CASE REPORT

Nabilone therapy for cannabis withdrawal presenting as protracted nausea and vomiting

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SUMMARY

Cannabis is one of the most commonly used recreational drugs worldwide. Psychoactive properties of the principal compound, δ -9-tetrahydrocannabinol include euphoria, a sense of relaxation and increased appetite. Chronic cannabis use has been associated with the development of a withdrawal syndrome on abrupt discontinuation. Withdrawal symptoms typically begin within 24 h of abstinence and manifest as irritability, nervousness, sleep disturbances and decreased appetite. There is growing evidence that supports the use of plant-derived and synthetic cannabinoids for the treatment of cannabis withdrawal. In this case report, we present 20-year-old woman who developed protracted nausea and vomiting secondary to cannabis withdrawal and was successfully treated with nabilone. Nausea and vomiting is not listed in the Diagnostic and Statistical Manual-5 diagnostic criteria for cannabis withdrawal syndrome and is an uncommon symptom presentation.

BACKGROUND

Cannabis is one of the most commonly used recreational drugs worldwide. In Canada, where the patient lives, the lifetime prevalence of cannabis use has been reported to be 24% in those between ages 15 and 24.¹ Psychoactive properties of the principal compound, δ -9-tetrahydrocannabinol (THC) include euphoria, a sense of relaxation and increased appetite. Common adverse effects associated with cannabis use include tachycardia, dry mouth and conjunctival injection.

Chronic cannabis use has been associated with the development of a withdrawal syndrome on abrupt discontinuation. The most common withdrawal symptoms reported in studies include irritability, nervousness, sleep difficulty, decreased appetite and restlessness.² Most symptoms appear within 24 h of abstinence, peak within 2–3 days and resolve over the course of 1–2 weeks. The development of withdrawal symptoms is thought to contribute to high relapse rates.³

There are currently no medications approved for the treatment of cannabis withdrawal. A variety of pharmacotherapies have been evaluated for the treatment of cannabis withdrawal with mixed results. Agents which have been studied include nefazodone, bupropion, lithium carbonate, divalproex, lofexidine and baclofen.⁴

Agonist substitution therapy refers to the replacement of the abused substance with a pharmacological agent having a similar mechanism of action in an attempt to reduce withdrawal symptoms and craving. This method has been successfully used to

treat withdrawal syndromes associated with tobacco smoking (nicotine replacement therapy) and opiate dependence (methadone maintenance treatment). Agonist substitution therapy has been applied to the treatment of cannabis withdrawal using plant-derived and synthetic cannabinoids with promising results.

CASE PRESENTATION

A 20-year-old woman with no medical or psychiatric history presented to the emergency department with a 6-day history of protracted nausea and vomiting. She also complained of tremors, decreased appetite and poor sleep. She did not take any medications regularly. She smoked 1 g of cannabis daily for several years. She had stopped abruptly 1 day prior to symptom onset because of inability to access the drug. The patient denied any other history of recreational drug use or coingestions. We were unable to obtain collateral history. She denied any fever, chills, abdominal pain, sick contacts or unique exposures. Her symptoms had led to several visits to emergency departments without resolution of symptoms. At our institution, vital signs were stable and the patient was afebrile. Physical examination was normal.

INVESTIGATIONS

She was mildly hypokalaemic (3.2 mmol/L). Serum β -human chorionic gonadotropin was negative. Abdominal X-ray was normal. Abdominal, pelvic and transvaginal ultrasound did not reveal any abnormalities. A toxicology screen was not performed for this patient.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for nausea and vomiting is broad, but important aetiologies to consider include oesophageal (eg, oesophagitis, gastroesophageal reflux disease), gastric (eg, gastritis, peptic ulcer disease), intestinal (eg, infections, mechanical obstruction) and extragastrointestinal (eg, raised intracranial pressure, vestibular disease, pregnancy, pyelonephritis). Clinical presentation and investigations did not point to any of these causes.

Toxic ingestions (such as alcohols, salicylates and acetaminophen) and withdrawal syndromes are also important considerations in a patient presenting with protracted nausea and vomiting. In our patient, there was no history of psychiatric illness, intent for self-harm or toxic ingestions and the accompanying biochemistry did not suggest any coingestions.

