

Chronic Cannabis Use with Hyperemesis, Epigastric Pain and Conditioned Showering Behavior

Karim Richard Masri, Ronnie Moussa, Heather Licke, Boutros El Haddad

Karim Richard Masri, Ronnie Moussa, Boutros El Haddad, Department of Internal Medicine; University of Kansas School of Medicine Wichita; 1010 N Kansas Wichita, KS 67214, USA

Heather Licke, Department of Family Medicine; University of Kansas School of Medicine Wichita, 1010 N Kansas Wichita, KS 67214, USA

Correspondence to: Karim Richard Masri, MD., Department of Internal Medicine, University of Kansas School of Medicine Wichita, 1010 N Kansas Wichita, KS 67214, USA. kmasri@kumc.edu

Telephone: +1-832 433-4475

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ABSTRACT

This report promotes awareness to an emerging cannabis-induced syndrome that is beguiling to primary care doctors and gastroenterologist specialists and a major expense on the healthcare system. It is also a diagnosis of exclusion. Four different young adults presented with recurrent admissions complaining of intractable nausea, vomiting, and epigastric pain with an incidental finding of excessive showering. They were all chronic heavy marijuana smokers. After extensive negative work up and observation of symptomatic cessation upon the discontinuation of marijuana, a diagnosis of exclusion was determined. Under the extrapolation of different animal model studies and basic science research, a hypothetical mechanism may explain why these patients present with these characteristic symptoms. The manifestation of chronic Δ 9-tetrahydrocannabinol (Δ 9-THC) may not show until after a long time and is reproducible when exposure to Δ 9-THC saturates the cannabinoid receptor-1 (CB-1). Chronic Δ 9-THC exposure appears to desensitize the gabanergic effects of CB-1 which is known to cause intestinal hypomotility, analgesia, and hypothermia. Extensive gastrointestinal workup is usually non-yielding and may impose financial burden on the healthcare system.

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Key words: Cannabis; Hyperemesis; Compulsive bathing; Abdominal pain; Nausea and vomiting

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INTRODUCTION

Cannabis is a plant that has been used for thousands of years dating back to the 3000 BCE^[1]. It was recently exploited during the Hippie Era of the 20th century as a widely yet illegal recreational drug due to its euphoric effect. Its use in the past century also entered the medical forum for chemotherapy patients with chemo-induced anorexia and refractory nausea because of its characteristic of promoting appetite and act as an anti-emetic^[2,3] by activating cannabinoid receptor 1 at the nucleus of the solitary nucleus in the dorsal vagal complex^[4]. Physiological responses from cannabis produce hypoactivity, analgesia and hypothermia^[5,6]. Unfortunately, many abuse this plant recreationally and become chronic cannabis users. There have been more than 10 case reports since the first documented incidence in Australia in 2004 by Allen *et al*^[2] of epigastric pain, hyperemesis with compulsive showering as a sequellae of chronic cannabis abuse. This is a case series with a possible mechanistic explanation of four individuals abusing cannabis and complaining of recurrent history of nausea, vomiting and abdominal pain, and frequent hot water showering.

CASE REPORT

Case 1

A 26-year-old white male presented to the hospital complaining of severe epigastric pain with nausea and vomiting. The patient had been admitted numerous times over the past three years with similar complaints, complicated with acute renal injury, and had undergone an extensive workup involving two normal EGD's, whole-body MRI and CT, MRCP, in addition to an elective cholecystectomy. EGD biopsies showed mild gastritis and negative *H. pylori* and celiac disease. MRI and CT abdomen demonstrated moderate stomach distention with otherwise normal findings. The MRCP was normal. Small bowel series and gastric swallow were unremarkable. Capsule endoscopy failed because it never left the stomach. Extensive laboratory data over the three years were negative, including acute intermittent porphyria and inborn errors in metabolism, except for

