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NARRATIVE REVIEWS

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Cannabinoids and the Gastrointestinal Tract

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The synthesis and degradation of endocannabinoids, location of cannabinoid (CB) receptors, and cannabinoid mechanisms of action on immune/inflammatory, neuromuscular, and sensory functions in digestive organs are well documented. CB_2 mechanisms are particularly relevant in immune and sensory functions. Increasing use of cannabinoids in the United States is impacted by social determinants of health including racial discrimination, which is associated with tobacco and cannabis co-use, and combined use disorders. Several conditions associated with emesis are related to cannabinoid use, including cannabinoid hyperemesis or withdrawal, cyclic vomiting syndrome, and nausea and vomiting of pregnancy. Cannabinoids generally inhibit gastrointestinal motor function; yet they relieve symptoms in patients with gastroparesis and diverse nausea syndromes. Cannabinoid effects on inflammatory mechanisms have shown promise in relatively small placebo-controlled studies in reducing disease activity and abdominal pain in patients with inflammatory bowel disease. Cannabinoids have been studied in disorders of motility, pain, and disorders of gut–brain interaction. The CB_2-receptor agonist, cannabidiol, reduced the total Gastroparesis Cardinal Symptom Index and increases the ability to tolerate a meal in patients with gastroparesis appraised over 4 weeks of treatment. In contrast, predominant-pain end points in functional dyspepsia with normal gastric emptying were not improved significantly with cannabidiol. The CB_2 agonist, olorinab, reduced abdominal pain in inflammatory bowel disease in an open-label trial and in constipation-predominant irritable bowel syndrome in a placebo-controlled trial. Cannabinoid mechanisms alter inflammation in pancreatic and liver diseases. In conclusion, cannabinoids, particularly agents affecting CB_2 mechanisms, have potential for inflammatory, gastroparesis, and pain disorders; however, the trials require replication and further understanding of risk-benefit to enhance use of cannabinoids in gastrointestinal diseases.

Keywords: Cannabis; Gastroparesis; Inflammatory Bowel Diseases; Nausea; Vomiting; Pain Disorders.

Cannabinoids are natural, endogenous, or synthetic compounds. The marijuana plants, *Cannabis sativa* and other species, have been used for medicinal and other purposes for millennia. The World Health Organization reported that 2.5% of the world population consumes cannabis annually.[1] Cannabinoids are used medically for the treatment of chronic pain and spasticity, nausea and vomiting due to chemotherapy, sleep disorders, Tourette syndrome, chronic neuropathic pain, and to enhance weight gain in human immunodeficiency virus infection.[2,3] More recently, studies have enhanced understanding of cannabinoids for diverse digestive disorders. Clinicians are encountering increasing numbers of patients who already are using cannabinoids or request information or guidance on their use for gastrointestinal indications.

The objectives of this review are to appraise the epidemiology of cannabis use; the synthesis and degradation of endocannabinoids; the location of cannabinoid receptors; cannabinoid mechanisms of action with specific attention to immune/inflammatory, neuromuscular, and sensory functions in digestive organs; and the role of cannabinoids in causation or treatment in diverse gastrointestinal diseases including the conditions associated with emesis, inflammatory bowel disease, disorders of motility and pain, and disorders of gut–brain interaction. In addition, the multiple effects of cannabinoids on diverse organs in the digestive tract including the pancreas and liver are evaluated.

Starting With a Word of Caution About Safety Before Mechanisms and Efficacy

Cannabinoids may cause short-term adverse events, including tachycardia, agitation, and nausea.[4] Effects of synthetic cannabinoid products are similar and may be more potent and longer lasting than those of Δ^9-tetrahydrocannabinol (Δ^9THC). Some cannabinoid compounds may cause psychosis, mania, and suicidal ideation.[5] With liberalization of cannabinoid use, there has been unintentional cannabis ingestion by children,[6] in utero effects on fetal neural development with use during pregnancy,[7] and cannabinoid hyperemesis

Abbreviations used in this paper: **AEA, anandamide; CB, cannabinoid; CHS, cannabinoid hyperemesis syndrome; CVS, cyclic vomiting syndrome; CWS, cannabinoid withdrawal syndrome; FAAH, fatty acid amide hydrolase; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IL, interleukin; NVP, nausea and vomiting in pregnancy; 2-AG, 2-arachidonoylglycerol; ^{9}THC, Δ^9-tetrahydrocannabinol.**

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syndrome.[8] Given these safety concerns, cannabinoids are regarded as third-line agents for chronic neuropathic pain management and should not be used in patients with a history of psychosis.[9] In July 2020, the National Institute on Drug Abuse reported that 9% of people who use cannabis will become dependent on it, increasing to approximately 17% in those who start using in their teens.[10]

Cannabinoids: Where, What, and How Do They Work?

Cannabinoid Receptors in the Digestive Tract

There are 2 G-protein–coupled membrane cannabinoid receptors, CB_1 and CB_2 receptors, as well as several other non–CB-receptor types (detailed later). The main active ingredient in cannabis is Δ^9THC, which activates both types of receptors. CB_1 receptors are located throughout the gut, mainly in myenteric and submucosal neurons, and in non-neuronal cells such as epithelial cells.[11] CB_1 receptors also are located in the brain. CB_2 receptors are located mainly in inflammatory and epithelial cells and, to a lesser extent, in myenteric and submucosal neurons.[12,13]

Endogenous ligands (called endocannabinoids, anandamide, and 2-arachidonoylglycerol [2-AG]) activate cannabinoid receptors. In the digestive tract, cannabinoid receptors are identified in cholinergic, tachykininergic, or vasoactive intestinal peptide–ergic nerves of the myenteric and submucosal plexuses[14]; in nerve fibers in circular and longitudinal muscles; in non-neuronal cells including crypt epithelial cells; and indirectly in smooth muscle cells through neuronal input.[14–16] Expression levels of the endocannabinoid system in intestinal diseases have been studied extensively.[17]

Endocannabinoid Biosynthesis, Retrograde Messengers, and Inactivation

The biosynthesis of endocannabinoids is derived from membrane phospholipids and occurs on demand, and is followed by immediate release extracellularly (eg, into a synapse). The endocannabinoids (anandamide [AEA] and 2-AG) are synthesized in postsynaptic neurons. The synthesis results from the action of synthetic enzymes, specifically N-arachidonoyl phosphatidyl ethanolamine–preferring phospholipase D for AEA and diacyl glycerol lipase-α for 2-AG (Figure 1).[18]

These endocannabinoids function as retrograde messengers and, after release into the synaptic cleft, AEA binds to CB_1 presynaptic receptors, whereas 2-AG binds to both CB_1 and CB_2 presynaptic receptors. Such receptor binding activates diverse intracellular effectors in the presynaptic neurons or other target cells, resulting in modulation of ion channels and reducing neurotransmitter (eg, acetylcholine) release. In addition to the effects on cannabinoid receptors, AEA also may activate the transient receptor potential, vanilloid type 1, in primary afferent neurons, which have important sensory functions, as well as the orphan G-protein–coupled cannabinoid receptor 55.[19] Having completed the activation of presynaptic cannabinoid receptors to induce a biological action, the endocannabinoids undergo reuptake by membrane transporters into the postsynaptic neuron (Figure 1). They undergo enzymatic degradation by fatty acid amide hydrolase (FAAH) for AEA or monoamine glycerol lipase for 2-AG. The common end product of these degradations is arachidonic acid, which undergoes further oxidative transformation by enzymes such as cyclo-oxygenase-2, lipoxygenase, or epoxygenase/cytochrome P450; the other metabolites are ethanolamine and glycerol.[20] Figure 1 also serves to contrast endocannabinoids and neurotransmitters. Endocannabinoids are synthesized on demand postsynaptically to act presynaptically to fine tune effects of a neurotransmitter on a postsynaptic receptor. Neurotransmitters are synthesized presynaptically and stored in vesicles to stimulate postsynaptic receptor, and the effect is modified by re-uptake or acting via presynaptic receptors to inhibit further transmitter release.[21]

In the normal gut, both CB_1 and CB_2 receptors and the respective synthetic and degradative enzymes for endocannabinoids are expressed in the enteric nervous system, smooth muscles, and blood vessels. In the gastrointestinal epithelium, there are CB_1 receptors in health, and increased expression of CB_2 receptors occurs in the gastrointestinal epithelium and lamina propria immunocytes, especially macrophages in inflammation.[22] CB_1 receptors are present on intrinsic primary afferents, as well as extrinsic spinal and vagal afferents, and enteric neurons involved in the peristaltic reflex.[23] Effects of CB receptors modulate intestinal ion transport and intestinal permeability, including perturbations by a high-fat diet.[24,25]