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Given her history of chronic cannabis use and onset of symptoms following abrupt cessation, cannabis withdrawal syndrome was considered the most likely diagnosis. Although nausea and vomiting were her predominant symptoms, she did meet the Diagnostic and Statistical Manual-5 (DSM-5) diagnostic criteria for cannabis withdrawal syndrome. Another diagnostic consideration in the case was 'cannabinoid hyperemesis', which is a unique entity in chronic cannabis users that presents with severe nausea and vomiting recurring in a cyclic pattern.⁵ Factors arguing against this diagnosis include the onset of symptoms following cessation (rather than ongoing use) of cannabis, no history of cyclic vomiting and the prolonged duration of emesis.

TREATMENT

She was admitted to hospital and treated with intravenous fluids, dimenhydrinate, ondansetron and metoclopramide which provided minimal relief. The synthetic cannabinoid nabilone was offered to the patient as a treatment option due to its documented efficacy in small randomised trials and the lack of current treatment guidelines for acute cannabis withdrawal. Nabilone was chosen because dronabinol is not commercially available in Canada. The patient was agreeable to this, and on day 1 of admission, she was administered nabilone 1 mg orally twice daily.

OUTCOME AND FOLLOW-UP

Two hours after initiation of nabilone therapy, her nausea subsided and she was able to tolerate an oral diet. Two days after admission, the patient was discharged with a 2 week prescription of nabilone at the same dose and was referred to an outpatient cannabis cessation programme. Her symptoms remained absent on nabilone therapy.

DISCUSSION

The cannabis plant contains over 60 cannabinoids, but the most potent and well studied compound is THC. THC exerts its psychoactive effects through the activation of cannabinoid type 1 (CB1) receptors, which are present on presynaptic neurons within the central nervous system. Endocannabinoids such as anandamide serve as the endogenous ligand for the CB1 receptor. CB1 receptor activation modulates the release of various neurotransmitters and has been shown in animal studies to stimulate dopamine release from the mesolimbic (reward centre) region of the brain.⁶ It is presumed that abrupt cessation of cannabis and CB1 activation results in the dysregulation of downstream neurotransmitter release and subsequent development of withdrawal symptoms. THC, dronabinol and nabilone all exert CB1 receptor agonism and therefore are potentially useful agonist substitution therapies for the treatment of cannabis withdrawal.

Dronabinol is a synthetic form of THC which is available as an oral formulation. Dronabinol has demonstrated efficacy in two small studies of non-treatment seeking cannabis users, reducing withdrawal discomfort, aggression, irritability and sleep difficulty with minimal side effects.^{7 8} Furthermore, a recent double-blind randomised controlled trial of 156 outpatient cannabis-dependent adults found that dronabinol significantly reduced withdrawal symptoms and improved treatment retention compared to placebo over a 12-week trial period.⁹

Nabilone is a synthetic cannabinoid that is a structural analogue of THC. It is currently licensed in Canada for the treatment of chemotherapy-associated nausea and vomiting. CB1 receptors are present in the dorsal vagal complex and nucleus of the solitary tract, areas which are involved in emesis and nausea.

Nabilone has been shown in a small study of 11 non-treatment seeking cannabis users to decrease withdrawal symptoms and a laboratory measure of relapse in the inpatient setting.¹⁰ Adverse effects at doses recommended for nausea and vomiting (1 mg/day) were found to be no different than placebo in a double-blind controlled pilot study.¹¹ Even at doses of 6–8 mg/day, it appears to be well tolerated.^{10 12} Compared to dronabinol, nabilone has greater oral bioavailability and its urinary metabolites are distinguishable from those of cannabis which can be useful in monitoring patients for relapse.¹² Given our patient's response to nabilone therapy, but not other antiemetics, we hypothesise that abrupt withdrawal of cannabis resulted in a dysregulation of CB1 modulated neurotransmitter release in the central nervous system resulting in the symptoms of nausea and vomiting.

Cannabis withdrawal presenting primarily as gastrointestinal (GI) symptomatology does not appear to be common. Current DSM-5 diagnostic criteria for cannabis withdrawal syndrome requires cessation of cannabis use that has been heavy and prolonged, and three or more of the following signs and symptoms that develop within 1 week after cannabis cessation: (1) irritability, anger or aggression, (2) nervousness or anxiety, (3) sleep difficulty, (4) decreased appetite or weight loss, (5) restlessness, (6) depressed mood, (7) at least one of the following physical symptoms: abdominal pain, tremors, sweating, fever, chills or headache.¹³ The signs or symptoms must also cause clinically significant distress or impairment in social, occupational or other important areas of functioning and cannot be attributable to another medical condition or mental disorder.¹³

