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The Role of Cannabis in the Management of Inflammatory Bowel Disease: A Review of Clinical, Scientific, and Regulatory Information

Commissioned by the Crohn's and Colitis Foundation

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There is significant interest among patients and providers in using cannabis (marijuana) and its derivatives to treat a number of chronic illnesses, including inflammatory bowel disease. Despite the Schedule I classification of cannabis by the federal government, state governments have sought ways to make cannabis available for specific medical conditions, and some states have legalized cannabis outright. This white paper summarizes the preclinical data, clinical data, safety data, and the regulatory landscape as they apply to medical cannabis use in inflammatory bowel disease. Animal models of cannabinoid chemistry and physiology give evidence of anti-inflammatory, antidiarrheal, and nociceptive-limiting properties. Human studies have found benefit in controlling symptoms and improving quality of life, but no studies have established true disease modification given the absent improvement in biomarker profiles or endoscopic healing.

Finally, this review describes the legal, regulatory, and practical hurdles to studying the risks and benefits of medical cannabis in the United States.

Key Words: cannabis, marijuana, THC, Crohn's disease, ulcerative colitis, inflammatory bowel disease

INTRODUCTION

Inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis, are chronic intestinal conditions characterized by uncontrolled inflammation[1] that results in gastrointestinal and extra-intestinal symptoms and, in many cases, progression to surgery or disability.[2] They are of unknown cause and have no medical cures. Therapy of these conditions has been focused on improvement of symptoms and quality of life, predominantly by control of inflammation with immune-based therapies.[3] More recently, the goal of management has included both symptom improvement and objective evidence of biochemical control, so-called "deep remission." Deep remission has been associated with improvement in disease control over time and is associated with reductions in hospitalization and surgery. However, despite significant advances in the effectiveness of medical therapies for patients with Crohn's disease and ulcerative colitis, there remain unmet needs and gaps in treatment options for many patients.[4, 5] In addition, despite substantial improvements in the ability to heal the bowel and even modify long-term outcomes of the disease,[6, 7] some patients with inflammatory bowel disease continue to suffer from a variety of nonspecific symptoms such as nausea, fatigue, weakness, loss of appetite, and coexisting psychosocial problems.[8]

Successful management of inflammatory bowel disease involves careful review by an appropriate specialist and coordination of medical, surgical, psychological, and complimentary therapies to address the complex needs of the individual patient.[9] There has been interest in the use of cannabis as a treatment for inflammatory bowel disease,[10, 11] but there is no definitive evidence to demonstrate that currently available formulations can control inflammation. However, the use of cannabis in various forms has been associated with improvements in nausea, abdominal pain, and appetite.[12–14] Therefore, there is great interest in the possibility of this therapy for additional

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use and further study. The legalization of cannabis for medicinal purposes in many states, and for recreational use in a few,[15] provides unique opportunities to further explore this treatment option.

Patients have expressed great interest in understanding the full therapeutic potential of cannabis and its derivatives,[16] and providers have struggled to know how to best support their patients' requests for authorization to use the therapy or consider it as an adjuvant therapy.

This white paper, commissioned by The Crohn's and Colitis Foundation, summarizes the available information about medical marijuana (MMJ) and its use in IBD and provides a review of the available literature and legal status in the United States. It also provides an outline of needed research initiatives and areas for further study, emphasizing the gaps in our current understanding in order to better define the potential and future utilization of this therapy.

CHEMISTRY AND PHYSIOLOGY OF CANNABIS

Cannabis, colloquially known as "marijuana," is a genus of flowering plant with multiple subspecies, including *Cannabis sativa*,[17] containing cannabinoids. Cannabis has generally been lumped into the category of "complementary and alternative medicine" when its medical application has been mentioned in the management of IBD.[18] Unlike many interventions included in this basket term, however, the effect of cannabis on the human body, which is mediated by the endocannabinoid system (ECS), has been studied in great detail.

Cannabis contains nearly 500 chemicals, the most well-known of which are cannabinoids cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC). THC is well known for its psychotropic effects, and CBD for its anti-inflammatory and immunomodulatory effects.[19–22] Broadly, the ECS system has been linked to visceral pain perception, nausea and vomiting, gastrointestinal motility, and intestinal inflammation and has been discussed elsewhere.[23]

Cannabinoids act at CB1 and CB2 receptors. CB1 is mainly expressed in the brain, where it causes its well-known psychotropic effects, and the enteric nervous system. In contrast, CB2 is absent in the brain but is still found in the enteric nervous system, immune cells (macrophages and plasma cells), and gastrointestinal epithelial cells. Endogenous cannabinoids, anandamide and 2-arachydonylglycerol (2AG), are produced and released locally to act on CB1/CB2 receptors.[23, 24] THC is a partial agonist of the CB1 and CB2 receptors. Although the mechanism of action of CBD is not specific, some of its downstream effects are potentiated through the prevention of reuptake of endogenous anadamide.[25–27]

Activation of the endocannabinoid receptors using CB1- and CB2-specific ligands results in decreased inflammation in animal models of colitis.[28–30] A systematic review of 24 individual cannabinoid compounds tested in murine colitis found them beneficial in reducing colonic inflammation in rats and mice.[19] A combination of THC and CBD was found to be additive in anti-inflammatory activity in a mouse model of colitis.[31]

Concentrations of CB1 and CB2 receptors increase in the human gut in the settings of colon cancer, diverticulitis, and celiac disease.[23, 29, 32] There is conflicting evidence regarding changes to the expression of endocannabinoid receptors in IBD. This may be due to small heterogeneous cohorts, lack of subclassification of disease types and activity, and variable tissue sampling sites.[24] This variance may also explain the conflicting effects seen in human experiments. Contrary to some other more recent studies in patients with chronic abdominal pain, administration of synthetic THC to healthy subjects has resulted in increased visceral sensitivity.[33] Oral THC administration was not beneficial in patients with chronic abdominal pain (postop pain, pancreatitis), and this is thought to be secondary to sensitization of nociceptive pathways in the central nervous system.[34]