Exogenous or administered cannabinoids can activate the same presynaptic receptors to modulate neurotransmitter release or sensory receptors. Cannabinoids are involved in diverse gut functions including regulation of food intake, nausea and emesis, gastric secretion and gastroprotection, inhibition of gut motility, ion transport with increased mucosal permeability, visceral sensation, reduction of intestinal inflammation, and cell proliferation.[26] Other than effects on intestinal permeability, which are mediated through CB_1 receptors, the other functions generally are mediated by both CB_1 and CB_2 receptors.[23,26]

Effects of Cannabis and Its Derivatives on Gastrointestinal Organs and Functions

Figure 2 summarizes the multitude of effects of cannabis and its derivatives in gastrointestinal organs and illustrates effects on the liver, metabolism, and

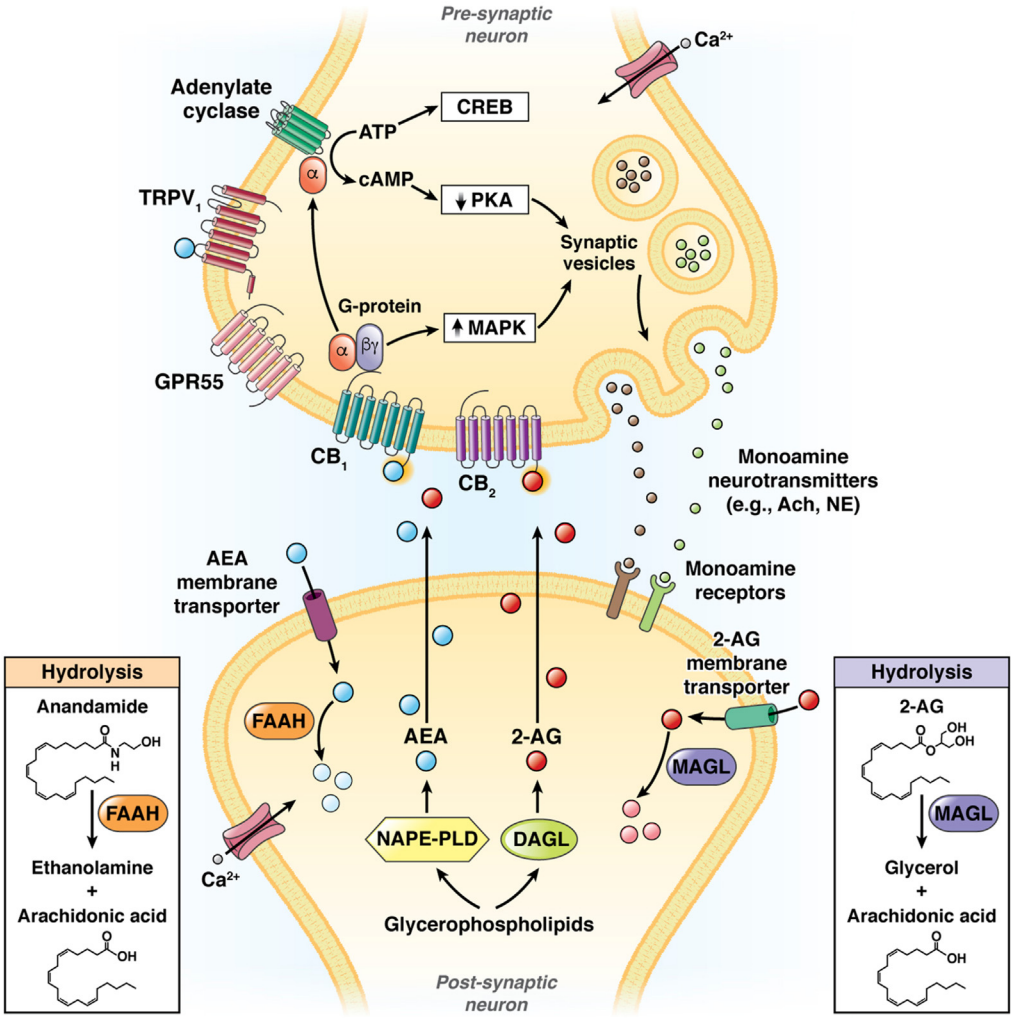

Figure 1. The biosynthesis of endocannabinoids is derived from membrane phospholipids and occurs on demand and is followed by immediate release extracellularly (eg, into a synapse). The endocannabinoids (anandamide [AEA] and 2-arachidonoylglycerol [2-AG]) are synthesized in postsynaptic neurons. The synthesis results from the action of synthetic enzymes, specifically N-arachidonoyl phosphatidyl ethanolamine-preferring phospholipase D (NAPE-PLD) for AEA and diacyl glycerol lipase-α (DAGLα) for 2-AG. Ach, ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CB, cannabis; CREB, cAMP response element-binding protein; FAAH, fatty acid amide hydrolase; GPR55, G-protein–coupled cannabinoid receptor 55; MAGL, monoacylglycerol lipase; MAPK, mitogen-activated protein kinase; NE, norepinephrine; PKA, protein kinase; TRPV1, transient receptor potential, vanilloid type 1. Reprinted with permission from Maselli and Camilleri.[18]

pancreas.[27] These effects are reviewed in greater detail in forthcoming sections.

Cannabinoid Use

Cannabis use in the US population is increasing, while an increasing number of US states and territories have legalized its medical and recreational use.[28] The percentage of cannabis users in the United States increased significantly from 11% (or 25.8 million people) in 2002 to 17.5% (or 48.2 million people) in 2019.[29]

Relationship to Cannabis Legalization

Many states in the United States have legalized cannabis for medicinal and/or recreational use. In a study from 17 health care institutions in 15 states, it was reported that states may experience an increase in cannabis-related emergency department visits with progression toward cannabis legalization. The differences between states were deemed likely to be multifactorial, including cultural norms, attitudes of local law enforcement, differing patient populations, legalization in surrounding states, availability of dispensaries, various ordering protocols in the emergency departments, and the prevalence of nonregulated cannabis products.[30]

A significant increase in prenatal cannabis exposure has been reported in recent years,[29] with an estimated 4% to 7% of women using cannabis during pregnancy (reviewed by Kitsantas et al[31]).

A systematic review involving 13 publications, reporting on 333,550 study participants and 855,630 presentations to emergency departments in North America,[32]

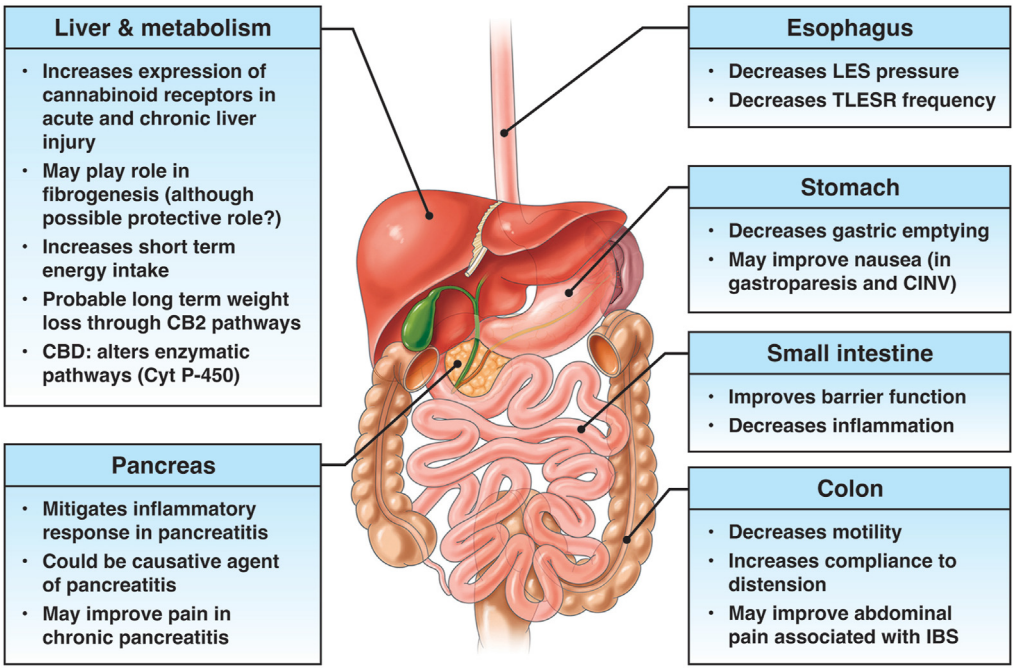

Figure 2. Summary of the multitude of effects of cannabis and its derivatives in gastrointestinal organs and effects on the liver, metabolism, and pancreas. CBD, cannabidiol; CB2, cannabinoid 2; CINV, chronic idiopathic nausea and vomiting; Cyt P-450, cytochrome P-450; IBS, irritable bowel syndrome; LES, lower esophageal sphincter; TLESR, transient lower esophageal sphincter relaxation. Adapted with permission from Gotfried et al.[27]

with the majority from western US states, documented that increased availability of legal cannabis was linked to increased current cannabis use and health-related outcomes (vomiting, psychosis, or cannabis-involved pregnancies) among both adults and adolescents. The positive correlation between cannabis availability and consumption was most pronounced among the groups who had been less exposed to cannabis before legalization.[32]