consistent $\Delta 9$ -THC in urine drug screens. Upon admission, the patient was found to be in the shower and the history was taken from the father until he came out of the shower. History goes back to the age of 14 when he smoked at least five KB marijuana joints per day. He reports that KB is high potency medical marijuana that has high $\Delta 9$ -THC levels. He reports suffering from the cyclical vomiting and epigastric pain with compulsive showering that resolved after cessation. Most recently, he reports that six months ago he was sober and asymptomatic, but then resumed smoking around 28 g (1 ounce) per week of Mexican marijuana three months later until the symptoms returned. He reported that he develops acute diaphoresis, stabbing epigastric pain, with severe nausea and non-bloody emesis. He then feels the urge to take a hot bath. He admits that as soon as the hot water touches his skin, he becomes asymptomatic. When asked why he initially resorted to hot bathes, he reported that he was conditioned in his youth by his mother to take warm baths when feeling ill. At home, he spends 3-4 h in a hot bath. In approximately 15 min after leaving the hot water, he reports that his symptoms return and feels the urge to have another hot water bath to sooth his symptoms. During this hospitalization, a quantitative analysis of the $\Delta 9$ -THC in urine was done. The patient responded to anti-emetics and narcotic analgesics. The acuteness of his symptoms abated after 48 h of marijuana abstinence which coincides with his reported history of "3 to 4 d" and was discharged with the diagnosis of cannabis-induced epigastric pain with cyclic vomiting and compulsive showering. He was informed that he should avoid using high amounts of marijuana and try to quit altogether. The patient was very receptive of this diagnosis and treatment plan.

Case 2

A 34-year-old black male previously healthy presented with nonspecific generalized abdominal pain, cyclic nausea and vomiting with subsequent decreased oral intake without diarrhea and a documented 20 pound weight loss over the past month, in addition to compulsive showering which after admission to hospital resolved. Patient had been taking hot baths up to six times per day and used heating pads because the heat seemed to relieve his abdominal pain. He has had a cholecystectomy. No recent travel, food related illness. He has tried narcotic for pain relief, gastric acid blockers, anti-emetics without improvement. Patient initially denied illicit drug use however his UDS tested positive for marijuana which was the same during his previous admissions. Patient reported having the same constellation of symptoms a few years ago but had been symptom free for the past 2 years. This had prompted an extensive workup by gastroenterology including upper and lower endoscopy with biopsies, small bowel series, gastric emptying studies, and acute intermittent porphyria which were all negative. CT abdomen and pelvis were negative. Workup for immunodeficiency was negative. Physical examination was unremarkable. A comprehensive laboratory workup showed electrolyte disturbances of metabolic alkalosis, hypokalemia and hyponatremia, starvation ketosis all consistent with decreased oral intake and vomiting. His symptoms and showering compulsions resolved quickly with intravenous fluids and cannabis abstinence and was discharged with the recommendation to minimize or stop his marijuana abuse. He was informed about the possible association of chronic marijuana abuse and his nausea, vomiting, and compulsive showering. Patient was not very receptive to his diagnosis and discharge plan.

Case 3

A 21-year-old black male presented with a three week history of vomiting up to 4 times a day and an 18 pound weight loss. This is

his second hospitalization within the past two months for similar symptoms, and was discharged with a diagnosis of ileus and acute gastroenteritis. He also complains of increased salivation during the day and excessive drooling at night. Past medical history positive only for depression. No past surgeries, medications, or allergies. On exam there was centralized diffuse abdominal tightness and on review of systems he reports "constantly" taking hot bathes to relieve his symptoms. His history of marijuana abuse started at age 18. He smokes marijuana at least three times per week. Labs were unremarkable except for a $\Delta 9$ -THC positive UDS, U/S gallbladder was normal, small bowel series and CT abdomen and pelvis showed some gas with possible ileus and no obstruction. Upper and lower scopes were preformed with normal colon and mild gastritis and esophagitis. Lipase, *H. Pylori* biopsies, celiac disease and acute intermittent porphyria workups were negative. Patient was treated with anti-emetics and intravenous fluids and was able to eventually tolerate oral foods. Patient was discharged with one month of omeprazole and to abstain from marijuana to which he was very receptive.

