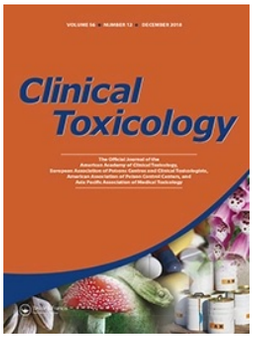

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

Efficacy and safety of topical capsaicin for cannabinoid hyperemesis syndrome in the emergency department

Samantha Wagner, Jason Hoppe, Matthew Zuckerman, Kerry Schwarz & Julie McLaughlin

To cite this article: Samantha Wagner, Jason Hoppe, Matthew Zuckerman, Kerry Schwarz & Julie McLaughlin (2019): Efficacy and safety of topical capsaicin for cannabinoid hyperemesis syndrome in the emergency department, Clinical Toxicology, DOI: 10.1080/15563650.2019.1660783

To link to this article: https://doi.org/10.1080/15563650.2019.1660783

Published online: 04 Sep 2019.

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2019.1660783

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

Efficacy and safety of topical capsaicin for cannabinoid hyperemesis syndrome in the emergency department

Samantha Wagner[a,b], Jason Hoppe[c,d], Matthew Zuckerman[c,d], Kerry Schwarz[a,b] and Julie McLaughlin[a,b]

[a]Department of Pharmacy, University of Colorado Hospital, Aurora, CO, USA; [b]University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA; [c]Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA; [d]Rocky Mountain Poison and Drug Center, Denver Health, Denver, CO, USA

ABSTRACT

Introduction: Cannabinoid hyperemesis syndrome (CHS) is a disorder of cyclic and recurrent nausea, vomiting, and abdominal pain associated with high-frequency and extended-duration marijuana use. Standard antiemetic therapy is often ineffective; however, capsaicin, an agonist of transient receptor potential vanilloid 1 (TRPV1), has shown promise in treating CHS.

Methods: This retrospective cohort analysis evaluated the safety and efficacy of topical capsaicin for patients presenting with CHS. The primary outcome was to assess if utilization of capsaicin for ED management of CHS decreased ED length of stay (LOS) as compared to a visit without capsaicin. Secondary outcomes included a cost analysis, use of rescue therapies, and adverse events.

Results: Forty-three patients met the inclusion criteria within the study period. ED LOS was reduced with capsaicin by a median of 22 minutes (201 vs. 179 min, $p = 0.33$). Patients received fewer additional medications if capsaicin was utilized (4 vs. 3 doses, $p = 0.015$), and 67% of visits where capsaicin was utilized required no further treatment prior to discharge. Additionally, opioid usage was less when utilizing capsaicin (166.5 vs. 69 mg OME). Forty-two percent of patients did not have a repeat CHS presentation to the ED after receiving capsaicin for an additional three months after the study period ended. Total medication cost was minimally more expensive (median difference of $3.26) in the capsaicin group. There were no significant adverse events reported with capsaicin.

Conclusion: There was no significant difference in ED LOS when capsaicin was utilized for CHS. However, there was a decrease in total medications administered and a reduction in opioid requirements. While medication costs for capsaicin visits were minimally more expensive, the utility of capsaicin as an over-the-counter (OTC) product may empower at home therapy with OTC products, decreasing potentially unnecessary healthcare encounters and costs.

ARTICLE HISTORY
Received 25 June 2019
Revised 29 July 2019
Accepted 23 August 2019
Published online 4 September 2019

KEYWORDS
Marijuana; capsaicin; cannabis; nausea; vomiting; cyclical vomiting syndrome

Introduction

Cannabinoid hyperemesis syndrome (CHS) is a disorder of cyclic and recurrent nausea, vomiting, and abdominal pain associated with high-frequency and extended-duration marijuana use. A hallmark sign of CHS is temporary symptom relief with hot water exposure [1,2]. Symptoms are often refractory to conventional treatment for nausea, vomiting, and abdominal pain. Initial agents utilized to manage CHS symptoms include antiemetics, opioids, benzodiazepines, and dopaminergic antipsychotics [2–9].

