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Cannabis Hyperemesis Syndrome in Palliative Care: A Case Study and Narrative Review

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Abstract

Background: Cannabis is increasingly used by persons at end of life to ameliorate symptoms such as pain, spasticity, anorexia, or anxiety. Cannabis hyperemesis is a distressing adverse effect of chronic use and may cause significant morbidity. Unfortunately, the clinical presentation of this syndrome may be subtle in a person with complex medical issues or disability. Providers must remain vigilant for possible variations in presentation in these populations.
Aim: To assess literature on cannabis hyperemesis and present unique considerations for clinical assessment and treatment for patients at end of life.
Design: Initial literature scoping yielded limited evidence on the subject in the setting of chronic disease and disability. A case of cannabis hyperemesis in a person with advanced amyotrophic lateral sclerosis is presented to illustrate challenges in diagnosis and management in this setting. A narrative synthesis of current literature on assessment and management and special considerations for evaluation and treatment for patients under palliative care was performed.
Results: Several unique considerations for the diagnosis and management of cannabis hyperemesis in palliative care patients are highlighted in the case presented, including: (1) Symptoms may possibly be abolished through decrease rather than complete abstinence from cannabis, (2) Frequent hot baths may not be present in patients with physical impairments in activities of daily living, and (3) Management of primary symptoms (pain, spasticity, nausea, and anxiety) in the end-of-life care patient must be considered to maximize comfort.
Conclusion: The presentation of cannabis hyperemesis may be atypical in palliative care patients due to disability. More work is needed to improve risk stratification for patients using cannabis for palliative care.

Keywords: amyotrophic lateral sclerosis; cannabis; medical marijuana; nausea; palliative care; vomiting

Highlights

What is already known about the topic?

- *Cannabis hyperemesis syndrome is associated with chronic cannabis use*
- *The syndrome is characterized by a triad of chronic cannabis use, cyclical nausea and vomiting, and relief of symptoms through hot baths*

What this article adds

- *The case presented illustrates a unique example where a patient with cannabis hyperemesis syndrome was able to ameliorate symptoms through decreasing, but not discontinuing use—this has not been previously described*
- *Challenges in diagnosing cannabis hyperemesis in patients receiving care due to medical complexity or disability are reviewed*
- *Proposed mechanisms for cannabis hyperemesis, as well as therapies to treat symptoms of the disorder and withdrawal, are presented*

Implications for practice, theory, or policy

- *Clinicians must be aware of atypical presentations of cannabis hyperemesis syndrome in the palliative care setting*
- *Complete abstinence from cannabis may not be required for resolution of cannabis hyperemesis syndrome*
- *Further study is needed to better define the optimal dose and route of administration of cannabis to maximize symptom control and minimize risk of adverse effects*

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Introduction

Cannabis hyperemesis syndrome is characterized by three typical features: chronic cannabis use, severe cyclical nausea and emesis, and frequent hot bathing. Although the hot bathing feature is common, it is a learned self-palliative behavior and may not be present in all instances. This syndrome was first reported in the literature in 2004.

Despite growing awareness, failure to recognize this syndrome often results in delays in diagnosis and costly medical procedures. Cases of acute renal failure[1] and even death[2] related to cannabis hyperemesis have been described. A large gap exists between the growing interest in cannabis-based medicine for palliative care and the dearth of literature to guide clinicians in appropriate use of this medication to alleviate symptoms,[3] as well as presentation of adverse effects related to cannabis use in patients with advanced disease or disability.

Materials and Methods

A unique case study is presented. The involved patient provided written informed consent, and formal approval was granted from the institutional review board. A scoping literature review failed to produce articles related to cannabis hyperemesis syndrome specifically related to palliative care, chronic disease, or amyotrophic lateral sclerosis (ALS). Therefore, a synthesis of current literature on cannabis hyperemesis syndrome without further limitations was performed. Literature published through September 2018 was searched in PubMed, CINAHL, and EMBASE using the MeSH (Medical Subject Headings) terms *cannabis* and *hyperemesis*. All relevant publications in English were included in this review.

Case History

A 31-year-old man with ALS presented to clinic requesting evaluation for abdominal pain, nausea, and vomiting of two months' duration. He described his pain as an epigastric dull aching and ''bloating'' sensation localized to the region around his radiographically-inserted gastrostomy tube (placed two years before presentation without previous complication). He reported that pain was worse after meals and with sitting upright and minimally alleviated with lying down and simethicone. He denied recent sick contacts or change in his usual daily bowel movements. A month before this visit, he presented to a local emergency room and was prescribed dicyclomine. This provided no relief of symptoms and was discontinued by the patient.

