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Pharmacologic Treatment of Cannabinoid Hyperemesis Syndrome: A Systematic Review

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Abstract

Objective: Cannabinoid hyperemesis syndrome (CHS) has become more prevalent with increasing cannabis use. CHS is often resistant to standard antiemetics. The objective of this study is to review the current evidence for pharmacologic treatment of CHS.

Methods: MEDLINE, PsycINFO, DARE, OpenGrey, Google Scholar, and the Cochrane Library were searched from inception to February 2017. Articles were selected and reviewed independently. Evidence was graded using Oxford CEBM guidelines.

Results: The search resulted in 1,262 articles with 63 of them eligible for inclusion (n=205). There were 4 prospective Level II and 3 retrospective Level III studies, 12 Level IV case series, and 44 Level V case reports. Among Level II studies (n=64),

tricyclic antidepressants (TCAs) and lorazepam were discussed as effective long- and short-term treatments, respectively, in two studies. Ondansetron, promethazine, diphenhydramine, and opioids were also mentioned, but the authors did not comment on their efficacy. Among Level III studies (n=43), one reported effective treatment with antiepileptics zonisamide and levetiracetam, but not TCAs. Another reported favorable response to morphine, ondansetron, and lorazepam, but did not specify the actual number of patients receiving specific treatment. Among the Level IV case series (n=54), benzodiazepines, haloperidol, and capsaicin were reported as helpful. For Level V case reports (n=44), benzodiazepines, metoclopramide, haloperidol, ondansetron, morphine, and capsaicin were reported as effective. Effective treatments mentioned only once included fentanyl, diazepam, promethazine, methadone, nabilone, levomepromazine, piritramide, and pantoprazole. Hot showers and baths were cited in all Level IVandV articles as universally effective.

Conclusion: High-quality evidence for pharmacologic treatment of CHS is limited. Benzodiazepines, followed by haloperidol and capsaicin, were most frequently reported as effective for acute treatment, and TCAs for long-term treatment. As the prevalence of CHS increases, future prospective trials are greatly needed to evaluate and further define optimal pharmacologic treatment of patients with CHS.

Key Words: cannabis; marijuana; hyperemesis; cannabinoid; cyclic vomiting; emesis

Introduction

Cannabis is the most commonly used illicit drug throughout the world, with over 180 million users.[1] From 2001-2013 in the United States, past-year cannabis use more than doubled from 4.1 to 9.5% of the adult population, and prevalence of cannabis use disorder rose from 1.5 to 2.9%.[2] Among college students, daily cannabis use has more than tripled in the past two decades from 1.8% in 1994 to 5.9% in 2014.[2] In 2013, there were an estimated 2.4 million persons aged 12 or older who had used cannabis for the first time within the past 12 months, or roughly 6,600 new users each day.[2] In 2011, there were 456,000 emergency department visits related to cannabis use, a 21% increase from 2009.[3]

According to the *Diagnostic and Statistical Manual of Mental Disorders V* (DSM-5), cannabis intoxication is defined by: 1) recent use of cannabis; 2) clinically significant problematic behavioral or psychological changes (eg, impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, social

withdrawal) that developed during, or shortly after, cannabis use; 3) at least two of the following signs developing within 2 hours of cannabis use: conjunctival injection, increased appetite, dry mouth, tachycardia; 4) symptoms not due to a general medical condition and not better accounted for by another mental disorder.[4]

As a result of the 2016 election, several states (California, Nevada, Maine, and Massachusetts) have legalized recreational cannabis, joining Washington, Oregon, Colorado, and Alaska. As the legalization and use of recreational and medical cannabis continues to rise, a variant of cyclic vomiting syndrome known as cannabinoid hyperemesis syndrome (CHS), has become increasingly recognized.[5,6] This is also reflected by the number of peer-reviewed articles regarding CHS, which have increased greatly since 2004 (Figure 1).

Cannabinoid hyperemesis syndrome is not recognized as a unique clinical entity in either the DSM-5 or the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).[4,7] As a specific diagnosis, CHS meets some criteria for "cannabis intoxication" as defined above, and/or "cannabis use disorder," which is characterized by at least two of the following 11 criteria: 1) cannabis often taken in larger amounts or over a longer period than was intended; 2) a persistent desire or unsuccessful efforts to cut down or control cannabis use; 3) a great deal of time spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects; 4) craving, or a strong desire or urge to use cannabis; 5) recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home; 6) continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis; 7) important social, occupational, or recreational activities given up or reduced because of cannabis use; 8) recurrent cannabis use in situations where it

is physically hazardous; 9) continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis; 10) tolerance, as defined by either (a) a need for markedly increased cannabis to achieve intoxication or desired effect or (b) markedly diminished effect with continued use of the same amount of the substance; and 11) withdrawal, as manifested by either (a) the characteristic withdrawal syndrome for cannabis or (b) cannabis is taken to relieve or avoid withdrawal symptoms.[4]

First described in 2004 by Allen and colleagues, CHS is characterized by recurrent, paroxysmal episodes of nausea and vomiting in chronic cannabis users that are mitigated by frequent hot bathing or showering and interspersed with symptom-free periods.[8] Complications from CHS may include acute renal failure, electrolyte derangement, and pneumomediastinum.[9-11]

Patients experiencing symptoms of CHS may visit the emergency department for intravenous antiemetics and rehydration. However, commonly used antiemetics are often ineffective for acute exacerbations, necessitating the use of multiple doses of different and unrelated pharmacologic agents until control of hyperemesis is achieved.[12] At present, the only proven long-term treatment is cessation of cannabis use.[13] The objective of this systematic review is to determine the most effective pharmacologic treatment for CHS.

