

# Concurrent Management of Adolescent Cannabinoid Hyperemesis Syndrome and Delirium With Haloperidol

**JEREMIAH HSU, MD; MAHAKSH KOTDAWALA, MD; and THOMAS PRIOLO, MD**

*Dr. Hsu is with Hackensack Meridian Health, Ocean University Medical Center, Brick Township, New Jersey. Drs. Kotdawala and Priolo are with Hackensack Meridian Health, Jersey Shore University Medical Center, Neptune City, New Jersey.*

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**ABSTRACT:** Cannabinoid hyperemesis syndrome (CHS) manifests in adults as severe nausea accompanied by episodic vomiting and intense abdominal pain, typically associated with prolonged, high-dose cannabis use. The clinical course of CHS is divided into 3 distinct phases: prodromal, hyperemetic, and recovery. Traditional antiemetic and antinausea medications, such as ondansetron and metoclopramide, are often used in the acute clinical setting to address these isolated symptoms. Discussions and occasional use of haloperidol have demonstrated a level of symptom relief in patients with CHS. In several instances, patients report complete resolution of symptoms previously refractory to, or only partially relieved by, traditional antiemetics and antinausea medications. This case report explores the hospital course of a 15-year-old female adolescent who presented to the emergency department with a recurrent episode of CHS. The patient reported symptoms of nausea, intense abdominal pain, compulsive bathing behavior, physical agitation, and delirium. In the setting of CHS symptoms refractory to traditional antiemetics and concurrent behavioral disturbances, the patient was started on a standing low dose of haloperidol. Within 6 days of starting haloperidol treatment, the patient reported complete resolution of her presenting symptoms and was subsequently discharged from the hospital. We conclude that patients presenting with CHS and concurrent delirium, as is often the clinical presentation, would further benefit from the off-label use of haloperidol. Although minimal literature exists on the management of CHS, there is almost no evidence examining CHS comorbid with delirium and/or agitation. This report seeks to demonstrate the underlying causality and explore the scientific mechanisms to show the clear benefits of haloperidol as an antiemetic and antinausea medication, in addition to any sequelae of delirium, and highlighting the need for a revision of pre-existing CHS treatment protocols, specifically in the emergency department setting. **KEYWORDS:** Case report, cannabinoid hyperemesis syndrome, haloperidol

Cannabis use has risen significantly in recent years, driven by increasing legalization and shifting social perceptions of its safety. Between 2008 and 2016, respondents in the United States aged 12 to 17 reporting cannabis use disorder increased from 2.18% to 2.72% when comparing to the number of respondents before the legalization of recreational marijuana.<sup>1</sup> This increased prevalence has been paralleled by a rise in cannabis-related psychiatric disorders, including cannabis-induced psychosis and cannabinoid hyperemesis syndrome (CHS). Moreover, emergency department visits for cannabis-related vomiting have increased by 50% in states with legal recreational cannabis.<sup>2</sup> The increased prevalence of CHS highlights the need for efficacious treatment modalities.

The clinical presentation of CHS is often through three distinct phases. The prodromal phase can last for months to years and is marked by early morning nausea, abdominal discomfort, and a fear of vomiting. Patients may increase consumption to manage symptoms, but they generally maintain normal eating behaviors and show minimal or no compulsive bathing.<sup>3</sup> In the hyperemetic phase patients experience consistent nausea and vomiting with decreased consumption of food and anxiety relating to eating. In this phase patients often self-treat through taking multiple warm showers to relieve the symptoms.<sup>3</sup> The recovery phase follows the discontinuation of cannabis use and may span from days to months, marked by the restoration of normal eating and the cessation

of compulsive bathing behaviors. However, reusing cannabis can lead to a resurgence of symptoms.<sup>4</sup> The pathogenesis of CHS remains unknown, although various studies suggest it to be multifactorial involving cannabinoid metabolism, exposure dose and tolerance resulting in changes in receptor regulation. One proposed mechanism explaining CHS symptoms is believed to result from dysregulation of the endocannabinoid system, particularly involving cannabinoid receptor 1 (CB1). Chronic cannabis use leads to receptor desensitization and paradoxical effects on gastric motility and the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the hallmark symptoms of intractable nausea and vomiting.<sup>5</sup> Haloperidol, a first-generation dopamine D2 receptor antagonist may prove beneficial in the use of cases presenting with concurrent agitation and delirium. Dopamine plays a key role in nausea and vomiting through its effects on the chemoreceptor trigger zone (CTZ) in the medulla, and haloperidol's blockade of D2 receptors in this region can provide rapid and sustained symptom relief.<sup>5</sup>

