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**Should Gastroenterologists Prescribe Cannabis? The Highs, the Lows and the Unknowns**

Should Gastroenterologists Prescribe Cannabis?

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## **Abstract**

Cannabis, commonly known as marijuana, is a drug extracted from the *Cannabis* plant known for its psychotropic and medicinal properties. It has been used for healing purposes during ancient times, although its psychoactive components led to its restricted use in medicine. Nonetheless, cannabis is found to have modulatory effects on the endocannabinoid system (ECS) exhibiting its medicinal role in the gastrointestinal (GI) system. Emerging animal and human studies demonstrate the influential effects of cannabis on a variety of GI diseases including inflammatory bowel disease (IBD), motility disorders and GI malignancies. It also has a regulatory role in GI symptoms including nausea and vomiting, anorexia, weight gain, abdominal pain, among others. However, both its acute and chronic use can lead to undesirable side effects such as dependency and addiction, cognitive impairment and cannabinoid hyperemesis syndrome. We will discuss the role of cannabis in the GI system as well as dosing strategies to help guide gastroenterologists to assess its efficacy and provide patient counseling before prescription of medical marijuana.

**Key Words:** Marijuana; cannabis; endocannabinoid system; side effects; gastrointestinal disorders

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**Core Tip:** Cannabis is becoming increasingly popular in the management of a variety of gastrointestinal disorders due to its active role in the endocannabinoid system. It provides anti-inflammatory, anti-emetic and analgesic effects indicating its potential use in treatment and symptom control. There is rising evidence on the therapeutic efficacy and short-term safety profile of cannabis but its long term safety profile remains to be explored. Before gastroenterologists consider prescribing medical

marijuana, gaining understanding of the benefits and associated risks and having an open and individualized discussion with patients are essential.

## **INTRODUCTION**

<sup>2</sup> Cannabis, also known as marijuana, is a substance derived from the cannabis plant consisting of <sup>7</sup> three species known as *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. The plant was well-known during the ancient times where it was traditionally used for therapeutic use in many countries. It was used for its anti-inflammatory, anti-septic and anti-epileptic properties written in the Ayurvedic texts from India. The Chinese culture would incorporate it in their tea for the treatment of gout, malaria, rheumatologic disorders and neuropathic pain. Marijuana would be given as a ceremonial sacrifice for Jewish priests <sup>[1]</sup>. In addition, Ancient Egypt and China utilized cannabis for the treatment of gastrointestinal (GI) disorders <sup>[2]</sup>. Currently, marijuana is a controlled substance that can be prescribed by licensed practitioners for the treatment of various GI disorders. Studies demonstrate its potential benefits but unfortunately also has undesired side effects.

### ***What is it?***

Although three species exist, marijuana is typically extracted from *Cannabis sativa*. It contains 60 aromatic hydrocarbon compounds known as cannabinoids. Two of the sixty compounds are often used and advertised: delta-9-tetra-hydrocannabinol (THC) and cannabidiol (CBD). Each strain of cannabis consists of varying compositions with some higher in CBD while others contain more THC. THC is frequently used for its psychotropic effects while CBD can aid with controlling pain, inflammation and improving motility <sup>[1, 2]</sup>.

## **HISTORY**

Cannabis has a complex history in the western culture due to both health and political concerns. It is currently classified as an illegal substance under federal law in the United States. The first cannabinoid receptor was identified in St. Louis, Missouri, USA in 1988

called cannabinoid receptor type 1 (CB1) followed by the discovery of cannabinoid receptor type 2 (CB2) in Cambridge, United Kingdom in 1993 [3, 4]. Anandamide was the first cannabinoid that was discovered in Israel in 1992, thus forming the endocannabinoid system (ECS) [5]. Since then, over 500 additional cannabinoids which function as neurotransmitters have been identified from the cannabis plant including THC and CBD. In the United States, THC was first authorized for medical use by the Food and Drug Administration (FDA) in 1986 for cancer patients who experienced chemotherapy induced nausea and vomiting or required appetite stimulants. The federal legalization of medical and recreational cannabis remains a divisive political topic but its use has become more widespread as more states continue to legalize the substance.

## PHARMACOKINETICS

### *Receptors*

THC and CBD interact with two receptors, <sup>3</sup> CB1 (cannabinoid receptor type 1) and CB2 (cannabinoid receptor type 2). CB1 and CB2 are G-protein-coupled receptors (GPR) found throughout the body but have varying effects that are still being elucidated in ongoing trials [6]. The main neurotransmitter that interacts with CB1 is anandamide and the key neurotransmitter that interacts with CB2 is 2-arachidonoylglycerol [5, 7].

CB1 receptors are commonly associated with the psychotropic effects of cannabis and are found in high concentrations in central neurons, including the cortex, hippocampus, basal nuclei and amygdala, and peripheral neurons, including the enteric nervous system and vagal and spinal neurons [3, 6]. Large concentrations of CB1 receptors were found in the colonic epithelium, smooth muscle and submucosal myenteric plexus using immunohistochemistry [8]. Aside from psychotropic effects, the activation of CB1 receptors can affect multiple processes including appetite stimulation, pain perception, metabolism and alterations in GI motility, contractility and secretions [9].

