Original Article

Cannabinoid Hyperemesis Syndrome

Shusen Sun, PharmD, BCPS,* and Anthony E. Zimmermann, PharmD†

Abstract

Background: The purpose of this review is to describe cannabinoid hyperemesis syndrome (CHS), which is thought to be induced by long-term cannabis use, and provide clinical pharmacists with information to manage the hyperemetic phase of CHS.

Method: Published literature was searched and reviewed using PubMed.

Results: CHS is characterized by intractable nausea and vomiting without an obvious organic cause and associated learned compulsive hot water bathing behavior. Patients often seek care in the emergency department (ED) for symptomatic relief.

Conclusion: CHS is potentially underrecognized and underdiagnosed in the ED, and it should be considered in the differential diagnosis in long-term cannabis use patients with CHS symptoms to avoid unnecessary extensive diagnostic workup including invasive radiologic imaging. Pharmacists have an important role in CHS recognition, education, and symptom management.

Key Words—cannabinoid hyperemesis syndrome, chronic cannabis use, clinical pharmacists, compulsive hot water bathing, intractable nausea and vomiting

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Cannabis is the most commonly used extra-medical drug in the United States, and its use is particularly prevalent among people under the age of 50 years.¹ Cannabis has various therapeutic properties including anti-emesis, appetite stimulation, and pain control. These properties have led to cannabis use in patients with cachexia associated with acquired immunodeficiency syndrome (AIDS), chemotherapy-induced nausea and vomiting, painful peripheral neuropathy, and muscle spasticity due to multiple sclerosis.² The number of states legalizing the use of medicinal cannabis is on the rise. Eighteen states and the District of Columbia have legalized the medical use of cannabis as of December 2012, although cannabis is still classified as a Schedule I drug.³

Cannabinoid hyperemesis syndrome (CHS) is a cluster of symptoms characterized by cyclic nausea and vomiting with abdominal pain without an obvious organic cause and compulsive hot water bathing behavior induced by long-term cannabis use (more than 1 year). Patients usually use cannabis on a daily or

weekly basis. The risk of developing CHS in long-term cannabis users depends on multiple known and unknown factors including, but not limited to, how much cannabis is used on a daily or weekly basis, the method of use, and confounding medical, psychiatric, ethnic, and socioeconomic conditions. Prior to the diagnosis of CHS, patients often suffer for years with potentially debilitating symptoms on a cyclic basis. These patients typically present multiple times to health care facilities with similar symptoms and receive multiple diagnostic tests and invasive procedures without a clear diagnosis or treatment plan.

The paradoxical adverse emetic effect associated with long-term cannabis use is under-recognized by health care professionals and the general public. CHS was first described in 2004 by Allen et al⁴ who reported a case series of 9 patients who were chronic daily heavy users of cannabis suffering from cyclic vomiting. Subsequent cases have been published worldwide in the medical literature.^{5–13} Increased availability of cannabis and its long-term use by patients as well as increased awareness of CHS among

*Clinical Assistant Professor, †Clinical Professor and Chair, Department of Pharmacy Practice, College of Pharmacy, Western New England University, Springfield, Massachusetts. Corresponding author: Shusen Sun, PharmD, BCPS, Department of Pharmacy Practice, College of Pharmacy, Western New England University, 1215 Wilbraham Road, Springfield, MA 01119; phone: 413-796-2424; e-mail: ssun@wne.edu

medical profession could result in the increased number CHS cases.¹⁴ It is important for health care providers and pharmacists to conduct focused history taking and consider CHS in the differential diagnosis of patients presenting with intractable cyclic nausea and vomiting plus abdominal pain as this may reduce the need for costly and invasive testing. The purpose of this brief review is to present a practical overview of CHS and to provide appropriate information to clinical pharmacists to effectively manage the hyperemetic phase of CHS in patients presenting to the emergency department (ED).

METHODS

Literature published between January 2004 and September 2012 was searched in PubMed using the terms “cannabinoid hyperemesis syndrome” and “cannabis hyperemesis syndrome”. All relevant publications in English were included in this review.

