Cannabinoid Hyperemesis Syndrome: Literature Review

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ABSTRACT

CHS is characterized by cyclic episodes of severe nausea, vomiting, and abdominal pain in individuals with a history of chronic cannabis use. Despite being paradoxical to the widely known antiemetic properties of cannabis, CHS continues to challenge healthcare professionals due to its often elusive diagnosis and mismanagement. The pathophysiology of CHS remains incompletely understood, but current research suggests that prolonged exposure to cannabinoids may disrupt the endocannabinoid system, resulting in dysregulated thermoregulation, gastrointestinal motility, and emesis. Additionally, genetic factors and individual variations in cannabis use patterns may contribute to the development of CHS. Diagnosis of CHS remains challenging, primarily based on clinical criteria, including a history of regular cannabis use, characteristic cyclic vomiting episodes, and symptom relief with hot showers or baths. Differential diagnosis must exclude other causes of cyclic vomiting, making CHS a diagnosis of exclusion. Management of CHS centers around discontinuing cannabis use, which typically leads to symptom resolution over time. Supportive care, including hydration and antiemetic medications, may be necessary during acute episodes. Capsaicin cream, a topical analgesic, has shown promise in alleviating symptoms in some cases. Behavioral therapy and substance abuse counseling may be essential to prevent relapse.

Introduction

With the legalization of recreational marijuana usage occurring across many states, questions of marijuana's effect on the human body also increased (*MARIJUANA LEGALITY BY STATE - Updated Aug 1, 2023*, n.d.). Classified as hallucinogens, cannabinoids exert antiemetic properties in the brain. This has led to the medical use of marijuana for conditions such as anxiety, chronic pain, and cancer (National Academies of Sciences et al., 2017). Over the past decade, a new disorder known as Cannabinoid Hyperemesis Syndrome (CHS) has gained increasing prevalence among young adults and adolescents. CHS is a condition characterized by severe bouts of vomiting and nausea. CHS can be potentially life-threatening due to severe dehydration. Other symptoms include frequent bowel movements, weight loss, and relief of nausea in showers (Galli et al., 2011). Usually, CHS occurs in chronic marijuana users whose onset is 3-5 years after chronic use, though recent data suggests that younger people may be at higher risk sooner (Reinert et al., 2021). Due to a lack of research and medical classification, CHS is frequently misdiagnosed due to overlapping clinical manifestations with other vomiting disorders such as Cyclic Vomiting Syndrome (CVS) and Hyperemesis Gravidarum (Eleonore & Denis, 2019). The mechanism for CHS is not clearly understood. However, recent evidence suggests a paradoxical effect on the gastrointestinal tract or susceptibility to genetic mutations (Perisetti & Goyal, 2022).

The purpose of this literature review is to clearly define CHS by analyzing the current clinical guidelines, understand the prevalence of CHS amongst certain populations, analyze the potential causes and diagnosis, and study the current treatment and management of the syndrome. The review aims to spread further awareness of CHS and offer recent insights to the scientific community to better understand this syndrome.
Inclusion criteria:

28 studies were selected from a bibliographic search of scientific articles from 2011 to 2022 in the PubMed database. Key search words used were “cannabinoid” “hyperemesis” and “cannabis.” All relevant articles were thoroughly evaluated and used.

Results

Section 1: How CHS is Defined and What Is It

CHS can be defined by three phases: prodromal, hyperemetic, and recovery. The prodromal phase often manifests as nausea (Eleonore & Denis, 2019). This may also lead users to intake more cannabis due to their belief that it will provide antiemetic effects. In the hyperemetic phase, users undergo severe episodes of nausea and vomiting, weight loss, loss of appetite, and a compulsive need for hot bathing. Patients can vomit up to 5 times per hour, causing fatal dehydration without treatment (Galli et al., 2011a). Relief by showering rapidly becomes a compulsive behavior that remains temperature dependent; the hotter the water the more relief is experienced (Eleonore & Denis, 2019). The hyperemic stage resolves within 48 hours, often with anti-emetic and fluid medications. At the recovery phase, the user returns to normal patterns of eating, bathing, and weight patterns. Recovery can be interrupted with cannabis use. Abstinence from cannabis is the only known effective treatment to prevent future occurrence of CHS (Galli et al., 2011).