OVERVIEW OF THE USE OF MMJ FOR THE TREATMENT OF IBD

There have been limited studies of cannabis in IBD. Prevalence studies in the United States, United Kingdom, Israel, Canada, and Spain suggest that 10%–12% of IBD patients are active cannabis users, with commonly expressed goals of mitigating abdominal pain, improving appetite, and limiting diarrhea.[12, 14, 16, 35] Nearly half of the nonusing patients in 1 study expressed interest in using cannabis to control symptoms when legally available.[14] A single-center study from Boston did not find any increase in medical use of cannabis among their IBD population over the 5 years since cannabis was decriminalized in that state.[36]

Several published studies assessing cannabis use in patients with Crohn's disease have been performed in Israel,[10, 12, 13, 37] where regulations surrounding cannabis are less restrictive (Table 1).[38, 39] Although medical cannabis is increasingly available in the United States, there has been no controlled prospective evaluation of cannabis in the management of IBD in the United States.

MMJ Effect on IBD Symptoms and Quality of Life

There have been several studies showing improvement in symptoms associated with IBD, leading to an improvement in quality of life. Cannabis use is common among IBD patients, with the majority of patients using cannabis to control IBD-related symptoms including pain, nausea, poor appetite, and sleep disturbances. In 1 study of 292 US patients, 12.3% of IBD patients reported current cannabis use. In this study, current users noted significant improvement in abdominal pain, poor appetite, nausea, and diarrhea.[14]

Lahat and colleagues performed an uncontrolled observational study of IBD patients refractory to conventional therapy.[12] Cannabis was provided as 50-g prepared cigarettes and

TABLE 1. SUMMARY OF STUDIES ON MEDICINAL CANNABIS USE IN IBD

Year/Author[Ref]	Country	Study Design	Cannabis Type	Patients	IBD Diagnosis	Outcomes
2011/Naftali[10]	Israel	Retrospective	Inhaled and oral	30	CD	Subjective improvement in symptoms
2012/Lahat[12]	Israel	Obsesrvational/ cohort	Inhaled (3 inhalations as needed for pain)	13	11 CD, 2 UC	Improvements in health perception, ability to work, social activities, emotional stress, abdominal pain
2013/Naftali[13]	Israel	RCT	Inhaled	11 treatment, 10 placebo	CD	Improvement in CDAI (not significant)
2017/Naftali[30]	Israel	RCT	Oral	10 treatment, 10 placebo	CD	Improvement in CDAI (not significant)

prescribed to be used as needed for pain. Thirteen patients with Crohn's disease were included in the study, with primary outcomes assessing quality of life and clinical disease activity indices after 3 months of treatment. Patients reported significant improvement in general health perception, social functioning, ability to work, pain, and depression. In addition, patients noted improvement in disease-specific symptoms measured through the Harvey Bradshaw Index (HBI), including general well-being, abdominal pain, and loose stools. Although there was no improvement in objective disease measures such as C-reactive protein (CRP), patients were able to gain weight from below an appropriate body mass index to normal or near-normal. There are several limitations to this prospective study, including lack of standardization of cannabis type and dosing and lack of a control group.

Naftali and colleagues performed a retrospective study of 30 patients with Crohn's disease refractory to conventional medical management who used cannabis in the management of their IBD for management of chronic pain, for persistent clinical symptoms, or for recreational use.[10] In this small retrospective study, the duration of cannabis consumption ranged from 3 months to 9 years, with varying forms of administration including cigarettes, water pipe inhalation, and oral. In this cohort, 30% of patients had no change in their clinical symptoms, measured by the HBI, yet many discontinued steroids while using cannabis. These studies suffered from multiple limitations, including selection bias, lack of standardized dosing and route of administration, absence of blinding, recall bias, and lack of a control population.

Naftali and colleagues subsequently performed the first randomized controlled trial assessing clinical and objective disease outcomes in patients with Crohn's disease.[13] Twenty-one patients with moderate disease activity were included; a majority were primary anti–tumor necrosis factor (anti-TNF) nonresponders or intolerant to anti-TNF therapy and were naïve to cannabis use. There was a standardized dose and administration among the treatment group. The primary outcome of this study was induction of clinical (symptomatic) remission at 8 weeks, defined as a Crohn's Disease Activity Index (CDAI) <150, and there were several secondary end points looking at objective disease assessment. The CDAI was calculated using 7-day recollection and recording of multiple weighted parameters including number of liquid stools, abdominal pain, general well-being, use of antidiarrheal agents, change in weight, hemoglobin, and the presence of abdominal mass. This small study failed to reach statistical significance of its primary end point, but 45% of the treatment group achieved CDAI scores below 150, compared with 10% in the placebo group. However, there were no differences in biochemical assessments, including hemoglobin levels and CRP. All patients in the treatment group were able to stop steroid-based therapy during the study. Importantly, cannabis use was associated with improved abdominal pain and quality of life scores. It is notable that all patients had clinical relapse within 2 weeks after discontinuation of cannabis. Although this was the first randomized controlled trial, the authors acknowledge that true "blinding" was difficult given the psychotropic effects of THC.[13] The possibility of general well-being driving the clinical improvement cannot be excluded. The same group from Israel, Naftali and colleagues,[37] published another placebo-controlled randomized trial of low-dose cannabidiol by oral administration in 20 patients with active Crohn's disease refractory to treatment with steroids, thiopurines, methotrexate, and anti-TNF agents. After 8 weeks of treatment, there was no significant reduction in CDAI scores between study patients and controls. Changes in laboratory parameters (blood count, liver and kidney functions) were not significantly different. Limitations to this study include the small sample size, the relatively low dose of cannabidiol used, route of administration (ingestion vs inhalation), and the use of a single cannabinoid (which minimizes the potential

anti-inflammatory synergistic effects that have been suggested with use of a combination of cannabinoids).

