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Cannabinoid Hyperemesis Syndrome

Jonathan A. Galli, MD, **Ronald Andari Sawaya, MD**, and **Frank K. Friedenberg, MD**
Department of Gastroenterology, Temple University School of Medicine, Philadelphia, PA

Abstract

Coinciding with the increasing rates of cannabis abuse has been the recognition of a new clinical condition known as Cannabinoid Hyperemesis Syndrome. Cannabinoid Hyperemesis Syndrome is characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and frequent hot bathing. Cannabinoid Hyperemesis Syndrome occurs by an unknown mechanism. Despite the well-established anti-emetic properties of marijuana, there is increasing evidence of its paradoxical effects on the gastrointestinal tract and CNS. Tetrahydrocannabinol, cannabidiol, and cannabigerol are three cannabinoids found in the cannabis plant with opposing effects on the emesis response. The clinical course of Cannabinoid Hyperemesis Syndrome may be divided into three phases: prodromal, hyperemetic, and recovery phase. The hyperemetic phase usually ceases within 48 hours, and treatment involves supportive therapy with fluid resuscitation and anti-emetic medications. Patients often demonstrate the learned behavior of frequent hot bathing, which produces temporary cessation of nausea, vomiting, and abdominal pain. The broad differential diagnosis of nausea and vomiting often leads to delay in the diagnosis of Cannabinoid Hyperemesis Syndrome. Cyclic Vomiting Syndrome shares several similarities with CHS and the two conditions are often confused. Knowledge of the epidemiology, pathophysiology, and natural course of Cannabinoid Hyperemesis Syndrome is limited and requires further investigation.

Keywords

Cannabinoid Hyperemesis Syndrome; Cannabis; Marijuana; Nausea; Vomiting

Epidemiology and Introduction

Cannabis is the most commonly used illicit drug in the United States with over 16.7 million users in 2009 [1]. The 18–25 year old age group has the highest prevalence of marijuana use [1]. Each year 2.6 million Americans become new users. The majority of these individuals are less than nineteen years of age [2]. Similarly in Europe, cannabis use is prominent among young adults, with a prevalence that has increased from 5% in 1990 to 15% in 2005 [3]. While the overall prevalence of marijuana use has remained stable in the United States at 4%, the prevalence of cannabis use disorders (i.e. cannabis dependence, cannabis abuse) has continued to rise [4]. Risk factors for developing cannabis use disorders include male race, lower income, living in a Western culture, and being separated, divorced, or widowed [5].

Coinciding with the increasing rates of cannabis abuse has been the recognition of a new clinical condition known as Cannabinoid Hyperemesis Syndrome (CHS). The syndrome was first described in 2004 by Allen and colleagues and is characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and the learned behavior of hot bathing [6]. This

Contact Info: Frank K. Friedenberg, MD, MS (Epi), Temple University Hospital, 3401 North Broad Street, Philadelphia, PA, 19140, Phone: 215-707-4391, Fax: 215-707-2684.

review will provide an overview of cannabinoid pharmacology that focuses on the properties that may contribute to CHS. We review a clinical description of CHS and a proposed clinical evaluation including differential diagnosis and treatment modalities. We conclude with a discussion regarding the shortcomings in our knowledge and suggestions for areas of future research

Pharmacology of Cannabinoids

The Cannabinoid Receptors

Two distinct cannabinoid receptors, CB_1 and CB_2, have been identified in human and animal models. The CB_1 and CB_2 receptors function as G-protein coupled receptors that act by inhibiting adenylate cyclase [7]. In the brain, CB_1 receptors are localized to the cerebral cortex, hypothalamus, anterior cingulate gyrus, hippocampus, cerebellum, and basal ganglia [8]. In the gastrointestinal system, CB_1 receptors are found on both intrinsic and extrinsic neurons, with the enteric nervous system serving as the major site of action [9]. Other organs where CB_1 receptors have been identified are the spleen, heart, liver, uterus, bladder, and vas deferens [10]. In comparison, much less is known about the effects of the CB_2 receptor. CB_2 receptors are expressed primarily by immune cells [11]. In the gastrointestinal system, CB_2 receptors are expressed by lamina propria plasma cells and activated macrophages, as well as by the myenteric and submucosal plexus ganglia in human ileum [9,12,13]. CB_2 receptors are likely involved in the inhibition of inflammation, visceral pain, and intestinal motility in the inflamed gut [9,14].