He was evaluated by interventional radiology in the facility where his gastrostomy tube was initially placed; examination revealed no evidence of feeding tube malfunction. Nausea symptoms continued to worsen over the ensuing months, and the patient described a new diurnal pattern to his nausea, involving morning retching, diaphoresis, and sensation of abdominal fullness. He denied any other alleviating factors for his symptoms and, when asked, reported that he never attempted hot showers, noting that mobility limitations prohibited bathing without direct assistance.

His past medical history was significant for a five-year history of limb-onset ALS, initially presenting as right leg weakness, but progressing to quadriparesis. In addition, he endorsed painful spasticity secondary to ALS involving the bilateral lower extremities. Previous treatments for spasticity symptoms included oral baclofen, tizanidine, and several benzodiazepines (diazepam, lorazepam, and clonazepam).

When prescription medications failed to alleviate his symptoms approximately one year after onset of symptoms, the patient initiated use of medical cannabis to manage spasticity-related pain. Initially, he used edible products (with an average self-reported use of 10 mg) three to five times per week. Four years after onset of symptoms (six months before presentation), as his spasticity symptoms progressed, he also inhaled through vaporization a cannabis extract tincture (specific Δ9-tetrahydrocannabinol (THC)/cannabidiol (CBD) content of this tincture not recorded), which he would use three to five times per night. Due to escalating symptoms, an intrathecal baclofen pump trial was offered but declined by the patient.

Premorbid medical history was notable only for chronic low back pain and military service-related post-traumatic stress disorder. Functionally, he required assistance for transfers and was ambulatory for household distances with a front wheeled walker. Regarding bulbar function, he had mild dysarthria and dysphagia, but was still taking all nutrition and hydration by mouth (feeding tube was placed early as per clinical practice guidelines based on pulmonary function results and only flushed daily to maintain patency of the tube).

At the time of his clinic presentation (two months after onset of increasing nausea/abdominal pain), physical examination revealed the patient to be afebrile with stable vital signs. His gastrostomy tube insertion site was well healed without purulence or erythema. Abdominal examination was benign with no tenderness to palpation, guarding, or rebound.

Complete cessation of cannabis use was recommended to determine if this was the underlying cause of his symptoms. The patient was advised to use diazepam for breakthrough spasticity symptoms as needed. As the patient related the marked increase in use of inhaled cannabis in the months preceding onset of nausea symptoms, he ceased use of cannabis oil, but continued the use of edible whole plant-based products. He reported infrequent use of diazepam during this transition. His nausea, vomiting, and abdominal pain symptoms completely resolved within three weeks of this change and remain completely resolved at one year follow-up despite ongoing cannabis edible use.

Discussion

An estimated 8.3% of the population above 12 years of age in the United States report active use of cannabis (defined as use within the past month).[4] Cannabis is also widely used by persons with life-limiting diagnoses, such as ALS, as a therapy for pain, anxiety, anorexia, and spasticity.[5,6] In 2004, Carter and colleagues found that 10% of 131 respondents to an online survey reported use of cannabis in the past year.[5] Since that time, the medicinal and/or recreational use of cannabis has been legalized by many U.S. states, although the use and possession of cannabis currently remain illegal under federal law. The effect of widespread legalization on the prevalence of cannabis use in the palliative care population is yet to be determined.

Clinical presentation

While cannabis is often used as a treatment for nausea, paradoxically, cannabis hyperemesis syndrome is a known

potential adverse reaction to chronic cannabis use. Cannabis hyperemesis syndrome was first described in 2004 and is characterized by the triad of chronic cannabis use, cyclical nausea and vomiting, and frequent hot bathing.[7] While this is generally regarded as a rare adverse effect of chronic cannabis use, a recent survey of 155 chronic cannabis users (≥20 days/month) presenting to an emergency room found that 32.9% endorsed experiencing cannabis hyperemesis symptoms (defined as nausea and vomiting relieved by hot showers in this population).[8]

The commonly described morning nausea and repeated vomiting of cannabis hyperemesis syndrome share similarities with cyclical vomiting syndrome, excepting the relief of symptoms with hot showers in cannabis hyperemesis syndrome. The differential diagnosis for cyclical vomiting syndrome (and thereby cannabis hyperemesis syndrome) is broad and includes medication or toxic effect, neurological disorders, gastrointestinal disorders, neurologic disease, and endocrine disorders.[9]

A large case series examining 98 persons with cannabis hyperemesis syndrome found a median age of 32 at diagnosis, abdominal pain in 86% of cases, epigastric location of pain in 61%, morning predominance of symptoms in 71%, relief with hot showers in 90%, and chronic use of cannabis for greater than or equal to two years for 67% of patients.[10] While this report helped define typically presenting symptoms of cannabis hyperemesis syndrome, absence of these symptoms clearly cannot exclude a diagnosis.