A systematic review and meta-analysis evaluating the use of cannabinoids for other chronic medical conditions, including neuropathic pain, cancer, diabetes, fibromyalgia, multiple sclerosis, musculoskeletal problems, and chemotherapy-related pain, showed moderate-quality evidence to support the use of cannabinoids for relief of chronic pain.[40] Inflammatory bowel disease was not included.

The underlying theme of the limited available evidence is that cannabis use may offer symptomatic benefit and improved quality of life when patients have poor or incomplete response to standard therapy. However, none of the available data demonstrate improvement in biochemical or disease activity scores.

Development of Commercial Compounds

There is increasing attention by the pharmaceutical industry to therapeutic manipulation of the endocannabinoid system.[41] A peripherally restricted CB1/CB2 receptor agonist, SAB378 (Novartis Pharmaceuticals, Basel, Switzerland), inhibits gastrointestinal motility in animal models but has not shown benefit in animal models of colitis.[42] Another commercially available CB1/CB2 receptor agonist and THC analog is dronabinol (Abbvie, Chicago, IL, USA), which has been approved for appetite stimulation in AIDS patients but has not been tested in IBD patients.[43] Nabiximol (GW Pharmaceuticals, Cambridge, UK), a commercially available buccal spray, also activates CB1/CB2 receptors and is currently approved outside the United States for neuropathic pain secondary to multiple sclerosis and cancer. This has not been tested in IBD patients.[44]

SAFETY AND ADVERSE EVENTS

The long-term safety profile of chronic cannabis use has not been well defined, mainly due to the heterogeneity of preparations, varying routes of administration, and the lack of controlled studies addressing safety, especially in IBD patients. In a retrospective study of more than 300 patients with Crohn's disease, cannabis use for more than 6 months was found to be an independent risk factor for surgery (adjusted odds ratio, 5.03; 95% confidence interval, 1.45–17.46).[45] Given the retrospective nature of this study and the lack of control for other risk factors for surgery, however, it is impossible to determine a causal relationship between cannabis use and surgery. In addition, there are population-based studies that have demonstrated an increased risk for motor vehicle accidents[46] and cannabis hyperemesis syndrome.[47, 48] Despite these reported safety concerns, there have been no deaths associated with cannabis use alone.

A Canadian multicenter retrospective study of 494 patients presenting to the emergency department for vomiting found that 19.4% reported recent cannabis use, suggesting that cannabinoid hyperemesis syndrome may be an overlooked diagnosis for vomiting.[49–52] The increase in potency of THC content in cannabis, from about 3% in the 1980s to 12% in 2012,[53] may potentiate adverse effects of cannabis use. For example, cannabis ingested in an edible form is more difficult to titrate, unlike vaping or inhaling, as the effect may be delayed, and therefore higher doses may be consumed, leading to intoxication. Heavy use may cause impaired memory for at least 1 week after abstinence, hyperemesis, and withdrawal symptoms. Acute psychotic symptoms during intoxication also have been reported.[54, 55]

In a separate study, Al-Shammari and colleagues evaluated the effect of MMJ legalization in the United States on trends of cannabinoid dependency (CDU) and persistent vomiting.[56] They collected hospital discharge data from the Healthcare Cost and Utilization Project before and after legalization of MMJ in 2009. Before legalization, there was an upward trend in the incidence of CDU, but the rate at which the incidence has been increasing grew by 6% after legalization. The effect is more striking in the incidence of persistent vomiting, which had a fairly stable incidence before legalization but has seen its growth rate increase by 8% since legalization. The investigators acknowledge that the defined 1-year washout period (2009) and the 5-year postlegalization period are relatively short to clearly define the legalization effect on these trends. Furthermore, the findings are based on administrative diagnosis codes and may be confounded by increased transparency in patient-reported symptoms after the legalization and decriminalization of cannabis.

Special Population: Safety in the Pediatric and Adolescent Population

The frequency of use of cannabis by adolescents in the United States has remained stable, with about 40% of 12th graders having used cannabis in the past 12 months.[57] In Colorado, a state with a robust cannabis industry, rates appear similar, with 38% of high schoolers having ever tried cannabis.[58] Both nationally and in Colorado, about 20% of adolescents report using in the past 30 days, and about 4%–6% use daily or almost daily. This suggests that 20%–25% of adolescents who use cannabis use it habitually, a trend that has been increasing over the past 10 years. Preliminary data from Colorado show that adolescents with IBD use cannabis at the same rate as their similarly aged peers without IBD, but they use it more intensely (50% weekly or more frequently vs 25% non-IBD adolescents).[59, 60] Similarly, in Connecticut, 75% of 18–21-year-olds with IBD who use cannabis do so weekly or more frequently.[61]

Along with the increase in use intensity, there has been a steady decline in perception of risk with regular use. Indeed, 60% of high school seniors perceive regular use of cannabis as not having great risk, and this figure has been increasing since 2004.[57, 62] However, emerging literature supports the view of significant adverse health effects with both short-term and long-term use, mainly on neurologic, cognitive, and mental health.[63] An increase in motor vehicle accidents among adolescents

combining recreational use of cannabis and alcohol has been reported but has not immediately translated to an increase in fatal crashes in states that have medical cannabis laws. Addiction risk may be higher for those beginning heavy use in adolescence, and this behavior may predict progression to harder drugs.[63, 64] Because of these short- and long-term negative effects, the American Academy of Pediatrics[65] and the Academy of Child and Adolescent Psychiatry[66] oppose cannabis legalization.