CB2 receptors are tightly associated with the immune system and inflammation. They are present in high concentrations in multiple cell lines including macrophages, neutrophils and some B and T lymphocytes [4]. CB2 receptors, when activated, are associated with reduced inflammation and pain and decreased intestinal motility.

### ***THC and CBD***

THC and CBD carry a similar structure to naturally occurring endogenous neurotransmitters, giving them various effects and potencies. Portions of THC mimic the active binding sites of the endogenous cannabinoid anandamide and CBD similarly mimics 2-arachidonoylglycerol [5, 7]. THC is a partial CB1 and CB2 agonist that is available in varying concentrations from 0.5-90+% depending on the product and modality. Metabolites of THC are commonly tested for in urine studies but can also be tested in hair and blood.

CBD effects on CB1 and CB2 receptors promote anti-inflammatory effects. CBD binds weakly to CB1 and CB2 receptors leading to strong antagonist effects, potentially explaining decreased inflammation through inverse agonism of immune cell activation [10]. CBD products are available in varying concentrations from 0.5-90+% depending on mechanism of use and is more readily available as it is not defined as a controlled substance.

### **THE ENDOCANNABINOID SYSTEM**

The endocannabinoid system (ECS) is moderated by lipid-based neurotransmitters in a complicated network of endogenous neurotransmitters and various receptors, including CB1 and CB2, and has effect on the enteric system [8]. Interestingly, the neurotransmitters act in a retrograde direction, meaning they are produced at the post-synaptic membrane and bind to receptors on the pre-synaptic membrane [11]. Cannabinoids are one of the most common retrograde neurotransmitters in the human body [12].

Activation of CB1 in the ECS results in an inhibitory effect on neurons *via* reduced acetylcholine release [13]. The reduction in acetylcholine can decrease gut motility or secretion and visceral pain sensation, which play a large role in symptom management including nausea, pain or diarrhea. Activation of CB2 is noted to be elevated in inflamed tissues, positing that CB2 plays an immunomodulatory role in gut inflammation [8]. There are also endocannabinoid-like receptors that have been discovered that fall under GPR including transient receptor potential vanilloid 1, peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ), GPR55, GPR119, among others [9]. In addition to endocannabinoid-like receptors, endocannabinoid-like compounds such as N-palmitoylethanolamine (PEA) and N-oleoylethanolamine stimulate similar receptors, resulting in anti-inflammatory and analgesic effects [14, 15]. Studies demonstrate a reduction in inflammatory cytokines in cannabis users through the activation of its receptors [16, 17].

## USE AND ONSET

There are many commercially available modalities on the market for use of cannabis and its concentrates. Types of cannabis include <sup>1</sup>cannabis or cannabinoid derivatives (inhaled and oral THC), cannabis derivatives including synthetic THC (dronabinol) or endocannabinoid ligands (palmitoylethanolamide) and phytocannabinoids (cannabidiol [CBD] oil). The different modes of application are visualized in Figure 1. Inhalation which is available through smoking cannabis flower, cannabis concentrates and vaping THC and/or CBD distillate, is a very common option, especially for patients with severe nausea. Effects after inhalation peak approximately 30 minutes after use and decrease over the following 2-3 h. Ingestion is another mode of use, available in commercial edibles such as candy or chocolate as well as cannabis infused products such as butter or beverages as well as tinctures. Onset after ingestion normally begins 30-90 minutes from intake, peaks at 2-3 h after intake and is slowly metabolized over 4-12 h.

## ROLE IN THE GASTROINTESTINAL TRACT

Cannabis is becoming more accepted and widespread for medicinal use. It shows therapeutic benefit in psychiatric and neurologic conditions as well as some gastrointestinal disorders. Its effects on the GI tract play an important role in a variety of digestive disorders including inflammatory bowel disease (IBD), GI motility, irritable bowel syndrome (IBS), cachexia and anorexia, neoplastic conditions and many more [Figure 2]. However, adverse side effects of marijuana are evident including its role in cognition and addictive properties. The long-term safety profile of cannabis is underrecognized and needs further investigation. We conducted an extensive literature review by searching PubMed and Google Scholar databases for current evidence on cannabis effects on GI disorders and symptoms. Citation mining was also utilized. We included 45 studies consisting of surveys, clinical trials, cohort and observational studies and meta-analyses to assess the outcomes and type and modality of cannabis used [Table 1]. Additional evidence such as animal models, systematic reviews and case reports were also compared.

### *IBD*

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Inflammatory bowel disease consists of two major chronic autoimmune inflammatory conditions: Crohn's Disease (CD) and Ulcerative Colitis (UC). They have a predisposition towards males between ages 15 to 30 or greater than 60 years old. Common medications used for treatment, induce remission and prevent reactivation are 5-aminosalicylate drugs, corticosteroids and immunosuppressive agents. Surgical intervention such as colectomy is typically the last line of therapy.

