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# Cannabinoid Hyperemesis Syndrome: An Update for Primary Care Providers

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**ABSTRACT**

Cannabis is the most commonly used recreational drug worldwide. Crossbreeding and genetic modification techniques have dramatically increased the delta-9-tetrahydrocannabinol content, with resultant increased rates of cannabis use disorders and other toxic effects among users. Cannabinoid hyperemesis syndrome (CHS) is a recently identified disorder and should be considered as a differential diagnosis in patients exhibiting recurrent symptoms of abdominal pain, weight loss, intractable vomiting, and compulsive bathing. Treatment includes vigorous rehydration with intravenous fluids, antiemetics, proton pump inhibitor administration, weight monitoring, and cannabis use cessation. Awareness of CHS symptomology and clinical management strategies can prevent extensive diagnostic workups and unnecessary hospitalizations.

**Keywords:** cannabinoid hyperemesis syndrome, delta-9-tetrahydrocannabinol, diagnosis, symptoms, treatment



Worldwide, cannabis is the most commonly used psychoactive drug. According to the World Health Organization,[1] cannabis is used for nonmedical purposes by an estimated 182 million people, or 2.5% of the world's population, annually. In the United States, more than 2.6 million Americans become new recreational users each year, and with more states sanctioning legalized usage, this number is increasing multifold.[2]

Cannabis comes from the female *Cannabis sativa* plant, which contains over 750 chemicals and over 100 different cannabinoids. The primary cannabinoids in the cannabis plant include delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol. Cannabinoids are used medicinally as antiemetics (THC and CBD), for seizure prevention (CBD), as a sedative (cannabinol), and for pain control (THC and CBD). Cannabis can be smoked, vaporized, and consumed whole or in oil extract form.[1]

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## PHARMACOKINETICS AND PHARMACODYNAMICS OF THE CANNABINOIDS

THC is the most psychoactive component of cannabis, causing euphoria, increased appetite, drowsiness, analgesia, and short-term memory loss. THC activates 2 receptors within the central nervous system, cannabinoid receptors type 1 (CB1) and type 2, which are located primarily in the dorsal ganglia, hypothalamus, hippocampus, cerebellum, and frontal limbic system of the brain. CB1 receptors are also found in the enteric plexus.[3]

The metabolism of THC occurs principally in the liver and is carried out by the CYP2C isoenzyme, which is a subtype of the cytochrome P450 complex. THC has a prolonged half-life of 20 to 30 hours; it is accumulated and stored largely in body fat. During times of lipolysis, which occurs during increased stress or food deprivation, the plasma levels rise and can cause reintoxication symptoms and toxic effects.[3]

## PHYSIOLOGIC EFFECTS OF CANNABIS USE

Over the past decade, crossbreeding and genetic modification techniques have dramatically increased the THC content of different cannabis strains, yielding

**Box 1. 3 Phases of Cannabinoid Hyperemesis Syndrome[2,6]**

Prodromal phase
Recurrent/persistent symptoms for months or years
Early morning nausea
Fear of vomiting
Abdominal discomfort
Normal eating pattern
May increase cannabis use to relieve nausea

Hyperemetic phase
Bouts of intense, persistent vomiting that is debilitating
Weight loss up to 14 kg
Compulsive warm bathing relieves nausea and

Recovery phase
Follows complete cessation of cannabis use*
Total resolution of symptoms within 12 hours to 3 weeks
Return of normal eating patterns
Weight gain
Regular bathing habits

*May require ongoing therapy/support for withdrawal and psychological dependence.

plants with much higher cannabinoid content. For example, the THC content may be increased from 3% content to upwards of 30%. This increased potency contributes to the increased rates of cannabis-related adverse effects, such as cannabis use disorder and acute intoxication, and toxic effects, such as cannabinoid hyperemesis syndrome (CHS).[1]

With the current trend of increased legal access to cannabis and the increased potency, it is necessary for the primary care provider to recognize and investigate cannabis usage patterns and related adverse side effects. For example, cannabis use disorder, occurring in 10% of regular cannabis users, is associated with cognitive impairment, poor school or work performance, episodic or chronic mood changes, and thought disturbances that may resemble non–drug-related psychiatric disorders.[4]

**Box 2. Treatment for Cannabinoid Hyperemesis Syndrome**

Vigorous rehydration and supportive therapy
Immediate and continued abstinence from cannabis in any form
Possible hospitalization during hyperemetic phase
Treatment with Haldol during hyperemetic phase
Administration of a proton pump inhibitor
Weight monitoring