Many patients also report that hot showers and/or baths relieve their symptoms, which can lead to compulsive bathing behavior observed in some patients.<sup>6</sup> This suggests THC inducing splanchnic vasodilation and cutaneous vasoconstriction and may be responsible for the abdominal discomfort reported by patients experiencing CHS.<sup>7</sup> However, the abdominal discomfort may also be attributed to a known property of

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**CORRESPONDENCE:** Jeremiah Hsu, MD; Email: [jhsu0807@gmail.com](mailto:jhsu0807@gmail.com)

THC, acting as an agonist at the transient receptor potential cation channel subfamily V member 1 (TRPV1), otherwise known as the capsaicin or vanilloid receptor. The receptor is integral in regulating antinociception in the descending pain pathways, as well as mediating nociception in the ascending pain pathways.<sup>8</sup> Central nervous system TRPV1 agonists, such as nabilone and dronabinol, have been approved by the US Food and Drug Administration (FDA) for treatment of cancer chemotherapy-associated nausea and emesis.<sup>9</sup> In the setting of CHS, overstimulation of TRPV1 from chronic cannabis use may downregulate TRPV1 and paradoxically produce symptoms such as nausea, emesis, and abdominal pain.

Given the unknown nature and the various, aforementioned hypotheses depicting the pathogenesis of CHS, symptomatic treatment in the acute setting may initially involve multiple unsuccessful medication trials using common antinausea and antiemetic agents, before utilizing offlabel or alternative treatment modalities.

## CASE PRESENTATION

A 15-year-old female adolescent with a past medical history pertinent for CHS presented to the ED, accompanied by her parents, for intractable vomiting and chest pain. The urine drug screen was positive for cannabinoids. A review of the patient's electronic medical records showed that she had presented to the same hospital 3 days prior and to another local hospital 1 day prior for similar symptoms. At the same facility 3 mornings prior, the patient received standard antinausea and antiemetic treatment (including pantoprazole, ondansetron, metoclopramide). At that time, it was also documented that the patient presented with behavioral disturbances and physical agitation, which prompted additional treatment with haloperidol. Subsequently, the patient was observed to be resting comfortably and tolerated a per os (PO) test with apple juice in the afternoon before being discharged at that time.

On this visit to the ED, the patient also reported experiencing intense shaking and stated that she had not eaten in 4 days due to frequent vomiting. Vital signs and routine labs (complete blood count, comprehensive metabolic panel, and urinalysis) were reviewed, with appropriate repletion of any metabolic

derangements secondary to the patient's recent history of poor nutrition. An intravenous (IV) line was inserted, and fluids, pantoprazole, and ondansetron were administered prior to the patient being admitted to the pediatric medical floor.

During the first 3 days of the patient's hospitalization, she presented with intermittent episodes of psychomotor agitation and reported severe nausea and abdominal pain. Although the patient reported that hot showers relieved some of the pain, her symptoms were poorly controlled, despite a robust combination of standing and as-needed medications (diphenhydramine, capsaicin cream, famotidine, acetaminophen, and toradol) for her refractory nausea and pain. By the end of the third day postadmission, the frequency and severity of the patient's behavioral disturbances increased. She exhibited fluctuating mentation with an inability to follow verbal redirection and was unable to engage in supportive therapy during her episodes of distress. Her psychomotor agitation intensified, resulting in her hitting herself against the backboard and side railings of her bed. The patient also began expressing passive suicidal ideation. She developed a compulsive bathing behavior, requesting to shower up to 3 times daily and becoming severely agitated if ancillary staff were unavailable to assist her immediately. As-needed lorazepam was added to the patient's medication regimen for management of severe agitation, and a psychiatry consult-liaison service was requested at this time.