Cannabis has potential analgesic effects for IBD patients. CB1 and CB2 receptor activation may minimize gut sensitivity and exert anti-inflammatory effects in the GI tract [1]. In rodent models studying IBD, CB receptor agonists reduced gut inflammation and improved IBD related symptoms [18]. Although several human studies have



evaluated the therapeutic effects on cannabis in IBD patients, evidence is mixed. A meta-analysis of 20 studies revealed that cannabis and cannabinoids improved quality of life in IBD patients with initially lower baseline quality of life and reported symptoms [19]. Supporting literature also demonstrates benefit in disease activity indices and decrease in alternative analgesics [20-22]. Subjective improvement in disease-associated abdominal pain, diarrhea and appetite in addition to anxiety and fatigue were reported in IBD patients [23-27]. In 2011, Naftali and colleagues led the first observational study in CD which demonstrated decreased disease activity scores and less need for corticosteroids and surgery [21]. In a small prospective placebo-controlled study, the authors found 90% of CD individuals using THC-rich cannabis had a greater than 100 point reduction in Crohn's Disease Activity Index. Quality of life, appetite, pain scores and satisfaction also improved [28]. However, a following study by Naftali and colleagues demonstrated no beneficial effects of CBD in CD [29]. It was also proposed CD patients who used cannabis for greater than 6 mo had an increased surgical risk but it was unclear if cannabis was used prior to or after surgery [24]. A nationwide study on inpatient outcomes found that although cannabis users with CD required less parenteral nutrition needs than nonusers (3% *vs* 4.7%) and had shorter hospital stays due to potential symptomatic improvement, there were higher complications of active fistulas or intraabdominal abscesses compared to nonusers (8.6% *vs* 5.9%) [30].

Conversely, a meta-analysis revealed cannabis had no effect on complications from Crohn's disease including stricture and fistula formation, abscesses, anemia, bowel obstruction and need for colectomy. Additionally, cannabis was concluded to be ineffective in achieving remission in IBD [19]. Small randomized controlled trials (RCT) demonstrated CBD-rich oil, although had significant clinical and quality of life improvement, exhibited no significant change in inflammatory parameters (C-reactive protein and calprotectin) or endoscopic score in IBD [31, 32]. In majority of the studies, cannabis was generally well-tolerated with some mild increased risk of side effects due

to its central actions including dizziness, dry mouth, and anxiety. The most reported reason to stop taking cannabis was dizziness [19]. In 2020, Cochrane reviews by Kafil and colleagues evaluated RCT studies for IBD patients and concluded cannabis safety and efficacy is uncertain so concrete conclusions cannot be made [33]. Overall, cannabis does offer symptomatic relief but there is scarce evidence that can support its use to control inflammation and achieve remission in IBD.

### ***GI motility/constipation***

Cannabis may reduce GI motility by its agonistic activity on the CB1 receptors of myenteric neurons. It is involved in presynaptic inhibition of the excitatory neurotransmitters, acetylcholine release and substance P, which decreases smooth muscle peristalsis and contractility. CB2 receptors, particularly during inflammatory states, can also decrease GI motility [34]. It slows down gastric emptying, upper GI transit and colonic propulsion [9]. A small RCT demonstrated THC delayed solid food in gastric emptying by decreasing smooth muscle activity *via* peripheral effect [35]. In an animal model, CBD reduced gut hypermotility under an inflammatory state by potentially activating the enteric CB1 receptor by fatty acid amide hydrolase (FAAH) inhibition, the enzyme involved in endocannabinoid degradation [36]. However, one study found no change in gastric emptying after administration of cannabis [37]. The foreseen physiologic effect of marijuana in gut motility contrasts with its apparent effect on constipation. An animal study found cannabis improved loperamide-induced constipation in mice likely due to gut microbiota changes [38]. Interestingly, a national cohort study in the United States demonstrated a 30% decrease in constipation with recent marijuana use compared to past or nonusers but lacked any association with diarrhea. This paradoxical effect may be explained by different cannabis compositions and presence of counteracting cannabinoids of the CB1 receptor [39]. Data is limited and conflicting in cannabis effects on GI motility and further studies are warranted.

### ***Paralytic Ileus***

Paralytic ileus is defined as the impairment of bowel muscle contractions that leads to intestinal obstruction. The pathogenesis of ileus may be affected by the release of endogenous cannabinoids. *In vivo* studies demonstrated cannabis may reduce or normalize GI motility. An animal model showed improvement in ileus after administration of CBD [40]. Targeted therapy towards endogenous cannabinoids may minimize the occurrence of ileus [9].

