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Cannabinoid hyperemesis syndrome: Prevalence and management in an era of cannabis legalization

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Abstract

As more states legalize cannabinoid products for recreational use and medicinal purposes, the prevalence of cannabinoid hyperemesis syndrome has become increasingly common. Yet, it remains unrecognized to many healthcare providers along with the most efficacious treatments. Cannabinoid hyperemesis syndrome most often presents with episodic vomiting secondary to chronic daily cannabis use over several months to years. Patients often complain of nausea and abdominal pain that is improved by taking hot showers or baths. Symptoms are alleviated with the cessation of cannabis use over a period of 6–12 months. Treatment for acute attacks often consists of parenteral benzodiazepines in the inpatient setting. Long-term management and prevention of further attacks are aided by tricyclic antidepressants such as amitriptyline with a dose range of 50–200 mg/d. Once a patient is in remission, amitriptyline can be tapered slowly. As cannabis becomes more widely available and accepted in the continental United States, so must education on the diagnosis of cannabinoid hyperemesis syndrome and treatment strategies.

Keywords

Cannabinoids, vomiting

Introduction

Cannabis has been a known psychoactive substance for millennia. One of the earliest mentions of cannabis can be found in the Ebers Papyrus from the 16th century BC.[1] Marijuana was introduced in the United States at the beginning of the 20th century and was officially banned in 1937 when the Anti-Marijuana law was passed after the US government bowed to pressure from drug enforcement agencies. This was done as agencies feared other restrictions on drugs such as cocaine, opiates, and chloral hydrate would cause Marijuana to become a replacement for those who relied on these substances.[2] Currently, 21 states have legalized marijuana for recreational use and 37 for medicinal use. In 2021, cannabis was a $15 billion industry and is expected to surpass $25 billion by 2025. Cannabinoid hyperemesis syndrome (CHS) was first reported in Australia in 2004.[3] As the use of marijuana increases, CHS has become increasingly prevalent with patients presenting to the hospital with abdominal discomfort, paroxysmal nausea, vomiting, and dehydration.

Cannabis use over a range of months to years has been found to predate the onset of episodes of cyclic vomiting. Along with the advent of growing and breeding cannabis, there has been an increase in the concentration of tetrahydrocannabinol (THC) and other marijuana compounds.[4] The authors speculate that shorter time periods prior to symptom onset can be expected. The frequency of marijuana use affects the onset prior to symptom manifestation. Patients who smoke monthly or weekly will have longer times of onset to symptomology than compared to those who smoke daily. One small-scale study completed by Allen et al. looked at nine patients with CHS and found that all patients had relief of their symptoms after discontinuing cannabis. Three of these patients later restarted using cannabis and had a return of their symptoms.[3]

Patients with CHS often seek hot baths or showers as it helps alleviate symptoms. In some cases, patients have been documented to bathe up to 20 times per

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day.[5] This may be due to the relaxing nature of heat or other central nervous system mechanisms that remain to be clarified. Another theory for hot showers alleviating symptoms is thought to be due to cannabinoids binding to cannabinoid binding receptor-1 (CB1) in the hypothalamus, causing a dose-dependent hypothermic effect in the thermoregulatory center of the brain.[6,7] Also proposed is the theory that cutaneous vasodilation from hot water alters both the core temperature and splanchnic circulation alleged to be contributing to abdominal discomfort, this theory has been coined as "cutaneous steal" syndrome.[5,8]

Episodes typically are cyclical in nature and can occur every few weeks or even months. Patients often report intense morning nausea and forceful vomiting which can be bilious in nature and can become intractable for hours with patients occasionally developing blood-tinged or frankly bloody emesis from a mucosal tear, at the gastroesophageal junction termed Mallory Weiss syndrome. Abdominal pain, specifically epigastric and periumbilical pain, accompanies the vomiting. Pain is consistently present from the onset of the vomiting cycle. Episodes most commonly last up to 48 h but occasionally can extend for several days.[9] CHS differs from cyclic vomiting syndrome in that patients are less likely to have a concomitant history of migraines or extreme stress in their lives and daily marijuana use dominates the clinical picture. Patients presenting to the emergency department are a real diagnostic challenge. Their accompanying abdominal pain often leads to extensive CT imaging or laboratory tests to exclude pancreatitis and even porphyria. Over time with recurrent emergency department visits, these patients are often stigmatized as opiate pain seekers. Narcotics do not provide symptomatic relief and may worsen symptoms which also adds to the stigma of pain-seeking as patients continue to request medication to help alleviate their symptoms.