Etiology of CHS

Cannabis contains at least 66 cannabinoids, with delta-9-tetrahydrocannabinol (THC) being the main active ingredient. THC binds to cannabinoid type 1 (CB1) and type 2 (CB2) receptors in human tissues. The CB1 receptor is highly localized to neuronal tissue and the CB2 receptor is generally found outside the CNS, in immune tissues such as the spleen, thymus, and various populations of immune cells.¹⁵ The exact mechanism of the anti-emetic action of THC is not known, but it probably relates to stimulation of the CB1 subtype of cannabinoid receptors on neurons in and around the vomiting center in the brainstem.¹⁶

The etiology of CHS is not well understood, and multiple theories have been proposed in the literature (see box, Proposed Etiologies of Cannabinoid Hyperemesis Syndrome). Patients exhibiting this syndrome may have a genetic variation in their hepatic

drug-transforming enzymes that results in excessive levels of cannabis metabolites that promote emesis.⁸ Alternatively, the main active ingredient of cannabis (THC) is highly lipophilic; long-term use likely causes THC to accumulate in cerebral fat, which may lead to toxicity and emesis in sensitive patients.¹¹ Nausea and vomiting are influenced by the balance between enteric and central nervous system effects. Cannabis binds to cannabinoid receptors in the brain and the enteric nervous system. Other theories propose that in long-term cannabis users, the peripheral CB1 receptors of the enteric nerves that are implicated in slowing gastrointestinal transit may cause cannabinoid receptors in the gut to override the antiemetic effect of cannabinoid receptor stimulation in the brain leading to paradoxical hyperemesis.^{8,10} The central effects of long-term cannabis use on the hypothalamic-pituitary-adrenal axis might play a major role in the development of CHS.¹² Cannabis toxicity may disrupt the balanced equilibrium of satiety, thirst, digestion, and thermoregulatory systems of the hypothalamus. Brain response to core body temperature changes from the hypothermic effects of THC or activation of CB1 receptors in the hypothalamus that regulates body temperature might explain the compulsive hot water bathing to relieve cyclic nausea and vomiting.^{7,12}

Clinical Presentation of CHS

CHS is an emerging clinical diagnosis that is often overlooked in the ED; the adverse effects of long-term cannabis use are not always recognized. The syndrome, characterized by a triad of long-term cannabis use, cyclic vomiting, and compulsive hot bathing, is divided into 3 phases: prodrome, hyperemetic, and recovery.

Prodromal phase

The prodromal phase^{4,17} can last for months or years, with patients developing early morning nausea,

Proposed Etiologies of Cannabinoid Hyperemesis Syndrome

- A genetic variation in cannabinoid metabolism leads to toxic accumulation.⁸
- The main active ingredient of cannabis, THC, is highly lipophilic, and long-term use causes THC to accumulate in cerebral fat, which may lead to toxicity and emesis in sensitive patients.¹¹
- Nausea and vomiting are influenced by the balance between enteric and central nervous system effects. The enteric pro-emetic effects of cannabis may override its central nervous system-mediated antiemetic effects to promote emesis.^{8,10}
- The central effects of long-term cannabis use on the hypothalamic-pituitary-adrenal axis might play a major role in the development of CHS.¹²
- The impairment of the physiologic thermoregulation provoked by cannabis use might account for the relief of symptoms with compulsive hot bathing.^{7,12}

Note: CHS = cannabinoid hyperemesis syndrome; THC = delta-9-tetrahydrocannabinol.

a fear of vomiting, and abdominal discomfort. Symptoms are most common in early middle-aged adults who have consistently been using cannabis since adolescence. Compulsive bathing is minimal or absent. Unlike anorexia nervosa or bulimia, these patients maintain normal eating patterns in this stage. They may increase their use of cannabis due to their belief in its beneficial effects in nausea relief.

