JPPT | State of the Art Review

Management of Pediatric Cannabinoid Hyperemesis Syndrome: A Review

Justin P. Reinert, PharmD; O'Neill Niyamugabo, PharmD; Kiersi S. Harmon, PharmD; and Norman E. Fenn III, PharmD

With significant increases noted in adolescent marijuana use across the United States, perhaps as a result of legislative changes over the past half-decade, clinicians must be increasingly aware of the potential negative health effects. One such effect that warrants concern is cannabinoid hyperemesis syndrome (CHS) in the pediatric population. A systematic review of the literature was performed to determine the safety and efficacy of management strategies for CHS using PubMed, Scopus, the Cumulative Index of Nursing and Allied Health (CINAHL), Web of Science, and Cochrane Library databases. Search terms used in each database were "pediatric OR child OR children OR adolescent" AND "cannabinoid OR marijuana" AND "hyperemesis OR cyclic vomiting OR vomiting" NOT "seizure OR chemotherapy OR pregnancy OR cancer OR AIDS OR HIV." Fourteen pieces of literature that described either effective, ineffective, or supportive management strategies for pediatric CHS were included in this review. Benzodiazepines were the most reported efficacious agents, followed by topical capsaicin cream and haloperidol. A total of 9 of the 14 studies described intravenous fluid resuscitation and hot bathing rituals as supportive measures, and 7 cases reported traditional antiemetics were ineffective for CHS. The heterogenicity of reported data, combined with the limited number of encounters, make it difficult to ascertain whether a definitive treatment strategy exists. Clinicians should be cognizant of pharmacotherapy agents that are efficacious, and perhaps more importantly, avoid using traditional antiemetic therapies that do not provide benefit.

ABBREVIATIONS CB, cannabinoid receptor; CHS, cannabinoid hyperemesis syndrome; D_2, dopamine$_2$; FDA, US Food and Drug Administration; H_2RA, histamine$_2$-receptor antagonist; IV, intravenous; PPI, proton pump inhibitor; THC, tetrahydrocannabinol

KEYWORDS cannabinoid hyperemesis syndrome; cannabis; hyperemesis; marijuana; pediatric; review; THC

J Pediatr Pharmacol Ther 2021;26(4):339–345

DOI: 10.5863/1551-6776-26.4.339

Background

Although derivatives and select formulations of cannabinoid-related medications have proven health benefits, such as with dronabinol for appetite stimulation in cancer patients and cannabidiol in pediatric seizure conditions, it is equally important for health care providers to be cognizant of the deleterious effects of recreational THC-containing products. As of January 1, 2020, eleven states have legalized recreational marijuana, and another 33 have processes in place to support prescriptions for medical marijuana.[1] With the legality of marijuana, cannabidiol oils, and other THC-containing products seemingly in a constant state of flux, health care providers must remain vigilant in preparing to treat toxicities associated with these substances.

One such toxicity of concern to pediatric patients is cannabinoid hyperemesis syndrome (CHS), which was first described in 2004 and may now be considered a subset of cyclic vomiting syndrome or an independent diagnosis.[2] Prevalence results from the Monitoring the Future study indicate statistically significant increases in the use of both synthetic and natural marijuana products for US students in the 8th, 10th, and 12th grades.[3] After Colorado became the first state to legalize recreational marijuana in 2014, cases of pediatric CHS doubled in emergency departments, a figure supported by the estimation that approximately 14% of adolescent Coloradoans are current marijuana users.[4,5]

The pathophysiology of CHS revolves around the physiologic role of 2 cannabinoid receptors, CB_1 and CB_2.[6] When activated by cannabinoids, these receptors inhibit adenylate cyclase, a rate-limiting step in the conversion of adenosine triphosphate to cyclic adenosine monophosphate, which is an important second messenger in intracellular signal transduction.[6,7] The slowing of normal functional cellular pathways is evidenced by mental dissociation, decreases in gastric motility, anxiety, and heart rate, and the slowing of nociceptive pain signals from their points of origin to the brain.[7] The CB_1 receptors are primarily located in the nervous system, but they have also been detected within numerous other organs and systems, including the spleen, heart, lungs, and bladder.[7] The CB_2 receptors are found on immune cells, as well as in the ileum, and are thought to be responsible for pain response mediation and gastric motility.[7] Centrally, these receptors mitigate anterior pituitary hormones as a result of induction from canna-

binoids, leading to decreased prolactin, gonadotropin, and growth hormone, while simultaneously increasing corticotropin secretions.

