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CANNABINOID HYPEREMESIS SYNDROME: PATHOPHYSIOLOGY AND TREATMENT IN THE EMERGENCY DEPARTMENT

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☐ **Abstract—Background: Cannabinoid hyperemesis syndrome (CHS) is a challenging clinical disorder. CHS patients frequently present to the emergency department and may require treatment for intractable emesis, dehydration, and electrolyte abnormalities. Thought to be a variant of cyclic vomiting syndrome, CHS has become more prevalent with increasing cannabis potency and use, as enabled by various states having legalized the recreational use of cannabis. Objective: This aim of this review is to investigate the pathophysiology of CHS and evaluate the published literature on pharmacologic treatment in the emergency department. This information may be helpful in providing evidence-based, efficacious antiemetic treatment grounded in knowledge of antiemetic medications' mechanisms of action, potentially precluding unnecessary tests, and reducing duration of stay. Discussion: The endocannabinoid system is a complex and important regulator of stress response and allostasis, and it is occasionally overwhelmed from excessive cannabis use. Acute episodes of CHS may be precipitated by stress or fasting in chronic cannabis users who may have pre-existing abnormal hypothalamic–pituitary–adrenal axis feedback and sympathetic nervous system response. The reasons for this may lie in the physiology of the endocannabinoid system, the pathophysiology of CHS, and the pharmacologic properties of specific classes of antiemetics and sedatives. Treatment failure with standard antiemetics is common, necessitating the use of mechanistically logical sedating agents such as benzodiazepines and antipsychotics. Conclusion: Despite the increasing prevalence of CHS, there is a limited body of high-quality research. Benzodiazepines and antipsychotics represent logical choices for treatment of CHS because of their powerful sedating effects. Topical capsaicin holds promise based on a totally different pharmacologic mechanism. Discontinuation of cannabis use is the only assured cure for CHS.** © **2017 Elsevier Inc. All rights reserved.**

☐ **Keywords—cannabinoid; cannabis; cyclic vomiting; emesis; hyperemesis; marijuana**

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INTRODUCTION

Cannabis is the most commonly used drug in the world, with 183 million users according to the 2017 United Nations World Drug Report (1). Based on the most recent National Survey on Drug Use and Health, an estimated 22 million Americans ≥12 years of age (8.3% of the population) in 2015 were occasional users of marijuana, and adult past-year cannabis use more than doubled from 4.1% to 9.5% over the past decade (2). There were 456,000 emergency department (ED) visits related to cannabis use in 2011, which represented a 21% increase from 2009 (3). As a result of the 2016 elections, California, Maine, Massachusetts, and Nevada have legalized recreational cannabis, joining Alaska, Colorado, Oregon, and Washington. As the use and legalization of recreational and medical cannabis continues to rise,

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cannabinoid hyperemesis syndrome (CHS), a variant of cyclic vomiting syndrome (CVS), has become increasingly widespread (4,5). First described in 2004 by Allen et al., CHS is characterized by recurrent, paroxysmal episodes of nausea, vomiting, and abdominal discomfort in chronic cannabis users, relieved by frequent hot bathing or showering, and followed by symptom-free periods (6). Patients experiencing these symptoms may visit the ED for intravenous (IV) antiemetics and rehydration.

Published case reports of complications from CHS have included acute renal failure, electrolyte derangement, esophageal injury, and pneumomediastinum (7–10). However, standard of care antiemetics are often ineffective for acute exacerbations, necessitating the use of multiple doses of different, unrelated, and off-label pharmacologic agents until control of hyperemesis is achieved (11). The only proven treatment is complete cessation of cannabis use (12). As a consequence, patients with CHS may undergo multiple rounds of different antiemetics, many with potentially significant side effects. They may also endure lengthy ED visits with extensive negative workups and misdiagnoses. In this review, potential explanations for the difficulties in treating CHS are reported. The function of the endocannabinoid system, pathophysiology of CHS, and the pharmacologic properties of specific classes of antiemetics and sedatives are illuminating in this regard. This knowledge may be helpful to clinicians who frequently care for CHS patients to help direct efficacious antiemetic selection, preclude unnecessary laboratory testing and imaging, and reduce these patients' duration of stay in the ED.