Capsaicin, an alkaloid extract from *Capsicum*, is responsible for the pungent, hot taste of chili peppers. Its analgesic properties make it useful for the treatment of a variety of nociceptive and neuropathic pain conditions. The proposed mechanism by which capsaicin works for CHS is related to its influence on transient receptor potential vanilloid 1 (TRPV1) within the endovanilloid system. Topical capsaicin binds to TRPV1, impairing substance P signaling which is often overstimulated in CHS [2,6,10]. Capsaicin is available as an OTC a cream in multiple strengths; the most frequently utilized strengths being 0.025%, 0.075%, and 0.1%. Capsaicin has a favorable safety profile with minimal side effects: local erythema, skin irritation, burning, and cough.

Evidence supporting the efficacy and safety of capsaicin for CHS is lacking. Most literature is limited to abstracts and case reports [11–15]. A case series discussed the role of capsaicin for CHS in 13 patients presenting to the emergency department (ED) at two academic medical centers. These patients received alternative treatment modalities without relief of symptoms but reported response to topical capsaicin within 45 minutes of administration. This study was limited by a small sample size, lack of control visits, and the inability to perform statistical analysis to determine if capsaicin is an effective and safe treatment for CHS [12]. The goal of this analysis was to evaluate the safety and efficacy of topical capsaicin for CHS in a larger population by assessing the impact on ED length of stay (LOS) as compared to a visit for CHS in which capsaicin was not utilized.

CONTACT Samantha Wagner srwagner211@gmail.com Nebraska Medicine, Omaha, NE, USA

Materials and methods

This retrospective cohort study was conducted through the University of Colorado Hospital in Aurora, Colorado, an academic medical center within the UCHealth system. Eleven UCHealth-affiliated EDs were included in this study. These sites encompassed both institution-based EDs and free-standing EDs comprising of a total of 404 beds, and approximately 300,000 ED visits annually. This retrospective analysis utilized electronic health record (EHR) (EPIC, Verona, WI) generated reports (pharmacy dispensing and clinical administration) to identify patients who received capsaicin in the ED from June 2017 through December 2017.

Patients were included if they were 18–89 years old with (1) a documented history of marijuana use, (2) had symptoms suggestive of CHS according to definitions proposed in previous literature (recurrent episodes of nausea, vomiting, and abdominal pain), (3) were treated with topical capsaicin, (4) had a previous visit for CHS in which capsaicin was not administered, and (5) were discharged from the ED [1,2]. Patients were excluded if they received capsaicin during the study period but did not have a prior visit for comparison. Because CHS tends to be a frequent and recurrent syndrome, a patient's previous ED visit for CHS when capsaicin was not administered served as their own control. Prior visit selection was determined by patient history. If the patient had a single prior visit, it was utilized for comparison against the visit in which capsaicin was utilized. For those with multiple prior ED visits, the visit closest to six months prior to the capsaicin visit was utilized. For those with multiple visits occurring over 2–3 days, the first encounter was utilized for comparison (Figure 1). Exclusion criteria included other acute major illness that could explain vomiting or nausea, admission, prisoners and pregnant women. Data abstracted from the EHR included patient demographics, past medical history, social history, ED chief complaint, frequency of marijuana use, history of improvement with hot showers, other illicit substance use, ED arrival/discharge date and time, capsaicin administration, administration of other medications, imaging during ED visit, and cost of medications received.

Due to the retrospective design of this study, and varying ED protocols for capsaicin use, there was no standard dosing or application. Multiple concentrations of capsaicin were utilized (0.025%, 0.075%, 0.1%), and administration most frequently occurred on the abdomen. Typical application of capsaicin included a 1-inch strip of cream distributed around the abdomen by the patient one time with a gloved hand; however, application of capsaicin without discrete directions and on the chest did occur in several patients.