The disruption of the hypothalamic-pituitary axis, and the downstream effects on the autonomic nervous system, are the hypothesized mechanisms of CHS.[6-8] Specifically, the loss of endogenous thermoregulation as a result of changes in the hypothalamic-pituitary-axis has been implicated in CHS.[7,8] Additionally, activation of cannabinoid receptors can activate TRPV1, a G-coupled protein that also plays a transient role in thermoregulation.[7] It is important to note that THC is lipophilic and will redistribute into body fat, resulting in a prolonged duration of action at both the CB_1 and CB_2 receptors.[6,7]

Regardless of the underlying pathophysiology, patients can be categorized into 1 of 3 distinct phases, although presentation to a health care facility typically occurs in phase 2.[4-9] The prodrome phase occurs as the patient recognizes the onset of nausea that accompanies imminent emesis. The patient may be diaphoretic, pale, and complain of abdominal pain. The vomiting phase begins upon the first bout of emesis. A patient may vary between the prodrome and vomiting phase as acute emesis attacks occur and subside; at a minimum, the vomiting phase commonly lasts 20 to 30 minutes.[4-9] Patients may present as unresponsive or with significant altered mental status, perhaps as a result of dehydration, in addition to experiencing significant abdominal pain in phase 3. Following the bout of emesis, the patient enters a recovery phase, where symptoms will dissipate and the patient will gradually return to their baseline.[4-9] Although adults and pediatric patients share similarities in presentation, pediatric patients are less likely to experience profound weight loss as a result of the cyclic vomiting.[9] Clinical considerations for diagnosis are described in Table 1.

The increasing availability of cannabinoid products opens the door for a potentially greater incidence of toxicity. Younger children may come across and accidentally ingest cannabinoid products, because most calls to poison centers involve children younger than 6 years.[10] In particular, adolescents are perhaps at a heightened risk based on their developmental stage, influential peers, and the experience-dependent plasticity of the evolving mind.[11] Because of the unconventional presentation of CHS, it is important for clinicians to be familiar with and prepared for management of this condition in a host of treatment settings, including the emergency department, intensive care unit, and general medicine floors. The primary objective of this review was to assess the effectiveness and safety of pharmacotherapies for CHS in the pediatric population.

Table 1. Clinical Criteria for Cannabinoid Hyperemesis Syndrome Diagnosis[9]

Major Features
Severe cyclic nausea and vomiting
Resolution of symptoms with cessation of THC products
Relief with external thermoregulation
Epigastric/periumbilical pain
Minimum frequency of weekly use of marijuana
Supportive Features
Age <50 yr
Weight loss >5 kg
Symptoms present on awakening
Normal bowel habits
Negative laboratory/radiographic studies

THC, tetrahydrocannabinol

Methods

Study Selection. A systematic review of the literature was performed using PubMed, Scopus, the Cumulative Index of Nursing and Allied Health (CINAHL), Web of Science, and Cochrane Library databases. Search terms used in each database were "pediatric OR child OR children OR adolescent" AND "cannabinoid OR marijuana" AND "hyperemesis OR cyclic vomiting OR vomiting" NOT "seizure OR chemotherapy OR pregnancy OR cancer OR AIDS OR HIV." All levels of evidence and study designs were evaluated for inclusion. Studies were retrieved by 2 study investigators. Titles and abstracts were reviewed for inclusion or exclusion in the review prior to discussion with the research team. All discrepancies were evaluated by the study investigators and resolved prior to data extraction.

Data Extraction. Studies that reached a definitive diagnosis of CHS in pediatric patients, as defined by the authors and health care providers of the respective case, and that described treatment modalities were included. Additionally, studies that evaluated both pediatric and adult populations were included if treatment of the pediatric patients was adequately described. Exclusion criteria were much more robust: reports of adult patients only, those in which symptoms were not related to cannabis use, and studies not available or readily translatable to English were not included. Data extracted from the studies included inclusion and exclusion criteria, study type and population, treatment modalities used, and any safety or efficacy data.