DISCUSSION

Pathophysiology of Nausea and Emesis

The pathophysiology of nausea and emesis is complex. Noxious stimuli, such as gastric distention, microbial toxins causing gastroenteritis, adverse drug reactions, drug withdrawal, trauma, motion sickness, emotional stress, malodor, unpleasant taste, irradiation, and toxic pharmacologic chemotherapeutic agents, can activate the chemoreceptor trigger zone of the medulla oblongata, otherwise known as the area postrema (13). This structure resides outside the blood–brain barrier and is sensitive to blood- and cerebrospinal fluid–borne chemicals. Other structures within the medulla comprising this "vomiting center" include the nucleus tractus solitarius and a central pattern generator that orchestrates the sequence of actions leading to emesis. Emesis initiated by the chemoreceptor trigger zone is relayed via the central pattern generator to efferent vagus nerve fibers and represents a complex and choreographed interplay between sensorimotor, parasympathetic, and sympathetic nervous systems (Figure 1) (14). The sequence of events begins with increased salivation, deep respiration, closure of the glottis, relaxation of the pyloric sphincter, then retroperistalsis from the small intestine to the stomach. Finally, contraction of the abdominal muscles results in emesis. Tachycardia, tachypnea, lacrimation, and diaphoresis occur concomitantly and may persist after emesis has completed (13,14).

The Endocannabinoid System and CHS

Endogenous cannabinoids bind to the G protein–coupled cannabinoid receptors CB_1 and CB_2. Located in the central nervous system (CNS) and in nerves throughout the gastrointestinal tract, CB_1 receptors modulate gastric secretion, motility, inflammation, and sensation (15). The CB_2 receptors are localized in lymphoid tissues in the periphery and are involved in immune system regulation (11). Activation of CB_1 receptors by endogenous cannabinoids results in the inhibition of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system response to stressful stimuli (16).

CHS is believed to be a variant of CVS that has been more extensively studied for a longer period than CHS but is still not completely understood (17). CVS usually develops after 3 years of age and resolves by adolescence, although it can extend into adulthood (18). No single mechanism exists to explain the pathogenesis of CVS, also referred to as "abdominal migraine" because of the high prevalence of concomitant migraine symptoms (17). Autonomic nervous system and neuroendocrine dysfunction, genetic and endophenotypic predisposition, affective disorders, and substance abuse have all been cited as potential factors (18,19). Differences between CVS and CHS include psychologic comorbidities, such as anxiety and dysphoria, associated migraine headaches, lack of hot water symptom relief, and higher gastric emptying rates (11,12).

The phases of CHS involve a prodrome, hyperemesis, and recovery. The prodromal phase is notable for early morning nausea, anorexia, fear of vomiting, and abdominal discomfort that can last for days. The hyperemetic phase is characterized by nausea, frequent emesis, and diffuse abdominal pain lasting $\leq$24 hours. The recovery phase involves resolution of nausea, emesis, and anorexia (11,12). Simonetto et al. developed diagnostic criteria based on their case series of 98 patients with CHS (Table 1) (20). CHS also represents a paradox, because the major psychoactive component of marijuana, Δ9-tetrahydrocannabinol, is an effective and widely used antiemetic (21). Δ-9-Tetrahydrocannabinol activates CB_1 receptors, noncompetitively inhibits emetogenic 5-hydroxytryptamine-3 ($5\text{-}HT_3$) serotonin

