www.neurogastrolatamreviews.com

PERMANYER

NeuroGastroLatam Rev. 2020;4(3):171-186

NeuroGastroLatam Reviews

REVIEW ARTICLE

Cannabinoids in disorders of gut-brain interaction and gastrointestinal motility

Cannabinoides en trastornos de la interacción intestino-cerebro y motilidad gastrointestinal

María F. Arboleda[1]*, Erin Prosk[1], Alain Watier[1], and Max J. Schmulson[2]

[1]Department of Research, Santé Cannabis Clinic, Montreal, Quebec, Canada; [2]Laboratorio de Hígado, Páncreas y Motilidad (HIPAM)-Unidad de Investigación en Medicina Experimental, Faculty of Medicine-Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico

ABSTRACT

While cannabis use and acceptance are increasing among patients with gastrointestinal disorders, medical cannabis education and training are still lacking. Several barriers have limited safe cannabis use and prescription. However, clinical research and real-world evidence developed over the past 20 years have shown the potential therapeutic benefits of cannabinoid-based medicines in various clinical settings. Advancements to elucidate the role of the endocannabinoid system in the regulation of gastrointestinal motility and secretion have been also critical for the clinical practice. This review aims to describe updated clinical evidence supporting the use of medical cannabis in disorders of gut-brain interaction (previously known as functional gastrointestinal disorders) and gastrointestinal disorders. It also provides practical considerations for cannabinoid-based medicines prescription. Finally, it explains relevant functional gastrointestinal and motility disorders related to problematic cannabis use such as cannabinoid hyperemesis syndrome.

Key words: Medical cannabis. Cannabinoids. Gastroenterology. Cannabinoid hyperemesis syndrome. Functional disorders. Gut-brain interaction disorders.

RESUMEN

A pesar del incremento evidente en el uso del cannabis medicinal y su mayor aceptación entre los pacientes con trastornos gastrointestinales, aún existen limitaciones significativas en el desarrollo de educación médica relacionada con los cannabinoides. En la actualidad, se conocen múltiples barreras que limitan la prescripción responsable y segura de los productos a base de cannabis medicinal. Sin embargo, el desarrollo de investigación clínica y de estudios observacionales de vida real durante los últimos veinte años, han mostrado los potenciales efectos terapéuticos de los cannabinoides en diferentes contextos clínicos. Por otra parte, avances en la investigación sobre el rol del sistema endocannabinoide en la regulación de la motilidad y la secreción gastrointestinal, han sido críticos para la aplicación de esta terapia coadyuvante en la práctica clínica. Este artículo de revisión tiene como objetivos principales, describir la evidencia clínica reciente que apoya el uso terapéutico de los cannabinoides en trastornos de la interacción intestino-cerebro (previamente conocidos como trastornos funcionales gastrointestinales) y de la motilidad gastrointestinal. Adicionalmente, indicar las consideraciones prácticas para la prescripción segura de productos a base de cannabinoides. Finalmente, mencionar información relevante sobre los trastornos de la interacción intestino-cerebro y de la motilidad gastrointestinal, que se relacionan con el uso problemático de cannabis, como el síndrome de hiperemesis cannabinoide.

Palabras clave: Cannabis medicinal. Cannabinoides. Gastroenterología. Síndrome de hiperemesis cannabinoide. Trastornos funcionales. Trastornos de la interacción intestino-cerebro.

Correspondence to:
**Maria F. Arboleda*
E-mail: mfarboleda@santecannabis.ca

NeuroGastroLatam Rev. 2020;4:171-186
Received in original form: 07-08-2020
Accepted in final form: 16-11-2020
DOI: 10.24875/NGL.20000021

INTRODUCTION

Access to cannabinoid-based medicines has been increasing at a rapid pace worldwide as more countries introduce specific regulatory frameworks for medical cannabis. Interest among patients and their families continues to increase as information spreads rapidly online. Consequently, patients with gastrointestinal disorders are seeking medical advice and support for the use of cannabinoid therapy to treat refractory symptoms or to replace conventional medications. Despite the use of cannabis in ancient medicine and the increasing understanding of cannabinoids' role in digestive disorders over the past 15-20 years, significant gaps in evidence-based information still exist and the majority of medical professionals report a lack of confidence to discuss the potential therapeutic benefits and risks with their patients[1,2].

There remains an important limitation related to medical cannabis knowledge and academic training among health-care professionals[3]. Despite evolving legal access frameworks and some limited training opportunities, the majority of patient cannabis use remains illegal and unregulated worldwide. Interestingly, a recent study demonstrated a significant reduction of inpatient health-care utilization among patients with irritable bowel syndrome (IBS) who are using cannabinoid-based medicines[4]. This finding requires further investigation to understand the implicated health-care factors and to validate the potential therapeutic benefits of cannabinoid therapy.

The need for more clinical research into the use of cannabinoids to treat gastrointestinal disorders cannot be over-emphasized. The wide distribution of the endocannabinoid system (ECS) within the gastrointestinal tract has been well-characterized in recent years, identifying the activity of cannabinoid receptors and endogenous ligands that participate in the regulation of gastrointestinal motility, secretion, inflammation, and maintenance of the epithelial barrier integrity[5,6].

Functional gastrointestinal and motility disorders represent significant global health-care costs and substantial burden of daily gastroenterology practice with more than 40% of people affected worldwide. The prevalence and severity of uncontrolled symptoms present an important negative impact in health-related quality of life[7]. Specifically, functional gastrointestinal disorders (FGIDs) have been renamed and are currently known as disorders of gut-brain interaction (DGBI). This updated classification utilizes the latest multicultural oriented Rome IV criteria and has been expanded to include cannabinoid hyperemesis syndrome (CHS), not a truly functional gastroduodenal disorder but considered suitable according to the criteria introduced in 2016[8,9].

Therefore, the aim of this article is to review the general properties of cannabinoids and the cannabis plant, the potential therapeutic benefits of cannabinoid-based medicines, the possible adverse effects, and the development of DGBI related to problematic cannabis use. To inform the discussion of proposed practical recommendations for the safe and effective clinical use of cannabinoid-based medicine, this manuscript draws from the clinical experience of a leading medical cannabis clinic in Canada established in 2014.