Results

A total of 165 studies were retrieved from the database searches, of which 151 were excluded using the predetermined criteria (i.e., duplicate entries [n = 63]; non-relevant entries [n = 43]; without patient cases [n = 36]; adult-only studies [n = 7]; and not available in English [n = 2]). In order to ascertain which therapies were the most efficacious in the cessation of CHS, pharmacotherapy interventions were classified as either effective, ineffective, or supportive by the authors. The quality of evidence from included studies is low,

Table 2. Results of Systematic Review

Source	Study Design (n)	Mean Age, yr (Pediatric Patients)	Effective Therapy	Ineffective Therapy	Supportive Care
Kelly[22]	Case (1)	16 (1)	None described	Omeprazole	Compulsive hot showers (≤ 10/day)
Wilson[21]	Case (1)	17 (1)	None described	Ondansetron; promethazine	IV fluid hydration Compulsive hot showers/baths
Besli[13]*	Case series (16)	15.4 (16)	Benzodiazepines	None described	IV fluid hydration
Allen[12]	Case series (10)	24.2 (3)	Benzodiazepines	None described	Cessation of cannabis abuse IV fluid hydration Compulsive hot showers/baths
Thomas[25]	Case series (3)	3.86 (3)	None described	None described	IV fluid hydration (40 mL/kg NS)
Pelissier[19]	Retrospective cohort analysis (7)	24.7 (2)	None described	Antiemetics; proton pump inhibitors	Cessation of cannabis abuse Compulsive hot baths
Jones[17]	Case (1)	18 (1)	Haloperidol 5 mg orally daily	Ondansetron; promethazine prochlorperazine; lorazepam metoclopramide; omeprazole	None described
Manoharan[20]	Case (1)	15 (1)	None described	Metoclopramide; ondansetron	Cessation of cannabis abuse Compulsive hot showers (≤ 6/day)
Gammeter[14]	Case (1)	5 (1)	Clonazepam 0.25 mg orally at bedtime, titrated to 0.5 mg orally at bedtime	Ondansetron; promethazine; lorazepam	Cessation of cannabis abuse IV fluid hydration (NS) Compulsive hot showers (≤ 20/day)
Miller[24]	Case series (2)	17.5 (2)	None described	Omeprazole	Cessation of cannabis use Compulsive hot showers
Solis-Garcia[23]	Case (1)	15 (1)	None described	None described	Cessation of cannabis abuse IV fluid hydration Compulsive hot showers
Sawni[15]	Case series (2)	15.5 (2)	Alprazolam	Antiemetics; omeprazole; analgesics	Cessation of cannabis abuse IV fluid hydration Compulsive hot showers
Desjardins[18]	Case (1)	17 (1)	None described	Metoclopramide; ondansetron; dimenhydrinate; pantoprazole	IV fluid hydration and potassium repletion Compulsive hot showers (≥ 10/day)
Graham[16]	Case series (2)	18 (1)	Capsaicin cream 0.025%, 1-mm–thick coating on abdomen	Metoclopramide; ondansetron; ranitidine; oxycodone	IV fluid hydration (NS, 1000-mL bolus) Compulsive hot showers

NS, normal saline

*Includes reports of synthetic cannabinoids.

because all represent either case reports or case series. A summary of included studies is provided in Table 2.

Of the 14 included reports, only 6 described effective treatment modalities in children.[12-15] Four described the effective use of a benzodiazepines as the primary treatment for CHS: 2 studies included medications and regimens, whereas another 2 did not specify a specific benzodiazepine. A single case series evaluated the efficacy of topically applied capsaicin cream for CHS refractory to antiemetics and analgesics.[16] One case study examined the efficacy of haloperidol.[17]

Nine of the reports included in this review discussed the use of various combinations of antiemetic therapies and subsequent treatment failures. Numerous formulations, routes of administration, and dosing strategies for ondansetron, promethazine, metoclopramide, and dimenhydrinate were described, although none of the regimens were found to be effective for the treatment of CHS.[12-25] Similarly, opioid analgesics and acid suppression therapy, including both proton pump inhibitors (PPIs) and histamine$_2$-receptor antagonists (H_2RAs), were found to be ineffective.[12-25] Although many investigators sought to create a cocktail of antiemetics, analgesics, and acid-suppressive medications, these were also found to be ineffective in the cessation of CHS symptoms.[12-25]