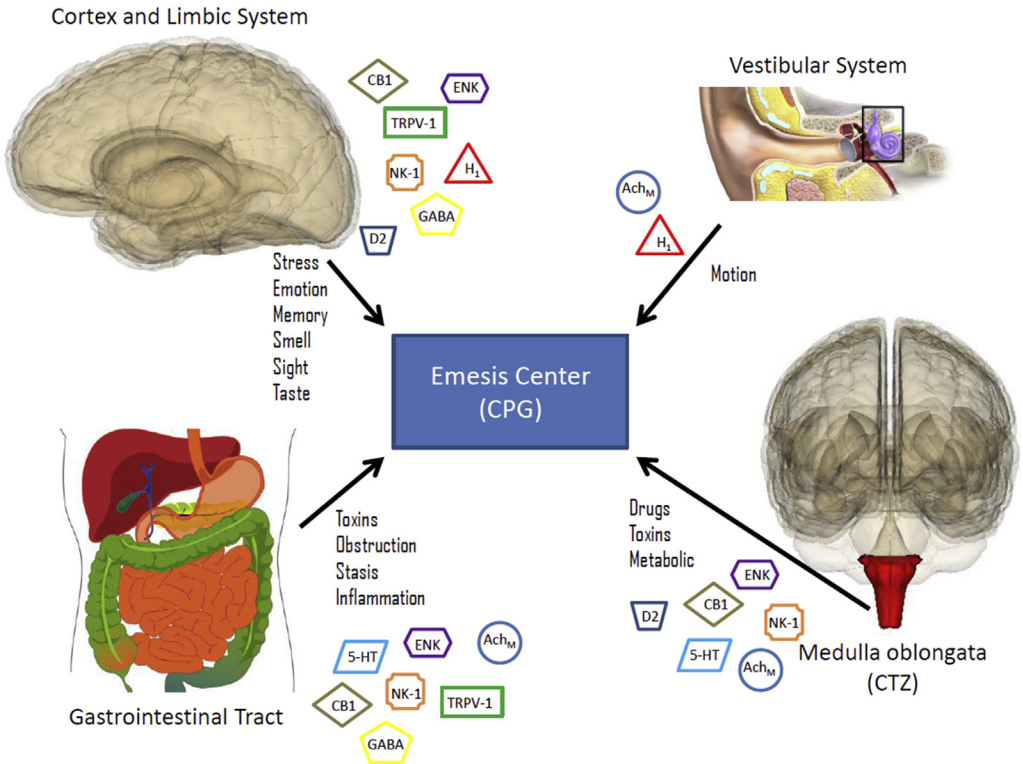

Figure 1. Potential stimuli and receptors involved in central and peripheral pathways of emesis. Adapted from medical images freely available through creative commons license from gallery of Blausen Medical, WikiJournal of Medicine, and WikiMedia Commons. 5-HT = serotonin; Ach_M = acetylcholine (muscarinic); CB1 = cannabinoid; CPG = central pattern generator; CTZ = chemoreceptor trigger zone; D_2 = dopamine; ENK = enkephalinergic (opioid); GABA = gamma-aminobutyric acid; H_1 = histamine; NK-1 = neurokinin; TRPV-1 = transient receptor potential vanilloid-1.

receptors, and may inhibit serotonin release via presynaptic CB_1 receptors (21). The activation of CB_1 receptors in the medulla inhibits gastric motor function and proemetic dopamine activity in the CNS (22,23). This in turn enables the stomach to accommodate food intake, which is helpful in patients with chronic disease states or those undergoing chemotherapy.

Table 1. Diagnosis of Cannabinoid Hyperemesis Syndrome: Proposed Clinical Criteria*

Essential for Diagnosis
Long-term cannabis use
Major features
Severe cyclic nausea and vomiting
Resolution with cannabis cessation
Relief of symptoms with hot showers or baths
Abdominal pain: epigastric our periumbilical
Weekly use of marijuana
Supportive features
Age <50 years
Weight loss of >5 kg
Morning predominance of symptoms
Normal bowel habits
Negative laboratory and radiographic and endoscopic test results

* Adapted from Simonetto et al. (20).

Several theories have been proposed to explain this paradox, such as downregulation, desensitization, or internalization of CB_1 receptors in response to chronic cannabis use (11,12). This may abnormally influence the HPA axis and sympathetic nervous system stress response, which may in turn induce hyperemesis (19). Cannabinoids are highly lipophilic, possess a long half-life, and over time accumulate in the CNS and peripheral adipose tissue (24). Another theoretical pathophysiologic mechanism is the metabolism or degradation of these stored cannabinoids into proemetic compounds capable of altering gastrointestinal motility (11,12). Genetic differences in the cytochrome P450 system may lead to the accumulation of cannabinoid metabolites in certain individuals, and this may explain why many chronic cannabis users do not experience CHS (19,25). Sympathetic system activation from stress or fasting results in lipolysis and release of stored cannabinoids, which may precipitate hyperemesis (19,26). The cannabis plant contains >400 different chemicals that accumulate in the body over time and may be emetogenic (24). Alternatively, cannabis withdrawal has also been proposed as a factor in CHS (27). Potential reasons for the increasing prevalence of CHS includes

increased availability and worldwide use of cannabis in the past decade and the development of highly potent strains with supranormal levels of Δ9-tetrahydrocannabinol, which has tripled from 4% to 12% since 1995 (28).