Since CHS does not have an official medical code, there have been multiple proposals of a diagnosis criteria to further the definition of CHS. A clinical criteria proposed by Simonetto et. al has been widely used across CHS studies, which encompasses a major and minor criteria for specific symptoms. The major criteria includes severe cyclical nausea and vomiting, resolution of symptoms upon stopping cannabis use, symptomatic relief by taking hot showers, abdominal, epigastric, or periumbilical pain, and weekly cannabis use. The minor criteria includes weight loss under 5 kilograms, age less than 50 years, morning predominance of symptoms, normal intestinal transit, negative laboratory results, radiological, and endoscopic tests. Although this criteria has been widely used, it is important to note that the Simonetto review is from 2012, and may require some updates.

Another widely used criteria is the Rome Base IV criteria, which was established in _____ as an attempt to improve existing CHS guidelines. Similar to the Simonetto criteria, the Rome IV criteria states that episodic vomiting resembling cyclic vomiting syndrome in terms of onset, duration, and frequency with presentation of prolonged excessive cannabis use and relief of vomiting episodes by cessation of cannabis use are symptoms to define CHS. The ROME IV criteria regards these symptoms as essential in terms of diagnosing CHS unlike Simonetto’s, viewing minor criteria symptoms from Simmoneto’s guidelines as having the potential to be a part of another disorder. Although the ROME IV criteria was more recently established than its predecessor, Simonetto, the guidelines may not be centered around real-world application, as they may be more tailored to clinical research and trials as noted in a study ((Perisetti & Goyal, 2022)).

There have been a multitude of unofficial proposals for CHS diagnostic criteria. A 2009 case study of a 22-year-old male by Sonteneti et al found that treatment with intravenous fluids led to improvement of symptoms. Although this cannot be generalized, the study proposed that cyclic vomiting, hydrotherapy, abdominal pain, and no evidence of pancreatic inflammation should be a part of the CHS diagnostic criteria. Rotella et al. used a standardized data collection tool to extract relevant clinical and demographic data including the patient’s age, sex, cannabis use history (amount, frequency, form used), and presence of cyclic vomiting to complement the Simonnetto criteria.

A highly debated component of CHS diagnostic criteria is the categorization of hot bathing as a main symptom. The heterogeneity among patient cohorts in terms of hot bathing prevalence makes it difficult to determine whether hot bathing should truly be considered as a main symptom. A study of 142 patients revealed

that relief from hot bathing was only found in 10% of CHS cases (Rotella et al., 2022). This is unlike Simonetto et's cohort, in which 91% of patients underwent hot bathing. In another study, bathing behavior was reported in 29 out of 31 previously reported cases of CHS (Osagie & Mirza, n.d.). The general consensus among medical professionals is the need to educate patients of the risk of severe burns while hot bathing (Lapoint et al., 2018). A recent case study analyzed a 36-year-old female who was diagnosed with CHS and reported severe chest burns from hot bathing (Osagie & Mirza, n.d.). Although this is the first of severe burn cases, the transparency of risks behind hot bathing should still be conducted. One study created a medical acronym for CHS diagnosis, CHUNDER: cyclical nausea/vomiting, history of regular cannabis use, under 50 years of age, normal lipase, diagnosis of exclusion, elevation of CRP less than 50 mmol/l, and reduction in symptoms after droperidol (Rotella et al., 2022). Generally, it can be concluded that CHS manifests as emesis, as in all patient cohorts reviewed, 100% had cyclic vomiting (Eleonore & Denis, 2019; Lapoint et al., 2018; Rotella et al., 2022; Simonetto et al., 2012).