More than half of the patients evaluated in this review received at least 3 different supportive therapies, with some being pharmacologic and others not. Intravenous fluid resuscitation was described in 9 of the 14 studies included in this review, with strategies differing between cases.[12-16,18,21,23,24] Although not all studies reported the fluid of choice, normal saline was described in 3 cases, including that of a 7-month-old patient who had been inadvertently exposed via breastmilk.[14,16,24,25] Bathing or showering with hot water was mentioned as effective by study participants, although authors of these studies noted the lack of feasibility of this strategy in most inpatient settings.[12,14-16,18-23]

Discussion

Significant heterogenicity exists between the studies evaluated in this review, making a conclusive and definitive treatment strategy elusive. Furthermore, a paucity of data exists in the pediatric literature of an appropriate medication regimen and duration. The single uniform consensus among investigators in managing CHS was the cessation of cannabis use.[12-24]

Effective Therapies. Benzodiazepines were the most commonly described pharmacologic therapy for managing CHS. These medications exert their effects by enhancing γ-aminobutyric acid activity, which inhibits neurotransmitters in the central nervous system and can decrease the activation of CB_1 receptors in the frontal cortex, leading to an antiemetic effect.[26] One study of 10 pediatric patients did identify that the maximum treatment period for benzodiazepines allowed should be 2 weeks in an effort to assist with withdrawal symptoms from cannabis.[12] An additional study of 2 pediatric patients discussed the successful use of alprazolam in complete resolution of the patient's symptoms, but it failed to disclose the dose or duration of treatment.[15] Finally, another study discussed the initial use of lorazepam, which was unsuccessful, but it was later switched to clonazepam 0.25 mg nightly titrated to 0.5 mg, which resulted in treatment success.[14] Although more information is required to inform treatment decisions in pediatric patients, it may be possible to extrapolate information from adult literature because benzodiazepines have demonstrated efficacy in this population. Two separate adult cases involving a 28-year-old male and a 35-year-old male reported immediate improvement in their nausea within 10 minutes of a single 1-mg IV dose of lorazepam.[27,28]

Topical capsaicin was also a reasonably effective treatment option in pediatric patients. The dysregulation of the thermoregulatory TRVP1 receptor has been implicated in the pathophysiology of CHS, and this may explain the efficacy of capsaicin.[16,22] The use of capsaicin was explored in 2 case studies involving a pediatric patient and a young adult. A 16-year-old female with recurrent nausea, vomiting, and abdominal pain experienced cessation of symptoms within 30 minutes of the application of a 1-mm–thick coating of 0.025% capsaicin cream to the abdomen.[22] Similarly, a 20-year-old-male experienced a resolution of symptoms in the same approximate time frame after receiving the same regimen.[16] Looking to adult literature, a case study by Moon et al[29] reported the use of 0.075% capsaicin cream applied to the abdomen in a 30-year-old patient, which again resulted in the resolution of symptoms associated with CHS. Further investigation is warranted to determine if a higher concentration can provide equal results without any adverse drug reaction in pediatric patients. Application of capsaicin to the abdomen has been well documented; however, the application of capsaicin to alternate anatomic structures has not yet been explored.

Despite haloperidol having supporting literature for adult patients, only 1 study evaluated its use in the pediatric population.[17] Haloperidol exerts its action by antagonizing dopamine$_2$ (D_2) receptors in the central nervous system.[30] There is a high concentration of these receptors in the chemoreceptor trigger zone, which is linked to haloperidol's antiemetic properties.[30] An 18-year-old female was treated with 5 mg of oral haloperidol daily in an effort to treat her CHS, and this was successful.[17] This report is encouraging in that it demonstrated the patient was able to start haloperidol in this hospital and transition to using it at home.[17] It is important to note that the patient did not stop using cannabis products during this time, making haloperidol a relatively attractive option in patients for whom cessation may not be an expectation. Furthermore, at follow-up visits,

the patient did not describe any adverse effects from the haloperidol, and she self-discontinued the drug 3 weeks after her symptoms subsided.[17]