Methods

All human trials, case series, or case reports of pharmacologic treatment of CHS were considered in the literature search. Data was abstracted systematically from an extensive query of MEDLINE, PsycINFO, and the Cochrane Library from inception to February 2017. The Preferred Reporting Items for Systematic Reviews and Meta-

analyses (PRISMA) guidelines were followed (Supplement 1).[14] Non-English language publications were included and translated when necessary. Our final search strategy included free-text words (TW) and controlled vocabulary terms using medical subject headings (MeSH) for these topics, their synonyms, abbreviations, and alternate spellings: ("cannabis"[TW] or "cannabinoid"[TW] or "marijuana"[TW] or "tetrahydrocannabinol"[TW] or "THC"[TW] or "cannabidiol"[TW] or "cannabigerol"[TW]) and (“hyperemesis”[TW] or “emesis”[TW] or “vomiting”[TW] or “cyclic”[TW] or “nausea”[TW]).

Additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL), and the Database of Abstracts of Reviews of Effects (DARE) were made. References in each selected publication were also carefully hand screened for any additional reports having relevance. In the development of specific treatment recommendations, all references are cited in appropriate context. A grey literature search was also performed using OpenGrey, Google, and Google Scholar. All authors reviewed the articles independently, and articles without mention of specific pharmacologic treatment of CHS were excluded. A meaningful meta-analysis was not possible due to the wide variety of pharmacologic treatments, protocols, study durations, and limited number of relevant trials. Therefore, we analyzed the data in a qualitative manner.

Results

The search resulted in 1,262 articles with 63 of them eligible for inclusion and involving 205 human subjects (Figure 2). Articles were graded using the Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence.[15] These levels are basically defined as: I = properly powered and conducted randomized clinical trial,

systematic review, or meta-analysis; II = well-designed controlled trial without randomization; prospective comparative cohort; III = case-control studies, retrospective cohort studies; IV = case series with or without intervention, cross-sectional studies; V = opinion of authorities, case reports. There were no high-quality (CEBM Level I) prospective, randomized, blinded studies. There were 4 higher-quality prospective (Level II) studies, 3 retrospective (Level III) studies, 12 case series (Level IV), and 44 case reports (Level V). The eligible articles are summarized in Table 1.

In the Level II studies involving 64 patients, Allen et al examined the association of chronic cannabis abuse and cyclic vomiting in nine patients treated specifically with benzodiazepines but did not report on the efficacy.[8] Hejazi and colleagues prospectively studied tricyclic antidepressant (TCA) treatment of 132 patients with cyclic vomiting syndrome.[16] There were 34 chronic cannabis users, of whom 25 (74%) responded favorably to amitriptyline, nortriptyline, or doxepin. During this study, several patients ceased using cannabis, which of itself may have resolved their hyperemesis. It is also unclear if TCA treatment directly ameliorated hyperemesis or enabled subjects to mitigate their cannabis use and/or facilitate cessation. Namin and colleagues investigated 31 patients with cyclic vomiting treated with amitriptyline, 13 of whom were chronic cannabis users.[17] Amitriptyline was effective as long-term therapy. At 3 months, 93% had decreased symptoms and 26% achieved full remission, and at 12 months there was a statistically significant mean improvement of 69% and 78% for nausea and vomiting, respectively. Of the cannabis subgroup, two were able to cease cannabis completely, and seven reported improvement in symptoms despite ongoing use, which is a lower rate of success than the overall study group. Based on this discrepancy, the authors stated that the

relationship between cyclic vomiting syndrome and cannabis use is inconclusive. Lorazepam was mentioned as the most effective acute therapy in the emergency department, but actual numbers treated were not specified.[17] Venkatesan and colleagues prospectively studied the relative serum levels of endocannabinoids and salivary cortisol and alpha amylase, which are markers for stress, in patients with cyclic vomiting.[18] Subgroup analysis revealed cannabis users had significantly higher cortisol and alpha amylase than non-users. Both groups were noted to respond to treatment with ondansetron, promethazine, diphenhydramine, lorazepam, and hydromorphone but further details were not given.[18]

In the Level III studies involving 43 regular cannabis users, Clouse et al. reported that 3 regular cannabis users among a cohort of 20 patients with cyclic vomiting reported effective treatment with the antiepileptics zonisamide and levetiracetam, but not with TCAs.[19] In a study of 28 patients, of whom 4 were cannabis users, Lee and co-workers reported favorable response to morphine, ondansetron, and lorazepam; however, the actual number of patients receiving specific treatment was unspecified.[20] In a multicenter review of emergency department visits in Europe following cannabis use, Dines and colleagues mention the use of benzodiazepines, olanzapine, chlorprothixene, and hydroxyzine for hyperemesis termination, but actual patient response rates are not given.[21]

