Cannabinoids and Opioids in the Treatment of Inflammatory Bowel Diseases

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In traditional medicine, *Cannabis sativa* has been prescribed for a variety of diseases. Today, the plant is largely known for its recreational purpose, but it may find a way back to what it was originally known for: a herbal remedy. Most of the plant's ingredients, such as Δ^9-tetrahydrocannabinol, cannabidiol, cannabigerol, and others, have demonstrated beneficial effects in preclinical models of intestinal inflammation. Endogenous cannabinoids (endocannabinoids) have shown a regulatory role in inflammation and mucosal permeability of the gastrointestinal tract where they likely interact with the gut microbiome. Anecdotal reports suggest that in humans, *Cannabis* exerts antinociceptive, anti-inflammatory, and antidiarrheal properties. Despite these reports, strong evidence on beneficial effects of *Cannabis* in human gastrointestinal diseases is lacking. Clinical trials with *Cannabis* in patients suffering from inflammatory bowel disease (IBD) have shown improvement in quality of life but failed to provide evidence for a reduction of inflammation markers. Within the endogenous opioid system, mu opioid receptors may be involved in anti-inflammation of the gut. Opioids are frequently used to treat abdominal pain in IBD; however, heavy opioid use in IBD is associated with opioid dependency and higher mortality. This review highlights latest advances in the potential treatment of IBD using *Cannabis*/cannabinoids or opioids.

INTRODUCTION

The marijuana plant, *Cannabis sativa*, has long been used by mankind for medical, ritual, and recreational purposes. Because of its anti-inflammatory, antiemetic, antidiarrheal, and analgesic properties, *Cannabis* extracts were prescribed for a variety of diseases until the beginning of the past century (1). At the same time, recreational use of the plant became increasingly popular, eventually leading to its banning (2). However, with the detection of Δ^9-tetrahydrocannabinol (THC) as the psychotropic ingredient of *Cannabis* (3) and the discovery of "endogenous cannabinoids" (and consequently of the endocannabinoid system) (4), the focus on *Cannabis* has shifted back to its role as a herbal remedy. More *Cannabis* ingredients except for THC are known nowadays, e.g., cannabidiol (CBD), tetrahydrocannabivarin, cannabichromene, and cannabigerol (5). In general, the term cannabinoid encompasses herbal cannabinoids, i.e., the ingredients of the *Cannabis* plant (*C. sativa* contains more than 100 cannabinoid ingredients (6)) and the synthetic cannabinoids, e.g., CP-55,940 and WIN55, 212 (7). In many preclinical models of intestinal inflammation, *Cannabis*/cannabinoids proved being highly effective in improving inflammation (8), supporting the notion of a potential treatment of people suffering from inflammatory bowel diseases (IBDs). Meanwhile, a small number of clinical trials and observational studies that investigated the effects of *Cannabis*/cannabinoids in patients with IBD have been completed. Beside the mechanistic understanding of cannabinoid actions, these studies will be discussed together with the adverse effects of *Cannabis*. In addition, caveats of opioid treatment will be highlighted.

INFLAMMATORY BOWEL DISEASES

Crohn's disease (CD) and ulcerative colitis (UC) represent 2 forms of IBD. Despite their unknown etiology, it is widely assumed that an exaggerated and misdirected immune response against bacterial antigens causes structural damage of the intestinal mucosa in genetically predisposed people (9). According to a recent systematic review, IBD has become a global burden, with incidences accelerating in newly industrialized countries (10). The prevalence of IBD now exceeds 0.3% in North America and many countries in Europe and Oceania. IBD poses a high symptomatic and psychological burden to the patient and a challenge to the society. It has been estimated that direct healthcare costs for IBD in Europe amount to 4.6–5.6 bn Euros/year (11). Between 15% and 40% of the patients with IBD display extraintestinal manifestations (e.g., peripheral arthropathies or cutaneous manifestations, such as erythema nodosum), and 30%–50% of patients with CD need surgical intervention (11). Depending on the severity of the flares and the response to medication, IBD therapy includes anti-inflammatory agents, such as aminosalicylic acid (5-ASA), corticosteroids, as well as immunosuppressants, azathioprine, and methotrexate. Antitumor necrosis factor (TNF)-α antibodies, vedolizumab (anti-α4β7 integrin antibody), and

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ustekinumab (interleukin [IL]-12/IL-23 antibody) are effective biological agents to treat severe forms of IBD. Conventional treatment with biologicals, however, can come with side effects such as opportunistic infections, malignancies, and infusion/injection reactions (12). Patients, therefore, often seek alternative forms of treatment. More than 50% of patients with IBD reportedly have sought treatment with complementary and alternative medicine, for instance, treatment with prebiotics, vitamins, probiotics, and Medical *Cannabis*, at some point of the disease (13).