Hyperemetic phase

The hyperemetic phase^{4,8,17} is characterized by intensely persistent nausea, vomiting, and retching, which are often described as overwhelming and incapacitating. Patients generally have decreased oral intake and may develop conditioned food aversion for fear of triggering these symptoms. They are extremely anxious about trying to increase or advance their oral intake given the painful episodes that food triggered in the past. The vomitus typically consists of whitish watery secretions, because patients cannot tolerate solid food. Patients frequently have abdominal pain and may experience weight loss and dehydration. During this hyperemetic phase, patients may take multiple hot water showers throughout the day or a single shower lasting for several hours in an attempt to quell the hyperemesis. This hot water bathing appears to be a learned behavior that is often not seen with the first few episodes of illness but, once established, rapidly becomes a compulsion. Symptomatic relief has been described as being temperature-dependent. The learned compulsive bathing behavior is a notable characteristics of CHS and should raise a “flag” to health care providers. This behavior is thought to relieve nausea and vomiting through the brain response to core body temperature changes resulting from the dose-dependent hypothermic effects of THC, the psychoactive component of cannabinoid, or activation of CB1 receptors in the hypothalamus, which regulates body temperature.⁷ Patients present to the ED numerous times throughout this phase, which can lead to unnecessary health care costs. In the ED, patients will typically undergo an extensive diagnostic work-up, including invasive imaging studies, but the results of these investigations are generally unremarkable. Reported tests included complete blood cell count, glucose level, liver biochemistries, pancreatic enzyme level, abdominal x-ray, abdominal computerized tomography (CT), abdominal ultrasound, esophagogastroduodenoscopy (EGD), colonoscopy, head CT, gastric emptying studies, upper GI with barium with or without small bowel follow through, capsule endoscopy, hepatobiliary iminodiacetic acid

scan (HIDA), and magnetic resonance cholangiopancreatography (MRCP).¹⁴

Recovery phase

The recovery phase¹⁷ begins with cannabis cessation and can last days, weeks, or months, and it is associated with relative wellness and normal eating patterns. Patients regain weight and return to a regular bathing frequency. Return to cannabis use at any time will lead to a recurrence of CHS.

Clinical Diagnosis of CHS

A set of clinical diagnostic criteria for CHS was proposed by Sontineni et al⁶ in 2009 based on case reports and was further modified by Simonetto et al¹² in 2012 after a review of a case series of 98 patients, the largest to date, diagnosed with CHS. The CHS diagnostic criteria consist of those essential for diagnosis (long-term cannabis use), major features, and supportive features of CHS (see box, Proposed Clinical Diagnostic Criteria for Cannabinoid Hyperemesis Syndrome). These diagnostic criteria can aid clinical pharmacists in the evaluation of patients presenting with cyclic vomiting with no obvious organic cause and a history of repeated ED visits for the same condition.

A diagnostic flow chart can be used by clinical pharmacists and clinicians for patients with suspected CHS to help reduce unnecessary costs and overutilization of health care resources. Diagnosis begins with a thorough physical examination and history for

Proposed Clinical Diagnostic Criteria for Cannabinoid Hyperemesis Syndrome¹²

Essential for diagnosis

Long-term cannabis use: more than 1 year

Major features

Severe cyclic nausea and vomiting

Resolution with cannabis cessation

Relief of symptoms with hot showers or baths

Epigastric or periumbilical abdominal pain

Weekly use

Supportive features

Age younger than 50 years

Weight loss over 5 kg

Morning predominance of symptoms

Normal bowel habits

Negative laboratory, radiographic, and endoscopic test results

all patients presenting with nausea, vomiting, and abdominal pain. This will help to rule out life-threatening causes or diagnoses that confer significant potential morbidity to the patient or to establish the presumptive diagnosis of CHS. Medical conditions that may cause the presenting symptoms include, but are not limited to, acute hepatitis, adrenal insufficiency, bowel perforation, bowel obstruction, cholangitis, cholecystitis, diverticulitis, ectopic pregnancy, gastroparesis, myocardial infarction, nephrolithiasis, pancreatitis, pelvic inflammatory disease, and ruptured or dissecting aortic aneurysm.¹⁴ Prompt and appropriate diagnostic testing and treatment should be pursued for patients with these conditions. History taking should include an inquiry about the patient's past and present medical illness, medication use, illicit drug use, and therapeutic or recreational use of cannabis. Denial of cannabis use by the patient is typically the biggest stumbling block for clinicians in making a proper diagnosis of CHS. A urine drug screen should be ordered if the patient presents with the typical symptoms of CHS, there is no noted other organic cause, and the patient denies cannabis use.