There were 12 Level IV case series involving 54 patients.[9,22-32] For these case series, the following CHS pharmacologic treatments were reported as helpful: benzodiazepines (n=6), topical capsaicin (n=5), haloperidol (n=5), and olanzapine (n=1).[24,27-32] There were 44 Level V case reports involving 44 patients.[10,11,33-74] For these case reports, the following CHS pharmacologic treatments were reported as effective: benzodiazepines (n=5), metoclopramide (n=4), haloperidol (n=4),

ondansetron (n=2), morphine (n=2), and topical capsaicin (n=2).[11,34,37,38,45,46,48,50,51,53,58,60,64,69,72,73] Other effective treatments mentioned only once included fentanyl, promethazine, methadone, nabilone, levomepromazine, piritramide, and pantoprazole.[37,38,43,56,66] Of note, hot showers and bathing were mentioned either by the authors or patients in all Level IV and V articles as universally effective at ameliorating CHS.

Discussion

Our systematic review revealed a lack of high-quality studies focusing on acute pharmacologic treatment of CHS, and the failure of many case studies and reports to clearly detail the efficacy of their chosen treatments. Benzodiazepines (most commonly lorazepam) were mentioned most frequently, followed by haloperidol and capsaicin for acute treatment of CHS among cannabis users. For long-term treatment, TCAs were utilized most frequently for mitigation of cyclic vomiting in patients who were also cannabis users. Given the complexity of the endocannabinoid system and hypothalamic–pituitary–adrenal (HPA) axis regulation of nausea and emesis, it is not surprising there is no one consistently effective class of antiemetics for the treatment of CHS.[12]

Endogenous cannabinoids bind to the G protein-coupled cannabinoid receptors CB1 and CB2. The CB1 receptors are located in the central nervous system (CNS) and nerves throughout the gastrointestinal (GI) tract and modulate gastroprotection, gastric secretion, motility, inflammation, sensation, as well as oral salivation.[75] CB2 receptors are localized in lymphoid tissues in the periphery and are associated with immune system regulation.[12] It is believed the antiemetic properties of cannabinoids are mediated by CB1 activation in the hypothalamus, and the proemetic properties

from CB1 activation in the GI tract.[11] Activation of the CB1 receptor by endogenous cannabinoids suppresses activation of the HPA axis and sympathetic nervous system to stress.[18]

It is paradoxical that cannabis has well-known antiemetic properties, yet chronic cannabis use may lead to CHS. The active compound in cannabis, Δ9-tetrahydrocannabinol (THC), binds to CB1 and CB2 receptors.[12] Chronic THC exposure leads to its accumulation in adipose cells. Prolonged supranormal levels of THC desensitize and down-regulate CB1 receptors, thus increasing the stress response which may in turn induce CHS.[11] Cannabidiol, a cannabinoid molecule in marijuana, is antiemetic in low doses but proemetic at higher doses.[76] Similar to THC, buildup of cannabidiol in chronic cannabis users may also be a factor in CHS. Patients with CHS may also have genetic variation in their hepatic drug-transforming enzymes, leading to excessive levels of proemetic cannabis metabolites.[23]

Gamma-aminobutyric acid (GABA) and its receptors reside in the CNS as well as in the GI tract, where GABA modulates motility, mucosal homeostasis, and release of histamine, acetylcholine, serotonin, and prostaglandins.[77] Benzodiazepines have GABA receptor agonist-like properties with antiemetic effects through anxiolysis, sedation, and inhibition of medullary and vestibular nuclei.[77] In our review, benzodiazepines, such as lorazepam and alprazolam, were touted as successful treatment for CHS in several articles.[17,20,24,29,30,32,38,46,58,64]

Dopamine receptors D2 and D3 in the medulla are also involved in the pathophysiology of emesis, and antagonists such as metoclopramide, prochlorperazine, and promethazine are commonly used antiemetics.[12] However, data suggest that metoclopramide is not an effective treatment for cyclic vomiting syndrome.[77] There were 13 metoclopramide treatment failures noted for CHS based

on our review.[10,23,27,30,36,42-44,56,58,63,69,72] The butyrophenone haloperidol was reported as effective in several case series and reports, and this may reflect its unique pharmacology relative to the other more common antiemetics.[27,31,51,69,73] Haloperidol is primarily an antipsychotic but has been used off-label as an effective general antiemetic.[78]

Serotonin, or 5-hydroxytryptamine (5-HT), is a major neuroendocrine transmitter in the regulation of emesis.[77] Histamine activates neurons in the medulla implicated with nausea, emesis, and motion sickness.[77] While the combined role of serotonin and histamine in CHS and cyclic vomiting syndrome is unknown, tricyclic antidepressants were shown to be effective for long-term treatment of both CHS and cyclic vomiting syndrome[16,17] This may be secondary to the inhibition of serotonin reuptake from TCA blockade of the serotonin transporter and TCA antihistamine effects.[77] Interestingly, the 5-HT3 antagonists, such as ondansetron, were used infrequently and/or not mentioned as successful treatment for CHS in the articles screened in our review.