The Endogenous Cannabinoids (Endocannabinoids)

Along with the discovery of the CB_1 and CB_2 receptors has been the identification of endogenous arachidonic acid derivatives that bind to these receptors (Figure 1). These compounds are referred to as endogenous cannabinoids, or endocannabinoids. The best characterized endocannabinoids are anandamide and 2-arachidonylglycerol (2-AG) [9]. The endocannabinoids are present in both the central nervous system [8] and enteric nervous system [15]. Anandamide and 2-AG are released locally on demand by neurons, are present in small quantities, and undergo rapid inactivation [8]. Endocannabinoids are thought to act as either neuromodulators or neurotransmitters [11]. Anandamide and 2-AG possess similar biochemical structures, but each has a distinct pathway for biosynthesis and degradation. Anandamide is synthesized from the precursor *N*-arachidonoyl phosphatidylethanolamine, while 2-AG is produced from an inositol-1,2-diacylglycerol precursor [8,16,17]. The metabolism of anandamide is principally carried out via fatty acid amide hydrolase (FAAH), whereas the major enzyme metabolizing 2-AG is monoacylglycerol lipase (MAGL) [18].

The Exogenous Cannabinoids

Δ^9-tetrahydrocannabinol (THC) is the principle active compound in cannabis (Figure 1). The metabolism of THC occurs mainly in the liver via oxidation and hydroxylation reactions. In humans this is carried out largely by the CYP2C isoenzyme subfamily of the cytochrome P450 complex [19]. The true elimination plasma half-life of THC has been difficult to calculate, but several studies have estimated it to be in the range of 20–30 hours [20]. THC is excreted mainly as acid metabolites, with 60–85% cleared through the feces and 20–35% in the urine [20,21].

THC accumulates largely within body fat which serves as a long-term storage site for the drug [20,22]. This characteristic partially explains its prolonged elimination half-life. A large reservoir of stored THC in fat tissue may produce a “reintoxication effect” secondary to increased lipolysis during times of increased stress or food deprivation [23]. These characteristics of THC may have implications in Cannabinoid Hyperemesis Syndrome as

these patients are chronic users of cannabis who likely have large lipid stores making them susceptible to increased cannabinoid levels in the plasma during times of stress.

Nearly 100 different metabolites have been identified for THC [24]. The two major metabolites found in humans are 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-THC- Δ^9-tetrahydrocannabinol (THC-COOH) [20]. 11-OH-COOH is a psychotropic metabolite that is equipotent to THC in terms of producing psychic effects and lowering intraocular pressure [25]. THC-COOH, in contrast, is a non-psychotropic metabolite that possesses anti-inflammatory and analgesic properties [26].

Cannabidiol (CBD) and cannabigerol (CBG) are two additional cannabinoids found in cannabis that appear to modulate the anti-emetic properties of THC. Cannabidiol, in contrast to THC, is non-psychotropic, has a low affinity for CB_1 and CB_2 receptors [27], and acts as a partial agonist at the 5-HT_{1A} receptor [28]. CBD enhances the expression of CB_1 receptors in the hypothalamus and amplifies the hypothermic effects caused by THC [29]. In animals the effect of CBD on toxin-induced vomiting displays a biphasic response with low doses producing an anti-emetic effect whereas higher doses enhance vomiting [30,31].

Cannabigerol (CBG) is a non-psychotropic cannabinoid that behaves as an antagonist at both the CB_1 and 5-HT_{1A} receptors [32]. This antagonism reverses the anti-emetic actions of low-dose CBD, which likely occurs at the 5-HT_{1A} receptor [33]. The pro-emetic properties of CBD (at higher doses) and CBG may play a role in the severe nausea and vomiting observed in patients with Cannabinoid Hyperemesis Syndrome (Figure 2).

