

# Cannabinoid Hyperemesis Syndrome

## What is cannabinoid hyperemesis syndrome?

Cannabinoid hyperemesis syndrome (CHS) is a condition in which patients who have been using cannabis or synthetic cannabinoids for a prolonged period of time develop a pattern of illness with episodes of severe vomiting (usually accompanied by abdominal pain) interspersed with prolonged asymptomatic periods.

CHS was first identified out of a cohort of adult cyclic vomiting syndrome (CVS) patients who were using cannabis frequently. It was shown that when they stopped using cannabis the episodes of vomiting went away. Therefore, some continue to view cannabis as a cause of CVS and others view CHS as a distinct but closely related disorder.

In adults with CHS, the episodes of vomiting usually last several days, but should not exceed 1 week in duration. The asymptomatic periods are usually quite long, in the range of one to several months, during which time the patient has no residual GI symptoms.

## How is cannabinoid hyperemesis syndrome diagnosed?

The official diagnostic criteria for CHS are based on the Rome IV criteria which require an episodic vomiting pattern with episodes lasting <1 week and asymptomatic periods >1 week between episodes, prolonged cannabis use, and evidence of relief of symptoms by sustained cessation of cannabis. Unfortunately, during an ED visit we will not be able to prove resolution of symptoms by stopping cannabis, making these criteria of limited utility.

A number of ED based diagnostic criteria have been proposed with overlapping features. There are three key components to look for when making the diagnosis:

1. An episodic pattern of vomiting
2. Prolonged cannabis use
3. Exclusion of alternative diagnoses

Since the formal criteria for CHS require cessation of cannabis to confirm the diagnosis, ED patients should be labelled as “probable” or “presumed” CHS. There are some other functional GI conditions which can mimic CHS including abdominal migraine and non-cannabis related CVS which may only be diagnosed after prolonged cessation from cannabis with ongoing symptoms.

## What causes cannabinoid hyperemesis syndrome?

CHS is thought to be caused by the THC component of cannabis, since it has been reported with isolated use of synthetic THC analogs and has not been reported from isolated CBD use. The cause of CHS may ultimately have multiple mechanisms contributing, but the pattern of illness does not correlate well with the amount of cannabis consumed which suggests that it is not related to a direct effect of the THC or from a withdrawal effect. There are two prevailing theories related to changes in neuro-signalling and receptor expression with chronic THC exposure which have the best supporting evidence.

The first theory revolves around downregulation of the CB-1 receptor which occurs with chronic THC use. This leads to dysregulation of the HPA stress axis. Endogenously produced cannabinoids are released in response to stress and have several important effects including negative feedback to reduce cortisol release, assisting cortisol in activating GABA inhibitory neurons, and direct anti-emetic effects. Chronic exposure to THC causes downregulation of CB-1 receptors, impairing the body's natural response to stress. It is thought that this leads to dysregulated sympathetic and vagal surges, often triggered by stress, which cause bouts of emesis. Since the normal negative feedback loops are impaired, it is difficult for these episodes to stop on their own and ultimately leads to unrelenting vomiting episodes. This theory helps explain why medications which have sedative or anxiolytic properties (eg. haloperidol, benzodiazepines) have been reported to be more effective than traditional antiemetics.

The second theory is based on changes in dopamine signalling. Dopamine release in the brainstem triggers nausea and vomiting in response to a noxious stimulus. Acute THC use triggers dopamine release. However, with chronic THC use rates of dopamine release are decreased. This may lead to upregulation of dopamine receptors and an increased downstream response to a dopamine signal. If this is the case the brain may become "hypersensitive" to dopamine, triggering exaggerated vomiting episodes in response to a dopamine signal. This theory is less well supported, but has been used to explain the beneficial effects of dopamine antagonists such as haloperidol. It does not fully explain why haloperidol appears more effective than other dopamine antagonists such as metoclopramide.

### **How should we treat cannabinoid hyperemesis syndrome in the ED?**

Traditional antiemetics have had low rates of success in treating CHS based on summaries of reported cases (ondansetron = 1.75%, metoclopramide = 4.35%, dimenhydrinate = 0.00%). While this data is likely impacted by reporting bias, clinical experience supports that CHS often does not respond well to these antiemetics. This is further supported by the fact that haloperidol was shown to be superior to ondansetron in the recently published HaVOC trial. There are downsides to using a "traditional antiemetics first" strategies in CHS since these medications have been shown to delay effective treatment, prolong ED length of stay, and prolong the QT interval.

Haloperidol is the only medication with a reasonable quality RCT supporting it as treatment for CHS. The HaVOC trial compared two different doses of haloperidol (0.05 mg/kg or 0.1 mg/kg) to ondansetron 8 mg IV for acute management of vomiting episodes in the ED. They found that haloperidol was twice as effective at reducing nausea and pain on a 10-point visual analog scale. Haloperidol also decreased rescue medication use (31% vs. 76%) and time from administration to ED discharge (3.1 hours vs. 5.6 hours). The trial was not powered to detect difference between the two haloperidol doses, but did not find any efficacy difference between high and low dose, with a trend towards higher adverse reaction rates in the high dose group. This led to a recommendation for 0.05 mg/kg to be the preferred dose. The evidence for haloperidol is further supported by a review of reported cases finding 84.6% effectiveness, and a retrospective study of droperidol which found a 50% reduction in ED length of stay and rescue medication use in CHS patients receiving droperidol. Haloperidol has both dopamine antagonism and  $\alpha$ -adrenergic blocking effects which may explain its beneficial effects based on the above theories of CHS pathophysiology.