The current literature on cannabis use should be interpreted with caution, as data from heavy and/or long-term users have potential confounding factors, such as other drug use, psychiatric comorbidities, and adverse psychosocial and economic conditions.[63] These retrospective and indirect studies should not be inferred as proof of causality for adverse outcomes associated with cannabis use.

Special Population: Safety in Conception and Pregnancy and Lactation

The role of the endocannabinoid system (ECS) in reproduction has been widely investigated, with evidence suggesting that cannabis use alters the female menstrual cycle and endometrial proliferation at the cellular and molecular levels.[67–69] Limited clinical data do not suggest any decrease in fertility associated with cannabis use. A web-based prospective cohort study (Pregnancy Study Online [PRESTO]) was conducted in North America whereby women between the ages of 21 and 45 years were enrolled, and their male partners were invited to participate.[70] Couples (n = 1125) completed lifestyle and behavioral questionnaires that included frequency of cannabis use. After 1-year follow-up, fecundability rates were comparable between those who used cannabis <1 and ≥1 time per week, and among women and men.

The American College of Obstetricians and Gynecologists does not recommend or endorse the use of cannabis in pregnant patients because observational data show that cannabis use was associated with low birth weight and preterm delivery.[71] There have been no studies looking at maternal cannabis use in IBD. However, a recent meta-analysis that compiled data from 31 observational studies looking at maternal cannabis use found no difference in rates of low birth weight, preterm delivery, or perinatal death when controlling for tobacco use and other confounding variables. The authors concluded that maternal cannabis use is not an independent risk factor for adverse fetal outcomes, citing tobacco use as the main driver for poor outcomes.[72]

Analysis of breast milk from mothers using cannabis detected THC up to 6 days after last use; the concentrations were directly related to the intensity and frequency of use, and the authors suggested that this may influence brain development during this period.[73]

OVERVIEW OF US STATE AND FEDERAL LAWS

As of January 2018, 30 states plus the District of Columbia have legalized medical cannabis,[74] and 16 states have legalized high-cannabidiol (CBD), low-THC forms of cannabis or hemp oil. Nine states and the District of Columbia, all with medical cannabis programs, have gone a step further and legalized recreational cannabis for adults over 21 years of age (Fig. 1).

At the same time, the possession or sale of cannabis remains illegal under federal law. Over the last several years, the federal government has mostly not enforced its cannabis prohibition, particularly against individuals acting in compliance with state laws, for 3 reasons. First, enforcement had been reduced significantly because of limited resources for law enforcement and prosecutors and the public's changing views about cannabis. For many years, the federal government has not prosecuted medical cannabis patients who were not growing or selling cannabis.

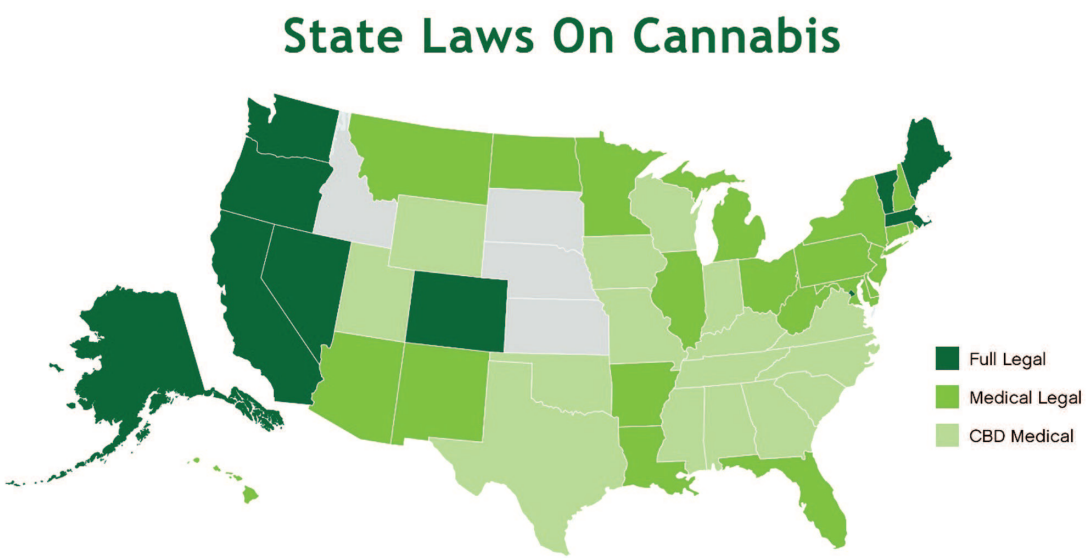

FIGURE 1. Legal status of cannabis by State in the United States—August 2018.

Second, in 2013, the US Department of Justice (DOJ) issued a memorandum (the "Cole Memo") that permitted federal prosecutors to use their discretion to decline to prosecute violations of federal cannabis laws as long as the crime did not implicate 9 federal priorities, such as preventing distribution to minors, diversion across state lines, drugged driving, and possession or use on federal land. On January 4, 2018, however, Attorney General Jeff Sessions issued a memorandum (the "Sessions Memorandum") that rescinded the previous DOJ guidance on the state legal cannabis industry, including the Cole Memorandum. Sessions wrote that the previous guidance on cannabis law enforcement was unnecessary, given the well-established principles governing federal prosecution that are already in place. As a result of the Sessions Memorandum, federal prosecutors may now be free to utilize their prosecutorial discretion to decide whether to prosecute even state legal adult-use cannabis activities.

Third, through the Rohrabacher-Blumenauer Amendment to omnibus spending bills, Congress has precluded the DOJ from interfering with state medical cannabis programs, including prosecuting anyone in strict compliance with state law. The protection was recently renewed in the fiscal year 2018 omnibus spending bill and remains in place. Future changes in federal enforcement are difficult to predict.