Other atypical clinical signs and symptoms have been described, including bradycardia and relief with cooling rather than heat.[11] Another case report detailed the presentation of a young man who developed rhabdomyolysis after he discovered running as a method to alleviate hyperemesis symptoms.[12]

In evaluating the cause of nausea, vomiting, and abdominal pain, palliative care patients may have an extensive differential diagnosis related to primary diagnosis, adverse effects of medications or treatments, and abdominal pathology or history of metastatic disease.[13] In addition, abdominal pain may result from adverse effects related to medication (e.g., constipation related to narcotics) and complications of medical interventions (such as prior abdominal surgeries or procedures such as gastrostomy tube placement). Use of noninvasive positive pressure ventilatory support may cause severe abdominal distension and discomfort secondary to aerophagia[14]—in more severe cases, this has been described to lead to abdominal compartment syndrome.[15] A careful history and physical examination is indispensable to exclude other acute conditions underlying the patient's symptoms.

Special consideration may also be given to potential drug interactions between cannabis and medications potentially used for the palliative care patient. THC and CBD serum concentrations may be impacted by other drugs that inhibit or enhance the activity of enzymes in the cytochrome P450 pathway (Table 1).[16]

Conversely, while not found to be a significant inducer or inhibitor of metabolic enzymes, cannabis has been found to increase serum levels of the anticonvulsant clobazam when administered concurrently.[17] Heavy cannabis smokers may lower serum concentrations of the antipsychotics fluphenazine and chlorpromazine; this interaction is the same as that with heavy tobacco smoking and thought to be related to an induction of the CYP1A2 enzyme.[18] Finally, pharmacodynamic additive effects have also been described between cannabis and anticholinergics (tachycardia and drowsiness), sympathomimetics (tachycardia and hypertension), and central nervous system depressants (drowsiness and ataxia).[19]

Table 1. Potential Drug Interactions with Cannabis

THC potentiators	
CYP2C9 inhibitors: Amiodarone, cimetidine, cotrimoxazole, metronidazole, fluoxetine, fluvoxamine, fluconazole, voriconazole	CYP3A4 inhibitors: Ketoconazole, clarithromycin, erythromycin, cyclosporine, verapamil, itraconazole, voriconazole, boceprevir
THC inhibitors	
CYP2C9 inducers: Barbiturates, carbamazepine, phenytoin	CYP3A4 inducers: Carbamazepine, dexamethasone, modafinil, phenobarbital, rifampin
CBD potentiators	
CYP2C19 inhibitors: Clopidogrel, fluoxetine, modafinil	CYP3A4 inhibitors: See above
CBD inhibitors	
CYP2C19 inducers: Barbiturates, phenytoin, rifampin	CYP3A4 inducers: See above

THC and CBD serum levels could be elevated by drugs that decrease activity of enzymes in the cytochrome P450 pathway (inhibitors). Conversely, serum levels could potentially be reduced as a result of medications that increase activity of enzymes in the cytochrome P450 pathway (inducers).

CBD, cannabidiol; THC, Δ9-tetrahydrocannabinol.

Pathophysiology

The underlying mechanism of cannabis hyperemesis syndrome is not entirely understood, but several potential mechanisms have been proposed based upon animal studies. Typically, cannabis acts as an agonist antiemetic by binding to the CB_1 G-protein endocannabinoid receptors in the central nervous system. Several theories center around the effect of cannabis on these receptors, either through acting as a partial agonist of the CB_1 receptor and blocking endocannabinoid function or causing downregulation of the CB_1 receptor.

Direct toxic effects and withdrawal have also been proposed as possible mechanisms for cannabis hyperemesis syndrome. One theory offers that lipid-soluble, nonintoxicating cannabinoids or metabolites accumulate over time in the central nervous system and subsequently exert a toxic effect. THC may exert an emetic effect, as observed with acute administration to cannabis-naive subjects, which is thought to be related to release of pro-inflammatory compounds and endocannabinoids. Cannabis is also known to

slow gastrointestinal motility, which may compound nausea and emesis. Another potential mechanism posits that cannabis withdrawal may cause these symptoms; this is less likely the case due to the long half-life of cannabis and failure of cannabis to resolve the symptoms following onset.[20] Finally, the possibility of a ''cannabinoid immune-type reaction'' has been suggested, related to production of an endogenous CB1 receptor antagonist; nausea and weight loss are known as adverse effects of synthetic CB1 receptor blockers, such as rimonabant.[21]