CHS Treatment Options

Standard antiemetics such as ondansentron and prochlorperazine are some of the most commonly used medications in acute care settings (14). A recent systematic review of pharmacologic treatment of CHS concluded that these drugs alone are frequently ineffective, and alternative agents used off-label, such as benzodiazepines, haloperidol, and topical capsaicin cream, have the greatest efficacy based mainly on cases series and reports (Table 2) (29). Another important consideration in the ED is that the selected agents may be administered parenterally, rectally, sublingually, or topically, because CHS patients may be unable to tolerate oral medication and will often require IV crystalloid hydration and electrolyte correction.

Dopamine antagonists. Activation of dopamine receptors D_2 and D_3 in the medulla is involved in the pathophysiology of emesis, and antagonists such as

Table 2. Published Studies to Date of the Pharmacologic Treatment of Acute Cannabinoid Hyperemesis Syndrome*

	Level of Evidence†	No. of Studies	Monotherapy Studies	Total No. of Subjects	Successful Treatment
Dopamine antagonists					
Metoclopramide	IV, V	23	3	46	4
Promethazine	II, IV, V	9	0	24	2
Haloperidol	IV, V	7	0	11	9
Prochlorperazine	IV, V	5	0	8	N/A
Olanzapine	III, IV	2	0	42	1
Chlorpromazine	IV, V	2	0	5	N/A
Propranolol	V	1	1	1	N/A
Chlorprothixene	III	1	0	36	N/A
Domperidone	V	1	0	1	N/A
Droperidol	V	1	0	1	N/A
Serotonin antagonists					
Ondansetron	II, III, IV, V	25	7	64	4
Granisetron	V	2	0	2	N/A
Antihistamines/anticholinergics					
Diphenhydramine	II, IV, V	3	0	13	1
Dimenhydrinate	V	2	0	2	N/A
Scopolamine	V	1	0	1	N/A
Clidinium	V	1	0	1	N/A
Hydroxyzine	III	1	0	36	N/A
Benzodiazepines					
Lorazepam	II, III, IV, V	12	1	36	21
Unspecified	II, III, IV	5	1	55	N/A
Diazepam	V	4	0	10	1
Alprazolam	IV, V	4	1	13	1
Clonazepam	IV	1	0	2	N/A
Chlordiazepoxide	V	1	0	1	N/A
Corticosteroids					
Dexamethasone	V	2	0	2	N/A
Unspecified	V	1	0	1	N/A
$TRPV_1$ agonists					
Capsaicin	IV, V	5	2	22	22
Opioids					
Morphine	III, IV, V	10	1	20	3
Hydromorphone	IV, V	2	0	9	1
Fentanyl	V	1	0	1	1
Tramadol	V	1	0	1	N/A
Methadone	V	1	0	1	1
Unspecified	IV	1	0	2	N/A

N/A, not applicable (treatment unsuccessful, unclear, or not documented); $TRPV_1$, transient receptor potential vanilloid-1.
* The small number of monotherapy articles and documented cases of successful treatment highlights the difficulty in treating this complex disorder. Adapted from Richards et al. (29).
† Based on Oxford Centre for Evidence-Based Medicine levels of evidence 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.

metoclopramide, prochlorperazine, promethazine, and trimethobenzamide are commonly used IV antiemetics (14). These drugs act on the dopaminergic regulation of the chemoreceptor trigger zone and have prokinetic effects on the motor function of the gastrointestinal tract. Several case series and reports have described the use of these standard dopamine antagonists for the treatment of CHS with variable success, often necessitating the use of several different unrelated antiemetics (7–9,25,29–55).