The current status of CHS shows that minimal progress has been made despite the growing number of cases in the U.S. There is no official diagnostic guideline or diagnostic code at present, making misdiagnosis common and patients often having to undergo unnecessary, invasive procedures such as radiation and advanced imaging (Lapoint et al., 2018). Treatment options remain relatively the same with complete abstinence from cannabis being the only truly effective option (Senderovich et al., 2022). It is estimated that 3 out of 10 people who use marijuana will develop a cannabis disorder, the risk growing higher if usage begins before 18 years of age (*Addiction | Health Effects | Marijuana | CDC*, 2022).

Section 2: Prevalence of CHS

Cannabis is the most widely used drug in the world, not only in the United States. CHS was first reported in Australia in 2004, with a series of cases that consisted of cyclic vomiting and nausea episodes with relief obtained through hot water bathing (Eleonore & Denis, 2019). Since then, 2.75 million Americans are estimated to have possibly suffered from CHS (Rotella et al., 2022). In a 2021 study, the number of adolescent (13-21 years old) visits to the ER or urgent care for cannabis-related issues has more than doubled since legalization. For adults, ER visits doubled for Cyclic Vomiting Syndrome (CVS), which is often confused with CHS. Hospitalizations for CVS increased from 46% to 100% (Cordova et al., 2021). A 2019 study based in Ontario, Canada confirmed that after commercialization of cannabis (full legalization and marketing), there was a large immediate increase in CHS visits per capita and per other types of ED visits (Myran et al., 2022). Younger individuals (below legal age) with CHS did not increase but those within the legal age did, suggesting legalization could increase more CHS cases as well as the possibility of higher potency.

CHS generally occurs in adults 50 years old or younger ((Rotella et al., 2022; Simonetto et al., 2012)). A 2021 research study of adolescents reported the median age was 17.7 years old. All patients reported use of marijuana within one month, mostly through inhalation or edibles. They also reported two-week emesis and abdominal pain (Cordova et al., 2021). A 2021 literature review solidified that adolescents mainly share the same major and minor diagnostic criteria as proposed by Simonetto et. al, with 21% of CHS adolescent patients having a history of anxiety and depression. It appears people are at a higher risk of CHS if they use cannabis as an adolescent. Overall, the CHS adolescent population is likely to increase due to the increasing access of cannabis amongst youth populations (Zhu et al., 2021).

It is regarded that CHS is more prevalent in males than females. A 2016 systematic review reported 154 males (72.9%) and 57 females (27.1%). The median age at diagnosis was 28 years (Sorensen et al., 2017). On the other hand, a 2018 study claimed that there is no notable difference in CHS demographics at all, noting that 53.6% of females and 46.4% of males met the CHS diagnostic criteria through a survey (Russo et al., 2022). CHS seems to be more prevalent in females when they are adolescents (Zhu et al., 2021).

A 2019 study proposed that young males are more than twice as likely to have schizophrenia with frequent cannabis use, and that there may be an association between CHS and schizophrenia (Eleonore & Denis, 2019). In 2023, the association of schizophrenia and cannabis use disorder was confirmed with a heavy emphasis on younger people. Manseu and Goth hypothesized that 30% of cases of schizophrenia among men aged 21-30 might have been prevented by averting cannabis use disorder, defined as someone being unable to use marijuana despite it causing social and health problems. (HALL & DEGENHARDT, 2008).

It's important to note that the majority of studies on CHS study patient cohorts that are predominantly self-reported as Caucasians. A longitudinal study that analyzed a predominately African American population (90%) reported a mean age 30 years of subjects. The common clinical manifestations included nausea, vomiting, chills, and diarrhea ((Ma et al., 2021)). The rate of CHS ED visits was highest in individuals aged 19 to 24 years and those living in the lowest income quintile neighborhoods in Canada. There is relatively little evidence confirming if CHS is predominant in one race or social class. CHS has varying evidence on median age and gender, raising more questions about the illness (Ma et al., 2021).