USE OF *CANNABIS*/CANNABINOIDS IN IBD
Surveys/questionnaires
Several questionnaires and surveys have indicated that "self-treatment" with *Cannabis* for symptom relief is common in patients with IBD and that *Cannabis* is generally well tolerated (14–16). However, 1 study also noted that in patients with CD, *Cannabis* use was associated with a higher risk for surgery (16). Surveys in young adults showed that a high number of patients with IBD were using *Cannabis* (17,18), but that they were unaware of adverse effects and usually did not inform their physician about its use (17). Most surveys suggest that *Cannabis* provides some benefit for patients with IBD, although the caveats of adverse effects and a higher risk for surgery in patients with CD remain. Interestingly, legalization of *Cannabis* did not prompt more patients with IBD to seek medical *Cannabis* therapy, although this may have been expectable (19). An overview of surveys on the *Cannabis* use in IBD and the main findings is given in Table 1.

Observational and prospective clinical studies
An early observational/retrospective study in patients with CD described *Cannabis* consumption as helpful (20). This observation was corroborated by Lahat et al. (21) who reported an improvement of disease activity index and quality of life in a small cohort of patients with IBD. Three prospective clinical studies followed; however, this time, placebo groups were included. Naftali et al. (22) investigated the effects of inhaled *Cannabis* in comparison to THC-free *Cannabis* (placebo group) in patients with CD and reported an improved CD activity index ($<$150) in 5 out of 11 subjects of the *Cannabis* group as compared to 1 of 10 subjects in the placebo group. However, there was no change in the levels of C-reactive protein, indicating symptomatic relief rather than reduction of inflammation. Two other trials investigated the effects of CBD in human IBD (23,24). Based on preclinical findings that CBD acts as an anti-inflammatory agent in models of intestinal inflammation (25–27), 2 clinical trials with CBD were carried out in patients with CD (23) and UC (24). CBD treatment did not have an influence on disease activity and C-reactive protein levels in patients with CD as compared to the placebo group (23). However, a trial that investigated the effects of CBD-rich botanical extract in patients with UC revealed that after per protocol analysis, quality of life outcomes were improved in patients taking the extract (24). So far, no clinical trial has investigated the effects of synthetic cannabinoids such as dronabinol or nabilone, but some case reports already suggest that nabilone, a THC analogue that is primarily used as an antiemetic, provides antidiarrheal effects which could be helpful in IBD treatment (28). An overview on clinical studies on *Cannabis* treatment in patients with IBD together with the main findings is given in Table 2.

CANNABIS/CANNABINOIDS AND IBD
The endocannabinoid system in the gut
Any IBD therapy with *Cannabis*/cannabinoids is based on cannabinoids such as THC acting through the body's endocannabinoid system (ECS) through activation of cannabinoid 1 (CB_1) and 2 (CB_2) receptors. In general, the ECS includes receptors (CB_1 and CB_2), their endogenous ligands (the so-called endocannabinoids, e.g., anandamide [AEA] and 2-arachidonoylglycerol [2-AG]), and the ligands' synthesizing (diacylglycerol lipase and N-acylphosphatidylethanolamine phospholipase D) and degrading enzymes (fatty acid amide hydrolase [FAAH] and monoacylglycerol lipase [MGL]). There are several other receptors—non-CB_1/CB_2 receptors—such as GPR55, GPR119, PPARα, PPARγ, and TRPV1 that are phylogenetically unrelated to the 2 CB receptors but have the ability to respond to (endo) cannabinoids (review. in Ref. (8)). They modulate CB receptor's actions and are considered part of a broader system, the "endocannabinoidome," a term that has been coined to unite the ECS, non-CB_1/CB_2 receptors, and endocannabinoid-like ligands (e.g., oleoylethanolamide and palmitoylethanolamide) in 1 system (29). All components of the "endocannabinoidome" are found in the gastrointestinal (GI) tract (30–32). CB_1 is primarily present in enteric cholinergic neurons where it inhibits neuronal hyperactivity (33), thus alleviating strong bowel contractions and secretion. CB_1 receptors are also present in enterocytes (30), where they are most likely involved in the regulation of mucosal permeability and wound healing (34,35). Unlike CB_1, CB_2 receptors are only little found in enteric neurons (30) but rather in B and T cells (30) as well as macrophages (35). One of the main purposes of the ECS in the gut is the maintenance of immune tolerance, and CB_2 plays an active role in it (36). We also found a high expression of MGL, the 2-AG degrading enzyme, in macrophages of the colon (30). Because pharmacological blockade of MGL was shown to reduce experimentally induced colitis, high MGL activity may promote intestinal inflammation (37). It should be noted that ECS components are also abundantly present in the brain and that centrally mediated cannabinoid effects may be involved in cannabinoid-induced improvement of intestinal inflammation. For instance, intracerebroventricular activation of CB receptors by WIN55, 212-2 was shown to inhibit whole gut transit in mice (38) and genetic deletion of CB_1 in the vagus caused an increase in GI motility (39), suggesting that the gut-brain axis can be manipulated by cannabinoids. In agreement with this concept, central application of CB receptor agonists was able to improve inflammation in a mouse model of colitis (40).