The primary objective of this study was to assess if utilization of capsaicin for ED management of CHS decreased ED length-of-stay (LOS) as compared to a visit for CHS without capsaicin. Secondary objectives included a medication cost comparison, utilization of rescue therapies, time-to-discharge from last medication, time-to-ED return, patient characteristics, and adverse events. Wilcoxon signed rank was used to evaluate continuous data and McNemar's test was used for

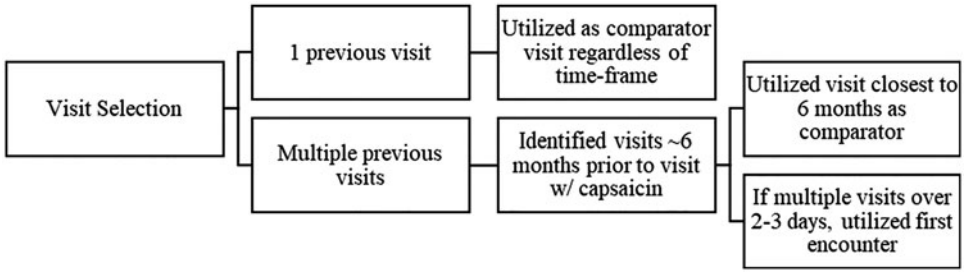

Figure 1. Visit selection criteria for patients with multiple prior emergency department visits.

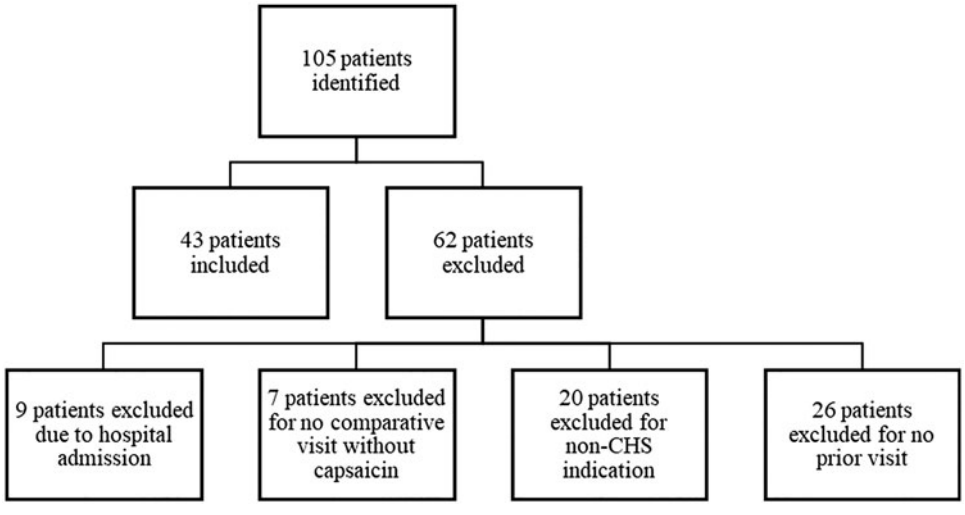

Figure 2. Patient inclusion.

categorical data. This study was approved by the institutional review board (IRB).

Results

Forty-three patients met the inclusion criteria within the study period (Figure 2). Baseline characteristics can be found in Table 1. Seventy-four percent of patients reported use of another substance, most commonly tobacco, alcohol, or opioids. The most common underlying comorbidities included anxiety (33%), gastroesophageal reflux disease (30%), cyclical vomiting syndrome (23%), depression (23%), and bipolar disorder (12%). Patients had a mean of 11 ED visits since EHR implementation in 2012. At presentation, the most frequent symptoms of CHS were nausea/vomiting (100%) and abdominal pain (85%). Forty-four percent of patients reported symptom relief with hot water exposure. Imaging at workup occurred in 19% of patients, all of which were normal or non-diagnostic by computerized tomography (CT), abdominal ultrasound (US), or x-ray (14%, 5.8%, and 4.6%, respectively). In addition, multiple patients had extensive imaging and work-up at prior ED visits and hospitalizations that was also normal or non-diagnostic. Median time between included ED visits was 4 months (range 0–11).