Causes of CHS

The exact cause of CHS currently remains unknown. However, there have been multiple proposed causes of CHS. CHS has been proposed to be a gut-brain axis disorder (Perisetti, 2020). There has been increasing evidence of cannabis's antiemetic properties that may trigger CHS, specifically with the endocannabinoid system (ECS). One of the most important factors in the pathophysiology of CHS is the downregulation of cannabis receptors-1 (CB1) in genetically at-risk individuals (Eleonore & Denis, 2019). The CB1 receptor has effects on anxiety, depression, gastrointestinal secretions, and appetite control. The CB2 receptor is associated with the immune system and has effects on nociception and inflammation due to being outside of the CNS. The ECS causes constant negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis. The stimulation of the CB1, CB2, and TRPV1 receptors can cause a loss of negative feedback, leading to increased vagal tone that leads to vomiting. Neurotransmitters, which are influenced by cannabinoids, exert their effect on the vomiting center of the brain stem (Eleonore & Denis, 2019; Iacopetti & Packer, 2014; Perisetti, 2020). Hyperemesis may be secondary to brainstem or neuronal effects. When there is chronic overstimulation of the CB1, CB2, and TRPV1 receptors, it could trigger vomiting. It is concluded that cannabis can cause a paradoxical effect, as it can be anti-emetic and pro-emetic at the same time (Galli et al., 2011b; Lua et al., 2019; Perisetti, 2020). Ingesting high amounts of cannabis along with a higher potency could contribute to a higher chance of the paradoxical effects of cannabis (Myran et al., 2022; Perisetti, 2020). The ECS in relation to the cannabinoid receptors is illustrated in Figure 1.