ECS and microbiota
Studies of adipogenesis and obesity have revealed a link between the ECS and the microbiome (41,42). By prebiotic and antibody treatment, authors demonstrated that gut microbiota could selectively modulate colonic CB_1, FAAH, and MGL expression in mice (41). CB_1 antagonists improved diet-induced metabolic dysfunction correlating with an increase in *Akkermansia municiphila* (43)—a strain known to have beneficial effects in the dextrane sulfate sodium (DSS)-induced colitis model (44). Most interestingly, genetic deletion of N-acylphosphatidyl-ethanolamine phospholipase D (and therefore, the production of AEA and related N-acylethanolamines) in intestinal epithelial cells drastically altered the composition of the gut microbiota (45), suggesting a physiological ECS-microbiota relationship. Another important

Table 1. Surveys on *Cannabis*/cannabinoid use in IBD

Study (ref.)	Survey type and patients	Main results	Conclusion
Lal et al. (14)	Questionnaire in 100 patients with UC and 191 patients with CD	In *Cannabis* lifetime users, 33% of the patients with UC and 50% of the patients with CD have used *Cannabis* to relieve IBD-related symptoms.	*Cannabis* use is common among patients with IBD for symptom relief.
Ravikoff and Allegretti et al. (15)	Questionnaire in 292 patients with CD, UC, or indeterminate colitis	16.4% of the patients with IBD that were current and past *Cannabis* users used *Cannabis* for disease symptoms. The majority felt that it was very "helpful" for relief of abdominal pain, nausea, and diarrhea.	A significant number of patients with IBD currently use *Cannabis*.
Storr et al. (16)	Questionnaire in 313 patients with CD, UC, or indeterminate colitis	*Cannabis* was used in 17.6% of the patients, specifically to relieve abdominal pain, cramping, and diarrhea. *Cannabis* use for more than 6 mo in patients with CD was a strong predictor of requiring surgery.	*Cannabis* use is common in patients with IBD, but patients should be cautioned about the potential harm.
Weiss and Friedenberg (88)	Retrospective survey using the NHANES database. The survey included 2,084,895 subjects with IBD and 2,013,901 control subjects	People with IBD had a higher incidence (67.3%) than that of control subjects (60.0%) of ever having used *Cannabis*. They also had earlier age of onset of *Cannabis* use.	Older, male patients with IBD have the highest odds of *Cannabis* use.
Phatak et al. (17)	Questionnaire in 18 patients with UC and 35 patients with CD (age 18–21 yr)	24% of the patients used *Cannabis* for IBD symptoms. 70% of the patients did not inform their physician. Half of the patients were unaware of *Cannabis* side effects.	There is a high rate of *Cannabis* use in young adults with IBD.
Hoffenberg et al. (18)	Cross-sectional study in 62 patients with CD, 27 patients with UC, and 10 patients with indeterminate colitis (age 13–23).	32% reported ever-use of *Cannabis*. Daily or almost daily *Cannabis* use was reported by 9%.	*Cannabis* use in young adults is common.

CD, Crohn's disease; IBD, inflammatory bowel disease; NHANES, National Health and Nutrition Examination Survey; UC, ulcerative colitis.

observation for the presence of ECS-microbiota interaction is that *Lactobacillus acidophilus* induced CB_2 receptor expression in intestinal epithelial cells and in the rodent gut mucosa (46). Manipulation of the ECS by *Cannabis*/cannabinoids may, therefore, contribute to an improvement of IBD symptoms.