Relationship to Discrimination and Prior Life Experiences

Racial/ethnic discrimination is associated with use of individual tobacco and cannabis products, and use outcomes were more profound for non-Hispanic White and non-Hispanic Black adults than adults from other racial/ethnic populations.[33] Moreover, there is significant substance misuse, including cannabis, opioids, stimulants, sedatives, and other drugs in older individuals; these were higher in Vietnam-era veterans than nonveterans. Veterans may be at particular risk owing to service-related experiences and later-life tribulations.[34,35] In addition, veterans with post-traumatic stress disorder and substance use disorders were more likely to have cannabis-positive urine drug test results.[36]

Among adult cancer survivors, approximately 50% used cannabis for medical reasons during the 2019 to 2021 coronavirus disease-2019 pandemic.[37] Among 162 adults with inflammatory bowel disease (IBD) at an IBD clinic in Puerto Rico, 37% reported use of cannabis, with 63% of users reporting use to relieve their IBD.[38] Several studies have documented the use of cannabis for relief of symptoms among patients with gastroparesis as well as hospital readmission rates among these patients.[39,40] Based on a nationwide inpatient sample database from January 2012 to December 2014 among patients with a primary diagnosis of gastroparesis, those with increased odds of cannabis use were younger and of African American, Asian, or Pacific Islander descent, and they had Medicaid insurance and a lower median household income.[41] On the other hand, among patients with gastroparesis hospitalized in 2016 and 2017 (99,695 hospitalizations), the inpatient mortality rate was 0.27%, and they had a shorter length of stay, lower total hospital charge, and lower sepsis rates.[42]

Cannabinoids and Gut Motility

Altered mechanisms of control of cannabinoid expression are associated with gut dysmotilities. For example, decreased FAAH is associated with slow-transit constipation[43] and there was increased expression of G-protein-coupled receptor 55 in a streptozotocin mouse model of gastroparesis.[44] Pharmacologic effects of cannabinoid mechanisms on human gut motility and sensation were shown with dronabinol, a synthetic nonselective cannabinoid agonist, which delayed gastric emptying of solids[45] and inhibited postprandial colonic motility and tone,[46] although no significant effect on colonic transit was noted.[45] Animal and in vitro studies showed cannabinoid inhibition of colonic contractility,[47] whereas inhibitors of synthesis of endocannabinoids accelerated colonic transit in mice.[48]

Cannabinoids and the Pancreas

Cannabinoid receptors are found on α and β cells of the endocrine pancreas, aiding in the release of insulin.[49] Acute pancreatitis is a rare complication of cannabinoid

use in human beings,[50,51] and the lifetime risk increases with the duration of cannabis use.[52] In animal models of cerulein-induced pancreatitis, CB_1-receptor activation worsened disease activity,[53] whereas CB_1- and CB_2-receptor agonists or selective CB_2-receptor agonists improved pain-related behavior, inflammation, and tissue damage.[54]

Cannabinoid modulation of pain in chronic pancreatitis has been associated with deactivation of proinflammatory pathways (p38 mitogen-activated protein kinase, mammalian target of rapamycin, and extracellular signal-regulated kinases pathways).[55] Clinical trials have shown contradictory information. Namisol (Echo Pharmaceuticals, Leiden, Netherlands) (which contains pure, natural Δ^9THC) showed no change in proinflammatory (tumor necrosis factor-α and interleukin [IL] 8) or anti-inflammatory (IL10) cytokines compared with baseline,[56] and Δ^9THC did not significantly reduce pain in chronic pancreatitis.[57] In contrast, 53 patients with chronic pancreatitis on opioid therapy showed a trend toward decreased daily average opioid use and decreased hospital admissions and emergency department visits compared with those not enrolled.[58] Concomitant cannabis use also was reported to reduce the odds of acute and chronic pancreatitis among individuals with abusive alcohol consumption.[59]

Antigrowth and pro-apoptotic properties have been observed in in vitro appraisals of cannabinoids in models of pancreatic cancer[60] and, particularly, effects of cannabidiol in pancreatic cancer cell lines.[61,62] However, there are no clinical studies of cannabinoid use to treat pancreatic malignancy.

Cannabinoids and the Liver

CB_1 receptors are expressed on endothelial cells and hepatocytes, and CB_2 receptors are expressed on Kupffer cells. Figure 2 depicts the mechanistic effects of the endocannabinoids, 2-AG and AEA, in liver diseases.[63] Endocannabinoids show multiple effects in the liver,[64] including inhibition of the inflammatory response of Kupffer cells, fibrogenesis, and activation of quiescent hepatic stellate cells through CB_2 receptors. On the other hand, CB_1 receptors promote fibrogenesis and activation of quiescent hepatic stellate cells, promote apoptosis in hepatocytes, increase lipogenesis and hepatic steatosis, and promote liver regeneration and immune tolerance in hepatocellular carcinoma (HCC).[65] Cannabidiol was shown to suppress HCC cell growth in vivo and in vitro and to induce HCC cell pyroptosis; thus, it could be considered as a potential compound for HCC therapy.[66]

Cannabinoid treatment has been studied in nonmalignant chronic liver diseases.[67] In nonalcoholic fatty liver disease, endocannabinoids and cannabinoid receptors are up-regulated in hepatic tissue. In rodent models of liver disease, CB_2-receptor agonists reduce the progression of inflammation and fibrosis.[68] Rimonabant, a CB_1 inverse agonist, reduced liver regeneration, portal pressure, and ascites in rodents with cirrhosis.[69] In patients with chronic hepatitis B infection, levels of CB_1 and CB_2 increased with the degree of fibrosis,[70] and were expressed by activated hepatic stellate cells.[70] Similarly, daily cannabis smoking is associated with progression of fibrosis in chronic hepatitis C.[71] In turn, CB_1-receptor expression was increased in patients with alcoholic liver fibrosis[72] and chronic hepatitis C infection, and was associated with fibrosis stage and cirrhosis steatosis.[73] Inhibition of CB_1 protected against alcohol-induced fibrosis.[71] On the contrary, a recent meta-analysis suggested a possible protective effect of cannabis (a CB_1 and CB_2 agonist) use in hepatic steatosis and possibly fibrosis.[74] Cannabidiol inhibited collagen gene transcription and synthesis and prevented transforming growth factor β– and IL4-induced fibroblast migration in a CCl_4 model of liver fibrosis.[75]

There may be a potential role of cannabinoids in autoimmune hepatitis, based on preliminary data and animal models,[76] although this has yet to be shown in human beings.

Cannabis use in patients with cirrhosis resulted in mixed outcomes regarding hospital admissions with hepatic decompensation. Those using cannabis after its legalization had a decreased rate of admissions related to hepatorenal syndrome and a trend to decreased hospital utilization and mortality. However, cannabis users with cirrhosis other than related to alcohol and hepatitis C had a higher risk of admission for hepatic encephalopathy.[77]

Cannabinoids and Vomiting Syndromes

Cannabinoids are associated with cyclic vomiting syndrome (CVS), cannabinoid hyperemesis syndrome (CHS), cannabinoid withdrawal syndrome (CWS), and nausea and vomiting in pregnancy.

