A Case Report on Cannabinoid Hyperemesis Syndrome in Palliative Care: How Good Intentions Can Go Wrong

Helen Senderovich\textsuperscript{a, b} Sarah Waicus\textsuperscript{c}

\textsuperscript{a}Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada; \textsuperscript{b}Baycrest Hospital, Toronto, ON, Canada; \textsuperscript{c}Department of Medicine, Trinity College Dublin, Dublin, Ireland

Established Facts

- Synthetic cannabinoids are commonly used to manage pain, nausea, and vomiting in oncology and palliative care.
- Recurrent cases of nausea and vomiting can lead to a distinct pathogenesis associated with chronic cannabis use known as cannabinoid hyperemesis syndrome.
- Effective antiemetic solutions for chronic hyperemesis syndrome are difficult to treat due to overlapping symptoms with other conditions such as malignancy and side effects of chemotherapy.

Novel Insights

- Drug-drug interactions between chemotherapy agents and nabilone can impair renal clearance leading to toxicity due to reduced metabolism of cannabinoids and contribute to hyperemesis.
- The stress and food deprivation induced by malignancy, comorbidities, and chemotherapy could contribute to the breakdown of fat-releasing cannabinoids perpetuating nausea and vomiting.
- Trial of withdrawing and reinitiation of synthetic cannabinoids and clinical signs of chronic hot-water bathing are important clinical markers of cannabinoid hyperemesis syndrome and can lead to a diagnosis.

Keywords
Small-cell lung cancer · Supportive care · Pain management · Palliative treatment · Cannabinoid hyperemesis syndrome · Chemotherapy

Abstract

Introduction: Synthetic cannabinoids are commonly used to manage pain, nausea, and vomiting in oncology and palliative care. Despite the current acceptance of cannabinoids as a treatment option for nausea and vomiting, there is a lack of data regarding the side effects of its prolonged use leading to possible toxicity due to accumulation, and as a result, exacerbation of nausea and vomiting rather than alleviation. 

Case Report Presentation: The patient, a 70-year-old female, was residing in the palliative care unit with the diagnosis of small-cell lung cancer. She underwent a course of chemotherapy consisting of paclitaxel, docetaxel, and cisplatin. She presented with hair loss, sore mouth, a loss of appetite, diarrhea, neuralgia, nausea, and vomiting which developed approximately 5 h after chemotherapy. Nabilone was used for the last 5 years to manage the patient’s neuralgia. As her cancer progressed, a dosage of nabilone was incrementally increased from 0.5 to 2 mg to control her pain;
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Introduction

Cannabis is the most used recreational drug worldwide, and it continues to grow due to legalization in many countries [1]. Synthetic cannabinoids are commonly used to manage pain, nausea, and vomiting in palliative care [1, 2]. Nabilone, sold under the brand name Cesamet is a synthetic cannabinoid with therapeutic use as an antiemetic and an adjunctive analgesic which is third-line therapy for persistent and problematic neuropathic pain [3, 4]. Although evidence is limited that nabilone may be better than placebo or known analogues in relieving chronic pain, nabilone has shown small but significant reduction in pain [5, 6]. Nabilone mimics delta (9)-tetrahydrocannabinol, the primary psychoactive compound found in natural cannabis. Despite the current acceptance of nabilone as a treatment option for refractory nausea and vomiting associated with cancer chemotherapy in patients who have failed to adequately respond to conventional antiemetic regimens, there is a lack of data regarding the side effects of its prolonged use leading to possible toxicity due to accumulation, and as a result, exacerbation of nausea and vomiting rather than alleviation.