Epidemiology

The profile of patients at risk of developing cannabis-related disorders is a broad spectrum with the commonalities being male gender and degrees of underlying stress in their lives.[10,11]

The United Nations estimated that 192 million persons had used cannabis in 2020 worldwide.[12] In North America, it has been estimated to be 12.4%.[13] Cannabis is the third most used controlled substance, only secondary to tobacco and alcohol. High-income countries have the highest prevalence of cannabis use with less but increasing use in low-income countries. Estimates show that 9.9% of individuals who reported cannabis use in the last year were daily or near-daily users.[12]

Marijuana crops can be susceptible to plant pathogens, such as hop latent viroid. This is known to cause painful sickness in very small quantities, regardless of whether it is ingested or inhaled. It has been suggested that having poor-quality crops has become the norm as crop disease has continued to be unchecked for many years.[14] Trichomes form a resin barrier that helps protect the plant and are generally where the highest concentration of THC is located.[15,16] Crops infected with Hop Latent Viroid often are found to have decreased resin in the trichomes (see Figure 1). Plants without resin are more susceptible to insects, pesticides, fungicides, and other diseases. It has been postulated that an increasing frequency of CHS can be related to the huge

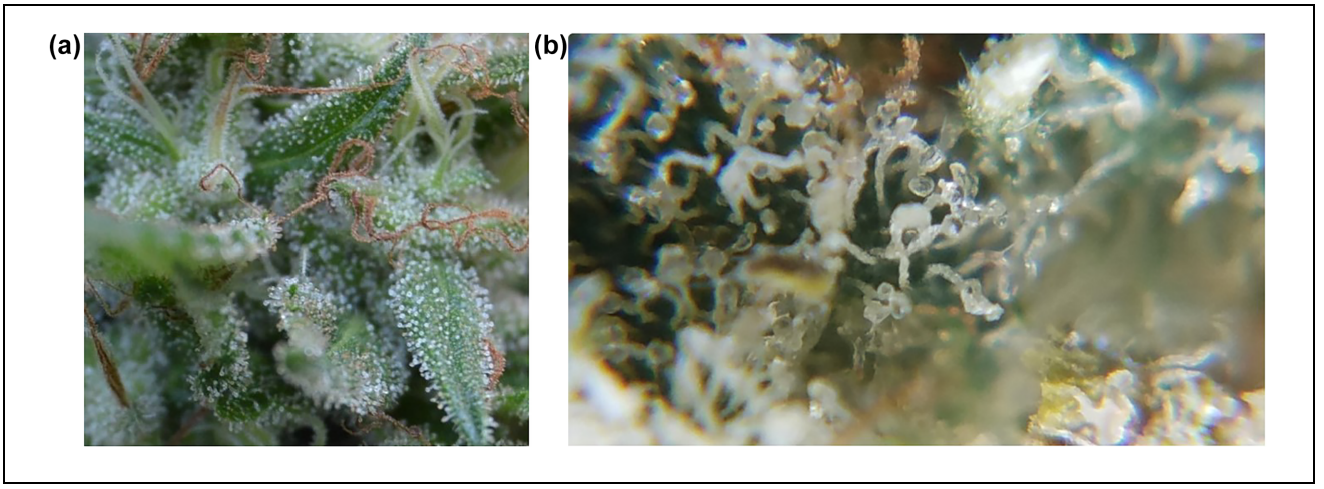

Figure 1. (a) A healthy marijuana plant with normal trichomes. (b) Abnormal trichomes with sparse resin secondary to Hop Latent Viroid Infection and its ingestion can cause toxicity.

surge in planting and growing marijuana and the resultant poor crop quality co-explained by contamination resulting in a toxic outcome.[17]

Pathophysiology

Researchers have postulated that one mechanism for CHS might be due to toxicity and disruption of the hippocampal–hypothalamic–pituitary level.[18–20] Pituitary hormones are affected by chronic cannabis use in that growth hormone, follicle-stimulating hormone, and luteinizing hormone levels have been reported to be decreased.[21] Cessation of cannabis use showed a return to baseline levels of pituitary hormones.[22]