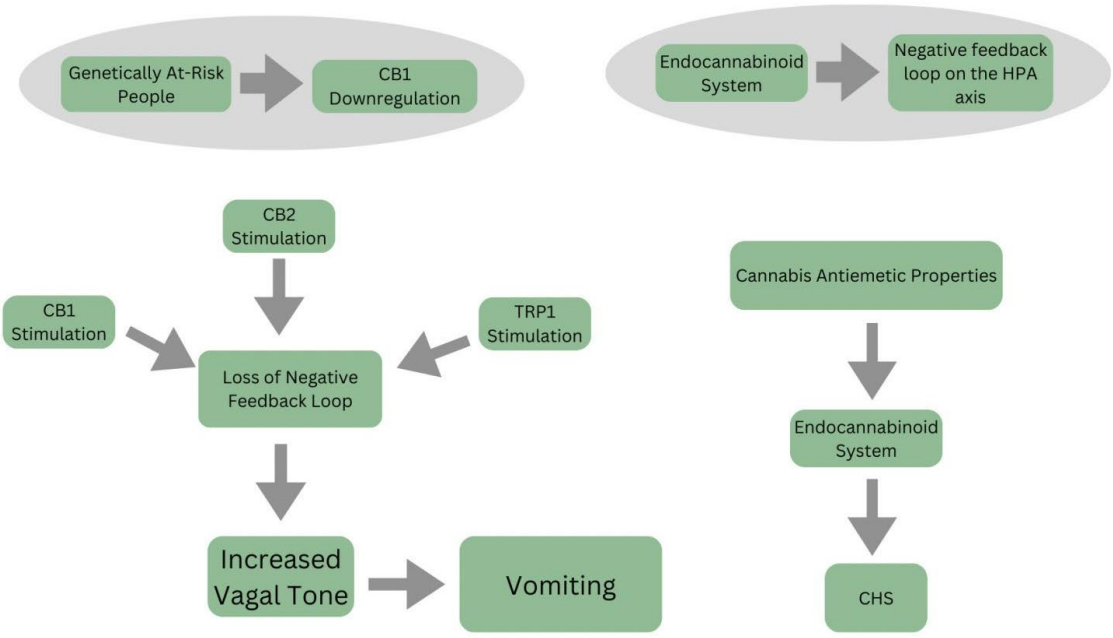

Figure 1. Potential pathophysiology of Cannabis Hyperemesis Syndrome

There has also been evidence of CHS occurring only in genetically at-risk individuals (Perisetti, 2020; Senderovich et al., 2022). In a genomic survey of 205 qualified participants from a CHS screening questionnaire revealed an association with CHS susceptibility and mutations in genes COMT, CRYPT9, transient receptor potential vanilloid receptor 1 (TRPV1), transient receptor potential vanilloid receptor 1 (DRD2), and ATP-binding cassette transporter gene (ABCA1). These genes affect the neurotransmitters, endocannabinoid system, and the cytochrome P450 complex associated with cannabinoid metabolism ((Russo et al., 2022). This could mean that CHS is a genetic disorder, but more studies need to be conducted to prove this significance.

Another crucial factor to consider is the current composition of the cannabis-stevia plant. The plant's composition has been increasingly changing, specifically with regards to higher THC levels. The potency has been increasing since 1970, increasing by approximately 5.7 milligrams each year, possibly due to a shift in the way cannabis is produced (ElSohly et al., 2016; Freeman et al., 2021). High potency cannabis can lead to dependency and increased risk of psychosis amongst other mental health disorders (Petrilli et al., 2022). There is no research to confirm that the level of THC is beneficial for a medical condition. Higher THC levels could possibly be contributing to chronic cannabis use, thus contributing to CHS. There have been no studies analyzing higher THC levels in relation to CHS specifically.

Misdiagnosis of CHS

Due to the lack of medical code and official diagnostic criteria, CHS patients are often misdiagnosed and are subject to invasive procedures. One of the most frequent causes of misdiagnosis of CHS is the lack of transparency in self-reported use of cannabis products by patients. In a pediatric study, nearly all 15 patients did not initially admit to marijuana use (Cordova et al., 2021). This could contribute to a delay in proper diagnosis. The most common misdiagnosis for CHS include migraine headaches, hyperemesis gravidarum, Addison's disease, psychogenic vomiting, bulimia, and Cyclic Vomiting Syndrome (CVS) (Eleonore & Denis, 2019).

CHS is accepted as a variant of CVS with chronic cannabis use as part of the differential diagnosis. However, this may also lead to multiple misdiagnoses due to their overlap in clinical symptoms. A study found that up to 6% of people who visited the emergency room (ER) for vomiting had CHS (Hernandez et al., 2018). Since CHS and CVS share many of the same symptoms, such as abdominal pain and relief from hot bathing, it can be difficult to differentiate the two disorders. Up to 50% of patients with CVS also find relief in hot showers. CVS, like CHS, affects young males more. However, CVS is not usually associated with substance use and is caused by psychological stressors or family history (Perisetti, 2020).

The misdiagnosis of CHS can cause a multitude of complications. Individuals with CHS have reported severe complications such as acute kidney injury, electrolyte disturbances, rhabdomyolysis, seizures, cardiac arrhythmias, and shock. Early diagnosis and rehydration therapy can prevent these complications (Perisetti, 2020.) Quantitative urinary THC-COOH levels obtained through gas chromatography or mass spectrometry may be able to help identify individuals at risk for CHS. The typical urine drug screen commonly used for THC is inadequate for determining frequency or timing of cannabis. The gas chromatography mass spectrometry urine testing showed that 14 out of 15 patients had urinary THC-COOH concentrations > 100 ng/ml, with seven individuals having >500 ng/ml. Urine immunoassay of THC-COOH levels corresponded to recent cannabis use. This could be an effective procedure in determining the diagnosis for CHS (Cordova et al., 2021).

Treatment and Management of CHS

Currently, the only known effective treatment of CHS is complete abstinence from use of cannabis products along with hydrotherapy for patients with active CHS (Sontineni et al., 2009). Medical professionals should assist in educating CHS patients about fatal risks of CHS and cannabis' paradoxical emetic effects. General awareness of CHS and dependency assistance may also be helpful.