The Effects of Cannabinoids in the Brain

Δ^9-tetrahydrocannabinol (THC) has several well-established effects in the central nervous system, such as alteration of psychomotor behavior, impairment in short-term memory, stimulation of appetite, and analgesia [8]. Rimonabant, a CB_1 antagonist, blocks the appetite stimulating qualities of the cannabinoids in the hypothalamus and has been marketed for the treatment of obesity and metabolic dysfunction [34]. THC exhibits an anti-emetic effect in the central nervous system. In animal models, CB_1 receptor activation in the dorsal vagal complex of the brainstem mediates this effect [35,36]. Dronabinol (synthetic THC) and nabilone (a CB_1 receptor agonist) are two commercially available cannabinoids for the treatment of chemotherapy-induced nausea and vomiting [37].

In the brain, the cannabinoid system helps regulate several aspects of the endocrine system. CB_1 receptor activation in the hypothalamus and pituitary gland results in modulation of all hypothalamic-pituitary axes [38]. Receptor activation leads to inhibitory effects on the release of growth hormone, thyroid hormone, prolactin, and luteinizing hormone [38]. In animal studies mice lacking CB_1 receptors demonstrate enhancement in circadian HPA axis activity peaks and impairment in glucocorticoid feedback [39].

The Effects of Cannabinoids in the Gastrointestinal System

The gastrointestinal actions of cannabinoids are mediated chiefly by CB_1 receptors (Figure 2). Activation of CB_1 receptors result in inhibition of gastric acid secretion, lower esophageal sphincter relaxation [40], altered intestinal motility [41,42], visceral pain, and inflammation [9,43]. CB_1 receptor activation reduces gastric motility and results in delayed gastric emptying in rat models [44,45]. In humans, THC given at doses used to prevent chemotherapy-induced nausea and vomiting causes a significant delay in gastric emptying [46]. These findings in humans are further supported by a randomized, placebo-controlled trial with dronabinol that resulted in a significant delay in gastric emptying [47]. In comparison to other adverse effects associated with cannabinoids, delayed gastric emptying appears to be particularly resistant to the development of tolerance [48]. Additionally,

intermittent administration of THC results in hypersensitization of the delayed gastric emptying effect [49]. THC's effect on gastric motility is a paradox, as a delay in gastric emptying would be expected to promote nausea and vomiting [50]. However, nausea and vomiting traditionally do not occur with cannabis use, likely due to the anti-emetic properties of THC on the central nervous system.

Clinical Presentation, work up and differential diagnosis of Cannabinoid Hyperemesis Syndrome

Two case series and numerous individual case reports have been published on Cannabinoid Hyperemesis Syndrome (CHS) (Table 1). Patients present with recurrent episodes of nausea, vomiting, and dehydration with frequent visits to the emergency department. [6,51–62]. Patients are typically young adults with a long history of cannabis use. In nearly all cases there is a delay of several years in the onset of symptoms preceded by chronic marijuana abuse [6]. In one study the average duration of cannabis use prior to onset of recurrent vomiting was 16.3 ± 3.4 years [62]. There are at least four reported cases where the time lag was equal to or less than three years [54,59,60]. Daily marijuana use is characteristic and often reported as exceeding three to five times per day.

CHS is a recurrent disorder interspersed with symptom-free intervals. It has been proposed to divide CHS into three phases: pre-emetic or prodromal, hyperemetic, and recovery phase [6,62]. The prodromal phase can last for months or years with patients developing early morning nausea, a fear of vomiting, and abdominal discomfort [62]. In this stage patients maintain normal eating patterns, and may increase or continue the use of cannabis because of the believed beneficial effects on relieving nausea [52,56]. The hyperemetic phase is characterized by paroxysms of intense and persistent nausea and vomiting, commonly described as overwhelming and incapacitating. Patients vomit profusely, often without warning and can vomit and retch up to five times per hour [62]. Most patients also present with diffuse but relatively mild abdominal pain. In one series approximately 70% of patients reported marked weight loss of at least 5 kg during their illness [6]. In the emergency department patients are found to be dehydrated but hemodynamically stable. They undergo an extensive diagnostic work up, including laboratory and imaging studies which, in the majority of cases, are unrevealing. During the hyperemetic phase patients stereotypically take numerous hot showers throughout the day. This idiosyncratic behavior appears to be learned and is repeatedly used as the only alleviating measure to control symptoms and rapidly becomes a compulsive behavior. The recovery phase can last for days, weeks, or months and is associated with relative wellness and normal eating patterns. Weight is regained and bathing returns to regular frequency.