CVS is a relatively frequent presentation (10.8%) among patients with intermittent episodes of nausea and vomiting seeking care in outpatient gastroenterology clinics. CVS is associated with younger age, tobacco use, psychiatric comorbidity, and symptoms compatible with other disorders of gut–brain interaction.[78] In a study of 140 patients with CVS at a specialized clinic, 72% were female and the mean age was 37 $\pm$ 13 years; 41% were current cannabis users and 21% reported regular use. The latter use pattern was more likely in males and was associated with report of an anxiety diagnosis and with smoking cannabis with higher Δ^9THC content and for a longer duration. Most users reported that cannabis helped control CVS symptoms, and abstinence rarely resolved the CVS episodes.[79] A recent review of CVS concluded that prophylactic therapy consists of tricyclic antidepressants (amitriptyline), antiepileptics (topiramate), and aprepitant in refractory patients, and abortive therapy consists of triptans, antiemetics (ondansetron), and sedation.[80] The review also showed

that treatment of comorbid conditions is extremely important to improve overall patient outcomes.[80]

CHS is characterized by the association of chronic cannabis use with persistent nausea and vomiting, abdominal pain, and (in the original article by Allen et al[8]) compulsive bathing.[8] It is noteworthy that the bathing is neither compulsive nor universal in CHS and is not deemed to be pathognomonic of cannabis use[81] because symptom relief with hot baths or showers was observed in 48% of CVS patients with no cannabis use compared with 72% who used cannabis.[82] In a series of almost 100 patients, approximately 75% of patients had used cannabis at least 4 days per week and approximately 68% for 2 or more years.[83] It has been proposed that a presumptive diagnosis of CHS may be considered when chronic (>1 year), daily use is encountered in the context of cyclic vomiting, and a failure to respond to standard prophylactic agents.[84]

Based on an internet survey of 157 CHS sufferers in Canada and the United States, there were 15 emergency department visits per 100,000 population before legalization, 21 after legalization, and 32 (95% CI, 31–35) during the beginning of the coronavirus disease-2019 pandemic, with treatment prevalence among chronic cannabis users as high as 6 per 1000 in the group aged 16 to 24 years.[85] In a study of 72 hospitalizations for CHS in Massachusetts, there was increased hospital resource utilization postlegalization, with increased length of stay, increased mean costs even after adjusting for medical inflation, increased intravenous fluid administration, and increased endoscopy costs.[86]

Among 271 cases of CHS evaluated between 2000 and 2018,[84] the mean age of patients was 30.5 ± 7.6 years, 68.6% were male, the mean duration of cannabis use before symptom onset was 6.6 ± 4.3 years (with daily use in 68%), and compulsive hot-water bathing in 71.5%. Moreover, case reports in the recent literature document rare complications of CHS, including pneumomediastinum for esophageal microperforation, hypophosphatemia, acute renal injury, nephrolithiasis, and even severe burns secondary to the hot baths. A systematic review of pharmacologic treatments for CHS could not identify optimal treatment. In general, benzodiazepines, haloperidol, and capsaicin have been efficacious for acute treatment, and tricyclic antidepressants for long-term treatment.[87] For both CHS and CVS, treatment with the neurokinin 1 antagonist, aprepitant, is reported to be efficacious.[88,89]

Just as it is important to recognize CHS and CVS, it is relevant that patients may develop symptoms on cessation through decreased central nervous system stimulation, or CWS, which also is recognized as International Classification of Disease, 10th revision, code F12.30. CWS affects women more frequently, occurring anytime from 1 to 10 days after last consumption, is associated less often with abdominal pain and vomiting (8.3% compared with 85.1% for CHS), and hot showers virtually exclude CWS. Psychological symptoms are extremely common and may impair quality of life,[90] and can get worse with time, up to 4 weeks, presumably the time for CB_1 receptors to return to their original state in the central dopaminergic pathways.[91]

Table 1 is an adaptation of a summary of the differences in the clinical history between CHS and CWS.[91] Treatment options for CWS include approaches to replace and taper by protocol oral THC with dronabinol, nabiximols, or nabilone combined with zolpidem to improve withdrawal symptoms (altered mood and sleep, nausea. and craving) and increase prolonged abstinence, or with gabapentin and behavioral therapies, which help improve symptoms while reducing relapse (reviewed by Razban et al[91]).

Cannabis is used to relieve nausea and vomiting in pregnancy (NVP); however, there is evidence suggesting aggravation of NVP by cannabis. Thus, among 220,510 pregnancies (2009–2016), of which 17.6% had a diagnosis of NVP, the rate of use was approximately 2-fold higher in those with NVP. The trends to increased use of cannabis over time increased similarly in NVP and non-NVP pregnant women.[92] Among 9250 participants, of which 5.8% had detectable urine Δ^9THC levels, those with positive test results had greater odds of moderate-to-severe nausea (20.7% vs 15.5% with undetected levels).[93]

Given that systematic reviews and meta-analyses found associations between cannabis use and adverse perinatal outcomes, especially with heavy cannabis use (eg, growth restriction, stillbirth, spontaneous preterm birth, and neonatal intensive care unit admission), women are advised to refrain from using cannabis during pregnancy and lactation.[94] Open discussion of cannabis consumption during pregnancy is very challenging for patients and maternity care providers in the current environment of variable legal status across states and variable degrees of personal and societal acceptance.[95] However, there is evidence of a therapeutic benefit of dose-dependent cannabis or its extracts in some post-partum depression symptoms.[96]

Cannabinoid Use in Patients With Gastroparesis

Δ^9THC delays gastric emptying of solid food in human beings.[97] Among 506 patients with symptoms of idiopathic or diabetic gastroparesis in the National Institutes of Health Gastroparesis Consortium database, 11.7% reported current cannabis use, particularly in those with severe nausea and abdominal pain, and they perceived it to be beneficial for their symptoms.[39] Use of cannabis was similar in idiopathic and diabetic patients, although users were younger; more often current tobacco smokers; and less likely to be a college graduate, married, or have income greater than $50,000. In a separate study, 24 patients with gastroparesis and refractory symptoms reported cannabis induced a significant improvement in every Gastroparesis Cardinal Symptom Index subgroup, as well as in abdominal pain score.[98]

Table 1. Adaptation of a Summary of the Differences in the Clinical History Between Cannabinoid Hyperemesis Syndrome and Cannabinoid Withdrawal Syndrome

Clinical history	Cannabinoid hyperemesis syndrome	Cannabinoid withdrawal syndrome
Onset of symptoms, from last consumption of cannabis	<24 hours	>24 hours
Compulsive hot showers, as symptomatic relief	Yes	No
Accompanying psychological symptoms	No	Yes
Clinical course/pattern	Well described, 3 phases, development of tolerance with escalating dosing	No
Quantity correlating with severity	No	Yes
Symptoms with cannabis consumption	Worse	Relief
Diagnostic criteria	Rome IV	DSM-V: ≥3 criteria within 1 week of reducing/ceasing cannabinoid use
	Criteria fulfilled for the past 3 months, symptom onset at least 6 months before diagnosis Stereotypical episodic vomiting resembling cyclic vomiting syndrome in terms of onset, duration, and frequency Presentation after prolonged, excessive cannabis use. Relief of vomiting episodes by sustained cessation of cannabis use Supportive feature: pathologic bathing behavior (prolonged hot baths or showers)	Irritability; anger or aggression Nervousness or anxiety Sleep difficulty Decreased appetite or weight loss Restlessness Depressed mood Somatic symptoms causing significant discomfort

DSM-V, Diagnostic and Statistical Manual of Mental Disorders, 5th ed. https://doi.org/10.1176/appi.books.9780890425596.
Reprinted with permission from Razban et al.[91]

Cannabis-related improvement in symptoms in patients with gastroparesis may be unrelated to slowing of gastric emptying in healthy volunteers by Δ^9THC[97] and by dronabinol,[45] although the latter study showed a trend to reduced postprandial fullness. Effects on visceral sensation[26] may contribute to improvement in symptoms.