Another proposed mechanism for CHS is through marijuana binding to CB1 receptor sites in the brain.[23] CB1 modulates gastric secretion, motility, inflammation, and sensation. Activation of the CB1 receptors causes inhibition of the hypothalamic–pituitary–adrenal axis and sympathetic systems.[24] CB1 receptors are localized in the cerebral cortex, anterior cingulate gyrus, hippocampus, cerebellum, and basal ganglia.[25] Within the gastrointestinal system, the enteric nervous system serves as a major sight of action with CB1 receptors being found on both intrinsic and extrinsic neurons.[26] Cannabinoid binding receptor-2 (CB2) is expressed in the lamina propria plasma cells and activated macrophages. CB2 activity is thought to play a role in inhibiting inflammation, visceral pain, and intestinal motility in the gut.[25,27] The chemoreceptor trigger zone sends a signal to the efferent vagus nerve and triggers a sensorimotor, parasympathetic, and sympathetic nervous system response through the afferent vagal nerves. This, in turn, triggers the emetic reflex which leads to increased salivation, deep respiration, and closure of the glottis, relaxation of the pyloric sphincter, and retroperistalsis from the stomach and small intestine. This is then followed by the contraction of the abdominal muscles (see Figure 2).[24]

Cannabis is thought to trigger the upregulation of the CB1 receptors in the hypothalamus and amplifies the hypothermic effects caused by THC.[29] The effect of cannabis is biphasic with low concentrations having an anti-emetic effect and high concentrations inducing vomiting.[30–32] Delta-9-THC has been found to act as a partial agonist on CB1 receptors.[33] This has led to the theory that high tissue concentrations, from chronic use, may lead to an antagonistic effect that could cause withdrawal symptoms which include vomiting.[34] An antagonistic effect of CB1 receptors could potentially cause the release and turnover of emetogenic transmitters such as serotonin, dopamine, and substance P.[35,36] It has been postulated that downregulation desensitization or internalization of CB1 receptors due to chronic cannabis use could be the cause of CHS.[6,7] This process may decrease the effectiveness of the endocannabinoid feedback inhibition and allow excess excitatory activity in the brainstem or the gastrointestinal system leading to hyperemesis.[34]

Another possible mechanism for CHS is sympathetic nervous symptom dysfunction. The hyperemesis phase of CHS often has tachycardia, diaphoresis, hot flashes, hypertension, and tremors, all of which support sympathetic nervous system dysfunction.[37]

Cannabinoids are extremely lipophilic and have a high propensity to bind to cerebral fat, which creates a reservoir of THC in adipose tissue and may produce a re-intoxication effect secondary to increased levels of stress or food deprivation.[38] Other studies have found that chronic marihuana use may inhibit or impair gastric emptying which could lead to nausea and even vomiting in the postprandial setting. This was demonstrated in a