Patients with CHS usually remain misdiagnosed for a considerable time period. In one case series the average number of emergency room visits (7.1 ± 4.3) prior to diagnosis and the delay in diagnosis (for up to 9 years) was substantial [62]. Not surprisingly, the early identification of patients with CHS leads to a reduction in morbidity and costs [6]. The differential diagnosis of nausea and vomiting is extensive and includes a broad range of pathologic conditions affecting the gastrointestinal tract, the peritoneal cavity, CNS, as well as endocrine and metabolic functions [63]. The initial approach to evaluate a patient with cyclical vomiting should start by excluding these vast disorders. In this context a comprehensive history along with initial screening tests should be performed to exclude acute conditions and emergencies (e.g pancreatobiliary disease, intestinal obstruction, pregnancy, etc). This includes laboratory tests (complete blood count and differential, glucose, basic metabolic panel, pancreatic and hepatic enzymes, pregnancy test), urinalysis, urinary drug screen, and plain flat radiographic series [63,64].

Further imaging and invasive testing must be tailored to the individual presentation. For example, associated symptoms like hematemesis should prompt an upper endoscopy, neurological findings would support brain imaging, and pronounced abdominal tenderness justifies an abdominal CT or abdominal radiographic series [64]. In the absence of positive findings on these diagnostic workups the possibility of an underlying motility disorder such as gastroparesis, intestinal pseudo-obstruction or small bowel dysmotility should be considered [63].

In clinical practice CHS is most often confused with cyclic vomiting syndrome (CVS). In fact patients with CHS are often mislabeled as having CVS and vice versa. Confusion exists in the medical literature secondary to a failure to recognize chronic marijuana use as a source of vomiting. For example, in two recently published series of adult patients with CVS, approximately one third of patients reported daily marijuana use [65,66]. Based on the categorization of functional disorders developed by Rome III, chronic marijuana use (CHS) is recognized as a mechanism for nausea and vomiting distinct from CVS [67]. Although both conditions share an astonishing similarity, there are several significant differences. For example, CVS patients usually have important psychological comorbidities including depression and anxiety [64,65]. In addition, CVS patients have a high prevalence of migraine headaches or a family history of migraines. Furthermore, gastric emptying rates in patients with CVS are often accelerated rather than delayed [46,65]. Table 2 summarizes some of the epidemiological and clinical characteristics that may help distinguish CVS and CHS.

Treatment

The treatment of Cannabinoid Hyperemesis Syndrome can be divided into therapy for the hyperemetic phase and the prevention of relapse. Patients may require hospitalization during the hyperemetic phase secondary to abdominal pain, volume depletion, and severe nausea and vomiting. Supportive therapy, albeit not very effective, serves as the mainstay of treatment during this phase of the syndrome [6,53,62]. For volume depletion aggressive resuscitation with intravenous fluids is needed [6,59,61,62]. Anti-emetic therapy can be tried with 5-HT_3 receptor antagonists, D_2 receptor antagonists, H_1 receptor antagonists, and neurokinin-1 receptor antagonists. However, all have been shown to provide minimal or no improvement in most patients with CHS [54–58,62,68]. Narcotics have also been attempted in a few cases to relieve associated abdominal pain [55,57]. Opioids should be used with caution, however, as they have the potential to cause emesis. [69,70]. Esophagogastroduodenoscopy findings from several patients with CHS have revealed varying grades of esophagitis and gastritis [6,54,57,60–62]. As a result, acid suppression therapy with medications such as proton pump inhibitors should be given routinely.

The most effective treatment during the hyperemetic phase of CHS is the use of hot showers by patients. The effects of this learned behavior are temperature-dependent [6], fast acting [6], but short-lived [6,56,62]. Hot showers improve symptoms of nausea and vomiting [6,52–56,60,62,68,71], abdominal pain [6,56,71], and decreased appetite [68] during the hyperemetic phase. The precise mechanism by which hot bathing produces a rapid reduction in the symptoms of CHS is unknown. It has been proposed that hot bathing may act by correcting the cannabis-induced disequilibrium of the thermoregulatory system of the hypothalamus [6]. Darmani has suggested that cannabis increases the core body temperature while concomitantly decreasing skin temperature thus increasing blood flow to the skin and dissipating excess core body heat [72].