Case 4

A 24-year-old black male presented to the hospital with abdominal pain associated with nausea, vomiting and epigastric pain. His past medical history included recurrent admissions to the hospital with the same complaints within the past seven years. He underwent an extensive workup which included computed tomography of the head, abdomen and pelvis, gastric emptying study, small bowel series, ultrasound of the gallbladder esophagogastroduodenoscopy with biopsy and was only found to have esophagitis with gastritis. The gastroenterologist had provided a preliminary diagnosis of functional abdominal pain. During this hospitalization, the patient was found to be taking frequent showers daily; more than five times. The admitting resident asked the patient's mother about this behavior and said that he was very clean. Upon questioning the patient, he did admit to smoking marijuana daily and had had frequent hot shower compulsions which made him feel better. Comprehensive laboratory studies including acute intermittent porphyria were negative and a urine drug screen positive for opiates, $\Delta 9$ -THC and TCA. The patient's nausea, vomiting and epigastric pain resolved within 24 h of marijuana abstinence during hospitalization and was discharged home. The patient was instructed to stop his chronic cannabis use because of the association between marijuana and his behaviors in addition to the resolution of his symptoms when stopped while hospitalized.

DISCUSSION

Cannabis is a flowering plant that is indigenous to Central and South Asia. It is known for its euphoric effect^[7]. The active ingredient is $\Delta 9$ -tetrahydrocannabinol, known as $\Delta 9$ -THC, is lipophilic and has psychoactive properties, which may manifest as depersonalization, derealization, fear of loss of control, or dying^[7]. Cannabis has been found to have three potential effects: (1) instilling a state of comfort; (2) stimulating the philosophical cognitive faculty in the form epiphanies; and (3) activating the autonomic nervous system for appetite and suppression of nausea^[8,9]. This is believed to occur when the liver metabolizes $\Delta 9$ -THC into 11-hydroxy-THC^[8].

The Cannabinoid Receptors

Cannabis works mainly on two receptors, cannabinoid receptor 1 and 2: CB-1 and CB-2 respectively^[10]. CB-1 has neuromodulatory gabaergic effect on the central nervous system which attenuates nausea, as well as on the enteric nerve plexus causing decreased intestinal motil-

ity and secretions^[10,11,12,13]. CB-2 has an immunomodulatory effect on leucocytes, which reduces inflammation and subsequently pain^[7,14].

Mechanism of $\Delta 9$ -THC against Nausea

Peripherally induced nausea is described, in animal models, to be caused by the activation of the vagal gastrointestinal plexus, which synapse with the dorsal vagal complex (DVC), found centrally in the brainstem. This activation results in vomiting. The DVC consists of the area postrema, the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus nerve. CB-1 receptors in the NTS are activated by $\Delta 9$ -THC and thus suppress nausea via its GABAergic effect^[11]. Parker *et al.*^[4] report that the anti-emetic effect of $\Delta 9$ -THC act centrally in lower doses and peripherally at higher doses.

The true mechanism of the effects of cannabis on the gastrointestinal system in humans is not truly elucidated.

Mechanism of Epigastric Pain with Hyperemesis

Medical marijuana has been used in chemotherapy patients because of its anti-emetic and hunger potentiating qualities^[3]. $\Delta 9$ -THC is lipophilic with a half-life up to 59 h and therefore accumulates in the body over time in chronic users^[15]. The true mechanism why patients develop epigastric pain with nausea and vomiting is uncertain, so the following is a proposed hypothesis.

Cyclical vomiting has been the labeled diagnosis for most of these patients and in other case reports. The Rome III criteria used to diagnose cyclical vomiting, needs the first three criteria for at least 3 months with the onset of symptoms six months prior to the diagnosis: (1) ≥ 3 recurrent discrete episodes of vomiting; (2) Varying intervals of completely normal health between episodes; (3) Episodes are stereotypical with regard to timing of onset, symptoms, and duration; (4) Absence of an organic cause of vomiting; And (5) personal or family history of migraine^[16].