WHY MEDICAL CANNABIS?

Although cannabis has been used for thousands of years to treat diverse medical conditions and symptoms[10], its clinical use, research, and development have been hindered by global prohibition throughout the last century. Significant barriers remain, including variable and complex regulatory restrictions, paucity of high-quality clinical evidence and limitations on research development, social stigma, and limited medical cannabis academic training of health-care professionals[11]. At present, < 13% of patients with gastrointestinal disorders consult with their physician about proper cannabinoid prescription and optimal medical guidance[12]. This could be due to fear and persistent stigma about cannabis use in medical environments. In most cases patients access illegal or unregulated medical cannabis products without any knowledge about dosage, indications and contraindications, potential drug-drug interactions, possible side effects, and the importance of using standardized and compliant cannabis-based medicines[13].

Meanwhile, many countries have adopted robust medical cannabis programs in the last decade. Canada's program was initiated in 2001 and now includes almost 400,000 registered patients. There has been an increasing development of medical cannabis clinics in emergent medical cannabis regulatory frameworks where a peer-supported, multidisciplinary approach may offer a rigorous clinical model of care including medical assessment, treatment recommendations, patient education, and follow-up and monitoring. In addition, the clinical experience supports the creation of continuing medical cannabis education programs for health-care professionals.

Recently, patient and health-care professional interest and an increase in published research have influenced an improved acceptance of medical cannabis use. A wave of investigative research has followed, including opportunities to study the cannabis plant, its main components and their mechanism of action in the human body. The main characteristics of the Cannabis plant are described in table 1[14,15].

INCREASED KNOWLEDGE OF THE ECS

The ECS is a complex endogenous lipid signaling system first characterized during the 1980s[16]. The main components of the ECS are:

- Cannabinoid receptors: described as 7-transmembrane-domain and G-protein-coupled receptors known as cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2). There is a higher density of CB1 receptors in the central nervous system. CB2 is mainly found in peripheral tissues such as the immune system. Other cannabinoid receptors have been characterized since the initial discovery of CB1 and CB2, these include the thermosensitive ionotropic transient receptor potential vanilloid 1 (TRPV1) and orphan cannabinoid receptors (GPR55);
- Endogenous ligands: compounds produced by the body that bind cannabinoid receptors are termed endocannabinoids, the two most studied N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG); and

Table 1. Main characteristics of the Cannabis plant

	Description
Origin	Central Asia
Family	Cannabaceae
Genus	*Cannabis sativa* L
Subspecies	*Cannabis sativa, Cannabis indica, Cannabis ruderalis*
Plant characteristics	Dioecious species (male and female flowers develop on separate plants)
Chemical compounds	More than 500 chemical compounds: cannabinoids, terpenes, flavonoids. More than 100 unique cannabinoids have been identified. Cannabinoids and terpenes are primarily produced in the glandular trichomes of female flower.
Therapeutic benefits	This will depend on the chemovar classification and main cannabinoid component: – THC-predominant (chemotype I) – THC-CBD balanced (chemotype II) – CBD-predominant (chemotype III)

THC: delta-9-tetrahydrocannabinol; CBD: cannabidiol.

– Regulatory metabolic and catabolic enzymes: such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).

The ECS has important regulatory functions and supports homeostasis in a broad number of physiological and pathophysiological processes such as cardiovascular function, immune function, inflammation, neurological development, synaptic plasticity and learning, bone development, mood, regulation of stress, wake/sleep cycles, pain, and reproduction and has a significant involvement in the gastrointestinal system[17].

CB1 receptors are found throughout the gastrointestinal tract, mainly in the enteric nervous system where receptor activity inhibits neurotransmission to reduce motility and gastric acid secretion[18], and produces relations of the lower esophageal sphincter (LES). CB2 receptors are mainly located in immunocytes, myenteric plexus neurons, and epithelial cells and may have an important role under pathophysiological conditions. TRPV1 and GPR55 receptors are also present in the gastrointestinal tract, though their activity has not been well-characterized[2]. Finally, endocannabinoids decrease intestinal hypermotility and hypersecretion by activation of CB1 receptors and could modulate intestinal inflammation and permeability[19].

BETTER UNDERSTANDING OF THC AND CBD

Recent advancements in research have illustrated the principal therapeutic benefits of the main plant-derived, or *phytocannabinoids*, in the cannabis plant, delta-9-tetrahydrocannabinol (THC), and cannabidiol (CBD). THC is a partial agonist of both CB1 and CB2 receptors and is responsible for the psychoactive, intoxicating effects of cannabis[20] whereas CBD does not appear to bind to these receptors at physiologically meaningful concentrations. Importantly, CBD is non-intoxicating and generally well tolerated[21]. One of the most

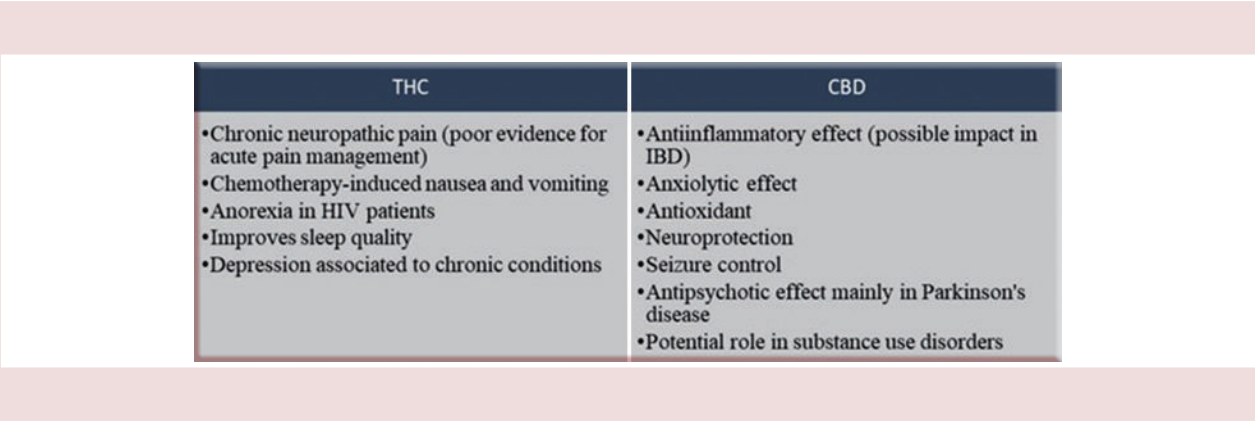

Figure 1. Therapeutic effects of THC and CBD.
THC: delta-9-tetrahydrocannabinol; CBD: cannabidiol; HIV: Human Immunodeficiency Virus; IBD: inflammatory bowel diseases.

frequent misconceptions is that CBD is for medical purposes whereas THC is for recreation or a drug of abuse. In fact, a great body of clinical evidence exists for the medical use of THC, yet persistent stigma and enduring prohibition continues to discredit the therapeutic use of THC.

