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Cannabinoid Hyperemesis Syndrome: An Unrecognized Cause of Nausea and Vomiting

Cannabinoid hyperemesis syndrome: An unrecognized cause of nausea and vomiting

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ABSTRACT

Cannabis has long been used for medical and recreational purposes due to its antiemetic, analgesic, and mood effects. Ironically, chronic use of cannabis can result in paradoxical effects, including a condition known as cannabinoid hyperemesis syndrome.

Patients with this syndrome are often seen the ED with cyclic vomiting, nausea, and epigastric pain. Although the definitive treatment of cannabinoid hyperemesis syndrome is discontinuing the causative agent, medical management that includes rehydration is important to prevent complications. Whereas common anti-emetic medications are ineffective, Haloperidol and lorazepam have been shown to be useful in some studies to be effective in the treatment of acute symptoms.

Keywords: cannabinoid hyperemesis syndrome, cannabis, cyclic vomiting, marijuana, antiemetic, side effects **[[AU: please suggest 3 more keywords- DONE]]**

Cannabis, known for its psychoactive and antiemetic effects, can be used to treat chemotherapy-induced nausea and vomiting, in addition to other medical conditions that

may lead to cachexia, weight loss, and chronic pain. Despite these antiemetic effects, chronic cannabis use can cause paradoxical effects from overstimulation of cannabis receptors. Cannabinoid hyperemesis syndrome (CHS), a type of cyclical vomiting syndrome, was first identified in 2004.[1] This syndrome is most frequently seen in young men and in studies is identified in patients who report recreational use of cannabis. **[[AU: please add reference] DONE – Please use Reference #3 Simonetto for this citation and renumber following references.]** Patient presentation may mimic acute pancreatitis, acute gastroenteritis, intestinal obstruction, pseudo-obstruction, and other functional diseases of the bowel. These medical conditions must be ruled out before making the diagnosis of CHS.

Clinicians who are aware of CHS can consider it in the differential diagnosis of patients with chronic nausea and vomiting.

Early diagnosis of CHS can minimize long-term morbidity, reduce costly emergency department (ED) visits and hospital admissions, and help clinicians provide quick, effective treatment.

A GROWING PROBLEM

Cannabis has been a commonly used recreational substance for centuries. The CDC surveys the general population yearly to identify US societal health trends.[2] Based on data from the 2015 national study on drug use and health, marijuana remains the most common illicit drug.[2] **[[AU: can this reference and statistics in this paragraph be updated?] RESPONSE: Done, See 2018 NIH/NIDA reference associated with data in the following sentence.]** Additionally, the National Institutes of Health, National Institute on Drug Abuse found an upward trend of cannabis use in the United States, with over 22.2 million US citizens age 12

and older having reported using marijuana within a month of taking the survey.**(NIH/NIDA)** The demographic with the highest number of individuals who use cannabis is age 18 to 25 years. A study that investigated trends of marijuana use between 2002 and 2014, indicated that prevalence is increasing among both men and women. Data from the US national survey on drug use and health show that 12.4 million men and 7.7 million women used marijuana in 2002. This number increased to 18.4 million men and 11.7 million women in 2014 ***(Carliner et al, 2017).** The most recent 2017 data from the CDC indicate that 10.6% of the male population surveyed **[[AU: is that all males or just those ages 18 to 25?] RESPONSE: Reworded for clarification]** and 6.2% of the female population surveyed use marijuana.[2]

In 2012, a study conducted in Minnesota reviewed 98 medical records of patients diagnosed with CHS**[[AU: please add**

reference] RESPONSE: Reference #3 Simonetto supports this statement. Please add this as the citation] with the goal of gaining a demographic perspective of patients with CHS.[3] Although the study corroborated findings from national studies completed by the CDC, clinically, CHS was seen to affect many demographics. This study found that 67% of patients with CHS are male with an average age of 32.3 years (standard deviation of +/- 9.9 years).[3] Another important finding of the study was that 68% of patients diagnosed with CHS had a history of using cannabis for an average of 2 years before the onset of symptoms. Additionally, 59% of the patients used cannabis daily, and 95% used it at least once per week.[3]

More recent trends show an increase in popularity among adolescents and younger adults of synthetic cannabis, with street names such as “K2” and “spice”. **[[AU: please add reference] RESPONSE: Done, please use**

reference #4 Ukaigwe as the citation to support this statement][4] Although surveys show that natural cannabis is preferred by users over its synthetic derivative, users are resorting to synthetics because they are undetectable in routine drug testing.[4] Few studies have investigated the relationship between synthetic cannabis and CHS, although a recent case report identified a patient with a history of chronic “spice” use and CHS.[4] CHS remains an important diagnosis to consider in patients who test negative on a drug screen despite clinical suspicion.