Table 1. Baseline characteristics.

Characteristic ($n = 43$)	Value
Age (y), mean ± SD	32 ± 9.7
Gender, *n* (%)	
Male	23 (53)
Female	20 (47)
Weight (kg), mean ± SD	73 ± 23.4
Height (in), mean ± SD	68 ± 5.4
Ethnicity, *n* (%)	
Caucasian	24 (56)
African-American	18 (42)
Native-American	1 (2)
Social history, *n* (%)	
Tobacco use	26 (60)
Alcohol use	14 (33)
Other	1 (2)
Marijuana use, *n* (%)	
<5 days per week	4 (9)
Daily	24 (56)
Multiple times per day	4 (9)
Not reported	11 (26)
Relief with hot water exposure, *n* (%)	19 (44)
Previous number of ED visits*, mean ± SD	11 ± 12.6
Previous number of hospitalizations*, mean ± SD	1 ± 1.7
Presenting symptoms, *n* (%)	
Nausea/vomiting	43 (100)
Abdominal pain	38 (88)
Diarrhea	9 (21)
Imaging at workup, *n* (%)	8 (19)

*Visits limited since electronic health record integration (2012 – present).

Overall, median LOS was 201 minutes (IQR 168, 310; range 56–1191) in the non-capsaicin group as compared to 179 minutes (IQR 147, 270; range 93–555) in the capsaicin group ($p = 0.33$). Median time to discharge following administration of the last medication was 92 minutes (IQR 47, 155; range 10–484) in the non-capsaicin group as compared to 60 minutes (IQR 35, 115; range 4–416) in the capsaicin group (p-value NS). Fewer additional medications were administered per patient visit if capsaicin was utilized (4 vs. 3 doses [IQR 2, 5; range 1–7 vs. IQR 2, 4; range 1–8], $p = 0.015$). The most frequently administered medications in both groups were anti-emetics, haloperidol, and diphenhydramine (Figure 3). Total opioid usage for all patients during duration of study, as measured by oral morphine equivalents (OME), was less when utilizing capsaicin (166.5 vs. 69 mg OME). In patients administered opioids, the median OME per patient was less when utilizing capsaicin (15 vs. 12 mg OME).

When analyzing visits with capsaicin administration, 0.075% cream was utilized most frequently followed by 0.025% and 0.1% ($n = 25$, 11, 7, respectively). Median time to capsaicin administration was 85 minutes (IQR 62, 132; range 8–277). Forty-two patients received alternate therapy prior to capsaicin, with an average of 3 medications per patient (range 1–6). Fourteen of the 43 patients required rescue therapy following capsaicin application, with an average of 2 medication administrations (range 1–4): 67% of visits in which capsaicin was utilized required no further medication interventions prior to discharge from the ED. Forty-two percent ($n = 18$) of patients did not have a repeat CHS presentation to the ED within 30 days of receiving capsaicin for an

