



Inflammatory Bowel Disease and Cannabis: A Practical Approach for Clinicians

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ABSTRACT

Although still not approved at the federal level for medical or adult recreational use, cannabis has been approved in the United States (USA) by individual states for both of these purposes. A total of 15 states now regulate cannabis for adult use and 36 states for medical use. In more recent years, cannabis has gained popularity for the treatment of chronic conditions, inflammatory bowel disease (IBD) being one of them. However, the exact role of cannabis in the treatment of IBD remains uncertain. While cannabis may help in some instances with symptom management, it has not been proven to help with inflammation or to fundamentally

correct underlying disease processes. Additionally, along with the perceived symptom benefits of cannabis come concerning issues like dosing inconsistencies, dependence, and cannabinoid hyperemesis syndrome. In this review article, we explore the nuanced relationship between cannabis and the treatment of IBD by summarizing the current research. We also use clinical vignettes to discuss the more practical considerations surrounding its use.

Keywords: Cannabis; Cannabidiol (CBD); Crohn's disease (CD); Inflammatory bowel disease (IBD); Marijuana; Tetrahydrocannabinol (THC); Ulcerative colitis (UC)

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Key Summary Points

Although classified as a Schedule I substance and not approved for medical or recreational purposes at the federal level, cannabis has now been approved by 36 states for medical use.

Through population studies, cannabis has been shown to alleviate symptoms associated with inflammatory bowel disease (IBD), like abdominal pain, joint pain, abdominal cramping, and diarrhea.

Although the clinical studies are limited, cannabis has not been shown to significantly reduce inflammation or improve endoscopic healing in patients with IBD.

Important considerations for patients with IBD who use cannabis include legal constraints, dosing inconsistencies, dependence, smoking, and cannabinoid hyperemesis syndrome.

Ultimately, the role of cannabis in the treatment of IBD is a decision that will be made on a case by case basis, taking into account the unique attributes of each individual patient, as illustrated through the clinical vignettes featured in this review.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to <https://doi.org/10.6084/m9.figshare.14625798>.

BACKGROUND OF MEDICAL CANNABIS USE

Although terms often used interchangeably, “cannabis” and “marijuana” do not refer to the same substance. Cannabis is a more general term that refers to the plant family *Cannabis sativa*, which includes both hemp and marijuana. The main difference between hemp and marijuana is that marijuana contains greater amounts of delta-9-tetrahydrocannabinol (THC). Hemp, which consists of little THC, is found to have higher levels of cannabidiol (CBD) [1].

In 2009, approximately 10.7% of North Americans between the ages of 15 and 64 years of age reported cannabis use [2]. As classified by the US federal government, cannabis is currently a Schedule I substance. On the federal level, it is not approved within the USA for recreational or medical purposes. Schedule I substances are defined as having no accepted medical use as well as high potential for abuse, and thus generally they cannot be used in research studies. However, despite these federal regulations, individual states within the USA have now gone on to pass laws approving cannabis for both medical and recreational use [3, 4].

Historically speaking, Proposition 215 in 1996 made California the first state to enable residents to use cannabis for medical purposes. Since then, 35 additional states, the District of Columbia, Guam, Puerto Rico, and the United States Virgin Islands have passed similar legislation. As of the November 2020 elections, Mississippi and South Dakota joined 34 states and four territories in sanctioning the medical use of cannabis. Arizona, Montana, New Jersey, and South Dakota also approved the regulation of adult recreational cannabis use, totaling 17 states, two territories, and the District of Columbia who have now done so [4].

Internationally, there is considerable variation in terms of the legality surrounding cannabis use. In the majority of countries and regions, however, cannabis is prohibited for medical and recreational purposes. To date, cannabis regulation is one of the more dynamic

regulatory issues, and some countries, like Canada, the Netherlands, and Uruguay, have even gone on to approve recreational consumption of cannabis at the national level [5].

PHYSIOLOGY OF CANNABIS

To understand the role of cannabis in the management of inflammatory bowel disease (IBD), it is essential to consider the physiological mechanisms of the substance. Cannabis contains a variety of cannabinoids, chemical compounds that have long been thought to have anti-inflammatory and analgesic properties. The two main cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The more pharmacologically active component of cannabis, 9-tetrahydrocannabinol (THC) possesses psychoactive properties [6]. Cannabinoid receptors, CB₁ and CB₂, are located in the nervous system, gastrointestinal tract, and immune cells, particularly within mast and plasma cells. These receptors are stimulated by the endogenous ligands anandamide and 2-arachidonoylglycerol (2-AG) in addition to THC, which is a partial agonist of CB₁ and CB₂ [7]. For this reason, it was hypothesized that cannabis might be a mediator within the gastrointestinal system, affecting inflammation, motility, and the secretory response.