Increasing evidence shows that THC has been used for the vast majority of chronic neuropathic pain studies[22], chemotherapy-induced nausea and vomiting (CINV) trials, anorexia in human immunodeficiency virus (HIV) patients, and among other medical conditions[23]. Initial studies of patients with IBD, mainly Crohn's disease utilized inhaled THC[24,25]. Conversely, CBD has been studied primarily as an anxiolytic[26] and has shown to reduce frequency and intensity of seizures in drug-resistant epilepsy[27]. Some preliminary investigation has identified potential anti-inflammatory effects[28]. Ongoing research for antipsychotic effects and a potential role to support treatment of substance use disorders is also promising[29-31].

The most important therapeutic benefits of THC and CBD are summarized in figure 1[32].

AVAILABILITY OF CANNABINOID-BASED MEDICINES

In practice, cannabinoid-based medicines are classified as *pharmaceutical* or *prescription cannabinoids* and *herbal cannabis* or *medical cannabis products*. Pharmaceutical cannabinoids are those have been approved for medical use for specific medical conditions and most randomized controlled trials (Phase I-III studies) to validate safety and efficacy have utilized pharmaceutical cannabinoids. However, the formulations of pharmaceutical cannabinoids are limited, and availability is restricted to select countries where the drug has been approved. Many patients and health-care professionals seek more diverse options for cannabinoid therapies and therefore, a growing number of countries now have legal access to unapproved herbal cannabis products including dried cannabis and cannabis derivatives. The classification of cannabinoid-based medicines is summarized in figure 2.

At present, there are four medications classified as pharmaceutical cannabinoids; their availability is variable across different jurisdictions[33]:

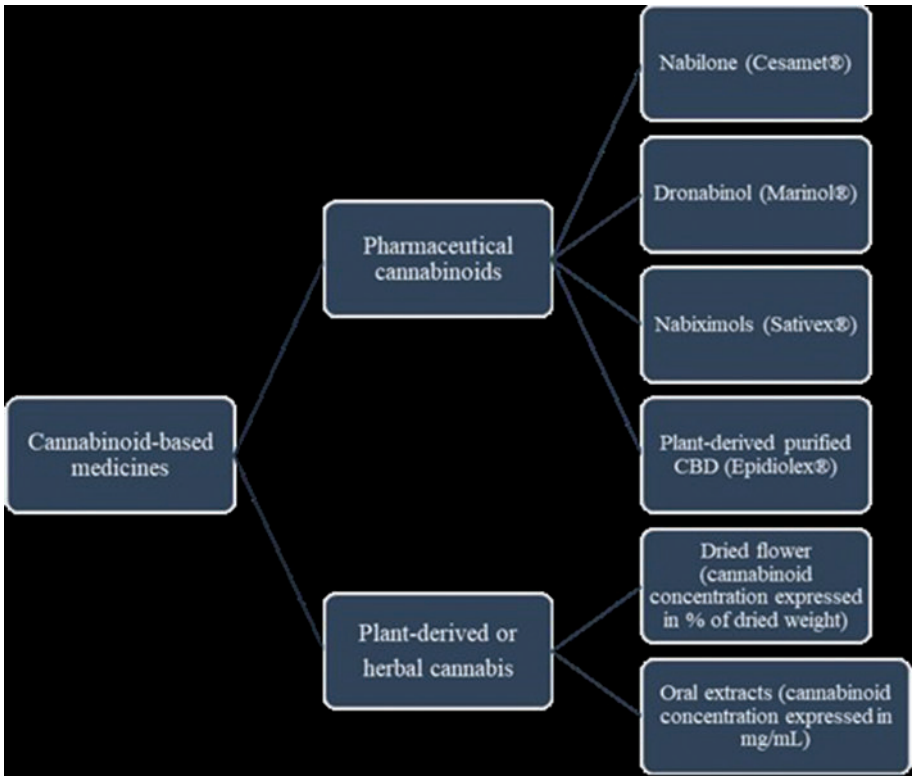

Figure 2. Classification of cannabinoid-based medicines.

Nabilone

A synthetic analog of THC administered in oral form; Food and Drug Administration (FDA)-approved since 1985 for CINV that has failed conventional treatments. It has been used off-label and studied for various medical conditions such as acute post-operative pain[34], chronic pain and fibromyalgia[35], post-traumatic stress disorder (PTSD)[36], neuropsychiatric symptoms of dementia[37], and refractory chronic diarrhea[38].

Dronabinol

A synthetic THC formulation is also administered in oral form; FDA-approved since 1992 for anorexia in HIV patients with weight loss and for CINV resistant to conventional antiemetics. The off-label use of dronabinol has been studied for the treatment of chronic pain[39], obstructive sleep apnea[40], substance use disorders[41], among other conditions.

Nabiximols (Sativex®)

A natural extract of *Cannabis sativa* formulated as an oromucosal spray. Each single 100 microliters spray contains 2.7 mg of THC and 2.5 mg of CBD so it is considered a balanced formulation. Nabiximols has been approved in more than 30 countries, including Latin-American nations such as

Colombia, Brazil, and Chile, as an adjunct for spasticity in multiple sclerosis (MS) patients[42], but it is considerably expensive and generally not covered by private or public health insurance plans. It has also been studied but still unapproved for the treatment of cancer pain[43].