A focused patient history should be prompted if the patient admits to the use of cannabis and/or the urine drug screen indicates such use. Details as to when cannabis use first began, how often and how much it is used, and when symptoms of nausea, vomiting, and abdominal pain were first experienced should be elicited. A diagnosis of CHS is likely if symptoms began after long-term cannabis use. Furthermore, if symptoms improved during cannabis cessation and reoccurred after resuming cannabis use, the diagnosis is further supported.¹⁴ The patient should be asked whether he or she is taking compulsive hot water showers in an attempt to relieve symptoms of nausea, vomiting, and abdominal pain. It is important to clarify the frequency and length of the hot water bathing; patients with CHS often take hot water baths or showers multiple times a day or a single hot shower lasting for several hours. The presence of compulsive hot water bathing is an important major diagnostic feature of CHS, because no other known vomiting syndrome shares this phenomenon.¹² It is advised that clinicians avoid unnecessary laboratory testing and imaging unless otherwise clinically indicated.¹⁴

Management of CHS Patients

No standard evidence-based regimen currently exists for the management of CHS patients. Most of the information in the literature is based on case reports, and treatment is targeted to the hyperemetic

phase.^{4,7,9,18,19} The therapeutic goal during the hyperemetic phase is to prevent dehydration and terminate the nausea and vomiting. Patients should be evaluated for signs and symptoms of volume depletion once a presumptive diagnosis of CHS has been made. If volume depletion is present and oral liquids cannot be tolerated, intravenous (IV) hydration is indicated. Conservative IV fluid replacement consisting of a 1 to 2 L bolus followed by a 150 to 200 mL/h infusion of 0.9% sodium chloride for 24 to 48 hours will generally lead to some improvement in the patient's condition.^{4,18} Analgesics such as morphine have been used to relieve abdominal pain if present.¹⁸ The use of medications including vitamin B6, ondansetron, promethazine, metoclopramide, dexamethasone, famotidine, and droperidol, alone or in combination, has been reported in the literature of CHS patients but has failed to effectively relieve the symptoms of nausea and vomiting.^{7,9,18}

Lorazepam's antiemetic, amnestic, and anxiolytic properties have made it useful for the treatment of anticipatory nausea and vomiting in patients undergoing chemotherapy²⁰ and in patients with cyclic vomiting syndrome.²¹ The effectiveness of lorazepam in the relief of nausea and vomiting symptoms in CHS patients has been reported in 2 recent case reports.^{18,19} Initial treatment with IV ondansetron and morphine was unable to keep a 28-year-old CHS patient from having breakthrough episodes of nausea, vomiting, and epigastric pain. After administration of IV lorazepam (1 mg), the patient exhibited an improvement in symptoms within 10 minutes and reported cessation of nausea, abdominal pain, and food aversion.¹⁹ The patient was transitioned to a regular diet with oral lorazepam (1 mg) and was able to discontinue all other analgesic and antiemetic medications over the next 12 hours. The addition of lorazepam to the patient's regimen allowed for rapid transition from a clear liquid to a regular diet and the ability to tolerate oral medications. The patient was discharged with a 7-day prescription of 1 mg oral lorazepam twice daily. The time from cannabis cessation to complete resolution of symptoms was approximately 3 weeks in this case. The patient was contacted at 3 and 6 months after discharge and reported sustained abstinence from cannabis; the symptoms had not returned. The effectiveness of lorazepam in the control of nausea and vomiting was also demonstrated in another patient case report where lorazepam (1 mg IV every 4 hours as needed) was added to promethazine (12.5 mg IV as needed) after minimal relief from ondansetron (4 mg IV as needed), droperidol (5 mg

IV), and promethazine (12.5 mg IV as needed) treatments.¹⁸

Based on published case reports of CHS, lorazepam could be considered as an agent of choice in the management of the acute hyperemetic phase of CHS to relieve symptoms of nausea and vomiting (Table 1). The role of lorazepam and its optimal dosing requires further clinical evaluation. Clinical pharmacists can play an important role in the management of CHS patients through therapy recommendation. Caution should be made against the overprescription of lorazepam, as it can cause physical and/or psychological dependence especially in CHS patients who are vulnerable to substance abuse.