In all Level IV and V articles, hot showers and bathing were reported to be universally effective at mitigating or abating CHS. Several theories have been suggested to explain this mechanism. One theory is the dose-dependent hypothermic effect of THC on the CB1 receptors of the hypothalamus, the thermoregulatory center of the brain.[22] A “cutaneous steal” syndrome is another putative mechanism, in which cutaneous vasodilation from hot water alters core temperature and splanchnic circulation, thus lessening abdominal discomfort.[12,64] Another possibility is the dysphoria and anxiety associated with CHS may be subjectively relieved with hot showering or bathing.

Capsaicin, or 8-methyl-N-vanillyl-6-nonenamide, is a chemical found in chili peppers that produces a sensation of heat on contact with skin. Available as a topical cream, capsaicin binds to transient receptor potential vanilloid-1 (TRPV1) receptors found widely throughout the body, often in proximity to CB-1 receptors and thus suggesting a functional interaction.[79,80] Such areas include the medullary vomiting center and GI tract. The TRPV1 receptors are also activated by low pH and high temperature, and may regulate release of substance P, an important mediator of nausea and emesis, from sensory nerves.[81] As such, TRPV1 receptors may play a teleological role in the efficacy of hot showers/baths for symptomatic relief of CHS. Seven patients with acute CHS successfully treated with topical capsaicin have been reported.[28,60,72]

Our systematic review has potential limitations. There are no large-scale randomized, multi-center, double-blind studies regarding the pharmacologic treatment of CHS. Therefore, any bias associated with the design or conduct of the included studies could have influenced the results of our systematic review. The overall number of patients is small. Because publication bias is a concern, we used a search strategy with a low inclusion threshold of all published and unpublished reports. For this reason, we also included case series and case reports to be as comprehensive as possible.

Conclusion

High-quality evidence for pharmacologic treatment of CHS is extremely limited. Benzodiazepines are most frequently reported as effective for acute treatment of CHS, followed by haloperidol and capsaicin. As the prevalence of CHS is likely to increase,

future prospective trials are greatly needed to evaluate and further define optimal pharmacologic treatment of CHS patients.

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REFERENCES

1. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2016. Available from www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf. Accessed December 1, 2016.

2. Azofeifa A, Mattson ME, Schauer G, McAfee T, Grant A, Lyerla R. National Estimates of Marijuana Use and Related Indicators — National Survey on Drug Use and Health, United States, 2002–2014. MMWR Surveill Summ 2016;65(No. SS-11):1–25.

3. Substance Abuse and Mental Health Service Administration. Highlights of the 2011 Drug Abuse Warning Network (DAWN) findings on drug-related emergency

department visits. Available from www.samhsa.gov/data/sites/default/files/DAWN127/DAWN127/sr127-DAWN-highlights.pdf. Accessed December 1, 2016.

4. Genen L. Cannabis-related disorders. Available from emedicine.medscape.com/article/286661-clinical. Accessed February 2, 2017.

5. Wilkinson ST, Yarnell S, Radhakrishnan R, Ball SA, D'Souza DC. Marijuana Legalization: Impact on Physicians and Public Health. Annu Rev Med. 2016;67:453-466.

6. Kim HS, Anderson JD, Saghafi O, Heard KJ, Monte AA. Cyclic vomiting presentations following marijuana liberalization in Colorado. Acad Emerg Med. 2015;22:694-699.

7. World Health Organization. Classification of diseases (ICD). Available from www.who.int/classifications/icd/en/. Accessed February 2, 2017.

8. Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis use. Gut. 2004; 53:1566–1570.

9. Cadman PE. Hypophosphatemia in users of cannabis. Am J Kidney Dis. 2016 Sep 27. pii: S0272-6386(16)30414-0.

10. de Moore GM, Baker J, Bui T. Psychogenic vomiting complicated by marijuana abuse and spontaneous pneumomediastinum. Aust N Z J Psychiatry. 1996;30:290-294.

11. Habboushe J, Sedor J. Cannabinoid hyperemesis acute renal failure: a common sequela of cannabinoid hyperemesis syndrome. Am J Emerg Med. 2014;32:690.e1-2.

12. Darmani NA. Cannabinoid-induced hyperemesis: a conundrum-from clinical recognition to basic science mechanisms. Pharmaceuticals (Basel). 2010;3:2163-2177.

13. Galli JA, Sawaya RA, Friedenberg FK. Cannabinoid hyperemesis syndrome. Curr Drug Abuse Rev. 2011;4:241-249.

14. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med 2009;6:e1000097.

15. Oxford Centre for Evidence-Based Medicine Levels of EvidenceWorking Group. OECBM Levels of Evidence System. Available from www.cebm.net/ocebm-levels-of-evidence. Accessed December 1, 2016.

16. Hejazi RA, Reddymasu SC, Namin F, Lavenbarg T, Foran P, McCallum RW. Efficacy of tricyclic antidepressant therapy in adults with cyclic vomiting syndrome: a two-year follow-up study. J Clin Gastroenterol. 2010; 44:18–21.

17. Namin F, Patel J, Lin Z, Sarosiek I, Foran P, Esmaeili P, McCallum R. Clinical, psychiatric and manometric profile of cyclic vomiting syndrome in adults and response to tricyclic therapy. Neurogastroenterol Motility. 2007; 19:196–202.