Cannabinoid Mechanisms and Intestinal Inflammation

Mechanisms related to endocannabinoids and their receptors participate in the pathobiology of IBD.[27,99] Cannabinoids protect against colonic inflammation in rodent[100] and human models, and they decrease the permeability of the human colon compared with controls.[101]

Several studies in animal models have documented the effects of cannabinoids in bowel inflammation. Thus, activation of both CB_1 and CB_2 receptors reduced colon weight gain, colon shrinkage, colon inflammatory damage score, and diarrhea induced by experimental colitis.[102] Genetic ablation of CB_1 receptors or CB_1-receptor antagonists rendered mice more sensitive to colitis.[100] FAAH-deficient mice as well as inhibitors of anandamide reuptake or enzymatic hydrolysis (all with presumed higher levels of anandamide) showed protection against colonic inflammation.[100,103] Anandamide levels and expression of cannabinoid receptors were increased in the inflamed colon.[100,103] CB_1 and CB_2-receptor activation reduced hypersensitivity and pain induced by experimental colitis.[104]

Patients with IBD show greater quantity used and an earlier age of onset of cannabis use compared with age- and sex-matched controls; thus, 6.8% to 17.6% of IBD patients use cannabis.[105] In multivariable logistic regression, the presence of IBD, male gender, and age older than 40 years predicted cannabis use.[105] Despite symptom relief, cannabis does not necessarily induce IBD remission. In fact, based on population studies, cannabis appears to be a predictor for the need for surgical intervention in Crohn's disease.[106] On the other hand, many patients with IBD who use cannabis experience improved symptoms and often do not disclose this use to their physicians.[38] Similarly, use of cannabis-based medicinal products was associated with short-term improvement in IBD patients with refractory symptoms.[107]

Several placebo-controlled studies in IBD have documented some benefits of cannabinoid treatments (including inhaled Δ^9THC or cannabis or cannabidiol-rich botanical extracts) on symptoms and quality of life (Table 2).[108–112] Ultimate proof of efficacy has not yet been documented. A systematic review and meta-analysis of these 5 trials documented borderline cannabinoid induction of remission based on randomized

Table 2. Several Placebo-Controlled Studies Documenting Some Benefits of Cannabinoid Treatments (Including Inhaled Δ^9THC or Cannabis or Cannabidiol-Rich Botanical Extracts) on Symptoms and Quality of Life in Inflammatory Bowel Disease,[108–112] Although Ultimate Proof of Efficacy Is Not Yet Documented

IBD	Cannabinoid used, *wk*	Patients, n	Primary outcome	Other comments	Study
Unresponsive Crohn's	Inhaled (cigarettes) containing 11.5 mg Δ^9THC; 8 wk	21	↓ CDAI score <150 *not* achieved	↓ CDAI score by >100 achieved in 10 of 11 vs 4 of 10 with placebo; improved QOL	Naftali et al[108]
Unresponsive Crohn's CDAI >200	10 mg CBD oil b.i.d. p.o.; 8 wk	20	No change in CDAI of CBD vs placebo at 8 wk and 2 wk later	AEs: no change between CBD and placebo groups	Naftali et al[109]
Left-sided UC on 5-ASA, Mayo score, 4–10	50 mg CBD-rich botanical extract; 10 wk	60	No Δ in number achieving Mayo score <2 on ITT analysis	39 completers; 21 withdrew (15 owing to AEs; 10 on CBD) Per-protocol analysis of total and partial Mayo UC scores and pain favored CBD-rich botanical extract	Irving et al[110]
UC; moderately active	Inhaled (cigarettes) 0.5 g dried cannabis (with 80 mg Δ^9THC) vs placebo 2 cigarettes/d; 8 wk	32	UC disease activity score by Lichtiger score and Mayo score	Clinical and endoscopic improvement relative to placebo: Lichtiger index ($P < .001$) and QOL improved ($P < .007$) Mayo endoscopic score changed in the CB group from 2.13 ± 1 to 1.25 ± 2 ($P = .015$), but the *P* value between groups was .17	Naftali et al[111]
Crohn's CDAI ≥200 and SES-CD ->2.	Oral CBD/THC 4:1 oil p.o.; 8 wk	56	CDAI, SES-CD, inflammation markers	Significant improvement in CDAI scores and median QOL scores No change in endoscopic score, CRP, or calprotectin level	Naftali et al[112]

AE, adverse event; b.i.d., twice daily; CB, cannabis; CBD, cannabidiol; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IBD, inflammatory bowel disease; ITT, intent to treat; p.o., orally; QOL, quality of life; SES-CD, Simple Endoscopic Score for Crohn's Disease; Δ^9THC, Δ^9-tetrahydrocannabinol; UC, ulcerative colitis.
Adapted with permission from Maselli and Camilleri.[18]

controlled trials, with an odds ratio of 1.56 (95% CI, 0.99–2.46) and significant effects on disease activity indices and improved scores on the short Inflammatory Bowel Disease Questionnaire.[113]

Management of pain in IBD is clinically challenging. Opiates increase the risk of death, and nonsteroidal anti-inflammatory drugs may induce stricture formation and ulceration. The potential of cannabis modulation of pain in Crohn's disease has been reported in a dose-related, open-label, parallel-group, multicenter, phase 2a study with the CB_2-receptor agonist, olorinab (pharmacologic actions detailed in the next section), for 8 weeks, administered at doses of 25 or 100 mg 3 times per day in 14 patients with quiescent Crohn's disease experiencing average weekly abdominal pain. The average abdominal pain score at weeks 4 and 8 improved compared with baseline, and other benefits included a higher number of pain-free days per week.[114] Further comparator-controlled studies are awaited.

Cannabinoid System Targets of Visceral Pain

CB_2 receptors are expressed in the brain, peripheral nervous system, and gastrointestinal tract,[115] and they are being targeted for potential analgesia without the psychic effects of nonselective cannabinoids such as Δ^9THC or dronabinol. $^9\Delta$THC was tested in 3 types of chronic pain: abdominal, pancreatic, and postsurgical pain, and proved ineffective relative to placebo.[57]

Palmitoylethanolamide is an endogenous fatty acid amide with a structure similar to anandamide, and binds to a nuclear receptor and has diverse biological functions related to chronic pain and inflammation. Palmitoylethanolamide/polydatin, 20 or 200 mg twice daily, was effective in reducing the severity of abdominal pain/discomfort compared with placebo in 54 patients with irritable bowel syndrome (IBS) and 12 healthy controls.[116]

Olorinab (formerly APD371) is a highly selective, full agonist of CB_2 receptors. Its visceral analgesic effects were shown in several preclinical models of pancreatitis, trinitrobenzene sulfonic acid colitis,[117] and chronic visceral hypersensitivity.[118]

The CAPTIVATE phase 2 trial[119] tested the efficacy of olorinab in patients with IBS. In a prespecified subgroup analysis of participants with a baseline average abdominal pain score of 6.5 or higher, 50 mg olorinab ($n = 35$) significantly improved the average abdominal pain score compared with placebo ($n = 30$), with greater efficacy in patients with constipation-predominant IBS.

Cannabidiol Pharmacology and Trials in Functional Dyspepsia, Irritable Bowel Syndrome, and Gastroparesis

Cannabidiol is a CB_2-receptor (CBR_2) agonist and CBR_1 antagonist that is nonpsychotropic and has significant anti-inflammatory effects. It modulates multiple receptors including being an agonist at serotonergic 5-HT1A, adenosine A1 and A2A, and transient receptor potential vanilloid type 1 receptor, and is an allosteric modulator of μ and δ opioid receptors.[120] It has been approved by the Food and Drug Administration (FDA) for seizure disorders affecting pediatric patients (Epidiolex [JAZZ/Greenwich Pharmaceuticals, Ireland]).

In a placebo-controlled trial in patients with functional dyspepsia and normal gastric emptying of solids, cannabidiol administered at a dose escalated to 10 mg/kg for 4 weeks (as recommended by the FDA for seizure indication) was not superior to placebo in terms of effects on gastric functions such as emptying of solids, fasting and postprandial gastric volumes, and postprandial satiation. It also did not result in improvement of pain-based patient response outcomes on the Nepean Dyspepsia Index (quality of life). A borderline cannabidiol treatment-by-genotype (CBR1) interaction was identified for one of the pain end points, the Leuven postprandial distress score, although the clinical significance will require replication.[121]

A cannabidiol chewing gum (containing 50 mg cannabidiol) was tested in patients with IBS in a placebo-controlled, crossover study based on visual analog scale scores just before and 30 minutes after the start of chewing a cannabidiol or placebo gum. Pain intensity was estimated with a visual analog scale device consisting of a stainless steel ruler. There was no significant effect on pain score or quality of life.[122]

The FDA-approved formulation of cannabidiol also was tested in 44 patients with gastroparesis and documented slow gastric emptying at baseline. In these patients, there was a significant slowing of gastric emptying. However, cannabidiol significantly reduced the total Gastroparesis Cardinal Symptom Index–Daily Diary score averaged over 4 weeks, as well as the perceived severity of gastroparesis, ability to finish a meal, and vomiting episodes per 24 hours. There was a borderline effect on upper abdominal pain. Cannabidiol also was associated with significantly higher kilocalorie ingestion to fullness and maximum tolerated calories during a nutrient drink satiation test (ingestion at 30 kcal/min).[123]

Conclusions

Cannabinoids are associated with cannabinoid hyperemesis syndrome and cyclic vomiting syndrome, and appear to aggravate nausea and vomiting in pregnancy, but many patients experience benefit in terms of relief of symptoms such as gastroparesis, nausea syndromes, and IBD. Liberalization of availability appears to be having some deleterious effects in terms of dependence and other addictive behaviors. Clinical controlled trials are documenting that cannabinoids, particularly those targeting CB_2 receptors, have the potential for

inflammatory and pain disorders as well as gastroparesis. Although the risk–benefit of cannabinoids in gastrointestinal diseases requires further research, there appear to be several promising leads that will individualize which disease states constitute the most appropriate indications for use.