## ACUTE CANNABIS INTOXICATION

The clinical manifestations of acute cannabis intoxication vary with age. In children, cannabis intoxication can produce neurologic abnormalities such as ataxia, hyperkinesia, lethargy, and coma.[5] After limited exposure, children may exhibit symptoms such as sleepiness, euphoria, nausea, vomiting, conjunctival injection, ataxia, or slurred speech. In large doses, coma with depressed respirations can occur, which may be life-threatening. Toxicity in children is usually from ingesting highly concentrated cannabinoid food products. In adolescents and adults, the signs of cannabis intoxication include tachycardia, hypertension, increased respiratory rate, conjunctival injection, dry mouth, increased appetite, nystagmus, ataxia, and slurred speech.[6]

## CHS

A relatively new clinical diagnosis, CHS, has emerged over the past 2 decades. In 2004, Allen first coined the term *cannabis hyperemesis syndrome* in a published case series of 9 patients in Australia.[7] In the US, primary care providers are just becoming aware of this disorder and its management. The Mayo Clinic study in 2012, the largest study to date with 98 patient case studies, has also contributed to the diagnostic criteria of CHS.[7]

## CLINICAL PRESENTATION

The knowledge and awareness of CHS symptomology can promote quick diagnosis and treatment of this condition and prevent unnecessary emergency department visits, hospitalizations, diagnostic testing, and

treatment trials.[7,8] The clinical presentation of CHS includes a health history of long-term, regular cannabis use with severe cyclic episodes of nausea, vomiting, and abdominal pain.[7] Often coupled with these gastrointestinal (GI) symptoms are patient reports of prolonged, repeated practices of bathing or showering in very hot water to relieve the symptoms.[8,9]

### The 3 Phases of CHS

**The Prodromal Phase.** CHS is characterized by 3 phases of illness. The prodromal phase can last for months or years with complaints of early morning nausea, a fear of vomiting, and abdominal discomfort. A normal pattern of eating is maintained, and cannabis use is ongoing and frequently increased for the assumed benefits of nausea alleviation.[2]

**The Hyperemetic Phase.** The second phase is the hyperemetic stage and includes bouts of intense and persistent nausea and vomiting that is debilitating. The patient may vomit bilious, nonbloody emesis up to 5 times per hour.[2] During this phase, the person may present to the emergency room where an extensive workup is completed.[7] Weight loss can be significant in many cases, with 1 study reporting 83% experiencing a mean weight loss of 14.2 kg.[7] Patients are commonly found to be dehydrated with orthostatic hypotension but otherwise hemodynamically stable. In cases of misdiagnosis and with symptoms of dehydration and intractable vomiting, multiple patient emergency room visits and hospitalizations for hydration and intravenous antiemetics over a period of several years may occur.[7]

**The Recovery Phase.** Lastly, the recovery phase follows cessation of cannabis use. The resolution of symptoms can occur within 12 hours of cannabis use discontinuation but can take as long as 3 weeks.[6] Patients must be advised that CHS symptoms will swiftly return with renewed cannabis consumption. With complete cessation of cannabis use, a return of normal eating patterns, weight gain, and regular bathing habits are obtained.[6]

### GI Manifestations of CHS

One hypothesis relating to the paradoxical symptoms of nausea, vomiting, and abdominal pain exhibited in CHS is that within the brain elevated or chronic levels of cannabinoids activate the CB1 receptor in the hypothalamic-pituitary-adrenal axis, causing autonomic instability. This process triggers the reduction of prolactin, gonadotropin, and growth hormone levels and increases corticotrophin levels, which are thought to be responsible for the physical manifestations of CHS.[7]

In addition, recent studies have also shown decreased intestinal motility after smoking cannabis, which may exacerbate GI symptoms. CB1 receptor activation within the gut inhibits gastric acid secretion, lowers esophageal sphincter relaxation, and decreases intestinal motility. The cannabinoid CBD, in large doses, increases the symptoms of abdominal pain, nausea and vomiting, and the cannabinoid THC also acts on CB1 receptors in both the brain and GI tract. CB1 gut activity may override brain activity in chronic users of high-potency cannabis products, stimulating an increase in nausea, vomiting, and abdominal pain.[4,6]

**Compulsive Bathing.** Compulsive hot water bathing is present in nearly all cases of CHS.[7,9] Patients report temperature-dependent, rapid, but transient symptom relief of CHS by taking hot showers or baths. Persons with CHS symptoms may spend up to 50% of their day bathing or showering.