18. Venkatesan T, Zadvornova Y, Raff H, Hillard CJ. Endocannabinoid-related lipids are increased during an episode of cyclic vomiting syndrome. Neurogastroenterol Motil. 2016;28:1409-1418.

19. Clouse RE, Sayuk GS, Lustman PJ, Prakash C. Zonisamide or levetiracetam for adults with cyclic vomiting syndrome: a case series. Clin Gastroenterol Hepatol. 2007;5:44-48.

20. Lee LY, Abbott L, Moodie S, Anderson S. Cyclic vomiting syndrome in 28 patients: demographics, features and outcomes. Eur J Gastroenterol Hepatol. 2012;24:939-943.

21. Dines AM, Wood DM, Galicia M, Yates CM, Heyerdahl F, Hovda KE, Giraudon I, Sedefov R; Euro-DEN Research Group., Dargan PI. Presentations to the emergency department following cannabis use--a multi-centre case series from ten European countries. J Med Toxicol. 2015;11:415-421.

22. Chang YH, Windish D. Cannabinoid hyperemesis relieved by compulsive bathing. Mayo Clin Proc. 2009;84:76–78.

23. Soriano-Co M, Batke M, Cappell MS. The cannabis hyperemesis syndrome characterized by persistent nausea and vomiting, abdominal pain, and compulsive bathing associated with chronic marijuana use: a report of eight cases in the United States. Dig Dis Sci. 2010;55:3113–3119.

24. Nicolson SE, Denysenko L, Mulcare JL, Vito JP, Chabon B. Cannabinoid hyperemesis syndrome: a case series and review of previous reports. Psychosomatics. 2012;53:212-219.

25. Torka P, Sharma R. Cannabinoid and hyperemesis. Mayo Clin Proc. 2012;87:502-503.

26. Fabries P, Ribaud N, Puidupin A, Coton T. Cannabinoid hyperemesis syndrome. Presse Med. 2013;42:1531-1533.

27. Witsil JC, Mycyk MB. Haloperidol, a novel treatment for cannabinoid hyperemesis syndrome. Am J Ther. 2014 Nov 12. [Epub ahead of print] PubMed PMID: 25393073.

28. Lapoint J. Case series of patients treated for cannabinoid hyperemesis syndrome with capsaicin cream (abstract). Clin Toxicol. 2014;52:707.

29. Bertolino J, Abdo L, Khau D, Meckenstock R, Sautereau N, Jean E, Greder-Belan A, Frances Y, Cabane J, Granel B. Cannabinoid hyperemesis syndrome: about 6 cases. Rev Med Interne. 2015;36:694-697.

30. Braver O, Leibman Y. Cannabinoid hyperemesis syndrome: descriptive overview of an under-recognized diagnosis. Isr Med Assoc J. 2015;17:324-325.

31. Contreras Narváez C, Mola Gilbert M, Batlle de Santiago E, Bigas Farreres J, Giné Serven E, Cañete Crespillo J. Cannabinoid hyperemesis syndrome. A report of six new cases and a summary of previous reports. Adicciones. 2016;28:90-98.

32. Sawni A, Vaniawala VP, Good M, Lim WY, Golec AS. Recurrent Cyclic Vomiting in adolescents: can it be cannabinoid hyperemesis syndrome? Clin Pediatr (Phila). 2016;55:560-563.

33. Boeckxstaens GE. Cannabinoid hyperemesis with the unusual symptom of compulsive bathing. Ned Tijdschr Geneeskd. 2005;149:1468-1471.

34. Alfonso Moreno V, Ojesa F, Moreno-Osset E. Cannabinoid hyperemesis. Gastroenterol Hepatol. 2006;29:434-435.

35. Chepyala P, Olden KW. Cyclic vomiting and compulsive bathing with chronic cannabis abuse. Clin Gastroenterol Hepatol. 2008;6:710–712.

36. Sannarangappa V, Tan C. Cannabinoid hyperemesis. Intern Med J. 2009;39:777–778.

37. Sontineni SP, Chaudhary S, Sontineni V, Lanspa SJ. Cannabinoid hyperemesis syndrome: clinical diagnosis of an under recognized manifestation of chronic cannabis abuse. World J Gastroenterol. 2009;15:1264–1266.

38. Price SL, Fisher C, Kumar R, Hilgerson A. Cannabinoid hyperemesis syndrome as the underlying cause of intractable nausea and vomiting. J Am Osteopath Assoc. 2011;111:166-169.

39. Sullivan S. Cannabinoid hyperemesis. Can J Gastroenterol. 2010;24:284-285.

40. Wild K, Wilson H. Cannabinoid hyperemesis. BMJ Case Rep. 2010;2010: pii:bcr0120102605.

41. Brenna Ø, Aasarød K, Gustafsson BI. A man in his 30s with recurrent vomiting and abdominal pain relieved by hot showers. Tidsskr Nor Laegeforen. 2011;131:2134-2136.