### ***Irritable Bowel Syndrome***

Irritable bowel syndrome is defined by Rome IV criteria as a functional disorder in which changes in bowel habits or defecation is associated with recurrent abdominal pain experienced at least once a week for the past 3 mo [41]. Although the pathophysiology is not completely understood, it is speculated that the gut-brain signaling system is impaired which leads to visceral hypersensitivity and motility disturbance. Alteration in gut microbiota can also lead to inflammation. Patients may experience abdominal discomfort, bloating and inconsistent bowel habits [9]. Cannabis may aid in symptomatic relief in IBS patients due to the effects on gut motility and tone [42]. Cannabinoid receptors are proposed to mediate abdominal visceral sensation. One small RCT study demonstrated lack of cannabis effect on reducing visceral hypersensitivity which contrasts with animal studies that demonstrate visceral pain reduction [43]. Dronabinol, a synthetic form of THC and nonselective cannabinoid receptor agonist, is proposed to ease colonic tone, inhibit gastric emptying and reduce colonic motility, although other studies differ [34, 44]. Wong *et al* concluded dronabinol inhibits colonic motility during the fasting phase and augments colonic compliance in IBS patients with diarrhea (IBS-D) or alternating predominant IBS. It either inhibits activity of excitatory motor mechanisms or activates the inhibitory neural mechanisms [45]. However the following study demonstrated dronabinol's lack of effect on colonic transit on IBS-D individuals but is postulated to inhibit transit in patients who have a specific genetic variation of CB1 [44]. Hospitalized cannabis users with IBS had lower symptomatic burden with shorter length of stay, lower rate of endoscopic procedure

utilization and overall decreased hospital cost [42]. Opposing data demonstrated cannabis users had increased odds for IBS-hospitalization and there was a rising trend of cannabis use disorder and related psychiatric comorbidities including anxiety and depression [46].

### ***Abdominal/Visceral pain***

The ECS is proposed to be involved in the modulation of stress through peripheral mechanisms and centrally by the hypothalamic-pituitary-adrenal (HPA) axis. Chronic stress is thought to lead to visceral hyperalgesia and chronic pain. Endocannabinoids effect on CB1 as well as inhibitors of endocannabinoid degradation can reduce stress-related hyperalgesia [47]. Many patients with GI disorders such as IBD and gastroparesis are burdened by abdominal pain in which cannabis is shown to provide symptomatic relief [18, 48]. Conversely a small phase 2 clinical trial demonstrated THC was not superior to placebo in patients with chronic abdominal pain [49]. Large clinical studies are needed to evaluate the efficacy of cannabis in chronic abdominal pain.

### ***GERD***

About 20% of adults in the United States are affected by gastroesophageal reflux disease (GERD) [50]. The vagovagal reflex mediates the actions of the lower esophageal sphincter (LES). LES transient relaxations can lead to GERD. Antacid is the mainstay of therapy but cannabis is also shown to provide some symptomatic relief in limited studies. CB1 and CB2 receptors are centrally expressed in the vagovagal nerve pathway and its inhibitory effect can reduce transient relaxations and control GERD symptoms [9]. Studies found that activation of CB receptors inhibits transient LES relaxations in dogs. It was translated to the human model and was shown that THC offered the same effect but only during the first hour post-meal in addition to basal LES pressure reduction. However, half the subjects had episodes of emesis, an undesired side effect [51, 52]. It was also demonstrated rimonabant, a selective CB1 receptor antagonist, increased postprandial LES pressure in humans but decreased transient LES relaxations which

contrasted a previous animal study. Different dosages, bioavailability and differing cannabis species could explain the discrepancy [52, 53]. More human clinical trials are needed to evaluate the effects of cannabis on GERD.

### *Nausea and Vomiting*

Nausea and vomiting have multiple triggers modulated by the central and peripheral nervous system. As a defense mechanism, these common GI symptoms can be induced by emotional and cognitive stimuli, disturbance in the proprioceptive system, ingestion of harmful contents and toxic drugs such as chemotherapy agents [54]. Serotonin receptor antagonists, steroids and neurokinin-1 (NK-1) inhibitors such as aprepitant are prescribed to manage nausea and vomiting [55]. Different medication classes such as metoclopramide, prochlorperazine or lorazepam may be used for breakthrough or refractory symptoms [56]. Cannabis and related cannabinoids also offer anti-emetic effects and can be utilized for refractory symptoms. They are often the primary or adjuvant therapeutic option depending on the disease state [55]. Literature demonstrates cannabinoids block both acute and delayed emesis and have been used as medicinal purposes for a variety of nausea and vomiting induced causes [57]. CB1 receptors affect the pathogenesis of emesis by its wide expression throughout the brain and in the dorsal vagal complex of the brainstem [1]. It is unclear if CB2 receptors play a role.

The FDA approved dronabinol and nabilone in the 1980s for intractable chemotherapy related nausea and vomiting [55]. Current guidelines recommend cannabinoids as an option for breakthrough or refractory chemotherapy-induced nausea and vomiting in addition to the standard anti-emetic regimen if other therapies failed [58, 59]. A meta-analysis of variable quality evidence demonstrated cannabinoids were highly effective to treat chemotherapy-induced nausea and vomiting but differences in symptoms were insignificant when compared with other anti-emetic drugs. Although dizziness was more commonly experienced with cannabinoid use, participants preferred it over traditional anti-emetics [56]. Side effects also included sedation and disorientation [60].