Preclinical evidence of beneficial effects of *Cannabis*/cannabinoids in IBD

Preclinical evidence for a beneficial effect of *Cannabis*/cannabinoids in colitis has been mostly received from mouse models and recently reviewed in a meta-analysis (47). There is a huge amount of literature that confirms the observation that *Cannabis*/cannabinoids diminish inflammation in rodent models of colitis. *Cannabis* extracts, phytocannabinoids (e.g., CBD), synthetic CB_1/CB_2 agonists (e.g., WIN55, 212-2), endocannabinoids (e.g., AEA), and inhibitors of FAAH and MGL (to raise endocannabinoid levels) all effectively diminished macroscopic disease index and myeloperoxidase activity (47).

Evidence that the ECS is involved in human IBD comes from studies in which blood and intestinal mucosal biopsies from patients with IBD were used to measure endocannabinoid levels (48) and expression of several other ECS components (31). From these studies, it can be assumed that the ECS is deranged in patients with IBD and could even play some role in the development of IBD. In intestinal mucosal biopsies of patients with CD, gene expression levels of diacylglycerol lipase α, the 2-AG synthesizing enzyme, were increased, whereas those of CB_1 and

GPR119 were decreased in comparison to controls (31), indicating a potential role for endocannabinoids and their receptors in IBD. How cannabinoids directly affect human tissue was shown in *ex vivo* assays with cultured human intestinal mucosal biopsies: CBD (49) and Δ^9-tetrahydrocannabinolic acid (50) prevented production of inflammatory cytokines, Cox-2, and metalloproteinase-9 in the colonic mucosal samples from patients with IBD. Interestingly, CBD and palmitoylethanolamide also strengthened the mucosal barrier in humans *in vivo* as evidenced by the inhibition of aspirin-induced absorption of lactulose and mannitol (51). Preclinical evidence, therefore, strongly suggests that ingredients of *Cannabis* are of benefit for patients with IBD, warranting further studies. Potential mechanisms of how *Cannabis*/cannabinoids may exert anti-inflammatory effects in the human GI tract are shown in Figure 1.

EVIDENCE, SAFETY, AND ADVERSE EFFECTS OF *CANNABIS*/CANNABINOID TREATMENT

Despite overwhelming preclinical data showing beneficial effects of cannabinoids in mouse models of intestinal inflammation, clinical data are only beginning to emerge. So far, clinical evidence for an improvement of patients with IBD by *Cannabis* is only based on surveys and a few clinical trials (Tables 1 and 2); most of the trials are uncontrolled and underpowered. Based on these few studies, *Cannabis* could have some therapeutic potential. *Cannabis* is particularly helpful in alleviating symptoms such as cramping, abdominal pain, and diarrhea. Patients also report an

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Table 2. Retrospective and prospective clinical studies

Study (ref.)	Study type and patients	*Cannabis*/cannabinoid treatment	Main results/conclusion
Lahat et al. (21)	Prospective, uncontrolled, single-arm trial. 13 patients with long standing CD, UC, or indeterminate colitis.	Inhaling *Cannabis* (by cigarette) for 3 mo whenever patients felt pain	Improvement of quality of life measurements and disease activity index. Weight gain and rise in the BMI of patients were also reported.
Naftali et al. (20)	Retrospective, observational study. 30 patients with CD included.	Inhaling *Cannabis* (mostly by cigarette or vapor). Average duration of *Cannabis* use was 2.14 yr. Most patients were using 0.5–1.5 mg/d THC	Significant improvement of the Harvey Bradshaw index in 21 patients. Significant reduction of other medication and requirement for surgery.
Naftali et al. (22)	Prospective, placebo-controlled. 21 patients with CD included (ClinicalTrials.gov NCT01040910).	*Cannabis* cigarettes 2× daily over 8 wk (115 mg THC). *Cannabis* flowers with THC extracted used as placebo.	Complete remission of 45% of the patients in the *Cannabis* group. Improved appetite and sleep. No significant side effects reported. CRP values, blood counts, and liver and kidney functions not different between groups.
Naftali et al. (23)	Prospective, placebo-controlled. 20 patients with CD included (ClinicalTrials.gov NCT01037322).	CBD (10 mg; 2× daily; orally) or placebo over 8 wk	No change in disease activity. CBD was well tolerated.
Irving et al. (24)	Prospective, placebo-controlled, randomized. 29 (CBD) and 31 (placebo) patients with UC included.	Starting with 50 mg CBD-rich botanical extract (or placebo) in hard gelatin capsules 2× daily orally, the dose was increased to 250 mg and maintained at this dose for 8 wk	Patients were less tolerant of CBD-rich botanical extract than placebo. Per protocol analysis of the total and partial Mayo score favored CBD. Quality of life outcome was improved in the CBD group.