42. Fleig S, Brunkhorst R. Hyperemesis and a high water bill. Z Gastroenterol. 2011;49:1479-1481.

43. Lieb M, Palm U, Nicolaus M, Reibke R, Baghai TC. Cannabinoid-induced hyperemesis. Psychiatr Prax. 2011;38:147-149.

44. Schmid SM, Lapaire O, Huang DJ, Jürgens FE, Güth U. Cannabinoid hyperemesis syndrome: an underreported entity causing nausea and vomiting of pregnancy. Arch Gynecol Obstet. 2011;284:1095-1097.

45. Bonnet U, Chang DI, Scherbaum N. Cannabis hyperemesis syndrome. Fortschr Neurol Psychiatr. 2012;80:98-101.

46. Cox B, Chhabra A, Adler M, Simmons J, Randlett D. Cannabinoid hyperemesis syndrome: case report of a paradoxical reaction with heavy marijuana use. Case Rep Med. 2012;2012:757696.

47. Hopkins CY, Gilchrist BL. A case of cannabinoid hyperemesis syndrome caused by synthetic cannabinoids. J Emerg Med. 2013;45:544-546.

48. Achanta L, Kelkhoff AJ. Cannabinoid hyperemesis--is it more common than we think? J Ark Med Soc. 2013;109:158.

49. Chen J, McCarron. Cannabinoid hyperemesis syndrome: a result of chronic, heavy cannabis use. Curr Psychiatry. 2013;12:48-54.

50. Enuh HA, Chin J, Nfonoyim J. Cannabinoid hyperemesis syndrome with extreme hydrophilia. Int J Gen Med. 2013;6:685-687.

51. Hickey JL, Witsil JC, Mycyk MB. Haloperidol for treatment of cannabinoid hyperemesis syndrome. Am J Emerg Med. 2013;31:1003.e5-6.

52. Mohammed F, Panchoo K, Bartholemew M, Maharaj D. Compulsive showering and marijuana use - the cannabis hyperemisis syndrome. Am J Case Rep. 2013;14:326-328.

53. Bonnet U, Stratmann U, Isbruch K. [No opiates against cannabis hyperemesis syndrome]. Dtsch Med Wochenschr. 2014;139:375-377.

54. Cha JM, Kozarek RA, Lin OS. Case of cannabinoid hyperemesis syndrome with long-term follow-up. World J Clin Cases. 2014;2:930-933.

55. Iacopetti CL, Packer CD. Cannabinoid hyperemesis syndrome: a case report and review of pathophysiology. Clin Med Res. 2014;12:65-67.

56. Lam PW, Frost DW. Nabilone therapy for cannabis withdrawal presenting as protracted nausea and vomiting. BMJ Case Rep. 2014;2014. pii:bcr2014205287.

57. Nogi M, Fergusson D, Chiaco JM. Mid-ventricular variant Takotsubo cardiomyopathy associated with Cannabinoid Hyperemesis Syndrome: a case report. Hawaii J Med Public Health. 2014;73:115-118.

58. Swanson M, Epperly T. Vomiting, abdominal pain, compulsive bathing--Dx? J Fam Pract. 2014;63:257-259.

59. Ukaigwe A, Karmacharya P, Donato A. A gut gone to pot: a case of cannabinoid hyperemesis syndrome due to K2, a synthetic cannabinoid. Case Rep Emerg Med. 2014;2014:167098.

60. Biary R, Oh A, Lapoint J, Nelson LS, Hoffman RS, Howland MA. Topical capsaicin cream used as a therapy for cannabinoid hyperemesis syndrome (abstract). Clin Toxicol. 2014;52:787.

61. Andrews KH, Bracero LA. Cannabinoid hyperemesis syndrome during pregnancy: a case report. J Reprod Med. 2015;60:430-432.

62. Bajgoric S, Samra K, Chandrapalan S, Gautam N. Cannabinoid hyperemesis syndrome: a guide for the practising clinician. BMJ Case Rep. 2015;2015.pii: bcr2015210246.

63. Desjardins N, Jamoulle O, Taddeo D, Stheneur C. Cannabinoid hyperemesis syndrome in a 17-year-old adolescent. J Adolesc Health. 2015;57:565-567.

64. Figueroa-Rivera IM, Estremera-Marcial R, Sierra-Mercado M, Gutiérrez-Núñez J, Toro DH. Cannabinoid hyperemesis syndrome: a paradoxical cannabis effect. Case Rep Gastrointest Med. 2015;2015:405238.

65. Wilson O, Lutton S, Doherty K. Diagnosing and treating cannabinoid hyperemesis. Emerg Nurse. 2015;23:22-25.

66. Bonnet U. An overlooked victim of cannabis: losing several years of well-being and inches of jejunum on the way to unravel her hyperemesis enigma. Clin Neuropharmacol. 2016;39:53-54.

67. Argamany JR, Reveles KR, Duhon B. Synthetic cannabinoid hyperemesis resulting in rhabdomyolysis and acute renal failure. Am J Emerg Med. 2016;34:765.e1-2.

68. Hinton KL, Chui JS, McWhorter KA, Jallad RH, Siple JF. Cannabinoid hyperemesis syndrome: a paradoxical case. Ann Pharmacother. 2016;50:1071-1072.