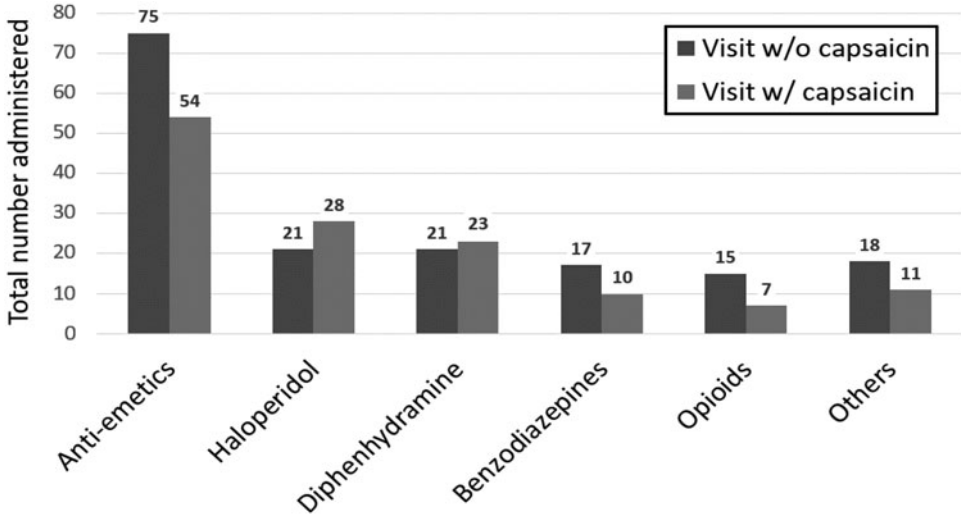

Figure 3. Medication administration by visit type.

additional three months after the study period ended. Of those that re-presented within 30 days, time to return was delayed when capsaicin was administered (8.2 vs. 10.7 days).

Total medication cost was minimally more expensive in the capsaicin group (median cost difference of $3.26). There were no significant adverse events reported with capsaicin. Two patients reported burning/itching following application and added capsaicin to their allergy list. Another patient utilized capsaicin at home inappropriately and returned to the ED for symptom management.

Discussion

Overall, the results of this investigation demonstrate no significant difference in ED LOS, decreased use of additional medications including opioids, and a minimal cost increase with the use of capsaicin for the management of CHS. Capsaicin's role in CHS management may continue to grow as recognition and knowledge of CHS increases and becomes a more widely recognized phenomenon. First established as a diagnosis in 2004, it was found that following legalization of marijuana in Colorado, the prevalence of cyclic vomiting presentation nearly doubled [16,17]. Patients were more likely to endorse marijuana use following liberalization, but it remained unclear if this was secondary to more accurate cannabis use reporting, increased cannabis use, or both [17–19]. As more states move towards legalization of medicinal and recreational cannabis, the incidence of CHS will likely continue to rise.

Multiple hypotheses have been proposed to explain the pathophysiology behind CHS. Dysregulation of the endocannabinoid system is the most widely recognized hypothesis, and while evidence is lacking, is it supported by both in vitro and animal studies [10,12]. The endocannabinoid system, specifically the CB1 receptor, has been recognized as playing a role in gastrointestinal motility, nausea/vomiting, appetite, inflammation, pain, and more. Transient receptor potential vanilloid1 (TRPV1), a receptor within the endovanilloid system, interacts with endocannabinoid receptors – often TRPV1 and CB1 are found on the same neurons in the area postrema of the medulla, as well as the enteric and vagal nerves. TRPV1 is also unique as it is found peripherally within the skin. Exogenous cannabinoids, including delta-9-tetrahydrocannabinoil, activate both CB1 and TRPV1. Prolonged exposure to exogenous cannabis can lead to dephosphorylation of TRPV1, subsequent receptor desensitization, and decreased signaling resulting in uncontrolled hyperemesis [11]. The counter-regulatory relationship of TRPV1 and CB1 not only play a role in nausea and emesis nociception, but also influence anxiety and stress maladaptation associated with cyclic vomiting syndrome and CHS [10,12,20,21].

TRPV1 is a nonselective cation channel activated by both capsaicin and noxious heat through direct agonism at the receptor site. Compulsive hot-water bathing may be an inadvertent attempt to normalize diminished TRPV1 activity, as the receptor is activated at temperatures above 43 °C [20,21]. It is known that activation of TRPV1 results in potent antiemetic effects potentially mediated by depletion of substance P within the neural circuits [2,10,11,20,21]. Therefore, the activation of TRPV1 by capsaicin may subsequently result in cessation of hyperemesis.

Definitive treatment of CHS focuses on cessation of cannabis use, however it may be difficult to convince patients that cessation will relieve their symptoms as patients may utilize cannabis for nausea relief and there is delay to resolution of symptoms following discontinuation [2,8]. For patients unwilling to cease cannabis use, management of CHS includes symptomatic treatment with anti-emetics, antipsychotics with dopaminergic activity such as haloperidol, olanzapine and droperidol, and modalities influencing TRPV1 [3–5,8,22].