Given the history of the patient in Case 1, an approximate of 28 g consumption of marijuana per week for three consecutive months accumulated and saturated $\Delta 9$ -THC in tissues. In basic cell biology, in a ligand-receptor interaction, when there are more ligands available for a particular receptor site, the cell reacts by decreasing the number of receptors, i.e. desensitization. When the ligand supply is diminished, the cell reacts by increasing the number of receptors, i.e. sensitization. Lundberg *et al.*^[15] describes that tolerance (desensitization) develops secondary to chronic cannabinoid receptor saturation by CB-1 receptor agonists, $\Delta 9$ -THC, and thus desensitizes the cells. CB-1 GABAergic effect in the enteric plexus by $\Delta 9$ -THC causes intestinal immotility and decreased secretions. With the above mechanism in mind, in the event of chronic $\Delta 9$ -THC saturation, the CB-1 receptors will decrease in number. If $\Delta 9$ -THC, therefore, decreases in concentration, due to cannabis smoking cessation, the autonomic and enteric nerve plexus GABAergic inhibition diminishes resulting with rebound nausea, gastric motility and secretions, which manifest as spasmodic pain and vomiting. The symptoms abate once the CB-1 receptors up-regulate, as a result of decreased $\Delta 9$ -THC concentration, and allow for potentiation for GABAergic effect by fewer $\Delta 9$ -THC ligands. A possible way to verify this is by acquiring gastric-neural sections in patients in the acute phase of epigastric pains and those who are no longer symptomatic, and to chemically label the number of receptors, in addition to quantifying the urine $\Delta 9$ -THC upon admission and upon resolution of symptoms.

Compulsive Showering versus Conditioned Showering Behavior

The showering behavior is poorly understood however four possible

mechanisms may help explain it. Patients report that they feel instant relief from hyperemesis and epigastric pain when in contact with hot water. Patient in Case 1 reported “the hotter the better”. Symptoms would relapse after 10 to 15 min away from hot water, and depending on how severe they were, another exposure of hot water showering may ensue.

The physiological responses by cannabis are intestinal hypoactivity, analgesia and hypothermia^[5,6]. In a study by Smirnov *et al.*^[17], doses of $\Delta 9$ -THC at 0.5 mg/kg, 2.0 mg/kg, and 8.0 mg/kg were administered to mice and a decrease in skin (peripheral) temperature by -0.6°C with an increase in temperature in the nucleus accumbans (central) was noted after the administration of the highest dose. Therefore, acute withdrawal of chronic $\Delta 9$ -THC exposure may cause central hypothermia^[15] and thus thermoregulation would be achieved from hot water exposure.

In general, thermoregulation is regulated by two variables: heat production and heat loss. $\Delta 9$ -THC had been found to decrease oxygen utilization and thus lower metabolism and consequently heat production. It is hypothesized that this inhibition of metabolism with heat production is the cause of hypothermia and not heat loss from vasodilation^[18].

The question about why and how the pain and nausea resolve when in contact to hot water is unknown. The theory of paradoxical response to heat states that cutaneous cold fibers, which are myelinated A delta fibers, fire rapidly in response to a noxious hot stimulus (hot water $>45^{\circ}\text{C}$); therefore skin perception of cold^[19]. Based on the theory of paradoxical response, acute withdrawal of chronic $\Delta 9$ -THC exposure may cause an elevation of skin temperature that feels cooler with hot water contact. This theory, though poorly understood, may help explain the association with hot water relief.

Allen *et al.*^[2] first reported compulsive showering behavior with cannabis use in 2004 seen in 19 patients in Southern Australia. In 2009, reported cases began to appear in the United States. The exact mechanism is unknown but physiologic studies in mice may shed light about human physiology. The DSM IV-TR defines compulsions as mental acts or repetitive behavior that drive a conscious urge to carry out an unwanted task in order to avoid a dreaded fate^[20].

Our patients stated that they felt relief when exposed to hot water during their epigastric pain and hyperemesis crises. They, therefore, became conditioned rather than forced to do so unwillingly to avoid “a dreaded fate”. Consequentially, labeling the act as a conditioned behavior instead of a compulsion, as described by DSM IV-TR, would be more appropriate.

CONCLUSION

The mechanism of hyperemesis, epigastric pain and conditioned relief showering in chronic cannabis use is poorly understood, but may be caused from CB-1 receptor desensitization. This desensitization manifests opposite to the hypoactivity, analgesia and hypothermia caused by the GABAergic effect of receptor-naïve exposure to THC. As a result, patients present with hyperemesis, epigastric pain, and severe thermoregulatory dysfunction described by the need for hot water exposure. The possible mechanisms for conditioned hot water showering are: (1) central hypothermia; (2) decrease in body metabolism; and (3) theory of paradoxical heat response. Therapy is geared towards symptomatic treatment, such as anti-emetics and analgesics such as opioids. Symptoms abate by conditioned hot water showering and marijuana cessation within 48 to 72 h. Finally, it is important to realize that this syndrome is a diagnosis of exclusion, which necessitates rigorous workup in order to rule out potentially fatal and reversible etiologies. Further research is necessary to clarify the CB-1

receptor desensitization and showering behavior.