Notably in animal models studying lithium and chemotherapy-induced vomiting, <sup>5</sup>THC suppressed vomiting in a dose dependent manner whereas CBD suppressed vomiting at low doses, yet triggered or enhanced vomiting at high doses [61, 62]. Cannabinoid hyperemesis syndrome is a well-established and paradoxical adverse effect of chronic cannabis use which can reverse its therapeutic role [54].

### ***Anorexia/Weight loss***

Marijuana can aid with appetite stimulation and weight gain. Cannabinoid signaling is involved in appetite stimulation pathways by the expression of CB1 receptors in the forebrain including the hypothalamus [63, 64]. Literature suggests that oral cannabis increases ghrelin levels, the hunger hormone that regulates appetite and food intake and modulates insulin sensitivity [65]. Marijuana has been used in disease related anorexia and cachexia such as in acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV) and malignancy. In 1985, the FDA approved dronabinol for the treatment of AIDS/HIV related cachexia [63]. In HIV positive patients, smoking cannabis demonstrated increases in body weight and caloric intake [66-68]. However, megestrol acetate, a synthetic progestin, led to greater weight gain than dronabinol in patients with AIDS associated anorexia [69]. In cancer patients, evidence suggests dronabinol can increase appetite and therefore weight gain but it was countered by Strasser *et al* who demonstrated cannabis use exhibited no changes in improved appetite [70, 71]. Dronabinol remains inferior to megestrol acetate in weight gain and appetite stimulation for cancer patients with no established benefit in combination therapy [72]. Smoking marijuana has not yet been studied in these patients. A meta-analysis concluded majority of the trials had low quality of evidence with potential reporting bias. Currently, there is no high quality evidence that supports cannabinoids in the treatment of cancer-related or HIV-related anorexia or cachexia [73].

### ***Obesity***

Obesity is a multifactorial disease and major health concern worldwide. Nearly one third of the population is defined as overweight or obese. It is associated with multiple comorbidities including diabetes mellitus and cardiovascular disease [74, 75]. Orlistat, an inhibitor of lipase enzymes, is one of the FDA-approved pharmacologic agents to target obesity. The role of cannabis is now being investigated in the management of obesity. Cannabis users generally have lower BMIs and are less likely to be obese than nonusers [76-79]. Marijuana is proposed to regulate body weight dependent on BMI and its acute *vs* chronic use [80]. Underweight individuals who use marijuana acutely may gain weight but individuals with normal or elevated BMIs may lose weight [80]. Moreover, although higher baseline BMI scores led to greater cannabis frequency, the increased cannabis use by adolescents led to greater decreases in BMI overtime [81]. Drugs and food compete for similar reward pathways in the brain which may explain the paradoxical effect of cannabis on BMI [78, 80]. Conversely, an observational study found no association between cannabis use and weight change in adolescents, although confounding factors may be present [82]. Withdrawal from cannabis use can also lead to weight loss. Discontinuation of chronic cannabis use downregulates CB receptors, which can therefore lower BMI [83]. An animal study demonstrated mice that lacked CB1 receptors were protected against obesity [84]. Abstinence from cannabis was found to decrease appetite and increase metabolic rates, but these effects were lost when CB1 receptors returned to normal levels [83]. Rimonabant, a CB1 receptor antagonist, was approved in Europe in 2006 for weight loss in obese patients. However its safety concerns, primarily psychiatric side effects, led to its discontinuation shortly after approval [83, 85]. The effects of marijuana on BMI is complex and more quality studies are needed to examine its long term use on obesity.

### *GI Malignancies*

Studies are investigating the impact of cannabis on GI malignancies. It may disrupt tumor signaling pathways through its pro-apoptotic, anti-inflammatory, anti-proliferative and anti-angiogenic effects. Inhibition of endocannabinoid enzymes may

also protect against metastasis [2]. Both anti-tumor properties and pro-tumorigenic activity are associated with the over- and under-expression of CB1 and CB2 receptors [86].

Due to CB2 receptor expression in pancreatic cancer cells, CB2 activation is theorized to induce apoptosis in these abnormal cells without affecting healthy cells. Additionally, low CB1 receptor expression demonstrated longer survival in pancreatic cancer [86, 87]. Notably, gemcitabine and cannabinoid receptor agonists provide a synergistic effect in pancreatic cancer cells *in vitro* and *in vivo* leading to apoptotic and antiproliferative effects [88]. In hepatocellular carcinoma (HCC), higher expression of CB receptors was associated with improved prognosis and disease free survival [89]. Interestingly, a population based study found cannabis users were less likely to have HCC than nonusers. CBD may offer protective effects against HCC by CB2 agonism [90]. Cannabinoids and cannabis extracts are also being investigated in the potential treatment of colorectal cancer [91]. Cannabidiol was shown to exert protective effects *in vivo* through multiple mechanisms and reduce cell proliferation through CB1 and CB2 activation [92, 93].