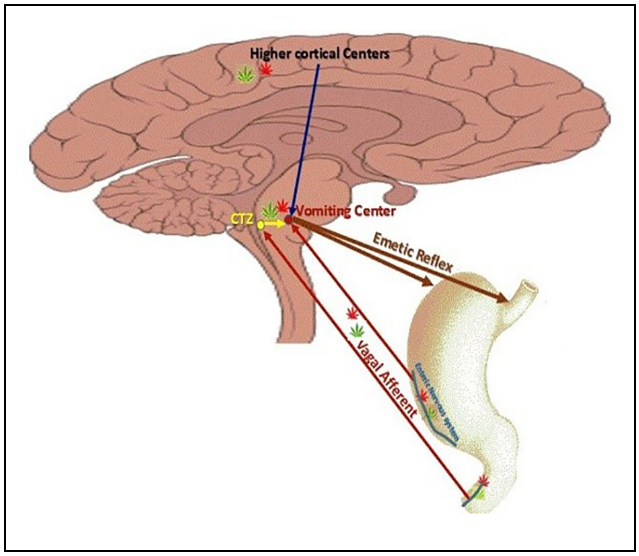

Figure 2. The nausea and vomiting pathways in the endocannabinoid network, and enteric nervous system. Both cannabinoid receptors 1 (green leaf) and 2 (red leaf) are located in the enteric nervous system as well as the enteric mucosa. The CB1 and CB2 receptors are found in the brainstem and the CNS which are the main centers of nausea and vomiting. The brainstem receives signals from the higher CNS centers which are involved in the processing of nausea and vomiting. The brainstem also receives signals from higher CNS centers involved in the processing of nausea and vomiting and is affected by endocannabinoid signaling. Activation of the cannabinoid-1 and cannabinoid-2 receptors alleviates nausea and vomiting through central and peripheral mechanisms. In cannabinoid hyperemesis syndrome, mechanisms related to the dysregulation of central neural pathways and neuroendocrine mediators involved in the afferent and efferent brain–gut pathways result in the induction of the chemoreceptor trigger zone which induces periodic nausea and vomiting.[28]
CNS, central nervous system.

study by McCallum et al. in 1999 when marijuana or placebo was administered to male volunteers prior to undergoing a radionuclide gastric emptying study.[39]

Clinical presentation

CHS has three proposed phases which include the following: the pre-emetic or prodromal phase, the hyperemesis phase, and a recovery phase. The prodromal phase can last for months with patients developing morning nausea, abdominal discomfort, or fear of vomiting.[40] In this phase, patients often continue to eat normally and maintain normal weight and functionality at work. During this phase, patients continue to use cannabis because of the believed antinausea properties.[41,42]

The hyperemesis phase evolves when patients present with dramatic symptoms which can build to a maximum within a few hours. Patients present with an upset stomach, paroxysmal persistent nausea, vomiting, and often feel episodes of imminent relapse. Patients often describe episodes as debilitating and overwhelming. During this phase, patients can vomit and retch up to five times per hour.[40]

The recovery phase can last from days to weeks, and patients can slowly resume normal eating and dietary habits. There can be days, weeks, or even months of complete quiescence where there is sustained relief.[37] This time frame is variable with a possible return to marijuana use inducing relapse. During these time periods, patients are functional and can maintain normal weight.

Upon presentation to the emergency department, patients in the hyperemesis phase are often found to have hypokalemia, volume depletion, acute renal failure, hypophosphatemia, and may have mild reactive leukocytosis. Mallory Weiss tears with hematemesis are another presentation due to multiple and forceful vomiting events, rarely leading to pneumomediastinum or Boerhaaves syndrome.[25,43,44] The abdominal pain usually begins as epigastric and then becomes more diffuse and often leads to an expensive workup including biliary scans to evaluate for acute cholelithiasis, choledocholithiasis, or CT imaging to exclude pancreatitis.

Acute treatment strategies and pharmacologic agents

Treatment of acute CHS flares should focus on IV rehydration and correction of electrolyte imbalances. Patients respond well to 1–2 mg of IV Lorazepam (Ativan), every 4–6 h. Ativan is thought to work by inducing sleep, decreasing CNS activity, and reducing the patient's awareness of pain. This decreases the need for narcotics, which should be avoided. If Ativan treatment fails or patients have allergies, Haloperidol can be used as an alternative second-line agent.[28] Haloperidol is a dopamine antagonist that has often been used as an IV antiemetic.[45] Similarly, Ativan is thought to work by inducing sedation in patients and by reducing pain and anxiety.[46,47] There is also some evidence that Haloperidol may possibly interact with the CB1 receptor.[46–50]

If patients do not obtain significant relief from either Ativan or Haldol, then Aprepitant is a medication that has shown efficacy in treating moderate to severe cyclic vomiting syndrome (CVS). It can be considered if other regimens are failing. Aprepitant is a Neurokinin 1 Receptor (NK1) antagonist. Blocking NK1 receptors found in the dorsal vagal complex in the brain stem blocks the ability of substance P to bind to the receptor thwarting its activation.[51]

In patients who are unable to keep medications down due to severe vomiting. A scopolamine patch can sustain an antiemetic environment for up to 3 days as it guarantees absorption between doses of oral and parenteral medications. Scopolamine is an antimuscarinic agent that has been commonly used as an anti-nausea medication and for motion sickness.[52]

Another treatment modality that has shown some efficacy is the topical application to the abdomen with Capsaicin as it binds to the Transient Receptor Potential Vanilloid-1 Receptor (TRVP-1). TRVP1 receptors are found in proximity to CB1 receptors, which may suggest a functionally combined mechanism.[47] Carnett's sign is the term used when abdominal pain is induced by tightening the abdominal muscles or by straight leg raising. Lidocaine patches have been proposed as a relaxant for the rectus muscle and could alleviate abdominal pain in acute flares.