The hyperemetic phase of CHS typically lasts for only 24–48 hours [6], but the risk for relapse is high if the patient returns to cannabis use. Case reports have demonstrated a

remission in CHS symptoms upon cessation of cannabis use for extended periods [6,51–54,57,59–62,68,71]. Unfortunately, many of these patients relapse upon resuming cannabis [6,59,61,62]. It has been suggested that many of these patients increase or continue their cannabis use because of their perception that it will have beneficial effects on nausea [52]. Patient education should therefore be provided with emphasis on the paradoxical nature of the symptoms of CHS. Furthermore, some authors have reported referring patients to drug rehabilitation programs in an attempt to raise the likelihood of long-term cannabis cessation [54,71]. Studies have demonstrated the efficacy of outpatient treatment options such as cognitive behavioral therapy and motivational enhancement therapy for marijuana dependence [73].

Shortcomings in our knowledge of CHS and areas for future research

There are several shortcomings in our understanding of CHS. There exists no epidemiological data regarding the incidence and prevalence of CHS among chronic marijuana users. The syndrome is likely underreported given its recent recognition [74,75]. With the large prevalence of marijuana use in the world, why does it appear that so few patients develop CHS? Certain individuals may have a genetic polymorphisms in the cytochrome P450 enzymes responsible for the metabolism of the cannabinoids [62,72]. This could result in excessive levels of pro-emetic cannabinoids or emetogenic metabolites. Such genetic variations have yet to be studied in patients diagnosed with CHS and represent an area for future research.

The mechanism by which cannabis induces hyperemesis is presently unknown. A recent review has explored numerous potential explanations regarding various pharmacokinetic and pharmacodynamic factors of the cannabinoids [72]. The cannabis plant contains over four hundred different chemicals, with sixty possessing cannabinoid structures [76]. The pro-emetic effects of two of these cannabinoids, CBD and CBG, have been discussed in this review and could conceivably play a role in the development of CHS. Additional pharmacological research is needed regarding the pro-emetic effects of additional cannabinoids and their metabolites. Another proposed explanation is that in susceptible individuals the pro-emetic effect of cannabis on the gut (e.g. delayed gastric emptying) overrides its anti-emetic CNS properties [62]. This hypothesis is supported by the demonstration of delayed gastric emptying on gastric emptying scintigraphy in some cases [6,55,62]. Further research is required to investigate the gastrointestinal physiology in these patients during both the acute attacks of hyperemesis and between episodes.

A lack of long-term follow-up is also a major shortcoming in our knowledge of CHS. The majority of reported cases that have provided follow-up included a period of less than one year [6,52,54,56–60,62,68,71]. A greater understanding of the natural course of the syndrome and response to marijuana cessation may be gained with longer lengths of follow-up. Future studies following patients longitudinally for extended periods of time are needed.

Conclusion

Cannabinoid Hyperemesis Syndrome is a new and under recognized clinical entity. Although its prevalence is unknown, numerous publications have preliminarily established its unique clinical characteristics. CHS should be considered as a plausible diagnosis in the setting of patients with recurrent intractable vomiting and strong history of cannabis abuse. Despite the well-established anti-emetic properties of marijuana, there is increasing evidence of its paradoxical effects on the gastrointestinal tract and CNS. Further initiatives are needed to determine this disease prevalence and its other epidemiological characteristics, natural

history, and pathophysiology. Additional treatments are needed and efforts to discontinue cannabis abuse are paramount.