Marijuana may also exert pro-neoplastic effects. It was found to be weakly associated with esophageal cancers [94]. In esophageal squamous cell carcinoma, CB1 receptor overexpression led to poor prognosis, cell proliferation and invasion [95]. One case report suggested chronic cannabis use may be a risk factor for Barrett's esophagus [96]. Studies of cannabis and its anti-tumor *vs* pro-tumorigenic activity are conflicting and strong data is lacking. More human trials are necessary to establish its potential protective or harmful properties in GI malignancies.

### ***Liver***

Cannabis is proposed to play a role in hepatic steatosis and fibrosis, hepatic encephalopathy and alcohol-associated liver disease [1]. CB1 receptor expression can



increase lipogenesis, fibrogenesis, decrease fatty acid oxidation and induce hyperphagia while receptor antagonists protect against hepatic steatosis [1]. On the other hand, CB2 receptor activation exerts antifibrogenic effects which can be an important target in cirrhosis treatment [97]. This is supported by animal models which demonstrate CB1 deletion improves hepatic fibrosis and steatosis and CB2 deletion increases inflammation and steatosis [98]. CB2 agonists can reduce oxidative stress and therefore inflammation [1, 99]. There was a decreased prevalence of non-alcoholic fatty liver disease in cannabis users proposing a potential benefit [99, 100]. There was also a reduced incidence of liver disease in concomitant alcohol and cannabis users likely from the anti-inflammatory properties of cannabis [101]. Evidence is scarce in cannabis' role in hepatic encephalopathy. Animal models suggest cannabis use improves hepatic encephalopathy due to its anti-inflammatory effects [102, 103].

Studies are conflicting in the role of cannabis in viral hepatitis, which may partially be explained by different endpoints and definitions. Cannabis use is thought to be associated with moderate to severe fibrosis in patients with chronic hepatitis C but there is opposing data [97, 104]. In HIV and hepatitis C co-infection, marijuana was associated with a decreased risk of steatosis [105, 106]. Currently, there is no evidence suggesting the association of cannabis with hepatitis B.

### ***Pancreas***

Pancreatitis is an acute inflammatory process of the pancreas that is commonly precipitated by gallstones and heavy alcohol use. Evidence suggests cannabis may lead to an increased risk of pancreatitis. CB1 and CB2 receptors in the pancreas are increased during inflammation but the pathogenesis remains unclear [34]. Several case reports suggest the association of cannabis-induced pancreatitis [107-109]. Multiple systematic reviews found cannabis use was related to acute and recurrent pancreatitis and cannabis cessation evoked no further episodes [110-112]. One study found no impact of cannabis on disease severity or mortality [113].

## **RISKS AND ADVERSE SIDE EFFECTS**

The risks and benefits of cannabis use and cannabinoids are highly debated in the United States. Significant research has been performed on the risk profile of marijuana and is still underway, although restricted by laws and regulations [Table 2]. In some countries where marijuana use is legalized, research guidelines were developed to ensure safe use and guide practitioner prescribing. One such recommendation is the evidence-based Lower-Risk Cannabis Use Guidelines (LRCUG). LRCUG consists of 10 recommendations including choosing a low concentration THC or balanced THC to CBD ratio products and avoidance of risky behaviors such as use under age 16 or daily use, synthetic compounds and driving while impaired <sup>[114]</sup>.

The recommendation to avoid cannabis use before the age of 16 is due to its potential adverse effects on the adolescent brain. *The New England Journal of Medicine* identified cannabis use can lead to abnormal brain development in the vulnerable adolescent population <sup>[115]</sup>. Longitudinal functional magnetic resonance imaging studies exhibited cannabis use decreased grey matter in multiple sites within the brain <sup>[116, 117]</sup>. Adolescent onset schizophrenia has also long been theorized to be related to altered grey matter development secondary to marijuana <sup>[116]</sup>. Multiple studies noted the probable, albeit mixed, evidence that chronic cannabis use decreases cognition, learning and memory <sup>[118, 119]</sup>. This poses significant concerns when experimentation and use of cannabis frequently occurs in the adolescent population <sup>[119]</sup>.

LRCUG also suggests avoidance of inhalation. Inhalation of cannabis has been closely compared to cigarette smoking. Some studies claim cannabis smoking contains approximately 2.8 times as much tar and up to 5 times as much carbon monoxide inhaled in comparison to tobacco smoking <sup>[120]</sup>. Wu and colleagues noted that cannabis smokers took two thirds greater and one third deeper of an inhale and four times longer of a breath hold resulting in longer exposure, although unaffected by THC

concentration <sup>[120]</sup>. However, there was no comparison of the density between commercial cigarettes and the various methods to smoke cannabis, as well as the purity, frequency and amount of cannabis consumed. Another complicating factor was the co-use of tobacco and cannabis, clouding what scarce research is available <sup>[120]</sup>. There was strong evidence that cannabis results in chronic cough and mucus production as well as a high risk of developing chronic bronchitis episodes, which likely improves with abstinence <sup>[121, 122]</sup>.