References

1. World Health Organization. Cannabis. Alcohol, drugs and addictive behaviours unit. 2022. https://www.who.int/teams/mental-health-and-substance-use/alcohol-drugs-and-addictive-behaviours/drugs-psychoactive/cannabis. Accessed July 30, 2023.
2. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 2015;313:2456–2473.
3. Meng H, Johnston B, Englesakis M, et al. Selective cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis. Anesth Analg 2017;125:1638–1652.
4. Tait RJ, Caldicott D, Mountain D, et al. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin Toxicol 2016;54:1–13.
5. Weinstein AM, Rosca P, Fattore L, et al. Synthetic cathinone and cannabinoid designer drugs pose a major risk for public health. Front Psychiatr 2017;8:156.
6. Richards JR, Smith NE, Moulin AK. Unintentional cannabis ingestion in children: a systematic review. J Pediatr 2017;190:142–152.
7. Grant KS, Petroff R, Isoherranen N, et al. Cannabis use during pregnancy: pharmacokinetics and effects on child development. Pharmacol Ther 2018;182:133–151.
8. Allen JH, de Moore GM, Heddle R, et al. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut 2004;53:1566–1570.
9. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag 2014;19:328–335.
10. National Institute on Drug Abuse. 2020. https://nida.nih.gov/download/1380/cannabis-marijuana-research-report.pdf?v=7fc7d24c3dc120a03cf26348876bc1e4. Accessed July 30, 2023.
11. Camilleri M. Cannabinoids and gastrointestinal motility: pharmacology, clinical effects, and potential therapeutics in humans. Neurogastroenterol Motil 2018;30:e13370.
12. Duncan M, Mouihate A, Mackie K, et al. Cannabinoid CB2 receptors in the enteric nervous system modulate gastrointestinal contractility in lipopolysaccharide-treated rats. Am J Physiol Gastrointest Liver Physiol 2008;295:G78–G87.
13. Wright KL, Duncan M, Sharkey KA. Cannabinoid CB2 receptors in the gastrointestinal tract: a regulatory system in states of inflammation. Br J Pharmacol 2008;153:263–270.
14. Duncan M, Davison JS, Sharkey KA. Endocannabinoids and their receptors in the enteric nervous system. Aliment Pharmacol Ther 2005;22:667–683.
15. Wright K, Rooney N, Feeney M, et al. Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing. Gastroenterology 2005;129:437–453.
16. Hinds NM, Ullrich K, Smid SD. Cannabinoid 1 (CB1) receptors coupled to cholinergic motorneurones inhibit neurogenic circular muscle contractility in the human colon. Br J Pharmacol 2006;148:191–199.
17. Lee Y, Jo J, Chung HY, et al. Endocannabinoids in the gastrointestinal tract. Am J Physiol 2016;311:G655–G666.
18. Maselli DB, Camilleri M. Pharmacology, clinical effects, and therapeutic potential of cannabinoids for gastrointestinal and liver diseases. Clin Gastroenterol Hepatol 2021;19:1748–1758.e2.
19. Brown AJ. Novel cannabinoid receptors. Br J Pharmacol 2007;152:567–575.
20. Hourani W, Alexander SPH. Cannabinoid ligands, receptors and enzymes: pharmacological tools and therapeutic potential. Brain Neurosc Adv 2018;2:2398212818783908.
21. Schlicker E, Feuerstein T. Human presynaptic receptors. Pharmacol Ther 2017;172:1–21.
22. Hasenoehrl C, Taschler U, Storr M, et al. The gastrointestinal tract – a central organ of cannabinoid signaling in health and disease. Neurogastroenterol Motil 2016;28:1765–1780.
23. Izzo AA, Camilleri M. Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. Gut 2008;57:1140–1155.
24. Cavin J-B, Cuddihey H, MacNaughton WK, et al. Acute regulation of intestinal ion transport and permeability in response to luminal nutrients: the role of the enteric nervous system. Am J Physiol Gastrointest Liver Physiol 2020;318:G254–G264.
25. Cuddihey H, Cavin J-P, Keenan CM, et al. Role of CB 1 receptors in the acute regulation of small intestinal permeability: effects of high-fat diet. Am J Physiol Gastrointest Liver Physiol 2022;323:G219–G238.
26. Sharkey KA, Wiley JW. The role of the endocannabinoid system in the brain-gut axis. Gastroenterology 2016;151:252–266.
27. Gotfried J, Naftali T, Schey R. Role of cannabis and its derivatives in gastrointestinal and hepatic disease. Gastroenterology 2020;159:62–80.
28. Haffajee RL, Mauri A. Cannabis liberalization in the US: the policy landscape. Health Affairs Health Policy Brief. Published online July 1 2021. https://doi.org/10.1377/hpb20210518.36548
29. Substance Use and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health (HHS publication no. PEP20-07-01-001, NSDUH series H55). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. 2020. https://www.samhsa.gov/data. Accessed July 30, 2023.
30. Tolan NV, Krasowski MD, Mathias PC, et al. Cannabis positivity rates in 17 emergency departments across the United States with varying degrees of marijuana legalization. Clin Toxicol (Phila) 2023;61:248–259.
31. Kitsantas P, Gimm G, Aljoudi SM. Treatment outcomes among pregnant women with cannabis use disorder. Addict Behav 2023;144:107723.
32. Manthey J, Jacobsen B, Hayer T, et al. The impact of legal cannabis availability on cannabis use and health outcomes: a systematic review. Int J Drug Policy 2023;116:104039.
33. Mattingly DT, Neighbors HW, Mezuk B, et al. Racial/ethnic discrimination and tobacco and cannabis use outcomes among US adults. J Subst Use Addict Treat 2023;148:208958.
34. Cypel YS, DePhilippis D, Davey VJ. Substance use in U.S. Vietnam war era veterans and nonveterans: results from the