Multiple case reports and case series have described symptom relief from CHS with capsaicin in adults, and more recently adolescents. There are limitations to the available literature and many patients still required administration of rescue therapy (ondansetron, promethazine, haloperidol, etc.) prior to discharge [11–15]. In addition, there was variability in how capsaicin was administered and used in conjunction with other anti-emetic medications. It appears that capsaicin is an effective tool for CHS management, but its exact place in therapy and patient population remains unclear.

While we did not detect a statistical difference regarding our primary outcome of difference in ED LOS, our study provided further evidence of potential benefit with capsaicin as part of a multi-modal treatment approach for CHS. The inability to detect a difference may be related to our sample size not being adequately powered to detect a statistical difference. Inability to meet sample size arose from the retrospective design and time frame constraints of this study. While the selection of emergency department LOS as a primary endpoint was unique, it could be used as a proxy for improvement since there is no reliable scoring system and LOS was the most consistent patient-centered outcome parameter available retrospectively to evaluate efficacy. The Age-Friendly Health System initiative, created by the John A. Hartford Foundation and supported by the Institute for Healthcare Improvement, recommends applying a "Time Is What Matters Measure (TWMM)" to evaluate patient quality of life [23]. This composite score includes readmissions, length of stay, and median time from ED arrival to departure, further supporting the selection of ED LOS as our primary endpoint. Additionally, our institution has a policy that each patient within the ED must have a disposition plan by hour two of ED stay, limiting the effects of unnecessary or prolonged time in the ED.

There are important limitations of this study. First off, this study is retrospective and with previous visit selection there is inherent selection bias regardless of standardizing the process for selection. There also is potential for provider bias when analyzing variability in capsaicin use in relation to a patient's healthcare exposure history, or provider bias in utilization of opioids. It is possible that in a patient with multiple previous ED visits, management of CHS was simplified resulting in faster capsaicin administration and a less extensive workup. While we identified similar trends to previous literature in regard to patient response to capsaicin, the

percent with positive response to hot water exposure may have been artificially low due to lack of documentation in the patient chart and retrospective design. Multiple patients did not require any additional abortive therapy after application of capsaicin; however, other patients had minimal relief from capsaicin. Multiple concentrations of capsaicin and a lack of standardization of administration between sites could also result in the variability of patient response to capsaicin. In addition, no unpredicted adverse effects arose from application of topical capsaicin and those reported were limited to minimal adverse effects of itching and burning. Importance of patient education was also highlighted in the study following the inappropriate administration of topical capsaicin by an outpatient after receipt of capsaicin in the ED.

Conclusions

Overall, there was no significant difference in ED LOS when capsaicin was utilized for symptom control in patients with repeat presentations to the ED for CHS. Patients received a reduced number of medications overall, which could be attributed to most patients requiring no further intervention after capsaicin administration prior to discharge and/or the inclusion of capsaicin as part of a multi-modal treatment approach. Differences in time to discharge following last medication could be due to the sedating effects of alternate medications which may prolong ED stay. Additionally, total opioid requirement was reduced. For this reason, capsaicin could be considered for addition to hospital's alternatives to opioids (ALTO) protocol and has been added at our site. While medication costs for visits utilizing capsaicin were minimally more expensive, the utility of capsaicin as an OTC product may empower at home therapy, decreasing long-term healthcare exposure, and costs. Future research is needed to further define capsaicin's role as a treatment modality and understand its effects and safety as we gain more experience with CHS.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Simonetto DA, Oxentenko AS, Herman ML, et al. Cannabinoid hyperemesis: a case series of 98 patients. Mayo Clin Proc. 2012; 87(2):114–119.

[2] Sorensen CJ, DeSanto K, Borgelt L, et al. Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment—a systematic review. J Med Toxicol. 2017;13(1):71–87.

[3] Jones JL, Abernathy KE. Successful treatment of suspected cannabinoid hyperemesis syndrome using haloperidol in the outpatient setting. Case Rep Psychiatry. 2016;2016:1–3.

