical attention.

Concluding remarks

CHS is an important manifestation of long-term cannabis use associated with episodic nausea and vomiting, similar to CVS. Rome IV criteria provide objectivity to CHS diagnosis as significant heterogeneity was noted in the previous cases for its diagnosis. Despite this, Rome IV may underestimate CHS cases because of the lack of details about the definition of chronic use and the duration of cannabis abstinence. Pathological hot water bathing is seen in CHS patients more often than in functional nausea and vomiting, but it is neither sensitive nor specific for CHS. The ECS and ratio of THC to CBs provide important insights about cannabis's biphasic effect on emesis, and its role in affecting brain stem and HPA axis signaling. The management of CHS is mainly conservative, with aggressive volume repletion, use of antiemetics, and cannabis cessation with rehabilitation. The prevalence of cannabis use disorder is poised to increase with the decrease in its legal thresholds for recreational use. Raising awareness and availability of further CHS data in the future will pave the way for targeted novel therapeutic interventions for CHS.

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