There are many medications that could serve as a potential treatment to CHS, but it should be cautioned that these drugs are not fully effective and may yield significant side effects. Topical capsaicin cream on the abdomen or back of the arms have shown short-term success with treating CHS, which interacts with the endo-cannabinoid system through TRPV1. Capsaicin cream works similarly to hydrotherapy and reduces nausea by 46% versus the placebo at 24.9% in a study of 30 patients. Some patients reported complete relief with capsaicin cream (Dean et al., 2020; Senderovich et al., 2022). Dopamine antagonists, such as Droperidol, can be used as an antiemetic and antipsychotic agent. Usage showed significantly decreased nausea and decreased need for other antiemetics (Senderovich et al., 2022). Haloperidol, an antipsychotic, has been used in management of CHS for severe cases. A single patient reported complete cessation of refractory nausea/vomiting and abdominal pain with no recurring symptoms after usage of haloperidol, but this has limited generalizability as most evidence was found in case studies (Senderovich et al., 2022). Propranolol and Aprepitant have worked for single case studies. Capsaicin and haloperidol are the only treatments with efficacy, but haloperidol should be used with caution as it can cause acute dystonia (Senderovich et al., 2022). Overall, capsaicin cream is the first-line of treatment to address CHS because of its low side effects and cost-effectiveness, but more studies need to be conducted as all of these treatments have mixed evidence Lapoint et al., 2018; Sabbineni et al., 2023; Senderovich et al., 2022).

Patients with comorbidities could face adverse side effects with the use of these drugs, such as drug interactions between chemotherapy drugs and cannabinoids can cause adverse effects (Senderovich et al., 2022). Supportive therapy such as hydration through IV could be helpful. If a patient suffers from CHS multiple times despite being aware of cannabis's effects, they may need to be referred to an addiction specialist (Lapoint et al., 2018). It should be noted that the sudden cessation of cannabis may cause intense withdrawal symptoms such as a decreased appetite, restlessness, and anxiety (Connor et al., 2022). In multiple case studies, patients who stopped using marijuana completely did not have another CHS episode (Lua et al., 2019; Sontineni et al.,

2009). Although death from CHS alone is rare, there have been two recorded deaths from CHS that could raise concern(Nourbakhsh et al., 2019).

Discussion

Due to the rising prevalence of CHS, more research should be conducted to discover why CHS occurs in some individuals and not others as well as treatment options. CHS is often regarded as a "mysterious illness" that is described as rare due to the high level of misdiagnosis. Healthcare providers should seek to further educate the general public of CHS with a focus on people aged 30 and younger. Awareness of marijuana's antiemetic effects and its relation to CHS should be emphasized as well as the risks and consequences of using cannabis daily.

There appears to be little to no data surrounding how frequent CHS is in specific regional areas. In states such as Massachusetts, recreational marijuana use is legal. It would be beneficial to conduct a regional study on CHS in the U.S to determine if it is more prevalent in one area and if legality affects the number of CHS cases. Further pediatric research of CHS would be useful in determining to what extent CHS needs to be talked about in primary education schools.

Many patients refuse to admit to using marijuana and often undergo invasive procedures as a result. Creating a comfortable environment for those who may have CHS as well as implementing new urinary tests may assist in reducing the number of misdiagnoses. Death from CHS is rare, but lack of awareness regarding the illness may lead to dangerous, recurring symptoms. Currently, there seems to have been no significant progress made to CHS other than more proposals for treatments, testing, and diagnostic criterias. This may be due to the lack of general knowledge about CHS or a lack of urgency for treating it.

While cannabis is generally considered to have relatively low potential for physical dependence compared to substances like opioids, CHS serves as a reminder that long-term and heavy use can still have significant and unexpected health consequences for some individuals. It is important to recognize CHS in hospitals and effectively treat it with the current information about CHS.

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