[4] Hickey JL, Witsil JC, Mycyk MB. Haloperidol for treatment of cannabinoid hyperemesis syndrome. Am J Emerg Med. 2013;31(6): 1003.e5–1003.e6.

[5] Lee C, Greene SL, Wong A. The utility of droperidol in the treatment of cananbinoid hyperemesis syndrome. Clin Toxicol. 2019; 57:773–777.

[6] Richards JR, Gordon BK, Danielson AR, et al. Pharmacologic treatment of cannabinoid hyperemesis syndrome: a systematic review. Pharmacotherapy. 2017;37(6):725–734.

[7] Lee LY, Abbott L, Moodie S, et al. Cyclic vomiting syndrome in 28 patients: demographics, features, and outcomes. Eur J Gastroenterol Hepatol. 2012;24(8):939–943.

[8] Lapoint J, Meyer S, Yu C, et al. Cannabinoid hyperemesis syndrome: public health implications and a novel model treatment guideline. WestJEM. 2018;19(2):380–386.

[9] Khattar N, Routsolias JC. Emergency department treatment of cannabinoid hyperemesis syndrome: a review. Am J Ther. 2018; 25(3):e357–e361.

[10] Richards JR, Lapoint JM, Burillo-Putze G. Cannabinoid hyperemesis syndrome: potential mechanisms for the benefit of capsaicin and hot water hydrotherapy in treatment. Clin Toxicol. 2018; 56(1):15–24.

[11] Moon AM, Buckley SA, Mark NM. Successful treatment of cannabinoid hyperemesis syndrome with topical capsaicin. ACG Case Reports J. 2018;5(1):e3.

[12] Dezieck L, Hafez Z, Conicella A, et al. Resolution of cannabis hyperemesis syndrome with topical capsaicin in the emergency department: a case series. Clin Toxicol. 2017;55(8):908–913.

[13] Graham J, Barberio M, Wang GS. Capsaicin cream for treatment of cannabinoid hyperemesis syndrome in adolescents: a case series. Pediatrics. 2017;140(6):e20163795.

[14] Biar R, Oh A, Lapoint J, et al. Topical capsaicin cream used as therapy for cannabinoid hyperemesis syndrome [abstract]. Clin Toxicol. 2014;5:787.

[15] Lapoint J. Capsaicin cream for treatment of cannabinoid hyperemesis syndrome [abstract]. Clin Toxicol. 2014;52:707.

[16] Allen JH, de Moore GM, Heddle R, et al. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut. 2004;53(11):1566–1570.

[17] Kim HS, Anderson JD, Saghafi O, et al. Cyclic vomiting presentations following marijuana liberalization in Colorado. Acad Emerg Med. 2015;22(6):694–699.

[18] Habboushe J, Rubin A, Haoming L, et al. The prevalence of cannabinoid hyperemesis syndrome among regular marijuana smokers in an urban public hospital. Basic Clin Pharmacol Toxicol. 2018;122:660–662.

[19] Bhandar S, Jha P, Lisdahl K, et al. Recent trends in cyclic vomiting syndrome–associated hospitalizations with liberalization of cannabis use in the state of Colorado. IMJ. 2018;49:649–655.

[20] Rudd JA, Nalivaiko E, Matsuki N, et al. The involvement of TRPV1 in emesis and anti-emesis. Temperature. 2015;2(2):258–276.

[21] Fernandes ES, Fernandes MA, Keeble JE. The functions of TRPA1 and TRPV1: moving away from sensory nerves. Br J Pharmacol. 2012;166(2):510–521.

[22] Ramos-Perdigues S, Gordillo MJ, Caballero C, et al. Cannabinoid hyperemesis syndrome, a treatment discussion. Eur Psychiatry. 2017;41:318.

[23] Haas S, Jacobs B, Schwartz M, et al. Measuring patient quality of life: time is what matters. NEJM Catalyst. 2018 [cited 2019 Apr 13; updated July 25]. Available from: https://catalyst.nejm.org/patient-quality-time-is-what-matters/