Although abdominal pain is listed as one of the physical symptoms, nausea or vomiting are not included. In a survey of 469 adult cannabis users, cannabis craving (75.7%), mood changes (33.7–50.1%), sleep disturbances (21.8–46.9%) and decreased appetite (38.8%) were the most prevalent psychological symptoms reported.¹⁴ Weight gain (23.5%) and headache (23.2%) were the most common physical symptoms, with nausea and vomiting reported in only 8.3% and 2.1% of surveyed individuals, respectively.¹⁴ One published case series describes three patients (one male patient 16-years-old and two female patients 17-years-old) who were referred to an eating disorder clinic for nausea, vomiting and decreased appetite.¹⁵ All three patients used cannabis chronically and were found to meet the criteria for cannabis withdrawal syndrome. Their GI symptoms improved with reintroduction of cannabis. This study suggested that GI symptoms may be under-recognised in the DSM-5 criteria for cannabis withdrawal in adolescents.¹⁵ However, the lack of inclusion of nausea and vomiting in the DSM-5 criteria is likely reflective of its limited diagnostic utility (due to its low prevalence) rather than an under-recognition of the symptom complex.

In any individual with non-specific symptoms and an unclear history of recreational drug use, clinicians should assess for a potential toxidrome or withdrawal syndrome. Suspicion for toxic ingestions should signal the clinician to perform a full toxicology screen. Collateral history from family members or acquaintances can provide crucial information regarding current or past drug use as well as any history of self-harm. In this particular case, although a lack of toxicology screen may weaken the certainty of the diagnosis, the pretest probability for cannabis withdrawal syndrome (based on the reliable history, lack of clinically apparent toxidrome and unremarkable investigations to exclude other causes) was high enough that we proceeded with empiric management.

Learning points

- ▶ Cannabis withdrawal syndrome typically presents within 24 h of abstinence with irritability, nervousness, sleep disturbances and decreased appetite usually lasting 1–2 weeks.
- ▶ Diagnostic criteria for cannabis withdrawal syndrome is a new addition to the Diagnostic and Statistical Manual-5 (DSM-5) classification system.
- ▶ This case contributes to the growing evidence for the use of plant-derived and synthetic cannabinoids in the treatment of cannabis withdrawal.
- ▶ Protracted nausea and vomiting is an uncommon presentation of cannabis withdrawal and is not listed in the DSM-5 diagnostic criteria.

Contributors PWL conducted a literature review and drafted the manuscript. DWF conceived the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Health Canada. Canadian Alcohol and Drug Use Monitoring Survey. 2011. http://www.hc-sc.gc.ca/hc-ps/drugs-drogués/stat/_2011/summary-sommaire-eng.php (accessed 1 Apr 2014).
- 2 Hesse M, Thylstrup B. Time-course of the DSM-5 cannabis withdrawal symptoms in poly-substance abusers. *BMC Psychiatry* 2013;13:258.
- 3 Budney AJ, Novy PL, Hughes JR. Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction* 1999;94:1311–22.
- 4 Weinstein AM, Gorelick DA. Pharmacological treatment of cannabis dependence. *Curr Pharm Des* 2011;17:1351–8.
- 5 Galli JA, Sawaya RA, Friedenbergh FK. Cannabinoid hyperemesis syndrome. *Curr Drug Abuse Rev* 2011;4:241–9.
- 6 Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. *Science* 1997;276:2048–50.
- 7 Haney M, Hart CL, Vosburg SK, et al. Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology* 2004;29:158–70.
- 8 Budney AJ, Vandrey RG, Hughes JR, et al. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend* 2007;86:22–9.
- 9 Levin FR, Mariani JJ, Brooks DJ, et al. Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend* 2011;116:142–50.
- 10 Haney M, Cooper ZD, Bedi G, et al. Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. *Neuropsychopharmacology* 2013;38:1557–65.
- 11 Lu S, Cameron K, Ganesan S, et al. A double-blind placebo control pilot study on the safety and tolerability of Nabilone in marijuana users. *Ment Health Subst Use* 2012;6:133–9.
- 12 Bedi G, Cooper ZD, Haney M. Subjective, cognitive and cardiovascular dose-effect profile of nabilone and dronabinol in marijuana smokers. *Addict Biol* 2013;18:872–81.
- 13 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th edn. Arlington, VA: American Psychiatric Association, 2013.
- 14 Levin KH, Copersino ML, Heishman SJ, et al. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. *Drug Alcohol Depend* 2010;111:120–7.
- 15 Chesney T, Matsos L, Couturier J, et al. Cannabis withdrawal syndrome: an important diagnostic consideration in adolescents presenting with disordered eating. *Int J Eat Disord* 2014;47:219–23.

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