Abstinence from cannabis use is the ultimate treatment for CHS. Cessation of cannabinoid use will lead to complete resolution of symptoms. The time to improvement varies from 1 to 3 months in the current literature.¹² Patients may be reluctant to accept that cannabis has played a role in their symptoms, and they should be educated about the nature of the disorder. This is an area where clinical pharmacists can play an important role.

DISCUSSION

CHS is a recently described condition of cyclic vomiting related to long-term cannabis use. It is potentially underrecognized and underdiagnosed given the prevalence of recreational and therapeutic cannabis use worldwide. Clinical pharmacists may encounter CHS patients in the ED and during the patients' brief hospital stay. These encounters provide

an excellent opportunity for clinical pharmacists to educate other health care providers about the paradoxical hyperemesis syndrome caused by long-term cannabis use. CHS should be considered in patients with long-term cannabis use who present with cyclic nausea and vomiting accompanied by abdominal pain and compulsive hot bathing behavior. Inclusion of this diagnosis in these patients may reduce the need for expensive and unrevealing workup tests and procedures when there are no other life-threatening signs or symptoms. Recently proposed clinical diagnostic criteria can be helpful in making the diagnosis of CHS. Clinical pharmacists can help to manage patients and provide pharmacotherapy consultation to ensure proper dosing of lorazepam once the diagnosis of CHS is made. Treatment goals during the hyperemetic phase include prevention of dehydration, vomiting cessation, and provision of symptomatic relief for associated abdominal pain. Clinical pharmacists can also educate CHS patients about the relationship between CHS symptoms and long-term cannabis use. Patients should be informed about the importance of complete cessation of cannabis use as the ultimate treatment of CHS. Clinical pharmacists can help to provide continuity of patient care by recommending and/or encouraging CHS patients to seek help from social workers and mental health providers.

Future studies are needed to better understand the etiology, prevalence, and risk factors for developing CHS (eg, understanding medical, psychiatric, ethnic, or socioeconomic conditions as well as amount and potency of cannabis). Randomized controlled clinical

Table 1. Summary of therapeutic options in the management of cannabinoid hyperemesis syndrome

Agent	Indication and dosing	Clinical outcome
IV Sodium chloride 0.9%	Hydration 1-2 L bolus and then 150-200 mL/h infusion for 24 to 48 hours	Demonstrated symptom improvement in case reports ^{4,18}
Morphine	Pain 4 mg IV as needed	Demonstrated pain control in case reports ¹⁸
Acetaminophen	Headache 650 mg as needed	Demonstrated headache relief in case reports ¹⁸
Lorazepam	Nausea/vomiting 1 mg IV x 1 OR 1 mg IV every 4 h as needed	Demonstrated symptom improvement in case reports ^{18,19}
Chlorpromazine	Hiccups 25 mg IV every 4 h as needed	Demonstrated symptom improvement in case reports ¹⁸

Note: CHS = cannabinoid hyperemesis syndrome; h = hour; IV = intravenous.

trials are needed to identify the optimal pharmacotherapy for managing CHS.

CONCLUSION

Although the mechanism of cannabis that leads to intractable nausea and vomiting is still unclear, CHS is well documented in the medical literature. With the widespread use of cannabis, both recreationally and therapeutically, the paradoxical effect of CHS deserves further attention. Clinical pharmacists should have heightened awareness when patients present to the hospital with intractable nausea and vomiting and report relief with hot showering. In addition to organic disease, long-term cannabis use should be considered as a possible cause. This consideration may prevent further unnecessary workup and health care costs for patients with CHS.

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