The underlying pathophysiology that explains why symptoms are relieved with this hot bathing ritual is unclear. One train of thought is that because the CB1 receptors are near the thermoregulatory center of the hypothalamus, chronic stimulation may be counteracted by warm bathing. Another theory is that the stimulation of vascular CB1 receptors in the splanchnic circulation causes vasodilation in the gut with regular cannabis use (causing GI symptoms), and the vasoconstrictive action of warming the body may help to relieve these symptoms.[7,9]

## DIAGNOSIS

According to Simonetto et al,[7] the patient with CHS is typically a young male between the ages of 14 and 48 years old with a history of more than 2 years of chronic cannabis consumption (uses cannabis daily or repeatedly during the week). Additional diagnostic criteria for CHS include weight loss of $\geq$ 5 kg (11 lb); predominance of symptoms in the morning; normal bowel habits; and negative laboratory, radiographic, and endoscopic results.[9]

Diagnosis begins with a detailed history and physical examination followed by a basic workup to rule out acute causes of nausea and vomiting, such as pancreatobiliary disease, intestinal obstruction, and pregnancy. The initial tests should include a complete blood cell count, a comprehensive metabolic panel, amylase, lipase, pregnancy test (female), urinalysis, urine toxicology screen, and abdominal radiographs.[6] More extensive diagnostic workups are often done and may include studies such as an abdominal computed tomographic scan, magnetic resonance imaging, gastric emptying scan, ultrasound, or esophagogastroduodenoscopy. These diagnostic tests usually reveal normal findings, although Mallory-Weiss lesions, esophagitis, or gastritis may be detected.[10]

Test results are generally negative, with the exception of electrolyte disturbances secondary to persistent vomiting, dehydration, and mild gastritis. Mild leukocytosis is less commonly found upon laboratory testing.[6,8] Acute renal failure has also been reported in some persons with CHS.[11] The unique combination of protracted vomiting and frequent hot showers, with exposure to temperatures approaching 49°C (120°F), puts patients with CHS at risk for severe dehydration and prerenal failure. In the cases cited, the creatinine level ranged from 3 mg/dL to 10 mg/dL on presentation (normal range, 0.6–1.2 mg/dL) and were more common in males and in persons over age 30. Fortunately, in all cases, the creatinine returned to normal after several days of rehydration and supportive measures.[11]

### Differential Diagnoses

Patients with CHS are often misdiagnosed with having cyclical vomiting syndrome (CVS) or another medical condition with similar nonspecific symptoms.[8] The Table describes other medical conditions with vomiting as a predominant symptom that may be considered in the differential diagnoses process.[12]

Although CVS and CHS have multiple similarities, there are several noteworthy differences. Persons with CVS usually have psychological comorbidities, including depression and anxiety. Additionally, CVS patients have an increased incidence of migraine headaches or a family history of migraines.[8] Chronic, frequent cannabis use is the major recognizable difference between CVS and CHS, along with the prevalence of compulsive bathing supporting the CHS diagnosis.

## TREATMENT

The treatment for CHS includes vigorous rehydration with intravenous fluids and supportive therapy. Patients may need hospitalization during the hyperemetic phase in order to treat the vomiting and

**Table. Differential Diagnoses for Intractable Vomiting[12]**

| Diagnoses to Consider | Associated Symptoms |
|---|---|
| Cannabinoid hyperemesis syndrome | Nausea, vomiting, abdominal pain, chronic and frequent cannabis use |
| Cyclic vomiting syndrome | Retching, vomiting, depression, anxiety, diarrhea, dizziness, fever, photophobia, family history of migraines |
| Psychogenic vomiting | Conversion disorder or major depression, vomiting |
| Bulimia | Binging/purging behavior, eating disorder |
| Hyperemesis gravidarum | Pregnancy, intractable vomiting |
| Addison disease | Weight loss, fatigue, hypotension, hyponatremia, hyperkalemia, myalgia, arthralgia, hyperpigmentation of skin, nausea, vomiting |
| Migraine headaches | Unilateral headache with/without aura, photophobia, nausea, vomiting |
| Bowel obstruction | Abdominal pain, distention, constipation, diarrhea, intermittent abdominal cramping, inability to pass stool, vomiting |
| Gastroparesis | Nausea, heartburn, bloating, feeling of fullness after small intake amount, vomiting, nausea, reflux, fluctuating blood glucose levels |

abdominal pain. Hospitalization will also ensure abstinence from cannabis.[8]