In light of the substantial deficit of pediatric data for this disease process, it is important to review clinical outcomes in adult cases to determine what, if any, treatment modalities can be extrapolated to adolescents. Besides avoiding traditional antiemetics because of a lack of efficacy attributed to differing pathologies, a single dose of 1 mg of IV lorazepam has been found to halt emesis, with additional doses up to 1 mg every 6 to 8 hours for sustained cessation of vomiting.[8,31] The same dosing information for haloperidol discussed in pediatric patients above has also been found to be efficacious in adult patients, although additional data exist regarding the duration of therapy. Following an initial oral, intramuscular, or IV dose of 5 mg of haloperidol, an oral maintenance dose of 2.5 to 5 mg may be required for up to 14 days in combination with cannabis cessation.[31,32] External thermoregulation with both hot bathing exercises and topical capsaicin have also been studied in adults. In a review of 98 patient cases, Simonetto et al[9] described the ability of 0.75% capsaicin cream, applied across the abdomen, to be efficacious within 20 to 30 minutes.

Ineffective Treatments. Contrary to the historic use of cannabis and its derivatives for antiemetic properties, a paradoxical effect is seen in patients diagnosed with CHS.[33,34] Traditional antiemetic therapies have been described in the literature as being ineffective when it comes to treating CHS. Seven of the studies included in this review trialed antiemetics from several medication classes, including 5-hydroxytryptophan, subtype 3 ($5HT_3$) receptor antagonists and D_2 receptor antagonists, as well as with the acid-suppressing H_2RAs, and PPIs.[14-20] Five of the studies attempted to use ondansetron, including IV, sublingual, and oral formulations, whereas patients from 2 studies attempted promethazine following ondansetron, which similarly did not provide relief.[14-20] Although management of esophagitis and gastritis secondary to repeated vomiting may warrant adjunctive therapy with a PPI or H_2RA, their use as part of other antiemetic combination therapies has not proven advantageous in the cessation of CHS symptoms.[16-19,24]

Information derived from adult literature may be able to further elucidate which therapies should not be attempted in the pediatric population because of a lack of efficacy. Droperidol, a structural analog of haloperidol, has been used for the management of CHS; however, its efficacy in managing hyperemesis has not been reported as favorably as with haloperidol.[9,32] Droperidol may have less direct antagonism of D_2 receptors as a result of differences in its molecular structure when compared to haloperidol.[31,32] Furthermore, droperidol has an FDA boxed warning for inducing arrhythmias. Although this may also occur with haloperidol and other traditional antipsychotics, literature suggests that it may be more likely to occur with droperidol.[9,32] Because CHS patients are commonly severely dehydrated and may have electrolyte abnormalities at baseline, furthering their risk for arrhythmia with droperidol is not likely to be warranted after a consideration of risks, benefits, and alternatives.

No evidence exists for the use of second-generation antipsychotics, such as quetiapine and olanzapine, for the acute or maintenance treatment of CHS. One possible reason for their lack of selection and utility may lie in their inherent difference in mechanisms of action when compared to haloperidol.[9] Although haloperidol and other first-generation antipsychotics almost exclusively antagonize the D_2 receptors, second-generation antipsychotics have a broader antagonistic spectrum of activity. 5-HT_{1A}, 5-HT_2, D_1, Histamine, subtype 1 (H_1), and adrenergic receptors are all antagonized by second-generation antipsychotics, leading to less specific activity at the D_2 receptor and thus a lack of efficacy in CHS.[9]

Supportive Care. The hyperemetic phase of CHS can lead to profound fluid loss and dehydration, especially in pediatric patients.[34] Furthermore, enteral supplementation is unlikely to be effective because of the nature of CHS, thereby making IV fluids a mainstay of supportive care for these patients.[12-16,18,21,23-24] Although the general role of fluid supplementation is understood as a standard of care, a fluid resuscitation strategy has not been clearly defined in the literature. Nine studies documented IV fluid resuscitation; however, there were significant discrepancies in the description of the volume, type, or infusion rate.[12-16,18,21,23,24] Although there is a report of a 16-year-old female receiving a 1000-mL bolus of normal saline as part of her care, this information is not easily extrapolated to the younger pediatric population at large.[16] Inferences can be made from the general management of pediatric dehydration, where an initial 10 to 20 mL/kg isotonic crystalloid, such as normal saline or lactated Ringer solution, may be appropriate.[35,36] It is imperative that clinicians invoke a rigorous rehydration strategy based on a thorough clinical assessment of the patient. Following a successful halting of emesis, it may be possible to use oral rehydration therapy.[37] Using the Holliday-Segar method, patients may require 50 to 100 mL/kg oral replacement therapy, given while the patient remains under observation.[38,39]