Epidiolex®

An oral solution of plant-derived purified CBD approved by the FDA in 2018[27] and the European Drug Agency in 2019[44] for the treatment of drug-resistant epilepsy, specifically Lennox-Gastaut Syndrome and Dravet Syndrome in patients aged 2 years or older.

On the other hand, *herbal cannabis* or *medical cannabis* or, in some jurisdictions *medical marijuana* refers to:

1. Dried cannabis that is administered by inhalation using a specific cannabis vaporizer device, or historically a pipe or rolled cigarette, more recently cannabis extracts in e-cigarette-type devices have been developed, though some significant safety risks have been observed, especially with unregulated products; inhaled cannabis has a rapid onset of effects of 1-10 min and shorter duration of effect of 2-4 h. THC and CBD dosages are measured in percentage of dried weight (% w/w)[45].
2. Oral extracts such as ingested cannabis oils, oromucosal sprays, and capsules; oral products have an onset of effects after 60-90 min and long-lasting duration of 8-12 h. THC and CBD dosages are measured in concentration (mg/mL) or fixed dosage (mg)[45]. Most Latin-American countries that have approved the use of cannabis for medical purposes only authorized oral extracts.
3. Topical products such as creams, salves, or patches; little is known about absorption of these products, onset time, and duration of effect remain unclear.

Despite the popularity of herbal cannabis for medical use, there remains limited evidence to confirm its actual efficacy, and obstacles to the development of randomized controlled trials to study medical cannabis products. To fill this need, collection of real-world evidence through medical cannabis registries and observational studies at dedicated medical cannabis clinics has provided valuable data which provide important validation of potential clinical uses and the observed adverse effects of medical cannabis products to inform clinical practice[46].

MOST SIGNIFICANT EVIDENCE FOR CANNABINOID-BASED MEDICINES AND CLINICAL EXPERIENCE

There has been an increasing development of systematic reviews and meta-analyses in the past 5 years to verify the efficacy of cannabinoid-based medicines in various clinical settings[47]. Despite limitations of randomized controlled trials, the most significant and conclusive evidence regarding safety and efficacy of cannabinoid-based medicines has been demonstrated for the treatment of chronic neuropathic pain, CINV, drug-resistant epilepsy, and spasticity in MS. According to the literature and clinical experience, the main therapeutic benefits of cannabinoids are summarized in table 2[32,48].

It is critical to keep in mind the following

Table 2. Cannabinoid-based medicines: clinical evidence and experience

Cannabinoid-based medicine	Medical condition or symptom	Evidence and clinical experience
THC (dronabinol, nabilone, natural)	Chronic pain	Potential to relieve chronic central and peripheral neuropathic pain conditions. – Short-term reductions in chronic neuropathic pain observed for 1 in every 5 to 6 patients treated. – Most studies have been done with THC-rich inhaled products (smoked cannabis). – Improvement of concomitant symptoms was observed, including insomnia, mood impairment, functionality, and health-related quality of life.
	PTSD	THC-rich products could improve nightmare frequency
	Insomnia	Improves sleep quality – Inhalation recommended mainly for sleep induction (rapid onset). – For sleep maintenance, oral administration (long acting effect) is suggested.
	CINV	– Antiemetic effects are associated to activation of CB1 receptors. – Administration of inhaled THC-rich products before chemotherapy infusion treatment has been recommended.
	Anorexia	– Most studies have been done in patients with HIV and cancer-associated anorexia; – Some evidence demonstrated appetite stimulation, taste improvement, and food enjoyment; – No significant improvement in weight was observed;
	Depression	– Very limited evidence to support the use of THC-rich products for depression as a secondary symptom; – High doses of THC have been shown to have negative effects on depression; – Low doses of THC-rich products could improve depression symptoms associated to chronic pain and cancer.
CBD	Anxiety	– Most studies have been done for SAD; Studies are of limited quality and further investigation is required.
	Drug-resistant epilepsy	– Lennox Gastaut syndrome and Dravet syndrome, Dravet Syndrome and Tuberous Sclerosis Complex
	Parkinson's disease	Most studies have shown improvement in: – Mood – Psychotic symptoms – Sleep (rapid eye movement sleep disorder)
	Substance use disorder	– Ongoing research for opioid and cannabis use disorder is promising.
	IBD	– Mainly anti-inflammatory effect from CBD. – It relieves IBD-related symptoms such as abdominal pain, nausea and diarrhea. – Improvement of health-related quality of life.

CBD: cannabidiol; CINV: chemotherapy-induced nausea and vomiting; HIV: Human Immunodef Virus; IBD: inflammatory bowel diseases; PTSD: Post-traumatic Stress Disorder; SAD: Social Anxiety Disorder; THC: delta-9-tetrahydrocannabinol.

recommendations when considering prescription of cannabinoid-based medicines[48,49]:

Medical cannabis is not a first-line treatment

Therefore, conventional pharmacological and non-pharmacological therapies must be considered before prescribing cannabinoid-based medicines. Some recent practice guidelines have proposed recommendations for the use of cannabinoids before opioid medications as a third-line treatment option for chronic pain.

There are specific indications and contraindications for medical cannabis use

For this reason, detailed medical history is always necessary to evaluate eligibility.

Clinicians should avoid THC-rich products in patients with anxiety, as well as potential contraindications of psychiatric disorders such as schizophrenia, psychosis, bipolar disorders, in patients with unstable cardiovascular conditions, and in patients under 25 years of age.

Always discuss therapeutic goals with your patient and family

This will help to manage treatment expectations and support patient compliance to treatment recommendations. In general, cannabinoids are used for symptom control as an adjunct to traditional treatments and must not be used for curative purposes.

Cannabinoids therapies are complementary and do not replace any conventional treatment

In some cases, once cannabinoid treatment is stable enough to provide therapeutic benefits, the reduction of concomitant medication dosage may be possible.

Always consider history of cannabis use for medical and non-medical purposes

Patients with the previous cannabis experience will require personalized recommendations and monitoring. It is also key to screen for cannabis use disorder (CUD) which is a condition included in the Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-5)[50]. Screening tools such as the CUDIT-r might be helpful, though it does not evaluate use of cannabis for medical purposes[51].