Upon an initial psychiatric evaluation, the patient was diagnosed with CHS and hyperactive delirium. Medical literature was reviewed, and haloperidol was discussed as an appropriate agent to concurrently treat delirium symptoms and CHS symptoms, especially given that the patient had already failed multiple trials of standard antiemetics and antinausea medications. Low-dose haloperidol was started on an as-needed basis, but the dose proved to be insufficient and was eventually uptitrated to 5 mg for behavioral disturbances. She continued to require the as-needed haloperidol on a daily basis over the next 2 days. In an effort to minimize the patient's risk of harm to herself and others in the setting of physical agitation due to delirium, the frequency of haloperidol was adjusted from an as-needed dose to a standing morning dose as a prophylactic

measure. The patient received the morning doses of haloperidol for an additional 2 days.

Nine days after admission and 5 days after initiating treatment with haloperidol, the patient no longer reported nausea and endorsed improved mood and sleep. Her delirious episodes also resolved. Her appetite improved, and she was able to tolerate a PO diet prior to discharge. A trial of removing standing haloperidol was enacted, and the patient remained symptom-free for 24 hours under observation, without requiring any as-needed haloperidol for behavioral disturbances or somatic complaints. Subsequently, the patient was safely discharged to return home with an appointment made for her to follow up in the outpatient child and adolescent psychiatry and substance-use clinic.

## DISCUSSION

Incorporating haloperidol as a front-of-the-line treatment for CHS, specifically in the ED setting, may decrease prolonged hospital admissions and even facilitate same-day discharges directly from the ED. Some of the current limited use of haloperidol in the setting of CHS stems from the risk of developing extrapyramidal symptoms (EPS), which has been demonstrated in a dose-dependent manner in meta-analyses.<sup>10</sup> Although the risk of EPS should warrant cautious use of any antipsychotic medication, the same concerns for EPS limiting haloperidol's current use for CHS may paradoxically lead to an increased need for additional haloperidol use if CHS symptoms were to worsen and remain refractory to standard first-line antiemetics and antinausea medications. By minimizing precipitating factors for delirium as a sequelae of undertreated CHS, advancing haloperidol in the therapeutic sequence of treating CHS might ultimately decrease the need for exposure to additional antipsychotic medication and therefore decrease the risk of patients developing EPS. An earlier administration of haloperidol might thus serve as a harm reduction strategy by alleviating CHS symptoms at the onset. Other strategies to consider minimizing risk of EPS development include the modality of administration, with some studies suggesting intravenous haloperidol to be better tolerated when compared to an oral administration.<sup>11,12</sup> Similarly, when considering the prevalence of hypokalemia secondary to hyperemesis, the

risk of QT prolongation with IV haloperidol do not significantly differ from placebo, and rates of torsades de pointes appear to be low.<sup>12</sup> Nonetheless, a careful consideration of individual patients' comorbid medical conditions should be factored into the decision when using any medication and understanding of its adverse effects.

Although there are multiple case reports highlighting the efficacy of haloperidol for the treatment of CHS, high-quality studies comparing the efficacy of haloperidol to other traditional antiemetics and antinausea medications remain sparse. This case report demonstrates a potential need for a treatment protocol for CHS in child and adolescent populations, as the aforementioned patient developed delirium likely exacerbated by a prolonged hospital course due to her initial, undertreated CHS symptoms refractory to traditional antiemetic and antinausea medications. The resolution of the patient's CHS symptoms (ie, nausea, severe abdominal pain) after the serial administration of haloperidol for delirium reinforces existing literature demonstrating the superior efficacy of treating patients with haloperidol for CHS symptoms vs using standard antiemetic and antinausea medications.<sup>5</sup> By aggregating these reports, a more comprehensive and reliable set of diagnostic criteria, insights into pathophysiological mechanisms, and evaluations of effective treatments can be established to develop formal treatment protocols for CHS.

## CONCLUSION

CHS is characterized by chronic cannabis use leading to cyclic episodes of nausea, vomiting, and abdominal pain. Traditional antiemetic treatments often prove ineffective in managing acute symptoms. Often, patients presenting with CHS have comorbid delirium and agitation. Examining a case of this adolescent presenting with the combination of aforementioned symptoms points in the direction of the benefits of haloperidol use. Further investigation to establish standardized treatment protocols that differ based on symptom presentation is necessary.

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