The butyrophenone haloperidol is a dopamine antagonist marketed as an oral and intramuscular (IM) antipsychotic, but it is frequently used off-label as an IV antiemetic (56). Haloperidol is an effective sedative and is commonly used for agitated patients in the ED (57). Its antipsychotic effects are caused by the antagonism of D_2 receptors in the mesolimbic and mesocortical pathways. Haloperidol has been used to terminate hyperemesis in CHS patients, and this may reflect its unique pharmacology with regard to sedation relative to the other more commonly used dopamine antagonists (34,36,46,54,58,59). In addition to its CNS effects, interactions between dopamine and CB_1 signaling mechanisms may be another explanation for the efficacy of haloperidol for this indication (23,60,61). Cannabis use may precipitate acute psychosis and unmask early schizophrenia symptoms, and antipsychotics such as haloperidol are efficacious for this adverse effect (62,63). It is interesting that the other butyrophenone droperidol, unlike haloperidol, is labeled for use as an antiemetic but has only appeared in 1 case report to date for the treatment of CHS (42). This may reflect restrictions upon its use from a controversial 2001 U.S. Food and Drug Administration black box warning of the drug's potential for QT prolongation, which was based on a handful of cases for whom extremely large doses were administered (64). There has not been a single case report in which droperidol at antiemetic dosage range ($\leq$2.5 mg IV/IM) has been associated with QT prolongation, dysrhythmias, or cardiac arrest (65). It is also important to note that the black box warning does not apply to doses <2.5 mg IV/IM (66). Other possible adverse side effects from dopamine antagonists include oversedation, extrapyramidal effects, neuroleptic malignant syndrome, hypotension, seizures, and agranulocytosis (14).

As mentioned earlier, sympathetic nervous system dysfunction and altered stress response have been proposed as potential contributory factors in CHS, thus making these patients more sensitive to emetogenic signals (16,19). The hyperemesis phase of CHS is often accompanied by tachycardia, hypertension, hot flashes, diaphoresis, and trembling, which are signs and symptoms attributed to sympathetic nervous system actuation. Patients with CHS often present to the ED in the early morning, which suggests that circadian variation of sympathetic nervous tone may also play a role (17). As such, dopamine antagonists with greater sedative properties, such as haloperidol, may be advantageous. The later-generation antipsychotic olanzapine has been reported to be an effective antiemetic for chemotherapy-induced nausea and vomiting but has appeared in only 2 articles for treatment of CHS (36,67,68). Lipophilic, nonspecific β-blockers may also be useful in this regard, and propranolol has been successfully used for the termination of CHS and CVS (69,70).

Serotonin antagonists. Serotonin, or 5-HT, is an important proemetic neuroendocrine transmitter (17). Enterochromaffin cells in the gastrointestinal tract release serotonin in response to pressure or noxious substances, activating afferent sensory neurons. Submucosal neurons are specifically activated by 5-HT_1P subtype receptors, whereas external afferent vagal neurons leading to the medulla are activated by 5-HT_3 subtype receptors. Potential antiserotonergic agents approved for IV use as an antiemetic and available in the ED include 5-HT_3 antagonists such as ondansetron, dolasetron, and granisetron. These have been used to treat CHS in numerous case series and reports, but details of efficacy are limited, and many describe the use of multiple alternative agents to achieve termination of hyperemesis (7,25,29–34,36,37,40,42–45,47–49,52–54,58,59,70–82).

Other drugs with antiserotonergic properties that are not available for parenteral use include cyproheptadine, a serotonin antagonist and antihistamine, as well as tricyclic antidepressants, which have been successfully used in the long-term treatment and prophylaxis of CVS (30,83). In general, serotonin antagonist antiemetics have been shown to have minimal significant side effects, most commonly headache, diarrhea, and fatigue. Transient elevation of hepatic enzyme levels has also been reported, as well as asymptomatic QT prolongation and QRS widening (14).

Antihistamines and anticholinergics. Antihistamines, such as diphenhydramine, meclizine, and dimenhydrinate, antagonize the action of histamine at the H_1 receptor. Anticholinergic agents, such as atropine and scopolamine, are muscarinic receptor antagonists inhibiting the action of acetylcholine. Both antihistamines and anticholinergics are effective for prophylaxis of motion sickness by blocking stimulation of the medullary vomiting center via the vestibular system of the middle and inner ear but have minimal effect on visceral stimulation (13,14). Compared to other classes of antiemetics, there are few published reports in which antihistamines were used for CHS, and none described

successful termination of hyperemesis using a single agent (31,34,42,43,48,52,68). There was 1 article detailing the use of the anticholinergic scopolamine (43). Both classes of medication are associated with significant CNS side effects, such as sedation, dizziness, incoordination, fatigue, dry mouth, urinary retention, blurred vision, and exacerbation of narrow-angle glaucoma (14).