While capsaicin is often discussed as a treatment, the evidence supporting its use is limited. In the initial case series supporting its use, all patients also received other antiemetics and there was no clear way to separate their effects. There was a small 2020 RCT published in support of capsaicin, but the small sample size led to large baseline differences in nausea scores between the capsaicin and placebo group, with the placebo group having much higher baseline nausea (8.5 vs. 6.0 on a 10-point scale). The study did not correct for any baseline differences, and the significant reduction in nausea they report with capsaicin would have been lost if statistical correction was performed. Overall, many patients with CHS may have previously tried capsaicin and if a patient previously responded positively to capsaicin, it would be reasonable to continue prescribing. However, the evidence supporting capsaicin is very limited, so its use should be a shared decision with patients.

Lorazepam has no specific studies assessing its utility in CHS. A summary of case reports suggests an efficacy of 58.3% in 19 patients. Despite the lack of evidence, clinical experience has led to lorazepam being recommended as an adjunct in recent CVS guidelines for patients who have an anxiety component to their presentation. Since 40-50% of traditional cyclic vomiting syndrome patients were chronic cannabis users, it is reasonable to extrapolate these guidelines to CHS until more specific literature is published. The use of anxiolytics such as lorazepam aligns with the theory that CHS is related to a dysregulated stress response.

Lastly, while there is limited evidence supporting olanzapine in CHS (only 6 reported cases), it has strong evidence supporting its antiemetic properties in the oncology literature and is worthy of consideration in cases where a patient has contraindications to haloperidol (ie. allergy, prolonged QT) or has had severe extrapyramidal effects leading to a haloperidol aversion. Olanzapine does not prolong the QT interval and has much lower rates of EPS compared to haloperidol. Olanzapine has dopamine, serotonin and histamine blocking effects which give it antiemetic properties through multiple pathways and its sedating effects may be beneficial for anxiolysis in the setting of CHS. Olanzapine would be used as a substitute for haloperidol and can be administered sublingually or intramuscularly. Dr. McGillis has anecdotally reported success in using olanzapine and prefers the IM route due to faster absorption.

To summarize, the current evidence would best support a haloperidol-first approach to treating vomiting episodes in CHS. Since haloperidol comes in a 5 mg/ml concentration, a dose of 2.5 mg is likely reasonable for smaller patients, with a dose of 5 mg for patients larger than 80 kg. This would approximate the 0.05 mg/kg dose from the HaVOC trial. The use of capsaicin should be a shared decision with patients since there is no strong evidence to recommend it. If the patient fails to respond to haloperidol, reassess their LOC and anxiety. In patients who have a strong anxiety component to their presentation, lorazepam is recommended in a dose of 1-2 mg IV. If the patient is already calm or drowsy (or fails to respond to lorazepam), traditional antiemetics such as dimenhydrinate and ondansetron can be added. Olanzapine could be a reasonable substitute for haloperidol in patients with a contraindication or aversion to haloperidol (dose = 5-10 mg IM or SL).

### **What should we be considering at time of discharge?**

The only long-term cure for CHS is prolonged cessation from cannabis use. It may take up to 6 months for episodes to cease after a patient stops using cannabis, so it is important to reinforce that episodes can still occur for some period of time after a patient stops using. The SBIRT approach of screening for substance use, providing a brief educational intervention, and referring for outpatient treatment is one

of the most well supported addictions management strategies in the ED. It is important to recognize cannabis use is often very engrained in patient's lives and social circles, making cannabis cessation more difficult than often recognized. If a patient is contemplating or ready to take action towards quitting cannabis, the RAAM clinic is the best available resource in Calgary. Patients can self-refer through the Addictions Services phone number, or physicians can refer patients. Physician referrals have the benefit that the clinic will actively call the patient to encourage follow through. The RAAM referral form and a RAAM information brochure with the self-referral number are available on the My ED App.

A second consideration is if home abortive medication may be a safe option to reduce recurrent ED visits. This will depend on which medications work for the patient, their comorbidities, and the patient's access to reliable follow up. There is no current evidence to guide outpatient treatment. Traditionally, GI has used SL Ativan and SL Zofran in combination to manage CVS patients at home. This may be reasonable if a patient has responded to these medications in the ED and the risk of misuse is felt to be low. The use of PO haloperidol at home is currently being studied, but there are no good protocols published to guide practice.

There have been no studies about using medications to reduce the frequency of CHS episodes. However, amitriptyline is recommended as a first line prophylactic treatment for adults with CVS. The studies which led to this recommendation demonstrated large reductions in both subjective symptoms scores, episode frequency and ED utilization. These studies were published before CHS was well recognized and had 40-50% of patients using cannabis, meaning they may have some applicability to CHS patients. Amitriptyline has several well recognized side effects, has to be slowly up-titrated and requires close follow-up. Therefore, it is not something which would be typically started in the ED should likely be deferred to a discussion between the patient and their primary care provider.

Lastly, while gastroenterology has a limited capacity to follow CHS patients chronically, it is reasonable to have patients referred for an EGD to rule out a structural cause for symptoms if this has never been done. This would be a non-urgent referral and is best arranged through a patient's primary care provider. Additionally, GI is actively recruiting patients for CHS studies through self-referral. If a patient with CHS is interested in research, please direct them to the [www.motility.ca](http://www.motility.ca) website where they can enter their information to be contacted about research opportunities.

## References Link