CASE 1

A 30-year-old man with Crohn's disease in remission on adalimumab maintenance therapy expresses an interest in using cannabis for occasional complaints of abdominal pain. He has intermittently smoked cannabis in the past and felt that it improved his symptoms. He works in advertising and travels throughout the USA frequently.

This case illustrates two important considerations. To begin with, this patient was forthcoming about his cannabis use, but as clinicians, it is essential to realize that many patients with IBD may not be. For this reason, clinicians should inquire about cannabis use in general in order to initiate a discussion of the risks and benefits surrounding it. In this specific

instance, the patient is currently in remission, and thus there is no need for additional therapy.

Secondly, given that this patient travels frequently for work, cannabis may not be an ideal adjuvant therapy for him. It is important to counsel this patient on the fact that while cannabis may be approved for medical use in his home state, if he were to travel to a different state for work, he would then be subjected to the legal constraints of that state. Furthermore, this patient should be informed that airports represent federal property and as a result it would be a criminal offense to have cannabis in his possession within any US airport.

CANNABIS AND IBD: POPULATION STUDIES

In order to understand the cannabis use patterns among patients with IBD, numerous population studies were performed. Lal et al. [8] performed a study of 100 patients with ulcerative colitis (UC) and 191 patients with Crohn's disease (CD), determining that 51% and 48% of patients with UC and CD, respectively, reported being lifetime users of cannabis. The patients cited symptom relief from diarrhea and abdominal pain in addition to increased appetite as benefits of cannabis. Patients with IBD with a history of abdominal surgery and long-term use of pain medications were also more likely to use cannabis, further highlighting its role in the symptom management of IBD.

One of the largest cannabis population studies consisted of 2,084,895 patients with IBD and 2,013,901 healthy controls from the National Health and Nutrition Examination Survey (NHANES) database. Survey data revealed that patients with CD and UC were more likely to use marijuana or hashish (67.3% versus 60.0%) and to begin doing so at a younger age (15.7 years versus 19.6 years) in comparison to healthy controls. Those with IBD were also found to consume cannabis less frequently than controls but in greater amounts at a time when they did use it. More specifically, male gender, age above 40 years, and history of

IBD were all predictive factors for cannabis use [9].

Storr et al. [10] collected survey data on 313 patients with IBD, discovering that 17.6% of these patients regularly used cannabis to alleviate IBD symptoms, with over 96% of this group preferring inhalation as the means of consumption. The most common symptoms mitigated by the use of cannabis were abdominal pain (83.9%), abdominal cramping (76.8%), joint pain (48.2%), and diarrhea (28.6%), all of which suggests that cannabis is beneficial in terms of symptom relief. One potentially concerning finding from this study was that patients with CD who consumed cannabis for more than 6 months were more likely to need surgery (odds ratio = 5.03, 95% CI 1.45–17.46). It is difficult to say why this was the case. However, one possible explanation is that cannabis use masks symptoms, which may be early signs of worsening inflammatory disease processes, thereby causing patients to delay in seeking treatment.

CANNABIS AND IBD: CLINICAL STUDIES

It has proven difficult to perform clinical studies on cannabis in the USA largely because of its Schedule I classification. For this reason, initial studies to assess the clinical benefit of cannabis in IBD were performed using mice models. In a study by Pagano et al. [11], colitis was induced in mice with intracolonic injections of dinitrobenzene sulfonic acid (DNBS). CBD was given to mice either intraperitoneally or by oral gavage. Regardless of administration route, it was found to decrease the extent of colonic damage based on myeloperoxidase activity (MPO) and reduce intestinal hypermotility. This study in conjunction with other mice studies suggested cannabis might help slow gastric motility and reduce inflammation [11–14]. However, one critique of this study was that the cannabis given to mice contained a high concentration of CBD, amplifying the effect seen, making findings less applicable to human models.

Many of the original human studies examining cannabis use and IBD were performed in Israel. One of the most promising was a retrospective observational study in 2011 involving 30 patients with CD. Outcome metrics such as disease activity (based on a Harvey–Bradshaw index), need for additional medications, and total number of surgeries were assessed both before and after cannabis use. This study found 21 of 30 patients experienced significant benefits from using cannabis. Overall, the average Harvey–Bradshaw index improved from 14 to 7 ($p < 0.001$) and fewer surgeries were required in the years after cannabis use. Furthermore, only 4 of the initial 26 patients on corticosteroids continued to require corticosteroids, and patients demonstrated less of a need overall for additional medications. While not double-blind or placebo-controlled, this study suggested cannabis might improve underlying disease [15].