Start with the lowest possible dose of cannabinoids

In general, it is recommended to start with 1-2.5 mg of THC and 5 mg of CBD at bedtime[49]. For elderly or otherwise vulnerable patients, the lowest dosage and a slower titration are recommended. If inhaled, patients should start with one inhalation from a low-THC cannabis variety (maximum THC 12% w/w) and wait for approximately 15 min to determine therapeutic effects. Slow titration is always necessary to avoid adverse effects.

CANNABINOIDS IN MOTILITY AND DGBI: WHAT HAS THE CLINICAL EVIDENCE SUPPORTED SO FAR?

There has been interesting development of clinical trials testing cannabinoid-based medicines for different gastrointestinal conditions[52]. However, there are still numerous, significant research gaps that need to be addressed. While pre-clinical findings in cellular and animal models show promising activity, preclinical research must be put in perspective when compared to human studies.

Cannabinoids and esophageal function

Several animal studies have confirmed that CB1 receptor agonists usually reduce motility of the GI tract[53]. It has also been

demonstrated that short-term THC administration relaxes the pressure of the LES. Conversely, chronic cannabis users have a high prevalence of hypertensive LES pressure. The administration of THC transiently reduces rates of transient LES relaxation[54]. Dronabinol, as a partial agonist of CB1, has been shown to increase pain thresholds and reduces pain intensity and odynophagia in patients with chronic chest pain of esophageal origin[55].

Cannabinoids and gastric emptying

The administration of dronabinol has also demonstrated delayed gastric emptying predominantly in females[56]. Nevertheless, a recent trial has elucidated the impact of cannabinoids, at dosages of up to 20 mg of dronabinol, inhaled cannabis, and oral extracts, on symptoms of refractory gastroparesis showing a significant improvement of Gastroparesis Cardinal Symptom Index and specifically abdominal pain[57]. A recent survey of patients with gastroparesis found that cannabis use was also associated with symptom improvement[58].

Cannabinoids and functional dyspepsia

The ECS controls early satiety, gastric accommodation, hypersensitivity to gastric distension, and cortical control of satiety and visceral pain. The clinical implications of cannabinoids in the treatment of functional dyspepsia should be evaluated[59].

Cannabinoids and colonic transit

As demonstrated in both animal and human studies, administration of cannabis delays colonic transit. Dysregulation of enzymes that synthesize and degrade endocannabinoids may be implicated in the physiopathology of slow transit constipation[60].

Cannabinoids and IBS

The ECS interacts with GI motility, pain, GI secretion, microbiota, visceral hypersensitivity, inflammation, and immune dysregulation, which are processes implicated in the pathogenesis of IBS[61]. Even if cannabis may help ease symptoms of IBS, there are limited human trials suggesting a potential benefit of cannabis in IBS. Further studies are needed.

Cannabis in gastrointestinal disorders: future research

As an important area for future research, cannabis has been reported to modify intestinal microbiome and seems to be implicated in the brain-gut-microbiota-endocannabinoid – axis[5].

There is still a role for cannabinoids in the current treatment paradigm of gastrointestinal disorders. Patient interest in medical cannabis treatments must be tempered by the reality of limited evidence and effective patient education and guidance to set realistic expectations. Considerable future research, specifically in human studies, is required to answer further questions about safety and

efficacy of existing treatment options and explore novel cannabinoid formulations.

CHS

Cannabis has been the most widely used illicit substance throughout the past 100 years, with more than 190 million users globally every year. Lifetime probability of transition from cannabis use to CUD has been estimated at 27%. Some significant risk factors to the development of CUD are male individuals, with early onset of cannabis use and an experience of three or more traumatic events during childhood; a correlation with psychiatric disorders such as personality or anxiety disorders and substance use disorders has also been reported[50].

Chronic and frequent cannabis use for non-medical purposes has been related to the development of a rare condition known as CHS. This condition was first described in 2004 in patients with chronic cannabis use and persistent, cyclical vomiting[62]. Importantly, patients displayed compulsive hot water bathing to control their symptoms and elimination of recurrent episodes of vomiting was observed on cessation of cannabis consumption. It is still unclear why cannabis produces antiemetic effects in some individuals; however, induces significant nausea and vomiting in rare circumstances.

Several theories have been proposed to explain the pathophysiology of CHS. It is thought that regular cannabis use may influence dysregulation of the ECS which consequently affects the gastrointestinal motility and gastric emptying. Another theory proposes that cannabinoid accumulation in the brain and fatty tissues could be responsible for observed toxicity and symptom presentation. Finally, it has been suggested that a genetic polymorphism of metabolic enzymes could explain the symptoms[63].

DIAGNOSTIC CRITERIA

In recent years, increased and recurrent emergency room visits by patients presenting with abdominal pain, nausea, and vomiting have been reported. With a growing interest in cannabis use both for recreational and medical purposes, health-care professionals must be familiar with CHS as a differential diagnosis. Since CHS is an unexpected and unrecognized cause of nausea and vomiting, patients are often exposed to multiple laboratory exams, advanced imaging, avoidable procedures, and uncertain discharge diagnosis, all at high risk and cost to both the patient and the medical system.

Recently, the Rome IV criteria included CHS as a new disorder, within the nausea and vomiting disorders category of the gastroduodenal disorders. Although CHS together with Narcotic Bowel Syndrome and Opioid Induced Constipation are different from other DGBI because of having substances (i.e., cannabinoids, opioids) that produce the symptoms, and their avoidance may lead to recovery, they are not truly "functional"[8]. However, they were included in the new Rome IV definition of DGBI: being characterized by altered function of the central nervous system or enteric nervous system; their clinical presentations are similar to FGIDs and thus need to

Table 3. Rome IV diagnostic criteria for cannabinoid hyperemesis syndrome

Must include all of the following: 1. Stereotypical episodic vomiting resembling cyclic vomiting syndrome (CVS) in terms of onset, duration, and frequency 2. Presentation after prolonged excessive cannabis use 3. Relief of vomiting episodes by sustained cessation of cannabis use
Criteria fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis
Supportive remarks: may be associated with pathologic bathing behavior (prolonged hot baths or showers).

be distinguished from them; and they have not yet been well characterized or reached acceptance in the field to be considered separate independent disorders[64]. The Rome IV criteria for CHS are depicted in table 3. However, patients may have associated symptoms such as abdominal pain. In addition, CHS has a male predominance and age < 50 is more frequent at onset of symptoms. Furthermore, patients have regular cannabis use for more than 1 year, with more than 4 times a week on average, but some patients are daily cannabis users[63,65].