With current political trends leaning toward the national legalization of cannabis for medicinal and recreational use, this once-rare syndrome has become increasingly prevalent. In 2000, Colorado amended its constitution to allow medical cannabis use. Alaska, California, Colorado, the District of Columbia, Maine, Massachusetts, Michigan, Nevada, Oregon, Vermont, and Washington

state have legalized recreational use of cannabis, and 23 other states have legalized it for medical use only. As of 2018, 33 states have legalized marijuana, some with restrictions for medical use and 11 having legalized it for recreational use.**(Governing, 2018) [[AU: 2018 stats, from www.governing.com/gov-data/safety-justice/state-marijuana-laws-map-medical-recreational.html] RESPONSE: Added these 2018 stats and included the above source (Governing) as a reference at the end of the existing references.]** Few studies have shown an increase of CHS secondary to legalization changes, however a single study in Colorado showed that the number of patients with CHS seen in the ED since the legalization of cannabis has doubled.[5]

More recently, a study using ICD codes was published in 2018 indicating an increased number of ED visits for cannabis-associated vomiting. This study reflects a time period

from 2006 to 2013 during which an increased number of states legalized medical and recreational use of marijuana. Marijuana-related cases of vomiting increased from 2,915 of 1,369,942 (.2%) total cases of vomiting in 2006 to 17,904 of 1,922,448 (0.9%)of vomiting cases seen in the ED in 2013. **(Bollom)**

PHYSIOLOGY

Two cannabinoid receptors (CB1 and CB2) have been identified in the autonomic and central nervous systems of humans and animals. These receptors also can be found in the spleen, stomach, small and large intestine, heart, liver, uterus, bladder, and vas deferens. The interaction between CB1 receptors and delta-9-tetrahydrocannabinol (THC), a chemical component of cannabis, triggers the psychoactive effects associated with cannabis use. These effects include altered consciousness, relaxation, euphoria,

perceptual disturbances, cognitive impairment, and intensified sensory disturbances. THC potentiates antiemetic effects by interacting with CB1 receptors located at the vomiting center in the medulla.

SIGNS AND SYMPTOMS

The classic signs and symptoms associated with CHS are recurrent episodes of nausea, vomiting, abdominal pain, and compulsive hot-water bathing. Because patients cannot hold food or liquid down, they may lose weight and become dehydrated. The specific mechanism of action of THC in patients with CHS has not been identified; however, physiologic concepts have been proposed to explain the symptoms.

Nausea and vomiting These symptoms could simply be a result of metabolites from impure or contaminated cannabis. However, the mechanism that most likely explains CHS

is that THC is a lipophilic molecule that accumulates in body fat (including cerebral fat) and is secreted over its extended half-life. This chronic exposure leads to hyperstimulation of the CB1 and CB2 receptors.[1] Down-regulation and desensitization of the CB1 and CB2 receptors increases the bioavailability of THC.[6] With excessive exposure to THC, antiemetic effects on the brainstem are overridden, reducing gut motility and inducing emesis due to gastroparesis.[6] Additionally, genetic variations of metabolic enzymes in the liver that may predispose a patient to experience the pro-emetic effects of cannabis after chronic cannabis use.[1] This variability offers a potential explanation as to why not every patients who uses cannabis chronically experiences CHS.

Abdominal pain Hyperstimulation of CB receptors in the gut may be the cause of abdominal pain associated with CHS;

hyperstimulation of CB1 and CB2 causes splanchnic dilation and increases blood volume, potentially leading to pain.[3] However, not all patients with CHS complain of abdominal pain. Studies show that most patients experience epigastric or periumbilical pain.[3]

Compulsive hot showers Compulsive bathing is a learned behavior intended to relieve symptoms of CHS; patients may or may not report this behavior during their initial history. Why hot showers appear to relieve the nausea, cyclic vomiting, and abdominal pain of CHS is unknown. However, the hypothalamus, the brain’s center for thermoregulation, contains CB1 receptors, and hot showers may counteract chronic hypothalamus stimulation caused by cannabis use**[[AU: stimulation caused by cannabis use?] RESPONSE: Yes. Sentence modified for clarification.]**.[7] Hot water may also stimulate CB1-mediated vasodilation,

redistributing blood flow from the splanchnic circulation to the skin, resulting in cutaneous steal syndrome and temporarily relieving symptoms.