The National Academies of Science, Engineering and Medicine (NASEM) conducted a systematic review in 2017 of the available research on cannabis use to also guide policy makers and physicians through evidence-based means. NASEM found no convincing evidence for associations between cannabis and heart disease, stroke, diabetes, COPD, asthma or worsening lung function <sup>[121, 122]</sup>. There was some evidence purporting that smoking cannabis does not increase risk of lung, head and neck cancer in adults <sup>[123]</sup>. However, cannabis use was associated with a 2.5 times risk of developing non-seminoma testicular cancer <sup>[124]</sup>. Additionally, cannabis has up to a 30% higher risk of motor vehicle accidents when driving under the influence <sup>[125, 126]</sup>. The risk of occupational injuries in cannabis users was unclear due to confounding variables by individual personal risks <sup>[127]</sup>. Unfortunately, the risk of childhood accidental exposure has increased. In states that legalized its recreational use, the estimated risk of unintentional overdose in children is as high as 2.8 times compared to states where cannabis is restricted <sup>[128, 129]</sup>. There was a 11-30% increase in calls to poison centers regarding childhood accidental exposure in states that legalized cannabis <sup>[130]</sup>.

Moreover, cannabis users may develop cannabis use disorder, which is the inability to discontinue use despite physical or psychological harms <sup>[131]</sup>. Cannabis use disorder affects approximately 10% of regular users and up to 33% of daily users but is likely underdiagnosed <sup>[131]</sup>. Dependence or addiction can occur in addition to cannabis withdrawal. The DSM-5 defines cannabis withdrawal as any 3 of the 7 following signs

or symptoms: nervousness/anxiety, irritability/anger, sleep difficulty, decreased appetite or weight, depressed mood, restlessness or physical discomfort (abdominal pain, tremors, sweating, fever, chills, and/or headache) [132].

A meta-analysis across 10 countries found a positive association between anxiety and cannabis use after accounting for confounding variables [133]. However, Blanco *et al* found no association between cannabis and anxiety disorder [134]. This relationship was further explored by Feingold *et al*, who used Blanco's data set, and demonstrated cannabis users have a higher risk of developing social anxiety disorder specifically [135]. There was no association between cannabis use and the development of mood disorder or major depressive disorder [136]. The type of cannabis can also lead to mixed effects due to differences in composition of varying cannabinoids. Studies demonstrate THC exhibited a pro-anxiety effect whereas CBD displayed an anti-anxiety effect [137].

Although cannabis can serve as a potential aid for patients who suffer from cyclic vomiting syndrome, this should not be confused with one its most notorious side effects, cannabinoid hyperemesis syndrome (CHS) [Figure 3] [138]. The exact mechanism of CHS is not fully understood. Cannabis is proposed to have an antiemetic effect at low doses but a pro-emetic effect at higher doses [139]. The Rome IV diagnostic criteria for CHS includes three features: stereotypical two or more episodes of intractable vomiting lasting hours to days over a period of at least 6 mo, history of prolonged cannabis use prior to symptom onset and relief of episodes from sustained abstinence [140]. A notable, learned behavior is prolonged hot bathing, which offers temporary symptom relief. This is thought to occur *via* multiple processes including chronic buildup of fat-soluble molecules reaching toxic levels, overstimulation of enteric neurons or hypothalamic disruption of digestion and thermoregulation [139]. Available therapeutics for CHS include serotonin antagonists (ondansetron), antipsychotics (haloperidol), benzodiazepines, aprepitant and topical capsaicin [141]. Haloperidol was found to be superior over ondansetron in managing abdominal pain and nausea in CHS leading to

early emergency department discharge <sup>[142]</sup>. Yet the most effective treatment is absolute abstinence from cannabis <sup>[141]</sup>.

Death from marijuana intoxication is complex. There have been cases of pediatric respiratory depression requiring intubation and cannabis triggered psychosis leading to erratic or dangerous behavior resulting in death <sup>[143]</sup>. A systematic review of epidemiologic data found that cannabis use and all-cause mortality were not statistically significant <sup>[125]</sup>. It should be noted that mice studies testing cannabis extracts estimated the lethal dose 50 to be greater than 1000 mg/kg <sup>[144]</sup>. Many side effects of marijuana have been established but the long-term safety profile needs further investigation.