69. Jones JL, Abernathy KE. Successful treatment of suspected cannabinoid hyperemesis syndrome using haloperidol in the outpatient setting. Case Rep Psychiatry. 2016;2016:3614053.

70. Srihari P, Liu M, Punzell S, Shebak SS, Rea WS. Cannabinoid hyperemesis syndrome associated with compulsive showering and acute kidney injury. Prim Care Companion CNS Disord. 2016;18(1).

71. Woods JA, Wright NJ, Gee J, Scobey MW. Cannabinoid hyperemesis syndrome: an emerging drug-induced disease. Am J Ther. 2016;23:e601-605.

72. Román F, Llorens P, Burillo-Putze G. [Topical capsaicin cream in the treatment for cannabinoid hyperemesis syndrome]. Med Clin (Barc). 2016;147:517-518.

73. Inayat F, Virk HU, Ullah W, Hussain Q. Is haloperidol the wonder drug for cannabinoid hyperemesis syndrome? BMJ Case Rep. 2017 Jan 4;2017. pii: bcr2016218239. doi: 10.1136/bcr-2016-218239.

74. Smith DA, Phillips HR 3rd. A patient with a curious case of cyclical vomiting. JAAPA. 2017;30:1-3.

75. Abalo R, Vera G, López-Pérez AE, Martínez-Villaluenga M, Martín-Fontelles MI. The gastrointestinal pharmacology of cannabinoids: focus on motility. Pharmacology. 2012;90:1-10.

76. Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. J Clin Pharmacol. 2002;42:11–19.

77. Bashashati M, McCallum RW. Neurochemical mechanisms and pharmacologic strategies in managing nausea and vomiting related to cyclic vomiting syndrome and other gastrointestinal disorders. Eur J Pharmacol. 2014;722:79-94.

78. Büttner M, Walder B, von Elm E, Tramèr MR. Is low-dose haloperidol a useful antiemetic?: A meta-analysis of published and unpublished randomized trials. Anesthesiology. 2004;101:1454-1463.

79. Ross RA. Anandamide and vanilloid TRPV1 receptors. Br J Pharmacol. 2003;140:790-801.

80. Yang F, Zheng J. Understand spiciness: mechanism of TRPV1 channel activation by capsaicin. Protein Cell. 2017 Jan 2. doi: 10.1007/s13238-016-0353-7. [Epub ahead of print]

81. Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. Pharmacol Ther. 2010;126:21-38.

Table 1. Summary of Evidence for Pharmacologic Treatment of Cannabinoid Hyperemesis Syndrome.

Source	Year	Type of Study/Trial	Treatment	Level of evidence	No. of subjects	Summary
Allen et al.[8]	2004	Prospective, longitudinal	Benzodiazepines (unspecified)	II	9	Study authors did not report success of specific treatments
Hejazi et al.[16]	2010	Prospective, longitudinal	Tricyclic antidepressants (Amitriptyline, nortryptilene, doxepin)	II	34	25 of 34 chronic marijuana users had successful response
Namin et al.[17]	2007	Prospective, longitudinal	Lorazepam, ondansetron, amitryptilene, phenothiazines (unspecified)	II	13	Lorazepam most effective acutely, amitryptilene long-term
Venkatesan et al.[18]	2016	Prospective, longitudinal	Ondansentron, promethazine, diphenhydramine, benzodiazepines, opioids (unspecified)	II	8	Study authors did not report success of specific treatments
Clouse et al.[19]	2007	Retrospective	Zonisamide, levetiracetam, tricyclic antidepressants (unspecified)	III	3	Improvement with antipileptics, tricyclic antidepressants prone to failure
Lee et al.[20]	2012	Retrospective	Morphine, ondansetron, lorazepam, acetaminophen, fluoxetine, codeine, buscopan, coenzyme Q, propranolol, carbamezapine	III	4	Morphine, ondansetron, lorazepam most helpful
Dines et al.[21]	2015	Retrospective	Benzodiazepines (unspecified), olanzapine, chlorprothixene, hydroxyzine	III	36	Study authors did not report success of specific treatments
Chang & Windish[22]	2009	Case series	Ondansetron, promethazine, metoclopramide, lorazepam, esomeprazole, morphine sulfate, erythromycin	IV	2	Multiple drugs given, but hot shower most effective
Soriano-Co et al.[23]	2010	Case series	Ondansetron, promethazine, proton pump inhibitors (unsepcified), metoclopramide, dilaudid	IV	8	Poor response to antiemetics in general
Nicolson et al.[24]	2012	Case series	Alprazolam, lorazepam, ondansetron, prochlorperazine	IV	4	Alprazolam improved symptoms for one patient, other antiemetics unhelpful
Torka & Sharma[25]	2012	Case series	Opioids (unspecified)	IV	2	Symptoms did not improve with opioids
Fabries et al.[26]	2013	Case series	Morphine	IV	7	Study authors did not report success or failure of morphine
Witsil & Mycyk[27]	2014	Case series	Halperidol, ondansetron, diphenhydramine, chlorpromazine, metoclopramide	IV	4	Haloperidol successful after other antiemetics failed
Lapoint[28]	2014	Case series	Capsaicin	IV	5	Successful treatment with 0.075% capsaicin cream
Bertolino et al.[29]	2015	Case series	Lorazepam	IV	6	Lorazepam prescribed for outpatient treatment with favorable outcome in 3 cases
Braver & Leibman[30]	2015	Case series	Diazepam, clonazepam, metoclopramide, nabilone	IV	2	Self-treatment with benzodiazepines minimally relieved symptoms, not metoclopramide
Cadman[9]	2016	Case series	Metoclopramide, ondansetron, alprazolam	IV	6	Author did not report success of specific treatments
Contreras Narváez et al.[31]	2016	Case series	Metoclopramide, ondansetron, diazepam, olanzapine, haloperidol	IV	6	Temporary improvement with haloperidol and olanzapine, other medications unclear
Sawni et al.[32]	2016	Case series	Alprazolam	IV	2	Successful outpatient treatment with alprazolam
de Moore et al.[10]	1996	Case report	Metoclopramide, prochlorperazine, benzodiazepines (unspecified), haloperidol	V	1	Medications ineffective
Boeckxstaens[33]	2005	Case report	Metoclopramide, domperidone, cisapride, amitryptiline, ondansentron	V	1	Author did not report success of specific treatments
Alfonso Moreno et al.[34]	2006	Case report	Metoclopramide, diazepam	V	1	Medications effective
Chepyala & Olden[35]	2008	Case report	Promethazine, alprazolam	V	1	Authors did not report success of promethazine
Sannarangappa & Tan[36]	2009	Case report	Metoclopramide, ganisetron, prochlorperazine	V	1	Medications ineffective
Sontineni et al.[37]	2009	Case report	Metoclopramide, morphine, pantoprazole	V	1	Combination treatment effective
Price et al.[38]	2010	Case report	Ondansetron, droperidol, diphenhydramine, promethazine, chlorpromazine, lorazepam	V	1	Promethazine and lorazepam most effective
Sullivan[39]	2010	Case report	Morphine, ondansetron	V	1	Author did not report success of specific treatments