BMI, body mass index; CBD, cannabidiol; CD, Crohn's disease; CRP, C-reactive protein; THC, tetrahydrocannabinol; UC, ulcerative colitis.

improvement of overall well-being, which (because effects on inflammation markers were unchanged) may be caused by central effects (22). Although significant side effects were not reported in that study (22), short-term side effects have been reported for *Cannabis*/cannabinoid treatment in other diseases and reviewed in a meta-analysis (52). Dizziness, dry mouth, nausea, somnolence, and euphoria were the most common short-term side effects; however, anxiety and hallucinations also occurred (52). These effects are caused by the activation of central CB_1 receptors by THC and are likely to be dose dependent, suggesting that application of low, but effective, doses might be a way to prevent/reduce them. In this context, nabilone, a THC analogue, decreased spasticity-related pain in a clinical trial at a dose as low as 1 mg/d causing only mild but well-tolerable side effects (53). Concerning the mode of application of THC, another caveat has recently emerged. After an outbreak of acute lipoid pneumonia associated with the use of electronic cigarettes (e-cigarettes) (54), the Center for Disease Control and Prevention has recommended that, because of the possibility of severe lung injury, persons should not use e-cigarette, or vaping, products that contain THC (55).

Little is known on medicinal long-term use of *Cannabis*. From recreational *Cannabis* use, we know that there is an 8.9% cumulative probability of a transition to dependence (22.7% for alcohol users) (56). Long-term *Cannabis* use increases the risk of psychotic outcomes (57) and of cardiovascular (58) and lung diseases (59). Male reproductive functions are also negatively affected by *Cannabis* use (60). Regular *Cannabis* use has been associated with a loss in grey matter in brain areas rich in CB_1 expression in people between 18 and 30 years (61); therefore, adolescence is a strong caveat for long-term use of medical *Cannabis*, which may be necessary for the an effective treatment

of IBD. There is also evidence that *Cannabis* use during pregnancy may cause problems in neurological development and cognitive functions of the child (62). The authors recommend that unless more evidence is available to counsel pregnant women on *Cannabis* use, they should not use *Cannabis* in pregnancy or while lactating (62).

USE OF OPIOIDS IN IBD
Similar to the ECS, the endo-opioid system, which is composed of mu- (MOR), kappa-, and delta-opioid receptors and their endogenous ligands (met-enkephalin, leu-enkephalin, β-endorphin, and dynorphin) regulates GI functions (63,64). Opioid receptors are expressed in smooth muscle cells, neurons, and blood vessels of the gut but are also encountered on lymphocytes and macrophages (64). Several preclinical studies suggest that the endo-opioid system could play an important role in intestinal inflammation. MOR, for instance, is increased in patients with active CD and UC (65), and MOR agonists have shown beneficial effects in preclinical models of intestinal inflammation (66–69). However, intestinal inflammation can also increase the antinociceptive tolerance to morphine (70).

Clinical implications
There are a majority of patients with IBD who experience pain (mostly abdominal and back pain) during the course of the disease (71). Opioids are, therefore, prescribed for the treatment of pain and diarrhea (72). However, IBD has also been identified as a risk factor for opioid misuse questioning the legitimacy of the wide-spread use of opioids in IBD (73). One study found that almost 45% of the patients with IBD received an opioid prescription during the study period (between 2009 and 2015) (72).
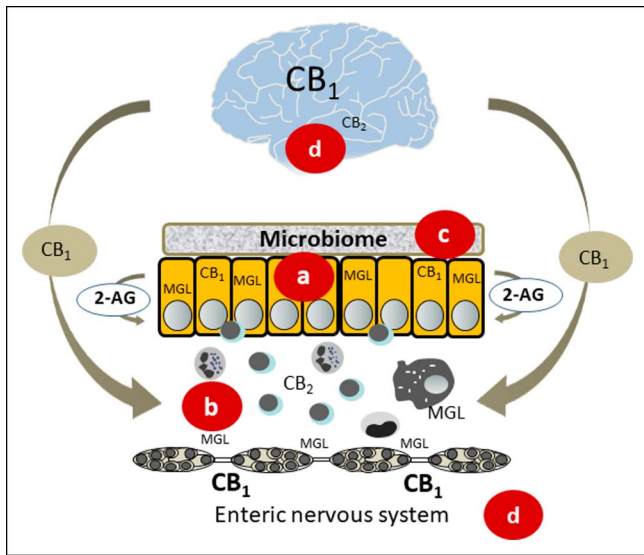
Figure 1. Potential mechanisms underlying beneficial effects of *Cannabis*/cannabinoids in inflammatory bowel disease. (**a**) Cannabinoids protect the mucosal barrier and promote wound healing (35). Blockade of MGL increases 2-AG levels, which promotes protection in colitis (37). (**b**) *Cannabis*/cannabinoids influence the activity of immunocytes and promote apoptosis in T cells (86). (**c**) The microbiome interacts with the endocannabinoid system in maintaining a healthy barrier (41,42). (**d**) CB_1 receptors are found in the brain (87) along the gut brain axis (39) and the enteric nervous system. CB_1 receptors in the brain may be essential in the protection against intestinal inflammation (40). 2-AG, 2-arachidonoylglycerol; CB1, cannabinoid 1 receptor; CB2, cannabinoid 2 receptor; and MGL, monoacylglycerol lipase.