Compulsive bathing or showering in high temperatures has been well documented in CHS literature, and external thermoregulation is one of the clinical criteria used to help support a diagnosis. Although marginally effective for the duration of the bathing ritual, cases exist in which patients have sustained thermal burns as a result of excessive showering or bathing.[12] Gammeter et al[14] describe patients taking hot showers or baths up to 20 times per day to obtain symptom relief, whereas Manoharan et al[20] describes a more conservative six

bathing times over the course of a day.

Unfortunately, the diagnosis of CHS is often one of excluding other common or insidious etiologies. Investigators studying CHS can unequivocally agree that relief from symptoms can be obtained through cannabis cessation.[12-25] Interestingly, cessation is also one of the characteristics evaluated in the diagnosis of the syndrome.[9] The conclusions from Allen et al[12] indicate that a patient's willingness to discontinue cannabis use will lead to the resolution of their symptoms. It is important to note that although the therapies discussed in this review may have the ability to manage acute symptoms, the sustained cessation of cannabis and cannabinoid products is the only intervention that has universally demonstrated longitudinal efficacy. A gap in knowledge exists as to the length of cessation time required until symptom dissolution. Although not strictly within the scope of this review, counselors, social workers, and other similar allied health professionals may have a lasting effect on cessation.

Future Investigation. Absent from the pediatric literature are reports of success or failure with aprepitant, despite the fact that the drug is used in the treatment of cyclic vomiting and chemotherapy-induced emesis in this patient population.[40] Aprepitant, a neurokinin-1 (NK_1) receptor antagonist, inhibits the endogenous function of NK_1 and Substance P in the dorsal vagal complex, thereby effectively controlling nausea and vomiting.[40,41] Parvataneni et al[41] described a report of a 30-year-old woman with CHS who previously failed treatment with antiemetics, PPIs, H_2RAs, and haloperidol. Following those treatment failures, the patient was successfully managed with aprepitant and was discharged. With the efficacy and safety profile of aprepitant and other NK_1 antagonists being well established in pediatric patients, future investigation for CHS is warranted. In addition to these agents, future studies that rely upon a set of codified diagnostic criteria and can define appropriate dosing of the other medications discussed in this review would be immeasurably beneficial.

Limitations. This systematic review of the literature has several limitations that warrant discussion. As with any investigation of this nature, it remains a possibility that a literature source may have been inadvertently overlooked or wrongfully excluded, although every effort was taken by the authors to prevent either happenstance. In addition, the strength of data evaluated in this review must be acknowledged as being relatively low, considering that our results describe management strategies derived from case reports, case series reports, and a single retrospective cohort analysis. It is equally difficult to make comparisons between the aforementioned cases because of the heterogenicity in outcome measures and pharmacotherapeutic interventions reported by the respective authors. Finally, the sheer lack of pediatric data for CHS makes reaching a definitive treatment algorithm difficult.

Conclusions

Investigative study of CHS in the pediatric population has not yet occurred, despite the assumption that the number of cases of CHS in this population will likely continue to increase amid heightened availability of cannabis and cannabinoid products in the United States and globally. At the current juncture, the greatest amount of efficacy data exists with longer-acting benzodiazepines, such as alprazolam and clonazepam, appropriate fluid resuscitation, and warm bathing and external thermoregulation. Traditional antiemetics, corticosteroids, and antipsychotic medications should be avoided once a diagnosis is confirmed. Clinicians must be cognizant of the relevant pathophysiology to effectively prescribe and manage acute symptomatology; however, only with sustained cannabis cessation can CHS be abated.

Article Information

Affiliations. Fisch College of Pharmacy (JPR, ON, KSH, NEF), The University of Texas at Tyler, Tyler, TX.