Current research has shown recurrent cases of nausea and vomiting with distinct pathogenesis associated with chronic cannabis use known as cannabinoid hyperemesis syndrome (CHS) may lead to toxicity due to the accumulation of cannabinoids [2]. This is a result of ingesting high amounts of botanical cannabis. The condition can cause distress for the patient, in addition to repetitive hospitalizations, and impact the quality of life of the patient and the cost of healthcare [3]. CHS is a prevalent health problem, as cannabis is readily available, and the abuse rate potential is high. Currently, the rate of cannabis consumption has rapidly increased due to COVID-19 and long stretches of quarantine have facilitated an environment which has seen a spike in cannabis, alcohol, and other drugs of abuse which were used to help with coping [4]. Finding effective antiemetic solutions for CHS have proven to be difficult due to the overlapping nature of the symptoms with other conditions such as malignancy, chemotherapy, cyclic vomiting syndrome, viral gastroenteritis, and bulimia nervosa [2]. This report aims to create awareness of the role of cannabis in the development of CHS.

Case Report

Case Presentation

The patient, a 70-year-old female, was residing in the palliative care unit with the diagnosis of small-cell lung cancer. She underwent a course of chemotherapy consisted of paclitaxel, docetaxel, and cisplatin soon after the diagnosis, complicated by hair loss, sore mouth, loss of appetite, diarrhea, neuralgia, nausea, and vomiting developed approximately 5 h after chemotherapy. Nabilone was used for the last 5 years to manage the patient’s neuralgia leading to a significant reduction in problematic nausea and vomiting that developed post-chemotherapy.

The patient’s past medical history is remarkable for long-standing dementia, depression, and coronary artery disease. Her medications included bupropion, bisoprolol, Haldol, lorazepam, and domperidone. Previous admissions to the acute care unit were unsuccessful in controlling her nausea and vomiting and only resulted in short-term improvement. Chronic hot bathing was temporarily relieving the patient’s nausea and vomiting.

She was initially started on 0.5 mg of nabilone orally once a day. As her disease progressed, nabilone was titrated up to 1 mg orally once a day which were controlling her pain and later on nausea, and vomiting. Unfortunately, nausea and vomiting recurs and became unmanageable in the community, and as a result admission to the palliative care unit was requested. A trial of increasing nabilone to 2 mg orally once a day exacerbated refractory nausea and vomiting and led to cognitive decline, but she was confident that the therapeutic benefits of nabilone outweighed the potential harms. Nabilone was discontinued 7 weeks after admission as per patient’s wishes, goals of care, and her reluctance to any changes to her treatment plan. At the request of the patient, nabilone was discontinued 7 weeks after admission as per patient’s wishes, goals of care, and her reluctance to any changes to her treatment plan.

Discussion/Conclusion

Successful recognition and management of cannabinoid hyperemesis syndrome is especially important in individuals with comorbid disorders in order to avoid cannabis toxicity.

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**Treatment**

Nabilone was discontinued 7 weeks after admission to the palliative care unit, nausea and vomiting resolved, but pain escalated. Attempt to reinitiate nabilone to help with the pain led to more severe episodes of nausea and vomiting. As CHS was suspected, she was switched to hydromorphone and gabapentin to control her pain. Serotonin and norepinephrine reuptake inhibitors were later added to augment analgesia.

**Outcome and Follow-Up**

The patient’s pain became well controlled with opioids, gabapentin, and selective serotonin reuptake inhibitors, and there has been no recurrence of nausea and vomiting since the cessation of nabilone. She died eventually in the palliative care unit while being comfortable with the support of the palliative care team and her loved ones at bedside.

**Discussion**

Clinicians should be aware of the risk of CHS with chronic use of cannabis [8]. Best practice guidelines assert that hyperemesis management should include adequate hydration and administration of non-cannabinoid-derived antiemetics as a first choice. In the patient’s case, nabilone led to the development of CHS, and as a result, she was switched to opioids, gabapentin, and selective serotonin reuptake inhibitors to target her pain. Nausea and vomiting subsided and no additional intervention was needed in this regard as time passed post chemotherapy. If she would become symptomatic from nausea and vomiting perspectives alternative antiemetics could be used as the drug of choice in this situation.