Particular States

Each medical cannabis state has a unique program with its own rules, some of which have been changing regularly. Approximately half list Crohn's disease or ulcerative colitis as qualifying conditions; some states do not list those conditions but instead list symptoms of IBD that can be treated by cannabis, such as chronic pain, anorexia, or nausea. For example, different states have different rules about the following: how patients can get certified to use medical cannabis; which medical conditions qualify; physicians' and other medical professionals' obligations; where patients may purchase cannabis; how, where, and in what form it may be used; rights with respect to employment, housing, and child custody; and how, where, and by whom cannabis may be grown, processed, and sold. Accordingly, patients should not assume that an activity that is legal in 1 state will be legal in another. For example, if a patient, after consultation with the treating physician, decides to use medical cannabis, the patient should understand particular laws' effects. In addition, only certain states provide reciprocity to patients licensed by another state.

A useful guide to the laws regarding how patients get approved to use medical cannabis under state laws can be found here: http://www.safeaccessnow.org/becoming_a_state_authorized_patient.

Legal Status of Medical Cannabis in the Rest of the World

Canada permits the use of medicinal cannabis and recently voted to legalize recreational use as well. This law will go into effect in October of 2018. European laws are varied; the following European countries have legalized medical cannabis in some form: Catalonia, Croatia, Cyprus, Czech Republic, Denmark, Finland, Germany, Greece, Italy, Luxembourg, Macedonia, Malta, Netherlands, Norway, Poland, San Marino, Switzerland, and Turkey. The following additional countries have legalized medical cannabis: Argentina, Australia, Chile, Columbia, Israel, Jamaica, Mexico, and South Africa. They have different levels of permissiveness. Spain has legalized cannabis for private use in private spaces. The Netherlands and Portugal are very permissive under decriminalization.[75]

Medical Professionals

Different states provide medical professionals different rights and obligations under each state's program. For example, state laws differ with respect to who may certify a patient, the extent of the medical relationship with the patient, what kind of exam is required, and the form of any written certification. State laws also differ on protections for medical professionals who help a patient administer medical cannabis, and whether and how patients may use cannabis in hospitals. A medical professional must assure compliance with state law, any medical malpractice insurance policy, and any policies by associated hospitals, medical groups, or institutions. Some malpractice insurance only covers the use of Food and Drug Administration (FDA)–approved medications and treatments.

Under federal law, physicians are protected from prosecution for recommending or suggesting that a patient use cannabis. They are also protected under the Rohrbacher-Blumenauer Amendment, as long as they are complying with the state medical cannabis law. Although the law is not entirely settled on whether writing a certification under state law could expose a medical professional to federal prosecution, the federal government has not prosecuted any medical professional merely for certifying a patient. Certifying medical professionals have faced prosecution only where there were exacerbating circumstances, such as a physician laundering drug money.

Medical professionals should be careful about submitting government claims relating to medical cannabis certification or treatment, because those particular claims may not be covered.

The Centers for Medicare and Medicaid Services can revoke an organization's federal Medicare and Medicaid funding for a violation of the certification institutions sign certifying compliance with federal law. In turn, the federal Medicare/Medicaid program has a "State Operations Manual" that sets forth all protocols that surveyors follow, but it does not discuss cannabis. Additionally, there are no publicized cases of any hospital being sanctioned or having their Medicaid/Medicare funding revoked on the basis of any kind of participation in a state medical cannabis program. Recommending or certifying a patient for medical cannabis does not violate federal law.

MEDICAL RESEARCH POLICY AND ADVOCACY

More research is needed on the potential medical benefits and the short-term and long-term effects of cannabis use. However, it is widely held that the US regulatory landscape makes it difficult to study MMJ. Cannabis is listed as a Schedule I drug by the Drug Enforcement Agency (DEA), the strictest scheduling category. According to the DEA, drug scheduling is not based on "severity" of the drug, but on select criteria identified in statute. Substances are listed in Schedule I if they meet all 3 of the below criteria. The substance:

- has no currently accepted medical use;
- has a high potential for abuse; and
- lacks accepted safety for use under medical supervision.

Because cannabis is considered a Schedule I drug, cannabis research is subject to additional registrations and security protocols compared with nonscheduled compounds. For example, 1 hurdle is the obtainment of research-grade cannabis from an authorized provider. In addition, it has been suggested that the scheduling of cannabis has led to stigma, making it difficult for researchers to find funding for research on the potential health *benefits* of cannabis, rather than the detriments. Below is a discussion of several research barriers, including regulatory hurdles, difficulties in obtaining research-grade cannabis, and availability of research funding:

- Regulatory Hurdles: To legally study cannabis in human subjects, a researcher must complete many steps with several federal and state entities. This process has been described as onerous, and many have argued that it has limited medical research on cannabis, thus limiting the availability of important information for policy decision-makers, medical professionals, patients, and other stakeholders. The process includes the below steps:
  - Submit an investigational new drug (IND) application to the FDA.
  - Obtain a letter of authorization (LOA) to obtain research-grade cannabis from the National Institute of Drug Abuse (NIDA).
  - Register with the DEA and obtain a Schedule I license.
  - Submit a research protocol to the DEA including security details for storing and dispensing cannabis. Security requirements may vary based on the amount of cannabis and the jurisdiction of the DEA office.
  - Comply with additional requirements by the researcher's state regulations.
- Cannabis Supply: Because cannabis is a Schedule I drug, researchers must contact NIDA to obtain the supplies they need. As of this writing, the University of Mississippi is the only licit provider, which has led to limits on the type and quantity of cannabis that researchers can obtain. As state-regulated cannabis has become more varied and potent, research-grade cannabis has remained limited and less potent. In response to concerns from the research community, the government took several steps to ease access to research-grade cannabis for approved researchers. In 2015, the DEA increased the aggregate production quota of cannabis; in 2016, the DEA increased the number of private entities allowed to provide research-grade cannabis; in 2016, NIDA released a Request for Information (ROI) on the strains and varieties of cannabis that researchers would want to access. According to NIDA, researchers wanted access to "marijuana strains and products that reflect the diversity of products available in state dispensaries." Lastly, research-grade cannabis can be expensive to obtain in the United States, although it is free for National Institutes of Health (NIH)–funded researchers.
- Research Funding: The National Academies of Sciences (NAS) asserts that not enough research funding on cannabis is spent on the potential benefits of cannabis. The NAS observes that most of the research on cannabis supported by the NIH is through NIDA, and NIDA's mission is to "advance science on the causes and consequences of drug use and addiction." Thus, much of the research funding is going toward the health risks of cannabis, and not the potential health benefits of cannabis that could be used to guide clinicians and patients. In fiscal years 2015 and 2016, the NIH spent just over $100 million on cannabis research, of which approximately $60 million was spent by NIDA.