Correspondence. Justin P. Reinert, PharmD; jreinert@uttyler.edu

Disclosures. The authors declare no conflicts or financial interests in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. JPR had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. Given the nature of this study, institutional review board/ethics committee review was not required.

Acknowledgments. The authors would like to thank Suzanne Abbey, professional librarian, for her assistance with literature search and retrieval.

Submitted. May 1, 2020

Accepted. October 19, 2020

References

1. State marijuana laws. Accessed January 24, 2020. https://www.governing.com/gov-data/safety-justice/state-marijuana-laws-map-medical-recreational.html
2. Campos-Outcalt D, Janousek A, Rosales C. The relationship between marijuana use and cyclic vomiting syndrome. University of Arizona College of Public Health. Guidance document for the Arizona Department of Health Services. 2013. Accessed 24 January 2020. https://azdhs.gov/documents/licensing/medical-marijuana/debilitating/cyclic-vomiting-syndrome.pdf

3. National Institute on Drug Abuse. Monitoring the Future survey: trends in prevalence of various drugs. 2019. Accessed 24 January 2020. https://www.drugabuse.gov/trends-statistics/monitoring-future/monitoring-future-study-trends-in-prevalence-various-drugs
4. Kim HS, Anderson JD, Saghafi O, et al. Cyclic vomiting presentations following marijuana liberalization in Colorado. *Acad Emerg Med*. 2015;22(6):694–699.
5. Habboushe J, Rubin A, Liu H, et al. The Prevalence of cannabinoid hyperemesis syndrome among regular marijuana smokers in an urban public hospital. *Basic Clin Pharmacol Toxicol*. 2018;122(6):660–662.
6. Iacopetti CL, Packer CD. Cannabinoid hyperemesis syndrome: a case report and review of pathophysiology. *Clin Med Res*. 2014;12(1–2):65–67.
7. Galli J, Sawaya R, Friedenberg F. Cannabinoid hyperemesis syndrome. *Curr Drug Abuse Rev*. 2011;4(4):241–249.
8. Budhraja V, Narang T, Azeez S. Cannabinoid hyperemesis syndrome: cyclic vomiting, chronic cannabis use, and compulsive bathing. *Prac Gasteroenterol*. 2008;6(3):79–81.
9. Simonetto DA, Oxentenko AS, Herman ML, et al. Cannabinoid hyperemesis: a case series of 98 patients. *Mayo Clin Proc*. 2012;87(2):114–119.
10. Anderson BD, Seung H, Klein-Schwartz W. Trends in types of calls managed by U.S. poison centers 2000-2015. *Clin Toxicol (Phila)*. 2018;56(7):640–645.
11. Yuan M, Cross SJ, Loughlin SE, et al. Nicotine and the adolescent brain. *J Physiol (Lond)*. 2015;593(16):3397–3412.
12. 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.
13. Besli GE, Ikiz MA, Yildirim S, et al. Synthetic cannabinoid abuse in adolescents: a case series. *J Emerg Med*. 2015;49(5):644–650.
14. Gammeter WB, Duke KA, Soundy TJ. Case report of intractable vomiting and abdominal pain related to heavy daily cannabis use. *S D Med*. 2016;60–63.
15. Sawni A, Vaniawala VP, Good M, et al. Recurrent cyclic vomiting in adolescents: can it be cannabinoid hyperemesis syndrome? *Clin Pediatr (Phila)*. 2016;55(6):560–563.
16. Graham J, Barberio M, Wang GS. Capsaicin cream for treatment of cannabinoid hyperemesis syndrome in adolescents: a case series. *Pediatrics*. 2017;140(6):1–4.
17. Jones JL, Abernathy KE. Successful treatment of suspected cannabinoid hyperemesis syndrome using haloperidol in the outpatient setting. *Case Rep Psychiatry*. 2016;2016:3614053. doi:10.1155/2016/3614053
18. Desjardins N, Jamoulle O, Taddeo D, et al. Cannabinoid hyperemesis syndrome in a 17-year-old adolescent. *J Adolesc Health*. 2015;57(5):565–567.