## LEGALIZATION

In the United States, legalization barriers limit cannabis medical research which creates gaps in medical knowledge. However cannabis use has become more increasingly accepted in the public eye as well as for medical use. In the United States, <sup>6</sup> 37 states, the District of Columbia and four US territories have legalized Cannabis for medical use in different degrees while <sup>2</sup> 21 states and District of Columbia legalized marijuana for recreational use. Some states decriminalized marijuana meaning legal consequences for possession of marijuana are minimal to none <sup>[145]</sup>. Several states approved medical marijuana for the treatment of a variety of disorders such as IBD, HIV/AIDS-related cachexia and chemotherapy-induced nausea and vomiting. Although states are legalizing marijuana, there is currently no federal legalization for its national use <sup>[18]</sup>. It is classified as a Schedule 1 substance indicating its high potential for substance abuse without acceptable medical use. This causes clinicians to feel hesitant in offering medical marijuana due to fear of prosecution. State laws designed systems to protect physicians when recommending marijuana use. Physicians require an active state medical license, must maintain a consistent relationship with the patient, and some states require certifications to recommend marijuana <sup>[6]</sup>. The barriers of legalization are

decreasing but investigators continue to face legal and administrative restrictions when attempting to perform research with cannabis and cannabinoids. The lack of knowledge has limited quality clinical research hindering potential novel findings that can inform both clinicians and the community of its therapeutic use and risk profile <sup>[18]</sup>. As research and patient interest on cannabis continues to grow, physicians must stay well informed on the substance in order to provide patients with appropriate education and guidance of its indications and safety profile.

### **TO PRESCRIBE OR NOT TO PRESCRIBE**

The question of whether gastroenterologists should or should not prescribe cannabis is raised [Figure 4]. Although limited data is available, with mixed results, evidence does show beneficial effects of cannabis in a variety of gastrointestinal symptoms and disorders. It can provide symptomatic control in diseases including IBD and IBS with tolerable side effects. However, research suggests it has no superior role over first line drugs in some disorders. Physicians should prescribe cannabis to patients through an individualized basis and a personalized treatment plan. Similarly to commonly prescribed medications, cannabis may provide therapeutic benefit in some individuals, while offering little to no benefit effect in others. Cannabis can be considered as an alternative agent in adults who failed first or second line therapies or for those who cannot tolerate oral intake, whereas inhalation or sublingual are suitable options. Although the side effects of cannabis are well-established, it is not sufficiently different than the side effects of federally approved drugs including biologic agents, anti-psychotic or anti-depressant medications. However, cannabis should be avoided in pregnancy and those under age 25 such as adolescents and the pediatric population due to its demonstrated effects on brain development. It should also be avoided in patients struggling with addiction or substance abuse due to its addictive properties. Once cannabis is prescribed, there should be initial close monitoring of the usage and side effects, similarly to opioid prescriptions. As evidence becomes more robust, medicinal and recreational legalization of cannabis will likely expand. This will allow for further

and more scrutinized research to guide and empower physicians to prescribe cannabis appropriately and safely with evidence-based knowledge of benefits and harms and without concern for legal recourse.

## **DOSING STRATEGIES**

Due to the limited data and risk of side effects, cannabis should be prescribed at the lowest dose. A CBD predominant regimen is encouraged to reduce risk of adverse events including psychotropic effects. CBD should be administered at a low dose of 5 mg once or twice daily. The modified Delphi approach, developed under the guidance of medical experts for chronic pain, recommend incremental increases of CBD 5-10 mg/day every 2-3 days. Once CBD dose reaches greater than 40 mg without achievement of goal, THC can be added. THC dosage of 1 mg/day should be the initial starting dose under the conservative protocol. Weekly incremental increases of THC 1 mg/day is recommended by the modified Delphi approach until goal is achieved or until maximum dose (40 mg) is reached <sup>[146]</sup>. Slow titration of THC will promote tolerance to the psychoactive properties. A THC predominant regimen can begin with prescribing 1.0-2.5 mg per day dependent on individual risk factors with incremental increases every 3-4 days until 40 mg is reached <sup>[147]</sup>. Ingestion over inhalation is the preferred route of administration. Another alternative is using equivalent dosing of THC:CBD with 2.5-5.0 mg of each cannabinoid daily and increase by 2.5-5.0 mg every 3 days until THC maximum dose is reached <sup>[146]</sup>. Caution is warranted when reaching the maximum limit of THC and high doses of CBD as majority of the studies on GI disorders lack data on high doses. Close monitoring every 2-4 wk is recommended to assess efficacy and side effects and need for upward titration or discontinuation of cannabis. Longer periods of follow-up can be done once patient is at a steady dose with tolerable effects <sup>[147]</sup>. Overall, a conservative approach of starting medical cannabis at a low dose and titrating upwards slowly is preferred due to the existing data available.

## **CONCLUSION**

Cannabis may offer therapeutic benefit in many GI disorders including inflammatory and neoplastic diseases but appropriate monitoring is essential due to the number of potential harmful side effects. Current evidence demonstrates mixed results due to small sample sizes, different formulations, dosages and routes of cannabis administration and outcome definitions. Its legal barriers cause further investigational obstacles but despite this, ongoing research continues. Further exploration of its safety profile and large randomized clinical trials are warranted to guide gastroenterologists on the effects of cannabis, appropriate indications and dosing as well as proper monitoring for efficacy and adverse side effects.

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