Public policy advocacy campaigns on medical cannabis are designed to remove barriers and increase the pace of research on medical cannabis. A popular approach is to advocate that the DEA de-schedule cannabis from Schedule I to Schedule II, because Schedule II drugs are subject to fewer research restrictions. As recently as August 2016, the DEA formally denied removing cannabis from Schedule I on the basis that there was no accepted medical use for cannabis in the United States. In their response letter, the DEA left the door open to consider future research advancements and announced the increase of authorized cannabis providers, subject to application. Some have argued that requirements like those outlined by the DEA are circular—the DEA needs more research to move cannabis from Schedule I but has established significant regulatory hurdles for conducting such research.[76]

Notable legislation to address research barriers under consideration by Congress include the Compassionate Access, Research Expansion and Respect States (CARERS) Act, and the Medical Marijuana Research Act. Among other provisions, the CARERS Act would exempt cannabis from Schedule I (similar to the alcohol and tobacco exemptions), limit federal intervention in state medical cannabis laws, and allow Veterans Administration physicians to prescribe MMJ. The CARERS Act is supported by voluntary health organizations including the Epilepsy Foundation, the National Multiple Sclerosis Society, the Michael J. Fox Foundation, and the National Women's Health Network. The Medical Marijuana Research Act would establish a new registration process to make it easier for researchers to access research-grade cannabis. Both bills have received bipartisan support, albeit with limited co-sponsorship.

Practical Advice for Clinicians

This review has summarized the limited experimental evidence suggesting that cannabis may play a role in controlling symptoms associated with IBD. There have been a few small studies that have demonstrated improvement of pain, nausea, appetite, and sleep. However, the medicinal use of cannabis has been limited by inability to perform quality research and concerns about cannabis' potential cognitive, psychiatric, and respiratory side effects. Patients who request cannabis for their symptom management or who share that they are using it already should be evaluated for further optimization of their medical or surgical management and control of their inflammatory disease. However, there appears to be a role for medicinal cannabis as complementary therapy for refractory or resistant symptoms. It is clear that more research is required to understand the short- and long-term benefits and risks of this therapy and to develop approaches to understanding dosing and monitoring patients.

Patients and providers considering the use of medicinal cannabis must consider the unique state laws pertaining to the prescription and use of cannabis, keeping in mind that it is still classified as a controlled substance by the Drug Enforcement Agency. Furthermore, patients must be aware of their employer's drug and drug testing policies.

We support policy changes that would facilitate further research into the potential therapeutic benefits of medicinal cannabis, including revising cannabis' status as a federal Schedule I controlled substance.

SUMMARY

This white paper summarizes the preclinical and clinical data and the legal and regulatory landscape as they apply to cannabis use in inflammatory bowel disease. The use of cannabinoid compounds in murine models of colitis demonstrates improvements in inflammation. Although the data are less robust in human studies, there may be benefit in symptom control and quality of life, though studies have been limited by small sample sizes and have failed to show improvements in biochemical markers or disease activity indices. Given the absence of data regarding disease modification by cannabis compounds, it may become important to monitor patients on medical cannabis who may take an improvement in clinical symptoms as a license to stop their standard therapies. A consequence of the conflict in state and federal status regarding cannabis is little oversight of quality, dose, frequency, or formulation, similar to herbal supplement use.

The conflict between federal law and state law has led to inconsistencies in the prescription of and access to medical cannabis. To date, there has been no prosecution for certification for, or possession of, medical cannabis in states where it has been legalized, but there remains an evolving tension in the legal and political landscape around this issue. Research regarding the benefits of medical cannabis has been hindered by the strict controls imposed for the study of Schedule I drugs. The need for medical cannabis in its current formulations may be obviated by drug compounds that similarly affect the endocannabinoid system, but these have not yet been tested in IBD patients.