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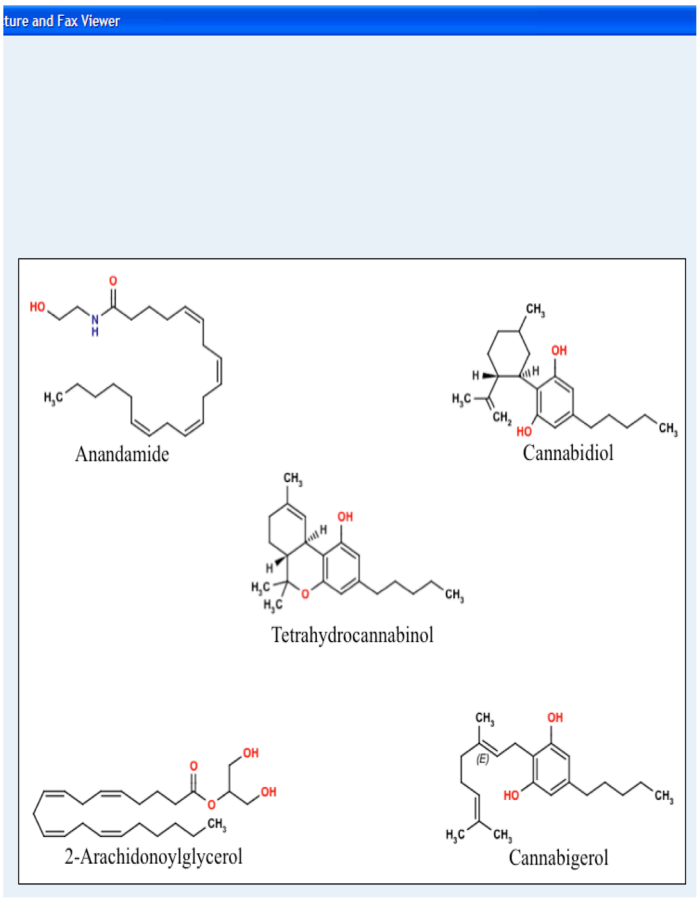

Figure 1.
Two well-characterized naturally occurring endocannabinoids are anandamide and 2-arachidonoylglycerol. Cannabinoids discovered in the cannabis plant with known effects on the regulation of emesis include tetrahydrocannabinol, cannabidiol, and cannabigerol.