Vietnam Era Health Retrospective Observational Study. Subst Use Misuse 2023;58:858–870.
35. Yockey RA, Hoopsick RA. National trends in past-year marijuana use among veterans in the United States, 2013-2019. Subst Use Misuse 2023;58:822–827.
36. Zaman T, Bravata DM, Byers AL, et al. A national population-based study of cannabis use and correlates among U.S. veterans prescribed opioids in primary care. BMC Psychiatry 2023; 23:177.
37. Sarkar S, Braun IM, Nayak M, et al. Cannabis use among cancer survivors before and during the COVID-19 pandemic, 2019-2021. JNCI Cancer Spectr 2023;7:pkad031.
38. Velez-Santiago A, Alvarez-Torres E, Martinez-Rodriguez R, et al. A survey of cannabis use among patients with inflammatory bowel disease (IBD). Int J Environ Res Public Health 2023; 20:5129.
39. Parkman HP, Sharkey EP, Nguyen LA, et al. Marijuana use in patients with symptoms of gastroparesis: prevalence, patient characteristics, and perceived benefit. Dig Dis Sci 2020; 65:2311–2320.
40. Shahsavari D, Zhao H, Ehrlich AC, et al. Factors associated with hospital admissions and readmissions in patients with gastroparesis using the nationwide readmission database. J Clin Gastroenterol 2020;54:801–805.
41. Saleem S, Tarar ZI, Aziz M, et al. Marijuana use in patients with gastroparesis. Cannabis Cannabinoid Res. Published online September 6, 2022. https://doi.org/10.1089/can.2022.0189.
42. Dahiya DS, Kichloo A, Shaka H, et al. Gastroparesis with cannabis use: a retrospective study from the Nationwide Inpatient Sample. Postgrad Med 2021;133:791–797.
43. Zhang SC, Wang WL, Su PJ, et al. Decreased enteric fatty acid amide hydrolase activity is associated with colonic inertia in slow transit constipation. J Gastroenterol Hepatol 2014; 29:276–283.
44. Lin XH, Wei DD, Wang HC, et al. Role of orphan G protein-coupled receptor 55 in diabetic gastroparesis in mice. Sheng Li Xue Bao 2014;66:332–340.
45. Esfandyari T, Camilleri M, Ferber I, et al. Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: a randomized, placebo-controlled study. Neurogastroenterol Motil 2006;18:831–838.
46. Esfandyari T, Camilleri M, Busciglio I, et al. Effects of a cannabinoid receptor agonist on colonic motor and sensory functions in humans: a randomized, placebo-controlled study. Am J Physiol 2007;293:137–145.
47. Hornby PJ, Prouty SM. Involvement of cannabinoid receptors in gut motility and visceral perception. Br J Pharmacol 2004; 141:1335–1345.
48. Bashashati M, Nasser Y, Keenan CM, et al. Inhibiting endocannabinoid biosynthesis: a novel approach to the treatment of constipation. Br J Pharmacol 2015;172:3099–3111.
49. Juan-Picó P, Fuentes E, Bermúdez-Silva FJ, et al. Cannabinoid receptors regulate Ca(2+) signals and insulin secretion in pancreatic beta-cell. Cell Calcium 2006; 39:155–162.
50. Jaiswal V, Mukherjee D, Batra N, et al. Acute pancreatitis as a rare adverse event among cannabis users: a systematic review. Medicine (Baltimore) 2022;101:e29822.
51. Azam C, Buscail L, Culetto A, et al. Cannabinoid-related acute pancreatitis: an update from international literature and individual case safety reports. Drug Saf 2022;45:215–235.
52. Han B, Gfroerer JC, Colliver JD. Associations between duration of illicit drug use and health conditions: results from the 2005–2007 national surveys on drug use and health. Ann Epidemiol 2010;20:289–297.
53. Dembiński A, Warzecha Z, Ceranowicz P, et al. Cannabinoids in acute gastric damage and pancreatitis. J Physiol Pharmacol 2006;57(Suppl 5):137–154.
54. Michalski CW, Laukert T, Sauliunaite D, et al. Cannabinoids ameliorate pain and reduce disease pathology in cerulein-induced acute pancreatitis. Gastroenterology 2007; 132:1968–1978.
55. Utomo WK, de Vries M, Braat H, et al. Modulation of human peripheral blood mononuclear cell signaling by medicinal cannabinoids. Front Mol Neurosci 2017;10:14.
56. Utomo WK, de Vries M, van Rijckevorsel DC, et al. Cannabinoid receptor agonist Namisol does not affect cytokine levels in chronic pancreatitis patients. Am J Gastroenterol 2015; 110:1244–1245.
57. de Vries M, van Rijckevorsel DCM, Vissers KCP, et al. Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase 2 placebo-controlled study. Clin Gastroenterol Hepatol 2017;15:1079–1086.
58. Barlowe TS, Koliani-Pace JL, Smith KD, et al. Effects of medical cannabis on use of opioids and hospital visits by patients with painful chronic pancreatitis. Clin Gastroenterol Hepatol 2019; 17:2608–2609.
59. Adejumo AC, Akanbi O, Adejumo KL, et al. Reduced risk of alcohol-induced pancreatitis with cannabis use. Alcohol Clin Exp Res 2019;43:277–286.
60. Sharafi G, He H, Nikfarjam M. Potential use of cannabinoids for the treatment of pancreatic cancer. J Pancreat Cancer 2019; 5:1–7.
61. Luongo M, Marinelli O, Zeppa L, et al. Cannabidiol and oxygen-ozone combination induce cytotoxicity in human pancreatic ductal adenocarcinoma cell lines. Cancers (Basel) 2020; 12:2774.
62. Emhemmed F, Zhao M, Yorulmaz S, et al. Cannabis sativa extract induces apoptosis in human pancreatic 3D cancer models: importance of major antioxidant molecules present therein. Molecules 2022;27:1214.
63. Caraceni P, Domenicali M, Bernardi M. The endocannabinoid system and liver diseases. J Neuroendocrinol 2008;20: 47–52.
64. Argemi J, Bataller R. Hepatocyte-stellate cell synapse in alcohol-induced steatosis: another role for endocannabinoids. Nat Rev Gastroenterol Hepatol 2020;17:5–6.
65. Choi WM, Kim HH, Kim MH, et al. Glutamate signaling in hepatic stellate cells drives alcoholic steatosis. Cell Metab 2019; 30:877–889.
66. Shangguan F, Zhou H, Ma N, et al. A novel mechanism of cannabidiol in suppressing hepatocellular carcinoma by inducing GSDME dependent pyroptosis. Front Cell Dev Biol 2021;9:697832.
67. Mboumba Bouassa R-S, Sebastiani G, Di Marzo V, et al. Cannabinoids and chronic liver diseases. Int J Mol Sci 2022; 23:9423.
68. Bazwinsky-Wutschke I, Zipprich A, Dehghani F. Endocannabinoid system in hepatic glucose metabolism, fatty liver disease, and cirrhosis. Int J Mol Sci 2019;20:2516.
69. Dibba P, Li AA, Cholankeril G, et al. The role of cannabinoids in the setting of cirrhosis. Medicines (Basel) 2018;5:52.