REFERENCES

1. Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. *World J Gastroenterol.* 2014;20:91–99.
2. Vester-Andersen MK, Prosberg MV, Jess T, et al. Disease course and surgery rates in inflammatory bowel disease: a population-based, 7-year follow-up study in the era of immunomodulating therapy. *Am J Gastroenterol.* 2014;109:705–714.
3. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol.* 2015;110:1324–1338.
4. Rubin DT, Mody R, Davis KL, et al. Real-world assessment of therapy changes, suboptimal treatment and associated costs in patients with ulcerative colitis or Crohn's disease. *Aliment Pharmacol Ther.* 2014;39:1143–1155.
5. Panés J, O'Connor M, Peyrin-Biroulet L, et al. Improving quality of care in inflammatory bowel disease: what changes can be made today? *J Crohns Colitis.* 2014;8:919–926.
6. Zallot C, Peyrin-Biroulet L. Deep remission in inflammatory bowel disease: looking beyond symptoms. *Curr Gastroenterol Rep.* 2013;15:315.
7. Christensen B, Rubin DT. Understanding endoscopic disease activity in IBD: how to incorporate it into practice. *Curr Gastroenterol Rep.* 2016;18:5.
8. Regueiro M, Greer JB, Szigethy E. Etiology and treatment of pain and psychosocial issues in patients with inflammatory bowel diseases. *Gastroenterology.* 2017;152:430–439.e4.
9. Rubin DT, Hanauer SB, Lichtenstein GR, et al. Refining treatment paradigms in inflammatory bowel disease: assessing the options for individualized therapy. *Am J Gastroenterol Suppl.* 2016;3:4–7.
10. Naftali T, Lev LB, Yablecovitch D, et al. Treatment of Crohn's disease with cannabis: an observational study. *Isr Med Assoc J.* 2011;13:455–458.
11. Hergenrather J, Mikuriya T, Bearman D. Clinical improvement and reduction of immunosuppressive drug therapy in cannabis treated patients with Crohn's disease. Paper presented at: International Association for Cannabis as Medicine 3rd Conference on Cannabinoids in Medicine; September 9–10, 2005; Leiden, the Netherlands.
12. Lahat A, Lang A, Ben-Horin S. Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. *Digestion.* 2012;85:1–8.
13. 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.
14. Ravikoff Allegretti J, Courtwright A, Lucci M, et al. Marijuana use patterns among patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2013;19:2809–2814.
15. *ProCon.org: The Leading Source for Pros and Cons of Controversial Issues*. 28 legal medical marijuana states and DC: laws, fees, and possession limits. https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881 (1 September 2018, date last accessed).
16. Lal S, Prasad N, Ryan M, et al. Cannabis use amongst patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol.* 2011;23:891–896.
17. Turner CE, Bouwsma OJ, Billets S, et al. Constituents of *Cannabis sativa* L. XVIII–electron voltage selected ion monitoring study of cannabinoids. *Biomed Mass Spectrom.* 1980;7:247–256.
18. Quezada SM, Briscoe J, Cross RK. Complementary and alternative medicine. *Inflamm Bowel Dis.* 2016;22:1523–1530.
19. Couch DG, Maudslay H, Doleman B, et al. The use of cannabinoids in colitis: a systematic review and meta-analysis. *Inflamm Bowel Dis.* 2018;24:680–697.
20. Van Sickle MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science.* 2005;310:329–332.
21. Kaplan BL, Springs AE, Kaminski NE. The profile of immune modulation by cannabidiol (CBD) involves deregulation of nuclear factor of activated T cells (NFAT). *Biochem Pharmacol.* 2008;76:726–737.
22. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology.* 2010;35:764–774.
23. Sharkey KA, Wiley JW. The role of the endocannabinoid system in the brain-gut axis. *Gastroenterology.* 2016;151:252–266.
24. Alhouayek M, Muccioli GG. The endocannabinoid system in inflammatory bowel diseases: from pathophysiology to therapeutic opportunity. *Trends Mol Med.* 2012;18:615–625.
25. Di Marzo V, Izzo AA. Endocannabinoid overactivity and intestinal inflammation. *Gut.* 2006;55:1373–1376.