PROPOSED MANAGEMENT

CHS presents with three phases: prodrome, hyperemesis, and recovery[66]. Despite its recent description there have been several proposed treatments and guidelines for the clinical management of CHS but they are not yet consistent[67]. The only standard and definitive treatment is cannabis cessation. On presentation, intravenous (IV) hydration is critical to avoid complications such as acute renal failure. Several case reports and case series[68] have shown a possible, but limited, effect of conventional pharmacologic antiemetics such as promethazine, ondansetron (4-8 mg IV), and metoclopramide; haloperidol (5 mg IV)[69], droperidol (0.625 mg IV)[70], benzodiazepines (i.e., clonazepam 0.5 mg PO)[71], and even aprepitant[72]. Such treatments may be considered when all other common antiemetics failed[67]. In practice, relief from pharmacological medications is inconsistent and generally rare.

While compulsive hot water bathing is a way to relieve symptoms through peripheral vasodilation, by diverting splanchnic circulation, several trials have proposed the use of topical capsaicin 0.075% concentration applied to abdomen or back of arms as an adjunct to treat CHS. This occurs through activation of TRPV1 receptors, neurohumoral regulation, and modulation of specific neurotransmitters such as histamine, acetylcholine, and serotonin[67,73,74]. It is important to be cautious when applying this treatment since it can produce significant skin irritation or chemical burns. Use of gloves and hand washing after application is highly recommended[67].

Use of opioid medications must be avoided under all circumstances as potential reduction bowel motility could worsen symptoms and, in some cases, may present risk of opioid use disorder[63].

Finally, detailed documentation of patient's cannabis use is very important for the management of CHS and in case of future visits to the emergency room. It is key to provide patient-centered education and support for cannabis cessation. While significant withdrawal symptoms are not expected on cessation, patients may experience headaches, decreased appetite, poor sleep, mood changes, and irritability. Additional medical support may be required from a

Figure 3. Cannabinoid hyperemesis syndrome: proposed treatment.

multidisciplinary team. Figure 3 compiles the proposed treatment for CHS.

CHS VERSUS CYCLIC VOMITING SYNDROME (CVS)

According to Rome IV criteria, CVS is also under the gastroduodenal disorders as a separate condition from CHS. In some cases, clinical differentiation between CHS and CVS may be difficult as both conditions present acute episodes of nausea and vomiting, multiple hospitalizations, and significant impact in health-related quality of life[65]. To add further complication, the use of cannabinoid-based medicines is frequent among patients with CVS as an antiemetic therapy. In fact, there has been a ten-fold increase of cannabis use in patients with CVS in recent years[75]. Thus, it is first critical to distinguish between heavy cannabis use for recreational purposes and medical cannabis use for antiemetic effects. This could help orient the differential diagnosis, though patients could be consuming cannabis for medical purposes without any medical supervision, dosing monitoring or proper guidance for chemotype selection. Consequently, there is still significant confusion and further research is needed to elucidate and determine the differentiation between CHS and CVS.

CONCLUSION

Cannabis use is prevalent among patients with gastrointestinal disorders for symptom

control; thus, health-care professionals must be familiar with its properties and the cannabis regulatory frameworks and legally available products in their countries. This knowledge will support medical supervision and potential to provide guidance and informed recommendations for the use of cannabinoid-based medicines. In addition, the role of the ECS in the regulation of gastrointestinal motility and inflammation should be acknowledged. Clinical evidence developed so far is critical to determine eligibility to this complementary treatment which requires specialized medical guidance and supervision. Since patient use is prevalent, screening for CUD must be considered before recommending this therapy; however, the presence of problematic cannabis use does not negate the need for medical supervision. Chronic cannabis use can lead to the development of motility and gastrointestinal DGBI such as CHS. Although CHS is often unrecognized by health-care professionals and still considered a rare condition, these recurrent episodes of vomiting may have significant negative impact on patients' health-related quality of life. It is still unclear why cannabis can elicit antiemetic effects in some clinical settings and may cause cyclic vomiting in chronic or heavy cannabis users. Further research, especially in well-designed, controlled human studies are still required to understand such rare adverse effects and to verify the potential therapeutic benefits of cannabinoid-based medicine in gastrointestinal DGBI and motility disorders.

FUNDING

None.

CONFLICTS OF INTEREST

Dr. Maria Fernanda Arboleda declares the following possible conflicts of interest: international Director of Medical Services, Khiron Life Sciences Corporation. Associate Research Director of Santé Cannabis, a medical clinic and research center.

Erin Prosk declares the following possible conflicts of interest: director of Santé Cannabis, a medical clinic and research center.

Dr. Alain Watier has no conflicts of interest to declare.

Dr. Max J. Schmulson W. has no conflicts of interest to declare.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

REFERENCES

1. Goyal H, Singla U, Gupta U, May E. Role of cannabis in digestive disorders. Eur J Gastroenterol Hepatol. 2017;29:135-43.
2. Hasenoehrl C, Taschler U, Storr M, Schicho R. The gastrointestinal tract-a central organ of cannabinoid signaling in health and disease. Neurogastroenterol Motil. 2016;28:1765-80.