Timing and associated symptoms A survey of 98 patients with CHS revealed that symptoms typically started in the morning.[3] Associated symptoms included diaphoresis, bloating, and weight loss.[3] Symptoms were not associated with specific foods.[3]

HISTORY AND PHYSICAL EXAMINATION

Other than abdominal discomfort or tenderness on palpation, patients typically have a normal physical examination. CHS is a clinical diagnosis, and an accurate and thorough patient history is essential.

The course of an episode of CHS occurs in phases. Clinicians should maintain a high suspicion of CHS when a patient presents with this sequence of events:

Pre-emetic phase Also called the prodromal phase, this phase can last for months to years and begins with intermittent diffuse abdominal discomfort, anxiety, agitation, morning nausea, and fear of vomiting. Patients also may exhibit autonomic symptoms of sweating, flushing, and increased thirst. During this phase, normal eating habits are maintained and patients continue to use cannabis because of its commonly known antiemetic and antinausea effects. Patients may then increase their cannabis use to self-medicate and to treat their nausea, not realizing that it could escalate the course of the episode.

Hyperemetic phase In this phase, which typically lasts 24-48 hours**,(Galli et al, 2011)** patients experience incapacitating nausea and cyclic vomiting. Patients begin vomiting profusely up to five times per hour and may experience mild abdominal pain. Patients begin to lose weight due to the

inability to hold down food. In the clinical setting, these patients usually present with dehydration but are hemodynamically stable. Additionally, during this phase, patients may report taking numerous hot showers throughout the day to help relieve their symptoms.

Recovery phase In this phase, a patient stops using cannabis and is placed on conservative treatment such as bowel rest, intravenous (IV) fluids, and electrolyte replenishment, and is slowly advanced to a normal diet. Patients regain their weight and their bathing habits revert to normal. Complete resolution of symptoms can take up to 1 month.

DIAGNOSTIC TESTS

The workup for chronic nausea and vomiting can be extensive and expensive. With an initial episode of CHS, a thorough workup to rule out medical emergencies is warranted.

Initial laboratory tests should include a complete blood cell count and differential, blood glucose, basic metabolic panel, pancreatic and hepatic enzymes, urinalysis, urinary toxicology screen, and abdominal radiographs. In female patients, a pregnancy test is critical to rule out hyperemesis gravidarum.

DIFFERENTIAL DIAGNOSIS

An algorithm is available to aid clinicians in obtaining a thorough history from patients who may have CHS (**Figure 1**).[8] Questions about cannabis use are essential. With compulsive bathing being considered a learned behavior, patients may or may not exhibit this behavior.

Providers should be mindful of two diagnoses that closely resemble CHS:

Cyclic vomiting syndrome Consider this diagnosis in patients without a history of chronic cannabis use. Patients with cyclic

vomiting syndrome typically present with migraine headaches, abdominal pain, and vomiting; psychologic stressors are pertinent in distinguishing this syndrome from CHS. The family history usually is positive for migraine headaches. Patients typically respond well to migraine abortive and or preventive relief medications; patients with CHS generally do not respond to these medications.

Psychogenic vomiting This condition usually is associated with a history of vomiting caused by psychologic stimuli in a patient with no obvious organic disease. It is common in patients with psychologic disorders such as depression or obsessive-compulsive disorder. The presentation of psychogenic vomiting is hyperemesis with emotional triggers but without an identified organic gastrointestinal dysfunction. In these patients, treating the underlying emotional issue with behavioral therapy,

antidepressants, and supportive psychotherapy causes resolution of the hyperemetic symptoms.

COMPLICATIONS

CHS is commonly underdiagnosed and misdiagnosed. For this reason, data on medical complications related to this syndrome are limited. Clinicians should be mindful of potential complications of CHS induced by natural and synthetic cannabis. With intractable vomiting, patients are at risk of becoming hypovolemic, leading to acute kidney injury and potential esophageal injury or Mallory-Weiss tear.