Unfortunately, traditional antiemetics are largely unsuccessful with CHS; the 5-HT3 receptor antagonists, D2 receptor antagonists, H1 receptor antagonist, and neurokinin 1 receptor antagonists provide minimal or no improvement.[8] Instead, the medication haloperidol (Haldol) has been found to be highly successful in treating the nausea and vomiting associated with CHS.[13]

Haloperidol is traditionally used for the treatment of psychosis and agitation but contains antiemetic properties, having been used by anesthesiologists for postoperative nausea and vomiting, as well as in hospice treatment.[13] Haloperidol acts on the D2 receptors in the chemoreceptor trigger zone of the brain, causing a decreased input to the medullary vomiting center. Given intravenously in the emergency department or by mouth in an outpatient setting, haloperidol decreases or completely resolves the nausea and vomiting associated with CHS.[13]

Capsaicin cream 0.075% applied to the abdomen has also been used successfully in patients with CHS to treat nausea and vomiting. The transient receptor potential vanilloid 1 receptors, located in the peripheral nervous system, are activated by scalding hot water and by capsaicin cream.[14] Activating the transient receptor potential vanilloid 1 receptors causes an antiemetic effect by decreasing activation of the medullary vomiting center. Symptoms resolve or are dramatically diminished within 45 minutes of applying the cream to the abdomen.[14]

Proton pump inhibitors are also given routinely because CHS patients have varying degrees of gastritis. Weight also needs to be monitored to ensure effective rehydration and sufficient caloric intake.[8]

## MANAGEMENT

The only remedy for CHS is complete cessation of cannabis use. However, high relapse rates are seen with CHS because of the euphoric effects produced by cannabis use.[8] Marijuana use disorders are managed in a similar manner to other substance use disorders. Behavioral therapies that have been used with some success include cognitive-behavioral therapy, contingency management, and motivational enhancement therapy.[15]

Although there are no medications approved for the treatment of marijuana use disorder, the hypnotic/sedative zolpidem (Ambien), the antianxiety medication buspirone (BuSpar), and the anticonvulsant drug gabapentin (Neurontin) have been used in some trials to improve sleep and, possibly, improve executive function.[15] The development of an allosteric modulator medication that will interact with cannabinoid receptors to inhibit THC's rewarding effects is currently under study.[15]

### The Role of the Nurse Practitioner

As cannabis use grows, primary care nurse practitioners need to be attentive and consider CHS as a differential diagnosis in patients presenting with abdominal pain, vomiting, frequent bathing in hot water, and a history of chronic and frequent cannabis use. Patients must be routinely asked about their use of recreational drugs, including marijuana, as part of the health history.

The early diagnosis of CHS can avoid repeated hospitalizations, invasive medical workups, and unnecessary costs to the patient and the health care system. Seeking consultation from a gastroenterologist to secure a prompt CHS diagnosis may decrease emergency department visits, extensive diagnostic workups, unnecessary hospitalizations, and increased patient symptomology. Patient education should describe what activates CHS symptoms and the likelihood of CHS symptoms returning upon resumption of cannabis product use.[16] Because of the high relapse rates, patients may require referral to a community substance abuse program for assistance with cannabis cessation.[8]

## CONCLUSION

In the US, 22.2 million people ages 12 and older are current users of cannabis, with an estimated 2.6 million new users annually.[13] The potency of THC has increased by a factor of 10 because of crossbreeding and genetic modification techniques over the past decade, which leads to an increase in cannabinoid toxicity and CHS occurrence.[1]

Further study of the endocannabinoid and P450 enzyme systems in humans is needed to better understand why only certain cannabis users develop

CHS. A genetic polymorphism may exist in the cytochrome P450 enzymes responsible for the metabolism of the cannabinoids. This polymorphism may result in excessive levels of proemetic cannabinoids.[3]

Currently, there are no effective treatment regimens available to assist patients to achieve and maintain cannabis abstinence, and research to find effective pharmaceutical agents that can directly affect endogenous cannabinoid receptor function is underway.[15] Research is also needed to find effective behavioral and pharmaceutical therapies for the treatment of refractory CHS.

Nurse practitioners play an important role in the diagnosis, treatment, and management of CHS. Reluctance on the part of health care providers to ask patients about their use of cannabis and other recreational drugs can contribute to underreporting of the incidence of CHS and other substance abuse disorders. Prompt diagnosis and treatment of CHS and management through sustained cannabis cessation will alleviate patient symptomology and decrease unnecessary overuse of the health care system. JNP

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