Benzodiazepines. Gamma-aminobutyric acid (GABA) and its receptors are located in the CNS and the gastrointestinal tract, and affect motility and mucosal homeostasis as well as the release of histamine, acetylcholine, serotonin, and prostaglandins (17,84). Exogenous cannabinoids reduce GABAminergic neurotransmission, increase extracellular GABA, enhance dopamine release in both the striatum and mesolimbic systems, and decrease extracellular glutamate (85–88). These effects may result in symptoms of paranoia, anxiety, and tremors experienced by some cannabis users. Abrupt cannabis cessation has led to catatonia from GABA and dopamine D_2 receptor hypoactivity and glutamate *N*-methyl-D-aspartate receptor hyperactivity, which has been successfully treated with benzodiazepines (89,90). Benzodiazepines have GABA receptor agonist–like properties with antiemetic effects through the inhibition of medullary and vestibular nuclei associated with nausea and emesis, and possibly of the gastrointestinal tract as well (84). The anxiolysis and sedation produced by benzodiazepines are also useful in this regard, especially in the setting of abnormal sympathetic nervous system response to stress. For treatment of CHS, benzodiazepines, most commonly lorazepam, were used in several articles (6,7,29–33,35,36,38,39,42,49,54,55,59,68,71,75,76,91–94). The adverse CNS side effects with benzodiazepines include oversedation, hypoventilation, dizziness, confusion, and incoordination.

Corticosteroids. Corticosteroids, such as dexamethasone and methylprednisolone, have been used as antiemetics for chemotherapy-induced nausea and emesis for several decades, but their mechanisms of action are still unknown (14). Some theories include antagonism of 5-HT_3 receptors, inhibition of serotonin and endogenous opioid release, activation of glucocorticoid receptors in the nucleus tractus solitarius, and inhibition of prostaglandin synthesis (17). The use of corticosteroids for the treatment of CHS appears in only 3 articles in which multiple agents were administered (44,45,95). Adverse short-term side effects include elevated blood glucose and psychosis, and long-term side effects include adrenal suppression, immunosuppression, delayed wound healing, and gastritis (14).

Capsaicin. Capsaicin, or 8-methyl-*N*-vanillyl-6-nonenamide, is a chemical found in several species of chili pepper that binds to transient receptor potential vanilloid-1 ($TRPV_1$) receptors. TRPV1 receptors are found throughout the body, often in proximity to CB_1 receptors, which suggests a functional interaction (96). These areas include the gastrointestinal tract and medullary vomiting center. $TRPV_1$ receptors are activated by low pH and high temperature and may regulate release of substance P, an important mediator of nausea and emesis, from sensory nerves (97). As such, $TRPV_1$ receptors have a theoretical role in the efficacy of hot showers/baths for symptomatic relief of CHS (98). Capsaicin is available as a topical cream that produces a sensation of heat on contact with skin. A small number of CHS cases treated with topical capsaicin in the ED have been reported (99–102). Side effects of capsaicin are most commonly skin irritation and blistering at the site of application. The neurokinin-1 (NK1) receptor antagonist aprepitant has been used as an antiemetic in children with CVS (103). The NK1 receptor is the endogenous receptor for substance P. Aprepitant is only available in oral form, and it has not appeared in any published articles for treatment of CHS to date.

Opioids. The endogenous opioid system consists of μ, δ, and κ opioid receptors and associated ligands, such as enkephalins and endomorphins, which are found widely throughout the body, including the gastrointestinal tract (104). Nausea and emesis are common side effects of opioids, and the mechanism is not completely understood (105). Some theories include opioid receptor activation in the chemoreceptor trigger zone, enhanced sensitivity of the vestibular system, and delayed gastric emptying (104). Opioid receptor antagonists, such as naloxone and alvimopan, have been studied for their antiemetic properties (104,105). However, these drugs reverse centrally mediated analgesia from both exogenous and endogenous sources. As such, opioid antagonists are inappropriate for patients with CHS, who frequently have concomitant abdominal discomfort. Opioids have been used in the treatment of CHS in several cases in which multiple agents were used (25,31,32,49,55,58,71,72,75,76,93,95,106–108). Because there is the potential to worsen hyperemesis and promote addictive behavior over multiple acute care visits, opioids should be used with caution in the treatment of CHS.