Long-term strategies

Long-term treatment in the recovery phase relies on sending patients home with tricyclic therapy. This can consist of amitriptyline with a dose range of 25–200 mg/d. If amitriptyline is not tolerated, which is usually due to sedation, then another tricyclic antidepressant such as doxepin may be used. The dose range starts at 10 mg and increases by a factor of 10 mg until symptoms are controlled.[53,54] Doxepin is generally better tolerated with less sedation than amitriptyline. Long-term treatment can be started in the emergency department or the hospital and dosage can be titrated during outpatient care. One study that compared CVS with CHS showed that both groups reported improvement in pain with a 70% improvement in the CHS group and an 80% improvement in the CVS group upon receiving treatment with amitriptyline.[28]

Patients must discontinue using cannabis to recover from CHS. Involving family to provide additional history, assist in monitoring the patient's progress and adherence to treatment, and provide therapeutic support can help aid a patient's recovery. The first-line strategy includes psychosocial interventions such as cognitive behavioral therapy or motivational enhancement therapy. The goal of helping patients recover is to enhance motivation to discontinue cannabis use, improve social interactions and skills, improve interpersonal functioning, manage painful feelings, and provide education about the consequences of cannabis use. Patients who do not have access to structured psychotherapy programs can be referred to addiction counseling and mutual-help groups such as Marijuana Anonymous.[55] Withdrawal symptoms can often play a role in the hesitancy of patients to stop using cannabis. Symptoms often include loss of appetite, anxiety, depression, physical tension, and insomnia.[56] Using amitriptyline and Lorazepam is an appropriate strategy to slow withdrawal symptomology.

Interview with JR who was diagnosed with CHS:

> One of the worst parts, for me at least, is the anxiety. Knowing once you start to vomit, you can't stop. It scares you. The anxiety builds up which compounds and leads to you being even sicker.
>
> I used to describe it as Pig Pen from Peanuts. How he's dirty and has that scramble around him. It feels like that and because you're anxious you can't calm down and it keeps spiraling. Sleep is the only thing that helps, but it is hard to calm down enough to sleep.
>
> For CHS, I think the worst thing is the patient care. Whenever hospitals hear it's about weed, they start to treat you like you're dumb or crazy. It's why I always ended up staying longer in the hospital, I always waited until the last moment to go in, dreading the whole experience.
>
> They usually treat you with some pain meds, anxiety meds, and something for nausea. But it's such a small dose that it doesn't last more than a couple of hours. They also often give Haldol. Which doesn't work for everyone or every time. The medical personnel always treated you like you were a drug seeker.
>
> To be honest, I never really paid attention to my symptoms until they got bad. I started using marijuana when I was in High School, so I was 15 or 16 years old. I was mistakenly diagnosed with cyclic vomiting syndrome before CHS. My first hospitalization, where I was diagnosed with CHS was almost 10 years later. I quit many times as everyone does, I told myself it wasn't weed. But every time I went back to it, I would be ok for a little while and then it would hit me harder than it did before.
>
> Usually, whenever I had an episode, my symptoms would alleviate in a couple of days to a week depending on how dehydrated I was. They would keep me in the hospital for a good week only because I'm diabetic and would usually end up in diabetic ketoacidosis.
>
> Also, I found that smoking weed as opposed to ingesting weed-infused food like gummies or brownies was worse. I'm a part of CHS recovery groups who also say that their episodes are triggered and worse when they smoke. My last ER visit was only an afternoon ordeal as opposed to a week because I only ingested a gummy.

Conclusion

As the use of cannabis expands with increased legalization in the United States for recreational and medicinal purposes, we can expect to see CHS prevalence become more commonplace. Although it has been almost 20 years since CHS was reported in Australia, CHS remains unfamiliar to many practitioners, as do the current acute and long-term treatment strategies. Continuing education and awareness of the disorder will be key in diagnosing and treating the disorder in the future as the prevalence of CHS continues to increase. This review article provides up-to-date information on the clinical spectrum of this entity highlighting management strategies as well as re-visiting concepts of its pathophysiology.

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