In addition to improving quality of life metrics, it has been proposed that regular cannabis use might stimulate appetite, thereby facilitating weight gain in patients with IBD. A prospective pilot study in 2012 by Lahat et al. [16] found that after receiving inhaled cannabis for 3 months, patients with IBD reported having less physical pain ($p = 0.004$), less depression ($p = 0.007$), and an improved ability to work ($p = 0.0005$). Patients on average gained 4.3 kg ($p = 0.0002$) and had lower average Harvey–Bradshaw index scores by a difference of 11.36 ($p = 0.001$). It is important to note though that this study only consisted of 13 patients in total. It was also susceptible to bias given that knowledge of having received cannabis might impact final results from self-reported questionnaire data.

Ultimately, the majority of subsequent studies on cannabis were unable to replicate these findings, concluding that while cannabis helped with IBD symptom management, it does not change inflammatory markers or affect endoscopic healing. Naftali et al. [17] performed a second study, this time a placebo-controlled study of 21 patients with a Crohn's Disease Activity Index (CDAI > 200), who had failed to respond to therapy. Patients were assigned to cannabis (THC cigarettes twice daily) or a

placebo group (flowers without THC) for 8 weeks. Though not statistically significant, 45% of those in the THC group achieved complete remission (CDAI < 150), whereas only 10% of patients in the placebo group achieved complete remission. Patients who received cannabis cited having improved sleep and appetite. As a result of the sample size, however, this study was underpowered, and no difference was seen between placebo versus THC groups in terms of C-reactive protein (CRP), a marker of inflammation.

Even if cannabis is beneficial for alleviating IBD-related symptoms, it is difficult to establish exactly what dose of cannabis would be optimal. Irving et al. [18] conducted a randomized control study of 60 patients with left-sided or extensive UC (Mayo score 4–10), who were assigned at random to either a cannabidiol (CBD) or placebo group. Patients were gradually uptitrated to a gelatin capsule dose of 250 mg twice daily, which they continued for 8 weeks. Interestingly, patients found the gelatin capsules difficult to tolerate, and tended to take one-third of the intended dose, resulting in inadequate exposure. Remission rates at the end of 10 weeks were 28% for the CBD group and 26% for the placebo group. However, patients in the CBD group endorsed significantly better quality of life than those in the placebo group. This study highlights that while cannabis might improve UC symptoms, additional research is needed to determine which dose achieves benefits and minimizes adverse effects.

Naftali et al. [19] also performed a randomized controlled trial of 20 patients with CD to further explore what dose might achieve a clinical benefit and still avoid side effects. Patients who had failed to respond to standard treatment and had a CDAI of greater than 200 were randomized to receive 10 mg of CBD or placebo twice daily. Patient's hemoglobin, albumin, creatinine, and liver enzymes were checked throughout the study. This study ultimately concluded that although safe, 10 mg of cannabis twice daily for 8 weeks did not produce a significant difference in average CDAI between cannabis and placebo groups. One possible weakness of this study is that 10 mg

twice daily is a relatively small dose of CBD in the first place.

More recently, a double-blind, randomized, and placebo-controlled trial involving 32 patients with UC observed that those in the cannabis group achieved clinical remission and reported better quality of life. Patients were given either cigarettes containing 0.5 g of dried cannabis flowers with 80 mg of THC or placebo cigarettes. The study determined that smoking cannabis did not contribute to an improvement in Mayo endoscopic score or a reduction in serum inflammatory markers, like CRP and calprotectin [20].

Another study from 2021 by Naftali et al. [21] that examined the relationship between CBD oil and CD reached similar conclusions. This study was also a double-blind, randomized, and placebo-controlled trial. It consisted of 56 patients with CD consuming CBD oil or placebo orally for 8 weeks. As seen in the prior study, patients in the cannabis group had a significant improvement in quality of life metrics and CDAI scores but did not exhibit less inflammation as evidenced by endoscopic appearance, CRP, or calprotectin.

CASE 2

A 23-year-old male graduate student with ileocolonic CD in clinical but not endoscopic remission currently requires 5 mg of prednisone daily to decrease his diarrhea symptoms. He says that he would like to try cannabis. His job is an NIH-funded position, for which he has to complete annual drug testing.