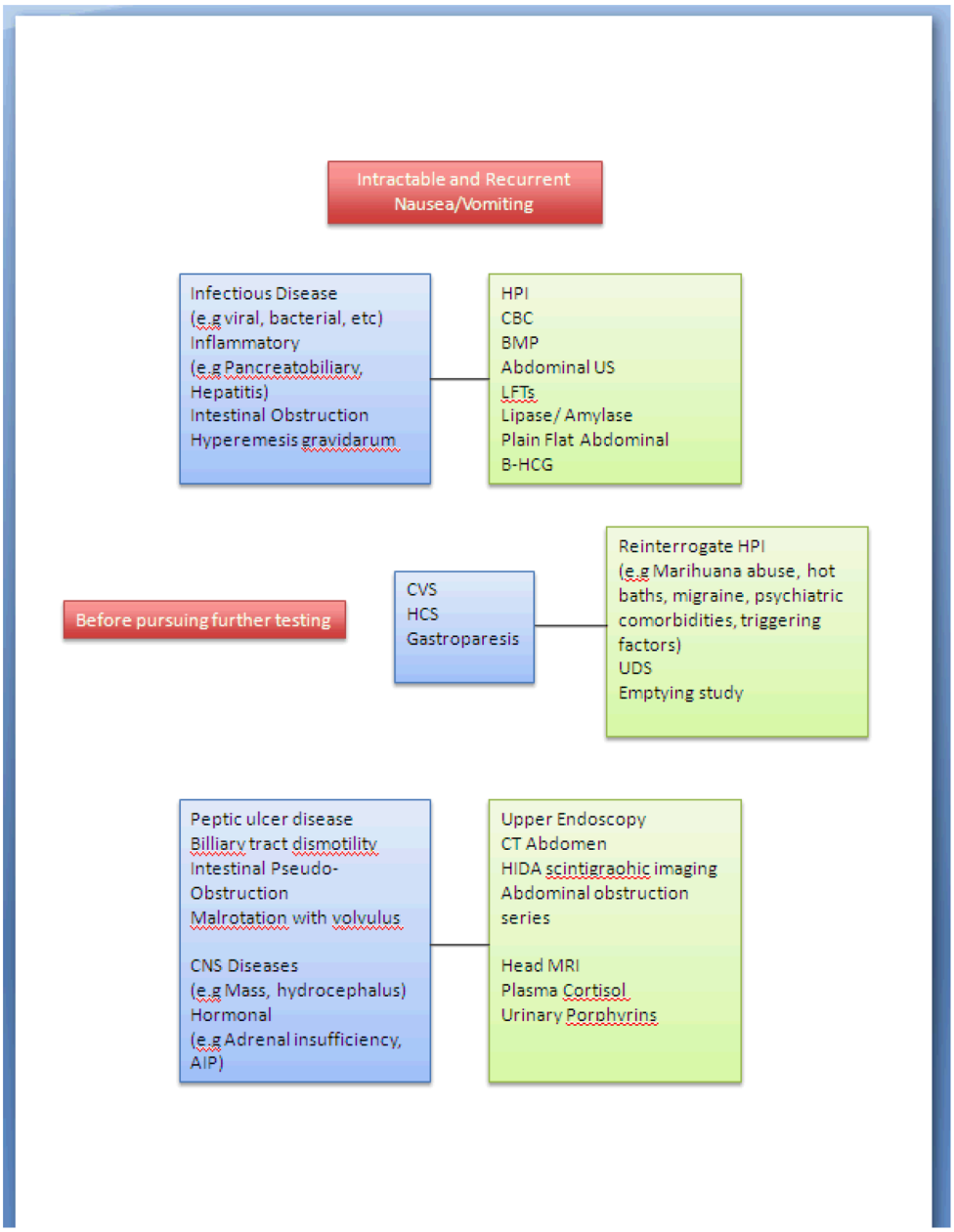

Figure 2.

The cannabinoids demonstrate opposing effects on the emesis response. A disruption in this balance causing the pro-emetic properties to overcome the anti-emetic effects may explain the paradox observed in cannabinoid hyperemesis syndrome. Abbreviations: CBD: cannabidiol, CBG: cannabigerol, THC: tetrahydrocannabinol.

Table 1

Epidemiology, clinical presentation and follow up of patients with Hyperemesis Cannabis Syndrome - Longitudinal case series and individual case reports

Publication	Year	Country	*n*	Gender	Age Started (y)	Frequency (joints/day)	Age of presentation (y)	Illness duration (y)	Prodromal Illness	Abdominal Pain	Hot Bathing (No./day)	Weight Loss (Kg)
Allen J. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse	2004	Australia	9	-	15.7 (12–19)	88% (≥5–10)	24.6 (14–44)	4.7 (0.5–12)	33%	-	77%	66% (≥10)
Soriano M. 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	2010	US	8	M (62.5%)	13.3 (9–20)	75% (≥3–10)	34.1 (21–35)	2.6 (1–8)	100%	100%	100% (≥3–8)	75% (≥10)
Patterson D. Cannabinoid Hyperemesis and compulsive bathing: A case series and paradoxical pathophysiological explanation	2010	US	4	M (100%)	18.7 (15–27)	75% (≥4) *	25.5 (18–39)	4.75 (8m–9)	-	50% *	50%	-
Donnino M. Cannabinoid Hyperemesis: A case series	2009	US	3	M (100%)	33.5 (23–51) *	66% (≥2–4)	29.6 (20–49)	2.3 (2–3)	-	Yes	Yes	-
Miller J. Pediatric Cannabinoid Hyperemesis	2010	US	2	M (50%)	17.5 (17–18)	Daily	16 *	2 *	-	Yes *	Yes	-
Chang Y. Cannabinoid Hyperemesis relieved by compulsive bathing	2009	US	2	-	16 (14–18)	Daily	17 (14–20)	8.5 (7–9)	-	Yes	Yes	-
Seraina M. Cannabinoid hyperemesis syndrome: an underreported entity causing nausea and vomiting of pregnancy	2010	Switzerland	1	F	23	Daily	20	3	-	-	Yes	-
Sannarangappa V. Cannabinoid hyperemesis	2009	Australia	1	M	19	8	24	10	-	-	Yes	-
Sontineni S. Cannabinoid hyperemesis syndrome: Clinical diagnosis of an underrecognised manifestation of chronic cannabis abuse	2009	US	1	M	16	Daily	22	2 months	-	Yes	Yes	-
Watts M. Cannabinoid hyperemesis presenting to a New Zealand hospital	2009	New Zeeland	1	M	18	Daily	29	3	-	Yes	Yes	-
Budhraja V. Cannabinoid Hyperemesis Syndrome: Cyclic vomiting, chronic cannabis use, and compulsive bathing	2008	US	1	M	16	Daily	18	8 months	-	Yes	Yes	-
Wallace D. Cannabinoid hyperemesis: marijuana puts patients in hot water	2007	Australia	1	M	14	≥1g/1–2 day	25	5	-	Yes	Yes	-
Singh E. Cannabinoid Hyperemesis	2006	US	1	M	Childhood	4	43	3	-	Yes	Yes	≥9
Roche E. Cannabinoid hyperemesis: not just a problem in Adelaide Hills	2005	UK	1	-	-	-	-	2	-	-	Yes	-