Of the opioid-naïve patients in that study, more than one-third became persistent opioid users (72). In addition to the risk of opioid misuse in IBD, use of strong opioids in patients with IBD is also associated with an increased all-cause premature mortality (74). Significant side effects of opioid intake primarily consist of constipation and nausea (75), whereas serious adverse events can include fractures, cardiovascular events, and bowel obstruction (76). Persistent use of opioids may lead to narcotic bowel syndrome, which is characterized by abdominal pain that worsens with continued or escalating dosages of narcotics (77).

Not only activation but also blockade of opioid receptors may provide some benefit for patients with IBD. A low dose of naltrexone (LDN), a MOR receptor antagonist, has been suggested to improve IBD. In a study by Lie et al. (78), LDN (4.5 mg naltrexone once daily) induced clinical improvement in almost 75% and remission in ~25% of conventional therapy-refractory patients with IBD. However, a systematic review in the Cochrane Database revealed that from the existing literature, there was not enough evidence to draw conclusions on efficacy and safety of LDN in CD (79). Persistent LDN usage may, however, favor a decline in the use of anti-inflammatory agents and immunosuppressants (80).

CONCLUSIONS AND RECOMMENDATION FOR CLINICAL USE OF *CANNABIS*/CANNABINOIDS AND OPIOIDS IN IBD

There is strong preclinical evidence that *Cannabis* and its ingredients improve experimentally induced intestinal inflammation. Although studies indicate a significant improvement of quality of life in patients with IBD after *Cannabis* use,

a reduction of independent anti-inflammatory markers has not been shown so far. As a major hurdle of treatment, THC is a psychotropic substance and causes strong side effects. As recently pointed out by 2 reviews from the Cochrane Library, the effects and safe application of *Cannabis*, *Cannabis* oil, and CBD in CD and UC are still uncertain until larger trials assess efficacy and safety. In addition, optimal doses and routes of application still need to be investigated (81,82), leaving health professionals with no clear recommendation. For more information on the legal status of medical *Cannabis* and practical advice for clinicians, the reader is referred to a position paper by the Crohn's and Colitis Foundation (83). As for medical *Cannabis*, its use as a complementary medicine for conventional therapy-resistant patients with IBD is quite possible, but the hope that (endo) cannabinoids find a way into the treatment of IBD probably lies in the future use of compounds that manipulate the ECS, such as FAAH and MGL inhibitors, with then minimal central side effects. It remains unclear whether cannabinoids may be a valuable tool as an add-on treatment when functional symptoms such as abdominal pain (despite good control of the inflammation) are a problem because the present clinical trials clearly show that cannabinoids are helpful in relieving functional symptoms in patients with IBD.

Prolonged opioid treatment in IBD not only increases the risk of misuse, severe adverse effects, and even premature mortality but also is an important predictor of emergent encounters and is associated with higher total health care costs (84). Therefore, pain, anxiety, and depression should be carefully assessed in patients with IBD to reduce comorbidities and adverse events. A recommendation by the Canadian IBD Network for Research and Growth in Quality Improvement in collaboration with Crohn's and Colitis Canada and the Canadian Association of Gastroenterology points out that while opioids can be used in select acute settings to manage abdominal pain, their long-term use for managing IBD-related abdominal pain should be avoided (85).

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