It is possible that this patient would benefit from cannabis from both the perspectives of symptom management and a reliance on steroids. Cannabis could decrease gut motility and in doing so would likely result in fewer episodes of diarrhea. Diarrhea was one of the most common symptoms that patients cited improved with cannabis use in population studies [10].

Additionally, in the Naftali et al. [15] study involving 30 patients with CD, it was found that after cannabis use, patients with CD needed fewer medications overall, particularly corticosteroids. For this reason, there may be some

role for steroid sparing with cannabis supplementation in this patient.

However, these proposed benefits would have to be weighed within the greater context of what is at stake for this patient professionally. Regardless of individual state laws, cannabis remains federally illegal, and this patient is routinely drug tested. Failure to pass an annual drug test might result in the patient losing his government funding if found to be in violation of a federal law.

CONCERNS FOR CLINICIANS WHOSE PATIENTS USE CANNABIS

Storr et al. [10] reported that more than a third of patients with IBD who were not cannabis users were worried about the possible side effects of the substance. Furthermore, even for patients who achieve a reduction in IBD symptoms with cannabis, there are still concerns among clinicians regarding the long-term consumption of it. One issue that must be viewed within the larger context of needing more standardized dosing is that of toxicity. When inhaled in doses of 2–3 mg or ingested in doses of 5–20 mg, THC has been found to impair attention, concentration, short-term memory, and executive functioning, which consists of more advanced cognitive tasks like planning and emotional self-regulation. Severe adverse effects are typically not seen until concentrations of higher than 7.5 mg/m², and include nausea, postural hypotension, delirium, panic attacks, anxiety, and myoclonic jerking. Given that cannabis is delivered through a multitude of means and formulations, it is challenging to ensure therapeutic dosing that entirely avoids toxic effects for individuals with varying levels of prior exposure [22].

Cannabis dependence and addiction potential are other facets that may limit the practicality and widespread use of cannabis. It was initially disputed whether or not cannabis possesses addictive properties. However, recent studies have proven that frequent cannabis users are at high risk of dependence. A prospective cohort study of 600 frequent cannabis users (ages 18–30) determined that 3 years

later, the incidence of dependence was 37.2% (95% CI = 30.7–43.8). Living alone, total number, and type of recent negative life events were all predictive of developing a dependence [23]. A 2012 National Survey on Drug Use and Health revealed that a total of 2.7 million people above the age of 12 met diagnostic criteria for cannabis dependence as defined by the DSM-IV [24]. Thus, the impact of daily cannabis use on the potential for addiction cannot be underestimated. For those dependent on cannabis, withdrawal symptoms commonly include irritability, poor sleep quality, dysphoria, craving, and anxiety [22].

The cannabis consumed today is thought to be between 6–7 times more potent than used in the 1970s. Among adolescent use, blunts, which contain purely cannabis, have become more popular than joints, which contain a combination of cannabis and tobacco, suggesting the amount of THC consumed overall per instance is much higher today than in past decades. Patients with IBD who are pregnant must be explicitly counseled to avoid the use of cannabis while pregnant. Although the research is limited, prenatal use of marijuana in particular has been connected to infertility, placental complications, and fetal growth restriction as well as long-term offspring effects on executive function and learning [25].

Additionally, for patients with psychiatric disease, cannabis is not an ideal adjuvant therapy for symptom control. Cannabinoid agonists have been shown to exacerbate the symptoms of patients with schizophrenia, for example, regardless of if being treated with an antipsychotic. This is not surprising given the connections between THC and psychosis. Laboratory studies have largely disproved the notion of cannabis as self-medication for those with schizophrenia, failing to identify any significant clinical benefit of cannabis in this patient population [26].

Chronic heavy use of cannabis can also predispose patients to cannabinoid hyperemesis syndrome (CHS), which only resolves with abstinence from cannabis. CHS is described as a cyclical vomiting illness that occurs within the context of regular cannabis use. The regular cannabis use typically predates the recurrent

episodes of nausea and vomiting. Further complicating this picture, the symptoms of CHS are similar to those of a CD flare with a partial small bowel obstruction [27]. However, one pathognomonic feature that distinguishes CHS is the fact that symptoms improve or temporarily resolve with hot showers or baths. Allen et al. [28] found that 9/10 patients with CHS took multiple hot showers or baths a day. They also found that of this group, only those who abstained from cannabis achieved resolution of symptoms, and once it was resumed, patients again suffered from CHS. This study illustrates that CHS symptomatology is disruptive to daily life and must be taken into account when considering long-term use of cannabis for medical purposes.