Patients with CHS are at risk of developing acute prerenal failure due to volume depletion. Severe dehydration can lead to acute kidney injury and rhabdomyolysis. One case study described a 25-year-old man who presented to the ED with complications of CHS.[9] He had an elevated blood urea nitrogen

to creatinine ratio of 24:3.21 that normalized after 24 hours of IV rehydration.[9] Another case study described a patient with CHS secondary to synthetic cannabis use. The researchers determined that this patient developed rhabdomyolysis because of either hyperemesis-induced electrolyte abnormalities or contamination of the cannabis.[10]

Patients who exhibit constant or forceful emesis are at risk of developing Mallory-Weiss tears. A case study investigated a 28-year-old woman who was pregnant at the time of presentation and complained of nausea, vomiting with hematemesis, and abdominal pain. Clinicians assumed she had hyperemesis gravidarum. It was not until the patient did not respond to antiemetic medications and had returned to the ED on multiple occasions for the same symptoms, that clinicians finally inquired about drug use **[[AU: and found out that she was used cannabis and was**

diagnosed her with CHS? what about the Mallory-Weiss tears? did she have those, too?] RESPONSE: DONE – YES, Thank you. Info added below] and confirmed chronic use of marijuana. Upon discharge she was diagnosed with Mallory-Weiss tears and CHS. Her symptoms resolved after cessation of marijuana.[11] This supports the recommendation that healthcare providers should inquire about drug use regardless of the patient's age, sex, or childbearing state.

TREATMENT

Rehydration, either orally or using IV fluids, is the first step in managing CHS. Because excessive fluid loss from hyperemesis causes patients to become hypovolemic, replenishing essential electrolytes can prevent acute prerenal injury and renal failure. Oral rehydration, if well tolerated, is the preferred route of rehydration. If the patient is unable to

tolerate oral intake, IV infusion of 0.9% sodium chloride solution or 5% to 10% dextrose, in addition to IV potassium, is adequate treatment in many cases. Because patients with CHS have been shown on endoscopy to manifest gastritis and esophagitis, treatment with a proton pump inhibitor is indicated for healing.**(Galli et al, 2011)** Bowel rest is essential in all patients. Cessation of cannabis use ultimately cures CHS. Studies show that once the patient completely stops using cannabis, symptoms resolve. Recommend that the patient participate in a 12-step program or support group as a means of recovery. A double-blind study conducted by the National Institute on Drug Abuse Clinical Trials Network examined the benefits of N-acetylcysteine (NAC), an antidote for acetaminophen overdose, in cannabis cessation.[12] They found it effective in promoting abstinence from cannabis in the subjects participating in the study.[12] NAC is

easily accessible, available over-the-counter, and is fairly inexpensive.

It is important to note that traditional antiemetic medications such as ondansetron, metoclopramide, prochlorperazine, and promethazine are ineffective for active symptom relief in patients with CHS. Haloperidol, a medication typically indicated for psychosis and agitation, may be effective in patients with CHS.[13] The mechanism of action for haloperidol's antiemetic effects in these patients is unknown; however, effectiveness may be attributed to complex interactions between dopamine D2 and CB1 receptors.[13] Haloperidol is a category C medication and its risks should be weighed against the benefits in pregnant patients. Early administration of haloperidol in acute episodes can significantly reduce symptoms, minimize time in the ED, and reduce the rate of hospital admissions.

Benzodiazepines may relieve nausea and vomiting in patients with CHS. In one case study, a patient with CHS did not respond to ondansetron and morphine, and could not tolerate taking anything by mouth. The providers administered an IV dose of lorazepam and his symptoms improved within minutes.[14] Lorazepam enabled the patient to advance to a regular diet.[14]

CONCLUSION

With national trends in legislation making cannabis more accessible, CHS will likely become increasingly common. More research is warranted to assess trends in the diagnosis and acute management of this condition. Moreover, with the increasing popularity of synthetic cannabis, additional studies are needed to improve drug toxicology screening. Because of the lack of synthetic cannabis screening, healthcare providers should remain suspicious of CHS in patients with

negative drug screening results. Once CHS is identified, education serves as the key to helping affected patients and making them accountable for their own health.

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