Hot shower or bath. Although not a pharmacologic or routine ED treatment, hot showers and bathing were mentioned in most articles regarding CHS as universally effective at abating CHS. Several theories have been suggested to explain this mechanism. One theory is the dose-dependent hypothermic effect of cannabinoids binding to

CB_1 receptors of the hypothalamus, the thermoregulatory center of the brain (19,98). "Cutaneous steal" syndrome is another putative mechanism in which cutaneous vasodilation from hot water alters core temperature and splanchnic circulation, thus lessening abdominal discomfort (11,94). Another possibility is that the dysphoria and anxiety associated with CHS may be subjectively relieved with hot showering or bathing (19,98).

Cessation and rehabilitation. Cessation of cannabis should be emphasized by the treating clinician as the only proven cure for CHS (109). Patients may be surprised to learn that the root cause for their episodic hyperemesis is long-term cannabis use, which may prevent future attempts at self-treatment with more cannabis (110). A discussion of how these patients integrate cannabis into their daily routine and social structure may be revealing with regard to cessation strategies. Information regarding local rehabilitation programs or specialists focusing on cannabis addiction should be provided if possible. Psychiatric treatment may be indicated if there is evidence of affective disorder, psychosis, or if the patient expresses interest in long-term treatment with benzodiazepines or tricyclic antidepressants, which may have efficacy. However, cannabis avoidance is the least risky way forward. Abstinence leading to sobriety is the best option to prevent recurrence.

CONCLUSION

As the legalization and availability of high-potency cannabis continues to increase, ED visits and hospital admissions for CHS and other cannabis-related disorders will likely rise in parallel. Despite the increasing prevalence of CHS, there is a limited body of high-quality research involving its pathophysiology and best pharmacologic treatment. Although standard antiemetics may be tried initially, treatment failure should be anticipated, as suggested by the large number of case studies and reports in which multiple unrelated agents were required. Parenteral benzodiazepines represent a logical choice for treatment of CHS, because hyperemesis may be precipitated by stress in patients with pre-existing abnormal HPA axis feedback and sympathetic nervous system response from chronic cannabis use. Haloperidol has been used off-label as an antiemetic in several case reports and may be advantageous because of its powerful sedating effects. Droperidol represents another potential agent, because it has been approved by the U.S. Food and Drug Administration as an antiemetic at doses to which the black box warning does not apply. Topical capsaicin also holds promise based on an entirely different pharmacologic mechanism.

Future studies are greatly needed to further define the etiology of CHS, which in turn should help define targeted pharmacologic treatment. Recognition of CHS and its resistance to standard antiemetic therapy will obviate extensive and futile diagnostic testing and irrelevant treatment in the ED and hospital wards, reduce morbidity, and decrease health care costs. Clinicians caring for CHS patients willing to consider cessation should also provide them with appropriate resources, because discontinuation of cannabis use is curative.

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ARTICLE SUMMARY

1. Why is this topic important?

Cannabis is used daily by millions of Americans. Cannabinoid hyperemesis syndrome (CHS) is becoming more prevalent as cannabis legalization, use, and potency increases. Emergency physicians should be aware of this complex clinical problem and its treatment options.

2. What does this review attempt to show?

This review provides a concise exploration of the physiology and pathophysiology that underlies the nausea and emesis of CHS (much of which is theoretical), and the best evidence linking drugs' mechanism of actions with pharmacological treatment of acute episodes of CHS in the emergency department.

3. What are the key findings?

Standard antiemetics often fail to terminate hyperemesis in CHS patients, who may have disordered hypothalamic–pituitary–adrenal axis and sympathetic nervous system responses to stress. As such, sedating agents such as benzodiazepines and antipsychotics appear to be the most efficacious. Topical capsaicin may also be effective based on entirely different pharmacodynamics.

4. How is patient care impacted?

Patients with CHS may be misdiagnosed and subjected to extensive and unnecessary laboratory testing, imaging, and procedures. This increases risks to the patient, duration of stay, and total health care costs to society. Questions regarding chronic cannabis use and frequent hot showering are facile methods to identify these patients in the emergency department to initiate appropriate directed care. Patients with emesis refractory to standard antiemetic agents should be queried about recent marijuana or other cannabinoid use, and potentially evaluated by screening for common drugs of abuse to detect cannabis use when CHS is suspected.