The clinical feature of hot showers used to alleviate cannabis hyperemesis syndrome is attributed to several possible mechanisms. Cannabis is thought to decrease core body temperature, either directly or through compensatory vasoconstriction. This may be an effect of direct CB_1 receptor stimulation in the hypothalamus or the effect of endocannabinoid and metabolite release following THC binding. In addition to increasing core body temperature through vasodilation, a hot shower may alleviate abdominal discomfort by diverting blood from the splanchnic circulation. Clues to the mechanism of heat analgesia in cannabis hyperemesis syndrome may also be gathered by observations regarding the use of topical capsaicin to mitigate symptoms of cannabis hyperemesis syndrome. Capsaicin binds and activates the transient receptor potential vanilloid 1 (TRPV1) receptor (a receptor which is also activated by heat >43°C). TRPV1 receptor activation results in a cascade of effects that may contribute to the antiemetic effects noted in this syndrome.[22,23]

Treatment. Definitive treatment of cannabis hyperemesis syndrome consists of cessation of cannabis use and supportive care. Abrupt cessation of chronic cannabis use can lead to significant withdrawal symptoms, including disruptions in sleep, appetite, mood, and—ironically—abdominal pain. Withdrawal symptoms are transient and typically resolve within two weeks of cessation.[24] Several medications have been used to prevent or treat hyperemesis symptoms including but not limited to benzodiazepines, haloperidol, capsaicin, tricyclic antidepressants, opioids, and antiemetics. Medications used to treat cannabis withdrawal include the cannabis derivative THC in the form of nabiximols or marinol,[25,26] gabapentin,[27] and lithium.[28] In addition, both extended release zolpidem and nitrazepam have been found to be effective for treating insomnia resulting from cannabis withdrawal.[29,30]

In the population of chronically disabled or medically complex end-of-life care patients experiencing cannabis hyperemesis syndrome, consideration for treating the primary symptoms for which the patient was using medical cannabis must be considered when advising abrupt cessation. Benzodiazepines, for example, may be a reasonable choice to attenuate both cannabis hyperemesis syndrome symptoms and spasticity in a person with a neurological disorder. Gabapentin or opioids may be more appropriate for individuals with pain experiencing cannabis hyperemesis syndrome.

Future directions. Estimating dose or quantity of marijuana use is challenging due to wide variation in forms of ingestion and variation in potency. Urine and blood assays are not reliable for estimating amount of cannabis ingested due to its long half-life. Studies have been performed to approximate weight of cannabis used by patient recall,[31] but these have mainly focused on smoked rather than ingested forms. Cannabis tinctures have vast variability in concentration based on solvent, storage, age, and variety or part of the plant used to make the extract.[32] These factors make it challenging to define safe versus toxic dose ranges for users of cannabis. Finally, the role that drug interactions play, specifically other pharmaceuticals impacting enzymes involved in cytochrome P450 drug metabolism, on adverse effects related to cannabis remains to be elucidated.

Conclusion

Although cannabinoid hyperemesis syndrome is becoming more widely recognized as a complication of chronic cannabis use, the case presented illustrates how the presentation of this disorder may be more subtle in a medically complex patient population. Delays in diagnosis may lead to significant patient morbidity and mortality, as well as costly and unnecessary diagnostic procedures and evaluations. Of note in this case, a marked decrease but not cessation of cannabis use was effective to interrupt the symptoms of cannabis hyperemesis syndrome. Symptoms were alleviated when the patient discontinued use of inhaled concentrated cannabis extracts, while continuing oral whole plant-based edible consumption. This is a unique observation not previously reported in the literature regarding cannabis hyperemesis syndrome.

Further studies may be useful to help determine the relationship between dose and toxicity of cannabis, as well as to determine whether the risk of cannabis hyperemesis syndrome varies based on formulation (whole plant versus extract), total THC or CBD doses, or route of administration (edible versus inhaled by vaporization).

There is a startling disconnect between the high prevalence of use of cannabis for recreational or medical purposes and the lack of standardized tools for clinicians to quantify use and understand risks of adverse events to best counsel patients. In addition, the proliferation of legalization in the United States has not been predicated on widely used standardization of labelling or quality metrics to provide consumers information about the content and quality of this highly variable product. This case highlights both the importance of monitoring quantity of medical cannabis used by palliative care patients for symptom management, as well as remaining vigilant for adverse reactions related to the use of cannabis in this population, so that they may be rapidly addressed and rectified.

Author Disclosure Statement

No competing financial interests exist.

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