There is an association between CHS and long-term cannabis usage which completely ceased with cannabis discontinuation [9]. In the described case, discontinuation of nabilone led to the complete resolution of nausea and vomiting, and reinitiation of nabilone resulted in more severe nausea and vomiting. It solidifies that the patient’s nausea and vomiting was induced by cannabis. Prolonged nabilone use can result in an increased level of synthetic cannabinoids in the blood, causing CHS [10]. The dosage of cannabis used by patients leading to CHS is undetermined, but the duration of cannabis usage varies between 6 months and 11 years has been shown to produce hyperemesis [10–13]. In the patient’s case, nabilone was used for 5 years to manage pain, nausea, and vomiting.

**Management of CHS**

Besides cannabinoids cessation, there are other solutions to manage nausea and vomiting in patients with CHS such as taking hot baths that provide temporary relief only. Delta (9)-tetrahydrocannabinol in cannabinoids may disrupt thermoregulation, and a hot shower may attenuate its symptoms [10]. Hot water may redirect blood to the skin and away from the guts, which can reduce nausea and vomiting. In the patient’s case, hot baths were used initially to alleviate nausea and vomiting which, provided relief only for a few hours, but had a diagnostic value. The unique clinical sign of compulsive hot water bathing should be highlighted in patient history, as an important diagnostic marker [10]. Side effects of chronic hot water bathing are associated with weight loss, volume reduction, and rupture of the esophagus [14].

Additionally, capsaicin cream has been used for induced cannabinoid hyperemesis relief and could be useful in patients like the patient to achieve the same effects without the burden of constant bath taking [2, 15]. In a randomized controlled trial, abdominal application of capsaicin has been shown to significantly reduce nausea and vomiting 60 min after administration [16]. Topical capsaicin has been shown to be cost-effective in managing CHS, as patients reported relief of nausea and vomiting and faster discharge [17, 18].

First-generation antipsychotics have also shown to be effective in managing CHS, including droperidol and haloperidol. Intravenous administration of droperidol significantly reduced nausea and vomiting, as well as the length of stay in the emergency department for older adults [19]. Similarly, intravenous use of haloperidol has been effective in treating severe refractory CHS in the emergency department. For individuals unresponsive to antiemetics, haloperidol rapidly led to the complete resolution of nausea and vomiting [20–22].

**Proposed Mechanisms of CHS**

The most common chemical in cannabis, delta (9)-tetrahydrocannabinol, has neuromodulatory antiemetic effects on CB1 and CB2 cannabinoid receptors. Delta (9)-tetrahydrocannabinol activation of these receptors is known to reduce gastric emptying [23]. It is hypothesized there is gastrointestinal CB1 overriding, where delta (9)-tetrahydrocannabinol activation in the central nervous system is overridden by its effect on the enteric system, leading to CHS, which was probably observed in the patient [23]. Prolonged CB1 agonist exposure has been shown to downregulate CB1 receptors, upregulating D2 receptors which may also predispose patients to nausea and vomiting [24].

Accumulation of the lipid-soluble delta (9)-tetrahydrocannabinol in cerebral fat has also been known to cause nausea and vomiting [11]. During stress or food deprivation the body breaks down fat and a large reservoir of stored delta (9)-tetrahydrocannabinol is released causing a “reintoxification effect” [25]. The stress and food deprivation induced by malignancy and chemotherapy in the patient’s case could have contributed to the breakdown of fat causing nausea and vomiting. The proposed mechanisms for CHS can be found in Figure 1.

**Drug-Drug Interactions and CHS**

For patients with cancer, drug-drug interactions between chemotherapy agents may contribute to nausea and
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Vomiting, which was possibly observed in the patient’s case. The interaction between nabilone and her other medications could lead to undesirable adverse events. Cisplatin and paclitaxel could increase the paclitaxel level by reducing drug clearance through the kidneys, resulting in delayed metabolism of nabilone and leading to toxicity, manifested by CHS [26]. Nabilone undergoes extensive first pass clearance, with active metabolites persisting greater than 20 h [27]. Additionally, nabilone elimination occurs in the feces (65%) rather than the urine (20%) [27], suggesting that reduced urine clearance by paclitaxel is unlikely, however, cannot be completely ruled out in this case. The structure of nabilone is similar to THC and CBD, as it is metabolized through CYP2C19 enzymes leading to multiple drug-drug interactions, including proton pump inhibitors, anti depressants, antiplatelet drugs, antifungals, and antinecancer compounds such as cyclophosphamide [24].