Publication	Laboratory	UDS (+)	EGD	GES	Psychiatric Dx	Cannabis Cessation (length)	Resolution of Symptoms	Weight Gain (Kg)	Cannabis Resumption	Recurrence of symptoms
Allen J. *et al* 2004	44% (Leukocytosis)	100%	44% (gastritis)	1 (delayed); 2 (normal); rest (N/A)	-	77% (9–48 months)	Yes	66% (≥5)	55%	Yes
Soriano M. *et al* 2010	12.5% (Leukocytosis)	-	75% (esophagitis)	1 (normal)	25% (depression, panic attacks)	62.5% (N/A)	Yes (80%)	80% (≥5)	25%	Yes
Patterson D. *et al* 2010	25% (Hypokalemia)	50% *	75% (gastritis)	-	-	100% (1m-1) °	Yes	-	100%	Yes
Donnino M. *et al* 2009	Hypokalemia	Yes	1 (Normal) *	-	-	66% (2–14 months)	Yes	-	-	-
Miller J. *et al* 2010	Hypokalemia	Yes	Esophageal rings, gastritis	-	ADHD, depression	1 month *	Yes	-	-	-
Chang Y, Windish D. 2009	Leukocytosis	Yes	Normal	Delayed	Bipolar Disorder	-	-	-	-	-
Seraina M. *et al 2010*	Normal	Yes	-	-	Psychogenic vomiting (?)	Yes °	Yes	-	-	-
Sannarangappa V, Tan C. 2009	Leukocytosis, AKI	-	Normal	-	-	2◆	-	-	-	-
Sontineni S. *et al* 2009	Normal	Yes	Esophagitis, Hiatal hernia	-	-	Yes °	Yes	-	-	-
Watts M. 2009	Normal	-	Normal	-	-	-	-	-	-	-
Budhraja V. *et al* 2008	Hypokalemia	Yes	Gastritis	-	-	5 months	Yes	-	-	-
Wallace D. *et al* 2007	Normal	-	Normal	-	Anxiety, depression, OCD	2	Yes	Yes	-	-
Singh E, Coyle W. 2006	Normal	-	-	-	-	4 months	Yes	-	-	-
Roche E, Foster P. 2005	Neutrophilia	-	Esophagitis	-	-	3	Yes	-	-	-

* Rest not reported or not available

° Period of time not specified

n Cases reported, OCD Obsessive Compulsive Disorder, Creat Creatinine, ADHD Attention deficit hyperactivity disorder

* Rest not reported or not available

° Period of time not specified

n Cases reported, OCD Obsessive Compulsive Disorder, AKI Acute Kidney Injury, ADHD Attention deficit hyperactivity disorder

Table 2

Comparison of cyclic vomiting syndrome in adults and cannabis hyperemesis syndrome

	Cyclical Vomiting	Cannabis Hyperemesis Syndrome
Age at diagnosis (y)	34.8	29.3
Delay in diagnosis (y)	7.9	3.1
Duration of episodes (days)	3.8	N/A
Cannabis use	Occasionally	Universal
Triggering factors (e.g. infections, psychological stress, etc)	Frequent	Absent
Prodrome	Common	Common
Clinical findings		
Vomiting	Universal	Universal
Abdominal Pain	Common (58–71%) – Moderate to severe	Common – Mild to moderate
Compulsive Bathing	Absent	Universal
GES	Accelerated	Delayed
Comorbidities Psychiatric	Common	Not common
Migraine headache	Common (24–70%)	Not common
Treatment	Abortive measures (antimigraine agents), supportive care, psychological support	Cannabis cessation, supportive care
Prophylaxis	Avoid triggers, TCA	Cannabis cessation

Data from Abell TL et al, Allen J et al and Soriano M et al.

N/A Not available, GES Gastric emptying study, TCA Tricyclic antidepressants

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