Cha et al.[54]	2014	Case report	Amitriptyline, paroxetine,	V	1	Medications ineffective
			sertraline, tegaserod			
Iacopetti & Packer[55]	2014	Case report	Ondansetron, omeprazole	V	1	Authors did not report success of
						specific treatments
Lam & Frost[56]	2014	Case report	Dimenhydrinate, ondansetron, metoclopramide,	V	1	Medications ineffective with exception
			nabilone			of nabilone
Nogi et al.[57]	2014	Case report	Ondansentron	V	1	Ondansentron ineffective
Swanson & Epperly[58]	2014	Case report	Ondansentron, hydromorphone,	V	1	Medications ineffective with exception
			metoclopramide, promethazine, lorazepam			of lorazepam
Ukaigwe et al.[59]	2014	Case report	Ondansentron	V	1	Ondansentron ineffective
Biary et al[60]	2014	Case report	Capsaicin, ondanseron	V	1	Ondansentron ineffective, successful
						treatment with 0.025% capsaicin cream
Andrews & Bracero[61]	2015	Case report	Metoclopramide	V	1	Authors did not report success of
						metoclopramide
Bajgoric et al.[62]	2015	Case report	Metoclopramide	V	1	Author did not report success of
						metoclopramide
Desjardins et al.[63]	2015	Case report	Pantoprazole, ondansetron,	V	1	Medications ineffective
			dimenhydrinate, metoclopramide			
Figueroa-Rivera et al.[64]	2015	Case report	Lorazepam, "antiemetic therapy"	V	1	Lorazepam improved symtoms, not
						antiemetic therapy
Wilson et al.[65]	2015	Case report	Ondansentron	V	1	Authors did not report success of
						ondansetron
Bonnet[66]	2016	Case report	Corticosteroids, prucalopride, clonidine,	V	1	Medications ineffective with exception
			fentanyl, "usual antiemetics"			of fentanyl patches
Argamany et al.[67]	2016	Case report	Morphine, ondansetron	V	1	Medications ineffective
Hinton et al.[68]	2016	Case report	Ondansetron, promethazine	V	1	Medications ineffective
Jones & Abernathy[69]	2016	Case report	Haloperidol, ondansetron, promethazine, prochlorperazine,	V	1	Haloperidol successful after patient
			metoclopramide, lorazepam, and omeprazole.			reported failure of other treatments
Srihari et al.[70]	2016	Case report	Diazepam, haloperidol,	V	1	Authors did not report success of
			ondansetron			specific treatments
Woods et al.[71]	2016	Case report	Promethazine, ondansetron, tramadol,	V	1	Authors did not report success of
			chlordiazepoxide/clidinium, amitrptyline			specific treatments
Román et al[72]	2016	Case report	Capsaicin, metoclopramide, granisetron	V	1	Metoclopramide and granisetron ineffective,
						successful treatment with 0.075% capsaicin cream
Inayat et al[73]	2017	Case report	Ondansetron, lorazepam, haloperidol	V	1	Ondansetron and lorazepam ineffective,
						successful treatment with haloperidol
Smith & Phillips[74]	2017	Case report	Lorazepam, ondansetron	V	1	Hyperemesis was refractory to lorazepam
						and ondansetron
			Total		**205**