19. Pélissier F, Claudet I, Gandia-Mailly P, et al. Cannabis hyperemesis syndrome in the emergency department: how can a specialized addiction team be useful?: a pilot study. *J Emerg Med*. 2016;51(5):544–551.
20. Manoharan SVR, Aggarwal R, Taneli T. Cannabinoid hyperemesis syndrome: a case report. *Asian J Psychiatr*. 2018;34:64. doi:10.1016/j.ajp.2018.04.013
21. Wilson L. Case 3: recurrent vomiting and 60-lb weight loss in a 17-year-old girl. *Pediatr Rev*. 2016;37(6):264–266.
22. Kelly E, Van Opstal E. Case 2: 16-year-old boy with intractable nausea and vomiting. *Pediatr Rev*. 2019;40(6):305–307.
23. Solis-Garcia G, González-Martínez F, Urbiola E, et al. Cannabinoid hyperemesis in adolescents: a poorly diagnosed syndrome. *J Paediatr Child Health*. 2019;55(10):1264–1266.
24. Miller JB, Walsh M, Patel PA, et al. Pediatric cannabinoid hyperemesis: two cases. *Pediatr Emerg Care*. 2010;26(12):919–920.
25. Thomas AA, Mazor S. Unintentional marijuana exposure presenting as altered mental status in the pediatric emergency department: a case series. *J Emerg Med*. 2017;53(6):e119–e123.
26. Kheifets M, Karniel E, Landa D, et al. Resolution of cannabinoid hyperemesis syndrome with benzodiazepines: a case series. *Isr Med Assoc J*. 2019;21(6):404–407.
27. Cox B, Chhabra A, Adler M, et al. Cannabinoid hyperemesis syndrome: case report of a paradoxical reaction with heavy marijuana use. *Case Rep Med*. 2012;2012:757696. doi:10.1155/2012/757696
28. Mahmad AI, Jehangir W, Littlefield JM, et al. Cannabis hyperemesis syndrome: a case report review of treatment. *Toxicol Rep*. 2015;2:889–890.
29. Moon AM, Buckley SA, Mark NM. Successful treatment of cannabinoid hyperemesis syndrome with topical capsaicin. *ACG Case Rep J*. 2018;5:e3. doi:10.14309/crj.2018.3
30. Witsil JC, Mycyk MB. Haloperidol, a novel treatment for cannabinoid hyperemesis syndrome. *Am J Ther*. 2017;24(1):e64–e67.
31. Sun S, Zimmermann AE. Cannabinoid hyperemesis syndrome. *Hosp Pharm*. 2013;48(8):650–655.
32. Hickey JL, Witsil JC, Mycyck MB. Haloperidol for the treatment of cannabinoid hyperemesis syndrome. *Am J Emerg Med*. 2013;31(6):1003.e5–e6.
33. Malik Z, Baik D, Schey R. The role of cannabinoids in regulation of nausea and vomiting, and visceral pain. *Curr Gastroenterol Rep*. 2015;17(2):429. doi: 10.1007/s11894-015-0429-1
34. Galli JA, Sawaya RA, Friedenberg FK. Cannabinoid hyperemesis syndrome. *Curr Drug Abuse Rev*. 2011;4(4):241–249.
35. Geurts D, De vos-kerkhof E, Polinder S, et al. Implementation of clinical decision support in young children with acute gastroenteritis: a randomized controlled trial at the emergency department. *Eur J Pediatr*. 2017;176(2):173–181.
36. Vega RM, Avva U. Pediatric dehydration. Accessed 22 April 2020. https://www.ncbi.nlm.nih.gov/books/NBK436022/
37. Canavan A, Arant BS. Diagnosis and management of dehydration in children. *Am Fam Physician*. 2009;80(7):692–696.
38. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19(5):823–832.
39. Holliday MA, Ray PE, Friedman AL. Fluid therapy for children: facts, fashions and questions. *Arch Dis Child*. 2007;92(6):546–550.
40. Cristofori F, Thapar N, Saliakellis E, et al. Efficacy of the neurokinin-1 receptor antagonist aprepitant in children with cyclical vomiting syndrome. *Aliment Pharmacol Ther*. 2014;40(3):309–317.
41. Parvataneni S, Varela L, Vemuri-reddy SM, et al. Emerging role of aprepitant in cannabis hyperemesis syndrome. *Cureus*. 2019;11(6):e4825. doi: 10.7759/cureus.4825