It is important to keep in mind that combined use of lorazepam and nabilone could lead to increase sedation, hence this combination should be monitored closely. Further, benzodiazepines should be used with caution due to the potential risk of addiction, development of delirium and falls in older adults [28, 29]. Haloperidol should be used with caution in patients with dementia and Parkinson’s disease, as dopamine blockade can dramatically worsen symptoms leading to Tardive dyskinesia, cognitive decline, and nonverbal fluency causing incapacitation [28, 29]. Interestingly enough, haloperidol has been associated with increased agitation in patients with dementia despite being frequently used to control responsive behavior in this population [30]. In the patient’s case, typical treatment with haloperidol for controlling nausea and vomiting was unsuccessful and only resulted in short-term benefits. Additionally, the use of haloperidol was associated with drowsiness and agitation. However, the reviewed data showed the efficacy of haloperidol in treating CHS as it acts as a sigma-1 receptor and D2 receptor antagonist and may counter the capsaicin targeted vanilloid receptor (TRPV1) and CB1 receptor activities [5]. Successful recognition and careful selection of pharmacological treatment for CHS is especially important in aged individuals with multiple comorbidities as was seen in the patient’s case.

Conclusion

Cannabinoid-induced hyperemesis can be a life-threatening situation. A recent study by Soota et al. [31] described three fatal cases presumably caused by CHS. Thus, it is important to keep in mind that using cannabis for over 6 months, especially in aged individuals with multiple comorbidities may lead to nausea and vomiting induced by cannabis toxicity [32], and urgent cannabis discontinuation should be considered. Medication interactions and polypharmacy in patients undergoing other treatments may impair renal function and results in drug toxicity manifested in described CHS [33]. Currently, there are high levels of misdiagnosis of CHS as it can be masked by other conditions such as malignancy, chemotherapy, cyclic vomiting syndrome, eating disorders, or drug-seeking behavior [34]. Healthcare professionals should be alarmed that patients using synthetic cannabinoids are more prone to the development of CHS compared to natural marijuana users [34].

With the worldwide growing usage of cannabis due to its legalization, cases of CHS are on the rise, and widespread awareness is vital for healthcare practitioners in order to recognize and appropriately manage nausea and vomiting induced by long-term cannabis intake, especially in palliative care settings while dealing with this frail population. Although the findings in this case report cannot be generalized to the whole population timely recognition, diagnosis, and management are imperative to mediate effects of cannabis toxicity. Further research is warranted to solidify the best management options for CHS.

Statement of Ethics

The authors declare this research complies with the guidelines in accordance with the World Medical Association Declaration of Helsinki. Baycrest Research Ethics Board granted an exception from requiring ethics approval, as a demonstrative case vignette was developed to illustrate potential applications of cannabis in clinical palliative care settings. The vignette presented involves the multifactorial utility of cannabis to control symptoms that are extremely valuable in palliative care, however, caution should be exercised due to the possibility of the development of cannabinoid hyperemesis syndrome which was observed in the presented vignette. Ethics approval was not required as it was a demonstrative vignette, and an exemption was granted from the Baycrest Research Ethics committee. Written informed consent was not required as the presented vignette is demonstrative only and no patients were involved in this case vignette, which was aligned to literature findings and supported by references.
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Helen Senderovich was responsible for the conception, design, drafting, clinical revisions, and final approval of a version to be published. Helen Senderovich is accountable for all aspects of the published work. Sarah Waicus was responsible for the drafting of the paper, interpretation of the data, and critical revisions of the paper.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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