70. Dai E, Zhang L, Ye L, et al. Hepatic expression of cannabinoid receptors CB1 and CB2 correlate with fibrogenesis in patients with chronic hepatitis B. Int J Infect Dis 2017; 59:124–130.
71. Hézode C, Roudot-Thoraval F, Nguyen S, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. Hepatology 2005;42:63–71.
72. Patsenker E, Stoll M, Millonig G, et al. Cannabinoid receptor type I modulates alcohol-induced liver fibrosis. Mol Med 2011; 17:1285–1294.
73. van der Poorten D, Shahidi M, Tay E, et al. Hepatitis C virus induces the cannabinoid receptor 1. PLoS One 2010;5: e12841.
74. Gangwani MK, Nawras M, Priyanka F, et al. Analytic cannabis effect on hepatic steatosis and hepatic fibrosis: a meta-analytic evaluation. Am J Ther. Published online February 28, 2023. https://doi.org/10.1097/MJT.0000000000001582.
75. Del Río C, Ruiz-Pino F, Prados ME, et al. Cannabidiol markedly alleviates skin and liver fibrosis. Front Pharmacol 2022;13: 981817.
76. Pandey R, Hegde VL, Singh NP, et al. Use of cannabinoids as a novel therapeutic modality against autoimmune hepatitis. Vitam Horm 2009;81:487–504.
77. Sobotka LA, Mumtaz K, Hinton A, et al. Cannabis use may reduce healthcare utilization and improve hospital outcomes in patients with cirrhosis. Ann Hepatol 2021;23:100280.
78. Sagar RC, Sood R, Gracie DJ, et al. Cyclic vomiting syndrome is a prevalent and under-recognized condition in the gastroenterology outpatient clinic. Neurogastroenterol Motil 2018;30.
79. Venkatesan T, Hillard CJ, Rein L, et al. Patterns of cannabis use in patients with cyclic vomiting syndrome. Clin Gastroenterol Hepatol 2020;18:1082–1090.e2.
80. Frazier R, Li BUK, Venkatesan T. Diagnosis and management of cyclic vomiting syndrome: a critical review. Am J Gastroenterol 2023;118:1157–1167.
81. Aziz I, Palsson OS, Whitehead WE, et al. Epidemiology, clinical characteristics, and associations for Rome IV functional nausea and vomiting disorders in adults. Clin Gastroenterol Hepatol 2018;17:878–886.
82. Venkatesan T, Sengupta J, Lodhi A, et al. An internet survey of marijuana and hot shower use in adults with cyclic vomiting syndrome (CVS). Exp Brain Res 2014;232:2563–2570.
83. Simonetto DA, Oxentenko AS, Herman ML, et al. Cannabinoid hyperemesis: a case series of 98 patients. Mayo Clin Proc 2012; 87:114–119.
84. Venkatesan T, Levinthal DJ, Li BUK, et al. Role of chronic cannabis use: cyclic vomiting syndrome vs cannabinoid hyperemesis syndrome. Neurogastroenterol Motil 2019;31(Suppl 2): e13606.
85. Andrews CN, Rehak R, Woo M, et al. Cannabinoid hyperemesis syndrome in North America: evaluation of health burden and treatment prevalence. Aliment Pharmacol Ther 2022; 56:1532–1542.
86. Marshall A, Fai C, Han J, et al. Rising inpatient utilization and costs of cannabis hyperemesis syndrome hospitalizations in Massachusetts after cannabis legalization. J Clin Gastroenterol Published online May 10, 2023. https://doi.org/10.1097/MCG.0000000000001857.
87. Richards JR, Gordon BK, Danielson AR, et al. Pharmacologic treatment of cannabinoid hyperemesis syndrome: a systematic review. Pharmacotherapy 2017;37:725–734.
88. Cristofori F, Thapar N, Saliakellis E, et al. Efficacy of the neurokinin-1 receptor antagonist aprepitant in children with cyclical vomiting syndrome. Aliment Pharmacol Ther 2014; 40:309–317.
89. Parvataneni S, Varela L, Vemuri-Reddy SM, et al. Emerging role of aprepitant in cannabis hyperemesis syndrome. Cureus 2019; 11:e4825.
90. Gorelick DA, Levin KH, Copersino ML, et al. Diagnostic criteria for cannabis withdrawal syndrome. Drug Alcohol Depend 2012; 123:141–147.
91. Razban M, Exadaktylos AK, Santa VD, et al. Cannabinoid hyperemesis syndrome and cannabis withdrawal syndrome: a review of the management of cannabis-related syndrome in the emergency department. Int J Emerg Med 2022;15:45.
92. Young-Wolff KC, Sarovar V, Tucker LY, et al. Trends in marijuana use among pregnant women with and without nausea and vomiting in pregnancy, 2009-2016. Drug Alcohol Depend 2019; 196:66–70.
93. Metz TD, Allshouse AA, McMillin GA, et al. Association of cannabis use with nausea and vomiting of pregnancy. Obstet Gynecol 2022;140:266–270.
94. Metz TD, Borgelt LM. Marijuana use in pregnancy and while breastfeeding. Obstet Gynecol 2018;132:1198–1210.
95. Galvin SL, Coulson CC. Addressing cannabis consumption among patients with hyperemesis gravidarum. AJOG Glob Rep 2023;3:100180.
96. Ayisire OE, Okobi OE, Adaralegbe NJ, et al. The use of cannabis and its effects on postpartum depression. Cureus 2022;14: e27926.
97. McCallum RW, Soykan I, Sridhar KR, et al. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double-blind, randomized study. Aliment Pharmacol Ther 1999;13:77–80.
98. Barbash B, Mehta D, Siddiqui M, et al. Impact of cannabinoids on symptoms of refractory gastroparesis: a single-center experience. Cureus 2019;11:e6430.
99. Ambrose T, Simmons A. Cannabis, cannabinoids, and the endocannabinoid system - is there therapeutic potential for inflammatory bowel disease? J Crohns Colitis 2019;13:525–535.
100. Massa F, Marsicano G, Hermann H, et al. The endogenous cannabinoid system protects against colonic inflammation. J Clin Invest 2004;113:1202–1209.
101. Couch DG, Cook H, Ortori C, et al. Palmitoylethanolamide and cannabidiol prevent inflammation-induced hyperpermeability of the human gut in vitro and in vivo - a randomized, placebo-controlled, double-blind controlled trial. Inflamm Bowel Dis 2019;25:1006–1018.
102. Kimball ES, Schneider CR, Wallace NH, et al. Agonists of cannabinoid receptor 1 and 2 inhibit experimental colitis induced by oil of mustard and by dextran sulfate sodium. Am J Physiol 2006;291:G364–G371.
103. D'Argenio G, Valenti M, Scaglione G, et al. Up-regulation of anandamide levels as an endogenous mechanism and a pharmacological strategy to limit colon inflammation. FASEB J 2006; 20:568–570.
104. Sanson M, Bueno L, Fioramonti J. Involvement of cannabinoid receptors in inflammatory hypersensitivity to colonic distension in rats. Neurogastroenterol Motil 2006;18:949–956.
105. Weiss A, Friedenberg F. Patterns of cannabis use in patients with inflammatory bowel disease: a population based analysis. Drug Alcohol Depend 2015;156:84–89.

106. Storr M, Devlin S, Kaplan GG, et al. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. Inflamm Bowel Dis 2014; 20:472–480.
107. Dalavaye N, Erridge S, Nicholas M, et al. The effect of medical cannabis in inflammatory bowel disease: analysis from the UK Medical Cannabis Registry. Expert Rev Gastroenterol Hepatol 2023;17:85–98.
108. Naftali T, Bar-Lev Schleider L, Dotan I, et al. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol 2013; 11:1276–1280.e1.
109. Naftali T, Mechulam R, Marii A, et al. Low-dose cannabidiol is safe but not effective in the treatment for Crohn's disease, a randomized controlled trial. Dig Dis Sci 2017;62:1615–1620.
110. Irving PM, Iqbal T, Nwokolo C, et al. A randomized, double-blind, placebo-controlled, parallel-group, pilot study of cannabidiol-rich botanical extract in the symptomatic treatment of ulcerative colitis. Inflamm Bowel Dis 2018;24:714–724.
111. Naftali T, Bar-Lev Schleider L, Benjaminov FS, et al. Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: a randomized controlled trial. PLoS One 2021;16: e0246871.
112. Naftali T, Bar-Lev Schleider L, Almog S, et al. Oral CBD-rich cannabis induces clinical but not endoscopic response in patients with Crohn's disease, a randomized controlled trial. J Crohn's Colitis 2021;15:1799–1806.
113. Doeve BH, van de Meeberg MM, van Schaik FDM, et al. Systematic review with meta-analysis of the efficacy of cannabis and cannabinoids for inflammatory bowel disease: what can we learn from randomized and nonrandomized studies? J Clin Gastroenterol 2021;55:798–809.
114. Yacyshyn BR, Hanauer S, Klassen P, et al. Safety, pharmacokinetics, and efficacy of olorinab, a peripherally acting, highly selective, full agonist of the cannabinoid receptor 2, in a phase 2a study of patients with chronic abdominal pain associated with Crohn's disease. Crohns Colitis 360 2020;3:otaa089.
115. Brierley SM, Greenwood-Van Meerveld B, Sarnelli G, et al. Targeting the endocannabinoid system for the treatment of abdominal pain in irritable bowel syndrome. Nat Rev Gastroenterol Hepatol 2023;20:5–25.
116. Cremon C, Stanghellini V, Barbaro MR, et al. Randomised clinical trial: the analgesic properties of dietary supplementation with palmitoylethanolamide and polydatin in irritable bowel syndrome. Aliment Pharmacol Ther 2017;45:909–922.
117. Lindstrom B, Ruckle J, Turner S, et al. Olorinab, a peripherally restricted, highly selective agonist of the cannabinoid receptor type 2 for the management of visceral pain in inflammatory bowel disease (IBD)—preclinical and early clinical development. Gastroenterology 2019;156:S92–S93.
118. Castro J, Garcia-Caraballo S, Maddern J, et al. Olorinab (APD371), a peripherally acting, highly selective, full agonist of the cannabinoid receptor 2, reduces colitis-induced acute and chronic visceral hypersensitivity in rodents. Pain 2022; 163:e72–e86.
119. Chang L, Cash BD, Lembo A, et al. Efficacy and safety of olorinab, a full agonist of the cannabinoid receptor 2, for the treatment of abdominal pain in patients with irritable bowel syndrome: results from a phase 2b randomized placebo-controlled trial (CAPTIVATE). Neurogastroenterol Motil 2023; 35:e14539.
120. de Almeida DL, Devi LA. Diversity of molecular targets and signaling pathways for CBD. Pharmacol Res Perspect 2020;8: e00682.
121. Atieh J, Maselli D, Breen-Lyles M, et al. Cannabidiol for functional dyspepsia with normal gastric emptying: a randomized controlled trial. Am J Gastroenterol 2022;117:1296–1304.
122. van Orten-Luiten A-CB, de Roos NM, Majait S, et al. Effects of cannabidiol chewing gum on perceived pain and well-being of irritable bowel syndrome patients: a placebo-controlled cross-over exploratory intervention study with symptom-driven dosing. Cannabis Cannabinoid Res 2022;7:436–444.
123. Zheng T, BouSaba J, Taylor A, et al. A randomized, controlled trial of efficacy and safety of cannabidiol in idiopathic and diabetic gastroparesis. Clin Gastroenterol Hepatol 2023;21: 3505–3514.e4.

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