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REFERENCES

- 1 Rudgley, Richard. *Lost Civilisations of the Stone Age*. New York: Free Press; 1998
- 2 Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut* 2004; **53**: 1566-1570
- 3 Mechoulam R. Plant cannabinoids: a neglected pharmacological treasure trove. *Br J Pharmacol* 2005; **146**: 913-915
- 4 Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. *Br J Pharmacol* 2011; **163**: 1411-1422
- 5 Malone DT, Taylor DA. Modulation of D9-tetrahydrocannabinol-induced hypothermia by fluoxetine in the rat. Modulation of D9-tetrahydrocannabinol-induced hypothermia by fluoxetine in the rat. *Br J Pharmacol* 1998; **124**: 1419-1424
- 6 Varvel SA, Bridgen DT, Tao Q, Thomas BF, Martin BR, Lichtman AH. Delta-9-tetrahydrocannabinol accounts for the antinociceptive, hypothermic, and cataleptic effects of marijuana in mice. *J Pharmacol Exp Ther* 2005; **314**: 329-337
- 7 McCallum RW, Soykan I, Sridhar KR, Ricci DA, Lange RC, Plankey MW. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double-blind, randomized study. *Aliment Pharmacol Ther* 1999; **13**: 77-80
- 8 Appendino G, Chianese G, Tagliatela-Scafati O. Cannabinoids: Occurrence and Medicinal Chemistry. *Curr Med Chem* 2011; **18**: 1085-1099
- 9 Van Sickle MD, Oland LD, Mackie K, Davison JS, Sharkey KA. Delta-9-Tetrahydrocannabinol selectively acts on CB1 receptors in specific regions of dorsal vagal complex to inhibit emesis in ferrets. *Am J Physiol Gastrointest Liver Physiol* 2003; **285**: G566-576
- 10 Pertwee RG. Cannabinoids and the gastrointestinal tract. *Gut* 2001; **48**: 859-867
- 11 Van Sickle MD, Oland LD, Ho W, Hillard CJ, Mackie K, Davison JS, Sharkey KA. Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. *Gastroenterology* 2001; **121**: 767-774
- 12 Johns A. Psychiatric effects of cannabis. *Br J Psychiatry* 2001; **178**: 116-122
- 13 Christie MJ, Vaughan CW. Receptors: Cannabis medicine without a high. *Nat Chem Biol* 2011; **7**: 249-250
- 14 Kaminski NE. Inhibition of the cAMP signaling cascade via cannabinoid receptors: a putative mechanism of immune modulation by cannabinoid compounds. *Toxicol Lett* 1998; **102-103**: 59-63
- 15 Lundberg DJ, Daniel AR, Thayer SA. Delta(9)-Tetrahydrocannabinol-induced desensitization of cannabinoid-mediated inhibition of synaptic transmission between hippocampal neurons in culture. *Neuropharmacology* 2005; **49**: 1170-1177
- 16 Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V. Functional gastroduodenal disorders. *Gastroenterology* 2006; **130**: 1466-79
- 17 Smirnov MS, Kiyatkin EA. Behavioral and temperature effects of delta-9-tetrahydrocannabinol in human-relevant doses in rats. *Brain Res* 2008; **1228**: 145-160
- 18 Fitton AG, Pertwee RG. Changes in body temperature and oxygen consumption rate of conscious mice produced by intrahypothalamic and intracerebroventricular injections of delta-9-tetrahydrocannabinol. *Br J Pharmacol* 1982; **75**: 409-414
- 19 Long RR. Sensitivity of Cutaneous Cold Fibers to Noxious Heat: Paradoxical Cold Discharge. *J Neurophysiol* 1977; **40**: 489-502
- 20 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000

Peer reviewers: Petar Ilija Ivanovski MD, PhD, Associate Professor of Pediatrics, subspecialist of hematology, General Pediatrics, University Children's Hospital Medical Faculty University of Belgrade 10 Tirshova str. 11000, Belgrade, Serbia; Sebastiano Antonio Bonventre, Department of Surgical and Oncological Sciences, University of Palermo, Via Resuttana Colli, 367, 90146 Palermo, Italy.