Lastly, patients contemplating cannabis use must be counseled on the need to avoid operating heavy machinery, as marijuana is the illicit drug most commonly associated with impaired driving and fatal accidents. The exact relationship between chronic cannabis use, lung cancer, and airway disease is less apparent. It is reasonable to conclude that patients who inhale cannabis long-term are more likely than non-users to incur lung damage. At the same time, cigarette smoking is known to be more carcinogenic than cannabis smoking [29].

It must be emphasized that one of the primary means by which cannabis is consumed is smoking, which alone poses inherent health risks. Smoking cannabis results in more rapid effects compared to oral ingestion. With smoking, a peak plasma concentration of THC can be reached in minutes versus with oral ingestion it may take hours [30]. A cohort study of young adults found that those who were cannabis-dependent exhibited respiratory symptoms at a similar rate as those who smoked between 1 and 10 cigarettes a day. Some of these symptoms included wheezing, exercised-induced shortness of breath, nocturnal waking with chest tightness, and increased sputum production. This study concluded that as early as 21 years of age, those who smoke cannabis heavily may experience respiratory symptoms and changes in spirometry [31]. Overall, cannabis is a treatment modality that requires thoughtful

evaluation of these potentially negative attributes prior to recommending it for patients with IBD.

CASE 3

An 18-year-old woman with a past medical history of well-controlled schizophrenia, intermittent alcohol bingeing, and Crohn's colitis, who is maintained on vedolizumab, lives in Tennessee, a state where cannabis remains fully illegal. She plans to cross state lines to obtain recreational cannabis and wishes to stop medical therapy, opting for "natural" remedies instead.

For multiple reasons, this patient should be advised to continue with her current treatment regimen, rather than stop it in favor of pursuing cannabis exclusively as therapy for Crohn's colitis. Although well-controlled, this patient's history of schizophrenia suggests that she would be a poor candidate for cannabis, as she might be more vulnerable to THC and its psychoactive properties than a patient without underlying psychiatric illness. Her history of binge drinking and desire to engage in risky behavior by traveling to a different state in pursuit of cannabis because it is illegal in her home state also raises concerns for cannabis dependence. In this particular scenario, it would be important to assess if she has been using cannabis, and if so, how much and how often. It is also essential to stress that cannabis should not be used in conjunction with alcohol, especially when consumed in large quantities.

Even aside from this issue of addiction potential in a patient who already engages in alcohol bingeing, cannabis should never serve as a replacement for standard maintenance therapy. Although cannabis might assist with symptom management, traditional therapy in the form of vedolizumab will provide greater benefit in terms of inflammation for this patient. Currently, there is no compelling evidence to suggest that cannabis alone would result in disease treatment.

CONCLUSION

In the USA, cannabis is classified as a Schedule I substance, which severely limits the scientific research that can be conducted on it. As cannabis gains popularity, both amongst patients and clinicians, governments will likely continue to pass laws at the state level approving its use, despite limited evidence of its clinical utility. By November of 2020, a total of 36 US states and four territories have already approved cannabis for medical use.

Patients with IBD often experience pain, nausea, and decreased appetite. As described here, in multiple studies, patients with IBD reported a significant improvement in symptoms and quality of life metrics with the use of cannabis. While initially promising, additional double-blind, placebo-controlled studies have found that even though CBD may improve perceived symptoms, it does not reduce inflammation or address underlying disease activity. These studies failed to demonstrate that when given cannabis, patients with IBD had an improvement in inflammatory markers or mucosal healing on endoscopy compared to patients with IBD in placebo conditions. Thus, in many circumstances, patients with IBD would benefit more from maintenance therapy optimization than from the initiation of cannabis as adjuvant therapy.

These studies also suggest that additional investigations are warranted to further elucidate the role of cannabis in the treatment of IBD. Changing the current classification of this substance would be the first step to facilitating more comprehensive studies on IBD and cannabis within the USA specifically. Overall though, from what is known, cannabis is a medication that offers benefits but also comes with appreciable legal considerations and potential side effects. When recommending it to patients for symptom relief, it is imperative to reflect on how issues of toxicity, dependence, and adverse effects from chronic use might impact a patient. As cannabis continues to become more widespread in consumption, it is essential for providers to ask patients about their cannabis use and have informed, non-

judgmental conversations about risks and benefits of it.

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