26. Alhouayek M, Muccioli GG. The endocannabinoid system in inflammatory bowel diseases: from pathophysiology to therapeutic opportunity. *Trends Mol Med.* 2012;18:615–625.
27. Elmes MW, Kaczocha M, Berger WT, et al. Fatty acid binding proteins (FABPs) are intracellular carriers for Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). *J Biol Chem.* 2015;290:8711–8721.
28. 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 Gastrointest Liver Physiol.* 2006;291:G364–G371.
29. Di Sabatino A, Battista N, Biancheri P, et al. The endogenous cannabinoid system in the gut of patients with inflammatory bowel disease. *Mucosal Immunol.* 2011;4:574–583.
30. 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.
31. Jamontt JM, Molleman A, Pertwee RG, et al. The effects of delta-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis. *Br J Pharmacol.* 2010;160:712–723.
32. Izzo AA, Capasso R, Aviello G, et al. Inhibitory effect of cannabichromene, a major non-psychotropic cannabinoid extracted from *Cannabis sativa*, on inflammation-induced hypermotility in mice. *Br J Pharmacol.* 2012;166:1444–1460.
33. 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 Gastrointest Liver Physiol.* 2007;293:G137–G145.
34. de Vries M, van Rijckevorsel DCM, Vissers KCP, et al; Pain and Nociception Neuroscience Research Group. 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.e4.
35. García-Planella E, Marín L, Domènech E, et al. Use of complementary and alternative medicine and drug abuse in patients with inflammatory bowel disease. *Med Clin (Barc).* 2007;128:45–48.
36. Merker AM, Riaz M, Friedman S, et al. Legalization of medicinal marijuana has minimal impact on use patterns in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2018;XXX:XXX–XXX.
37. 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.
38. Mechoulam R, Gaoni Y. A total synthesis of DL-delta-1-tetrahydrocannabinol, the active constituent of hashish. *J Am Chem Soc.* 1965;87:3273–3275.
39. Ablin J, Ste-Marie PA, Schäfer M, et al. Medical use of cannabis products: lessons to be learned from Israel and Canada. *Schmerz.* 2016;30:3–13.
40. Martín-Sánchez E, Furukawa TA, Taylor J, et al. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med.* 2009;10:1353–1368.
41. Ewan S. Weeding out new drugs. *Drug Discov Today.* 2005;10:1336–1337.
42. Cluny NL, Keenan CM, Duncan M, et al. Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone (SAB378), a peripherally restricted cannabinoid CB1/CB2 receptor agonist, inhibits gastrointestinal motility but has no effect on experimental colitis in mice. *J Pharmacol Exp Ther.* 2010;334:973–980.
43. NDA 18–651/S-021 Marinol (dronabinol) capsules. Marietta, GA: Solvay Pharmaceuticals, Inc.; 2004.
44. Wade DT, Makela P, Robson P, et al. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler.* 2004;10:434–441.
45. 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.
46. Li MC, Brady JE, DiMaggio CJ, et al. Marijuana use and motor vehicle crashes. *Epidemiol Rev.* 2012;34:65–72.
47. Allen JH, de Moore GM, Heddle R, et al. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut.* 2004;53:1566–1570.
48. Wang T, Collet JP, Shapiro S, et al. Adverse effects of medical cannabinoids: a systematic review. *CMAJ.* 2008;178:1669–1678.
49. Hernandez JM, Paty J, Price IM. Cannabinoid hyperemesis syndrome presentation to the emergency department: a two-year multicentre retrospective chart review in a major urban area. *CJEM.* 2018;20:550–555.
50. Aydelotte JD, Brown LH, Luftman KM, et al. Crash fatality rates after recreational marijuana legalization in Washington and Colorado. *Am J Public Health.* 2017;107:1329–1331.
51. Del Balzo G, Gottardo R, Mengozzi S, et al. "Positive" urine testing for cannabis is associated with increased risk of traffic crashes. *J Pharm Biomed Anal.* 2018;151:71–74.
52. Santaella-Tenorio J, Mauro CM, Wall MM, et al. US traffic fatalities, 1985-2014, and their relationship to medical marijuana laws. *Am J Public Health.* 2017;107:336–342.
53. ElSohly M. *Potency Monitoring Program Quarterly Report No. 123-Reporting Period: 9/16/2013-12/15/2013*. Vol. 123. Oxford, MS: University of Mississippi, National Center for Natural Products Research; 2014.
54. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. *Ann Intern Med.* 2017;167:319–331.
55. Vadhan NP, Corcoran CM, Bedi G, et al. Acute effects of smoked marijuana in marijuana smokers at clinical high-risk for psychosis: a preliminary study. *Psychiatry Res.* 2017;257:372–374.
56. Al-Shammari M, Herrera K, Liu X, et al. Effects of the 2009 medical cannabinoid legalization policy on hospital use for cannabinoid dependency and persistent vomiting. *Clin Gastroenterol Hepatol.* 2017;15:1876–1881.
57. Johnston L, O'Malley P, Miech R, et al. *Monitoring the Future National Survey Results on Drug Use, 1975–2015: Overview, Key Findings on Adolescent Drug Use*. Ann Arbor, MI: Institute for Social Research, The University of Michigan, The National Institute on Drug Abuse at the National Institutes of Health; 2016.
58. Hall K, Vigil D, Anderson A, et al. *Monitoring Changes in Marijuana Use Patterns in Colorado: 2015 Update*. Denver, CO: Healthy Kids Colorado Survey; 2015.
59. Hoffenberg EJ, Newman H, Collins C, et al. Cannabis and pediatric inflammatory bowel disease: change blossoms a mile high. *J Pediatr Gastroenterol Nutr.* 2017;64:265–271.
60. Hoffenberg A, Hopfer C, Markson J, et al. Marijuana use in adolescents and young adults with and without inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2013;57:e64 #227.
61. Phatak UP, Rojas-Velasquez D, Porto A, et al. Prevalence and patterns of marijuana use in young adults with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2017;64:261–264.
62. Schuermeyer J, Salomonsen-Sautel S, Price RK, et al. Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003-11. *Drug Alcohol Depend.* 2014;140:145–155.
63. Volkow ND, Baler RD, Compton WM, et al. Adverse health effects of marijuana use. *N Engl J Med.* 2014;370:2219–2227.
64. Simonetto DA, Oxentenko AS, Herman ML, et al. Cannabinoid hyperemesis: a case series of 98 patients. *Mayo Clin Proc.* 2012;87:114–119.
65. Committee on Substance Abuse, Committee on Adolescence. The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics.* 2015;135:584–587.
66. Committee on Substance Abuse, American Academy of Child and Adolescent Psychiatry. *AACAP Marijuana Legalization Policy Statement.* Washington, DC: American Academy of Child and Adolescent Psychiatry; 2014.
67. Brents LK. Marijuana, the endocannabinoid system and the female reproductive system. *Yale J Biol Med.* 2016;89:175–191.
68. Yao JL, He QZ, Liu M, et al. Effects of δ(9)-tetrahydrocannabinol (THC) on human amniotic epithelial cell proliferation and migration. *Toxicology.* 2018;394:19–26.
69. Almada M, Amaral C, Diniz-da-Costa M, et al. The endocannabinoid anandamide impairs in vitro decidualization of human cells. *Reproduction.* 2016;152:351–361.
70. Wise LA, Wesselink AK, Hatch EE, et al. Marijuana use and fecundability in a North American preconception cohort study. *J Epidemiol Community Health.* 2018;72:208–215.
71. Braillon A, Bewley S. Committee opinion no. 722: marijuana use during pregnancy and lactation. *Obstet Gynecol.* 2018;131:164.
72. Conner SN, Bedell V, Lipsey K, et al. Maternal marijuana use and adverse neonatal outcomes: a systematic review and meta-analysis. *Obstet Gynecol.* 2016;128:713–723.
73. Bertrand KA, Hanan NJ, Honerkamp-Smith G, et al. Marijuana use by breastfeeding mothers and cannabinoid concentrations in breast milk. *Pediatrics.* In press.
74. *State Marijuana Laws in 2018 Map*. http://www.governing.com/gov-data/state-marijuana-laws-map-medical-recreational.html. Accessed January 3, 2018.
75. Kilmer B. *New Developments in Cannabis Regulation*. Lisbon, Portugal: EMCDDA; 2017.
76. Nutt D. Illegal drugs laws: clearing a 50-year-old obstacle to research. *PLoS Biol.* 2015;13:e1002047.