3. Karanges EA, Suraev A, Elias N, Manocha R, McGregor IS. Knowledge and attitudes of Australian general practitioners towards medicinal cannabis: a cross-sectional survey. BMJ Open. 2018;8:e022101.
4. Desai P, Mbachi C, Vohra I, Salazar M, Mathew M, Randhawa T, et al. Association between cannabis use and healthcare utilization in patients with irritable bowel syndrome: a retrospective cohort study. Cureus. 2020;12:e8008.
5. Sharkey KA, Wiley JW. The role of the endocannabinoid system in the brain-gut axis. Gastroenterology. 2016;151:252-66.
6. Camilleri M. Cannabinoids and gastrointestinal motility: pharmacology, clinical effects, and potential therapeutics in humans. Neurogastroenterol Motil. 2018;30:e13370.
7. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome foundation global study. Gastroenterology. 2020;S0016-5085(20)30487-X.
8. Schmulson MJ, Drossman DA. What is new in Rome IV. J Neurogastroenterol Motil. 2017;23:151-63.
9. Suzuki H. The application of the Rome IV criteria to functional esophagogastroduodenal disorders in Asia. J Neurogastroenterol Motil. 2017;23:325-33.
10. Pisanti S, Bifulco M. Modern history of medical cannabis: from widespread use to prohibitionism and back. Trends Pharmacol Sci. 2017;38:195-8.
11. Arboleda MF, Prosk E, Cyr C, Gamaoun R, Vigano A. Medical cannabis in supportive cancer care: lessons from Canada. Support Care Cancer. 2020;28:2999-3001.
12. Kerlin AM, Long M, Kappelman M, Martin C, Sandler RS. Profiles of patients who use marijuana for inflammatory bowel disease. Dig Dis Sci. 2018;63:1600-4.
13. Wheeler M, Merten JW, Gordon BT, Hamadi H. CBD (cannabidiol) product attitudes, knowledge, and use among young adults. Subst Use Misuse. 2020;55:1138-45.
14. Klumpers LE, Thacker DL. A brief background on cannabis: from plant to medical indications. J AOAC Int. 2019;102:412-20.
15. Lewis MA, Russo EB, Smith KM. Pharmacological foundations of cannabis chemovars. Planta Med. 2018;84:225-33.
16. Di Marzo V, Piscitelli F. The endocannabinoid system and its modulation by phytocannabinoids. Neurotherapeutics. 2015;12:692-8.
17. Health Canada. Information for Health Care Professionals Cannabis (Marihuana, Marijuana) and the Cannabinoids: dried or Fresh Plant and oil for Administration by Ingestion or Other Means Psychoactive Agent; 2018. Available from: http://www.publications.gc.ca/collections/collection_2018/sc-hc/H129-19-2018-eng.pdf.
18. Duncan M, Davison JS, Sharkey KA. Review article: endocannabinoids and their receptors in the enteric nervous system. Aliment Pharmacol Ther. 2005;22:667-83.
19. Pertwee RG. Cannabinoids and the gastrointestinal tract. Gut. 2001;48:859-67.
20. Russo EB. Current therapeutic cannabis controversies and clinical trial design issues. Front Pharmacol. 2016;7:309.
21. Russo EB. Cannabidiol claims and misconceptions. Trends Pharmacol Sci. 2017;38:198-201.
22. Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. J Pain. 2015;16:1221-32.
23. Abrams DI. Should oncologists recommend cannabis? Curr Treat Options Oncol. 2019;20:59.
24. Naftali T, Lev LB, Yablekovitz D, Half E, Konikoff FM. Treatment of crohn's disease with cannabis: an observational study. Isr Med Assoc J. 2011;13:455-8.
25. Naftali T, Schleider L, Dotan I, Lansky EP, Benjaminov FS, Konikoff FM. Cannabis induces a clinical response in patients with crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol. 2013;11:1276-80.e1.
26. Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacology. 2011;36:1219-26.
27. Cannabidiol (epidiolex) for epilepsy. Med Lett Drugs Ther. 2018;60:182-4.
28. Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. Bioorg Med Chem. 2015;23:1377-85.
29. Zuardi AW, Crippa JA, Hallak JE, Pinto JP, Chagas MH, Rodrigues GG, et al. Cannabidiol for the treatment of psychosis in Parkinson's disease. J Psychopharmacol (Oxford). 2009;23:979-83.
30. Batalla A, Janssen H, Gangadin SS, Bossong MG. The potential of cannabidiol as a treatment for psychosis and addiction: who benefits most? A systematic review. J Clin Med. 2019;8:1058.
31. Hurd YL, Spriggs S, Alishayev J, Winkel G, Gurgov K, Kudrich C, et al. Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial. Am J Psychiatry. 2019;176:911-22.
32. Abrams DI. The therapeutic effects of cannabis and cannabinoids: an update from the national academies of sciences, engineering and medicine report. Eur J Intern Med. 2018;49:7-11.
33. Schrot RJ, Hubbard JR. Cannabinoids: medical implications. Ann Med. 2016;48:128-41.
34. Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain. Can J Anaesth. 2006;53:769-75.
35. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008;9:164-73.
36. Jetly R, Heber A, Fraser G, Boisvert D. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology. 2015;51:585-8.
37. Bahji A, Meyyappan AC, Hawken ER. Cannabinoids for the neuropsychiatric symptoms of dementia: a systematic review and meta-analysis. Can J Psychiatry. 2020;65:365-76.
38. Pellesi L, Verga MC, De Maria N, Villa E, Pini LA, Guerzoni S. Nabilone administration in refractory chronic diarrhea: a case series. BMC Gastroenterol. 2019;19:105.
39. Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol. 2017;78:320-9.
40. Carley DW, Prasad B, Reid KJ, Malkani R, Attarian H, Abbott SM, et al. Pharmacotherapy of apnea by cannabimimetic enhancement, the PACE clinical trial: effects of dronabinol in obstructive sleep apnea. Sleep. 2018;41:zsx184.
41. Levin FR, Mariani JJ, Pavlicova M, Brooks D, Glass A, Mahony A, et al. Dronabinol and lofexidine for cannabis use disorder: a randomized, double-blind, placebo-controlled trial. Drug Alcohol Depend. 2016;159:53-60.
42. Yadav V, Bever C, Bowen J, Bowling A, Weinstock-Guttman B, Cameron M, et al. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American academy of neurology. Neurology. 2014;82:1083-92.
43. Boland EG, Bennett MI, Allgar V, Boland JW. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. BMJ Support Palliat Care. 2020;10:14-24.
44. Wise J. European drug agency approves cannabis-based medicine for severe forms of epilepsy. BMJ. 2019;366:L5708.
45. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy. 2013;33:195-209.
46. Graham M, Lucas CJ, Schneider J, Martin JH, Hall W. Translational hurdles with cannabis medicines. Pharmacoepidemiol Drug Saf. 2020;29:1325-30.
47. Montero-Oleas N, Arevalo-Rodriguez I, Nuñez-González S, Viteri-García A, Simancas-Racines D. Therapeutic use of cannabis and cannabinoids: an evidence mapping and appraisal of systematic reviews. BMC Complement Med Ther. 2020;20:12.
48. Cyr C, Arboleda MF, Aggarwal SK, Balneaves LG, Daeninck P, Néron A, et al. Cannabis in palliative care: current challenges and practical recommendations. Ann Palliat Med. 2018;7:463-77.

49. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med 2018;49:12-9.
50. Feingold D, Livne O, Rehm J, Lev-Ran S. Probability and correlates of transition from cannabis use to DSM-5 cannabis use disorder: results from a large-scale nationally representative study. Drug Alcohol Rev 2020;39: 142-51.
51. Artigaud L, Fener C, Bisch M, Schwan R, Schwitzer T, De Ternay J, et al. Screening tools for cannabis use disorders and their adaptation to DSM-5: a literature review. Encephale. 2020;46:382-9.
52. Gotfried J, Naftali T, Schey R. Role of cannabis and its derivatives in gastrointestinal and hepatic disease. Gastroenterology. 2020;159:62-80.
53. Izzo AA, Mascolo N, Pinto L, Capasso R, Capasso F. The role of cannabinoid receptors in intestinal motility, defaecation and diarrhoea in rats. Eur J Pharmacol. 1999;384:37-42.
54. Gotfried J, Kataria R, Schey R. Review: the role of cannabinoids on esophageal function-what we know thus far. Cannabis Cannabinoid Res. 2017;2:252-8.
55. Malik Z, Bayman L, Valestin J, Rizvi-Toner A, Hashmi S, Schey R. Dronabinol increases pain threshold in patients with functional chest pain: a pilot double-blind placebo-controlled trial. Dis Esophagus. 2017;30:1-8.
56. Esfandyari T, Camilleri M, Ferber I, Burton D, Baxter K, Zinsmeister AR. Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: a randomized, placebo-controlled study. Neurogastroenterol Motil. 2006;18:831-8.
57. Barbash B, Mehta D, Siddiqui MT, Chawla L, Dworkin B. Impact of cannabinoids on symptoms of refractory gastroparesis: a single-center experience. Cureus. 2019;11:e6430.
58. Jehangir A, Parkman HP. Cannabinoid use in patients with gastroparesis and related disorders: prevalence and benefit. Am J Gastroenterol. 2019;114:945-53.
59. Ameloot K, Janssen P, Scarpellini E, Vos R, Boesmans W, Depoortere I, et al. Endocannabinoid control of gastric sensorimotor function in man. Aliment Pharmacol Ther. 2010;31:1123-31.
60. Zhang SC, Wang WL, Su PJ, Jiang KL, Yuan ZW. Decreased enteric fatty acid amide hydrolase activity is associated with colonic inertia in slow transit constipation. J Gastroenterol Hepatol. 2014;29:276-83.
61. Storr MA, Yüce B, Andrews CN, Sharkey KA. The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome. Neurogastroenterol Motil. 2008;20:857-68.
62. Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut. 2004;53:1566-70.
63. Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA. Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment-a systematic review. J Med Toxicol. 2017;13:71-87.
64. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology. 2016;150:1262-79.
65. Venkatesan T, Levinthal DJ, Li BU, Tarbell SE, Adams KA, Issenman RM, et al. Role of chronic cannabis use: cyclic vomiting syndrome vs cannabinoid hyperemesis syndrome. Neurogastroenterol Motil. 2019;31:e13606.
66. Galli JA, Sawaya RA, Friedenberg FK. Cannabinoid hyperemesis syndrome. Curr Drug Abuse Rev. 2011;4:241-9.
67. Lapoint J, Meyer S, Yu CK, Koenig KL, Lev R, Thihalolipavan S, et al. Cannabinoid hyperemesis syndrome: public health implications and a novel model treatment guideline. West J Emerg Med. 2018;19:380-6.
68. Richards JR, Gordon BK, Danielson AR, Moulin AK. Pharmacologic treatment of cannabinoid hyperemesis syndrome: a systematic review. Pharmacotherapy. 2017;37:725-34.
69. Witsil JC, Mycyk MB. Haloperidol, a novel treatment for cannabinoid hyperemesis syndrome. Am J Ther. 2017;24:e64-7.
70. Lee C, Greene SL, Wong A. The utility of droperidol in the treatment of cannabinoid hyperemesis syndrome. Clin Toxicol (Phila). 2019;57:773-7.
71. Kheifets M, Karniel E, Landa D, Vons SA, Meridor K, Charach G. Resolution of cannabinoid hyperemesis syndrome with benzodiazepines: a case series. Isr Med Assoc J. 2019;21:404-7.
72. Parvataneni S, Varela L, Vemuri-Reddy SM, Maneval ML. Emerging role of aprepitant in cannabis hyperemesis syndrome. Cureus. 2019;11:e4825.
73. McConachie SM, Caputo RA, Wilhelm SM, Kale-Pradhan PB. Efficacy of capsaicin for the treatment of cannabinoid hyperemesis syndrome: a systematic review. Ann Pharmacother. 2019;53:1145-52.
74. Richards JR, Lapoint JM, Burillo-Putze G. Cannabinoid hyperemesis syndrome: potential mechanisms for the benefit of capsaicin and hot water hydrotherapy in treatment. Clin Toxicol (Phila). 2018;56:15-24.
75. Siddiqui MT, Bilal M, Singh A, Olivier-Cabrera S, Lebovics E, Schorr-Lesnick B, et al. Prevalence of cannabis use has significantly increased in patients with cyclic vomiting syndrome. Neurogastroenterol Motil. 2020;32:e13806.