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Expert Review of Clinical Pharmacology

ISSN: 1751-2433 (Print) 1751-2441 (Online) Journal homepage: https://www.tandfonline.com/loi/ierj20

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To cite this article: Nienke Halbmeijer, Michael Groeneweg & Lissy de Ridder (2019): Cannabis, a potential treatment option in pediatric IBD? Still a long way to go., Expert Review of Clinical Pharmacology, DOI: 10.1080/17512433.2019.1582330

To link to this article: https://doi.org/10.1080/17512433.2019.1582330

Accepted author version posted online: 15 Feb 2019.

Publisher: Taylor & Francis

Journal: *Expert Review of Clinical Pharmacology*

DOI: 10.1080/17512433.2019.1582330

Review

Cannabis, a potential treatment option in pediatric IBD? Still a long way to go.

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Abstract

Introduction: The onset of inflammatory bowel disease (IBD) in children is rising. Current treatment options are based on immunomodulatory therapy. Alternative treatment options are upcoming since they appear to be effective in individual patients. Cannabis might relief IBD symptoms in these cases and improve quality of life. Recent evidence suggests a potential anti-inflammatory effect of cannabis.

Areas covered: This review presents an overview of recent literature on the use of cannabis in IBD focussing on pediatric IBD patients. Background information on the role of the endocannabinoid system within the gastro-intestinal tract is presented. Other modalities of cannabis and its purified ingredients will be discussed as well, with attention to its applicability in children with IBD.

Expert opinion: More research is needed on the efficacy and safety of cannabis in pediatric IBD. Studies are well under way, but until then the use of cannabis in pediatric IBD cannot be recommended.

Keywords: adolescents, cannabis, cannabidiol, children, endocannabinoid system, inflammatory bowel disease, medical marijuana, pediatric

Article highlights

- Incidence of pediatric IBD is rising, while conventional treatment in many patients fails. Alternative treatment options have to be explored.
- The endocannabinoid system is involved in gut homeostasis and can be altered in an inflamed gastro-intestinal tract.
- Questionnaires in adolescent and young-adult IBD patients report relieve of IBD symptoms and improved quality of life when using cannabis.
- Cannabis seems to have a potential immunomodulating effect on IBD in murine colitis models.
- Preclinical data suggest a relevant role for endocannabinoid-degrading enzymes, such as FAAH and MAGL. To what extent inhibitors of these enzymes will cause decreased inflammation in humans needs to be further investigated.
- Until there is sufficient data about the efficacy and safety profile of cannabis, cannabis use needs to be actively discouraged in children with IBD.
- Further research needs to focus on clinical response and evaluation of mucosal healing due to cannabis or its purified ingredients.

1.0 Introduction

The incidence of pediatric inflammatory bowel disease (IBD) is steeply rising globally [1]. IBD includes Crohn's disease and ulcerative colitis, both diseases affect the gastro-intestinal tract by immune mediated inflammation. These diseases are characterized by relapsing and remitting episodes of active disease, which may be accompanied by abdominal pain, nausea, loss of appetite and diarrhoea. The current treatment options are based on reduction of inflammatory processes, by using immunomodulatory therapies, such as corticosteroids, thiopurines, methotrexate and/or TNF-a blockers. Despite improvement in therapy, many IBD patients report ongoing symptoms (abdominal pain, fatigue, poor appetite) with significant impact on quality of life. Cannabis has been studied as an alternative treatment to relief IBD symptoms. Over the past decades, cannabis or also known as medical marijuana has gained more acceptance for conditions like chemotherapy-related nausea and vomiting and chronic pain but also for spasticity and tremor in neurological diseases. Cannabis may be promising in improving the quality of life of IBD patients, by ameliorating symptoms like: abdominal pain, nausea, diarrhoea and poor appetite. Recent evidence suggests there also might be a potential anti-inflammatory effect of cannabis on IBD disease activity. So cannabis is of high interest for this medical condition.

Population based surveys show that many adult and adolescent IBD patients use cannabis to relieve abdominal symptoms [2-6]. About ten – twenty percent of patients are still under the age of 18 years when diagnosed with IBD [1, 7]. In this population 32% of the IBD patients use cannabis [8]. As a result, pediatric gastroenterologists will more frequently be confronted with patients who will use cannabis to relieve IBD-related symptoms. Therefore, we conducted a review to summarize the present scientific evidence about the efficacy and safety of cannabis in the treatment of pediatric IBD.

For this review a literature search was performed in Pubmed and EMBASE on trials who evaluated the effect of cannabis on IBD until September 2018. Keywords used were 'inflammatory bowel diseases', 'Crohn disease', 'Ulcerative colitis', 'Cannabis', 'Medical Marijuana' and 'Cannabinoids'.

2.0 The endocannabinoid system and the gastrointestinal tract

The effect of cannabis on the gastrointestinal tract is based on involvement of the endocannabinoid system in gut functioning. The endocannabinoid system contains receptors, endogenous cannabinoids, synthesizing and metabolizing enzymes that are active in both the central and peripheral nervous system but also in many other organs. They modulate neuronal signalling and influence physiological processes as sleep, mood and emotion, appetite, pain perception and memory [9]. Two endogenous ligands of the endocannabinoid system have been discovered: anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Both ligands are responsible for endocannabinoid signalling. They are inhibited by their metabolizing enzymes, fatty acid amine hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. The most thoroughly investigated part of the endocannabinoid system is

the cannabinoid 1 and 2 (CB1 and CB2) receptors, which are widely distributed in the gastrointestinal tract. They are found in the enteric nervous system and epithelial cells. Particularly CB1 receptors are expressed in the mucosa of the stomach and colon. In contrast, in non-inflamed human intestinal epithelium CB2 receptors are absent or only weakly expressed [10, 11]. CB2 receptors are mainly expressed by immune cells (neutrophils, plasma cells, activated macrophages and subsets of B and T cells) and to a lesser extent by enteric neurons [11]. Activation of CB1 receptors leads to relaxation of smooth muscle and to decreased gut motility and gut secretion. Based on the current knowledge, the endocannabinoid system as a whole is seen as a physiological entity that controls gut homeostasis [12-14].

In addition, the endocannabinoid system has a role in gut inflammation. The endocannabinoid system probably serves as an endogenous gastrointestinal defence system by affecting the regulation of the endogenous cannabinoids. Furthermore, inhibition of the metabolizing enzymes (FAAH, MAGL) ensures ongoing activity of the endocannabinoids ligands (AEA and 2-AG) and CB receptors [15]. Activation of CB2 receptors causes suppression of inflammation, resulting in improvement of mucosal healing in murine colitis models [15-17]. So, potentially the endocannabinoid system is a target for new therapies in IBD.

2.1 Role of cannabis on gastro-intestinal inflammation

Recent evidence suggests that an anti-inflammatory effect can be attributed to cannabis [14, 18-20]. Cannabis contains phytocannabinoids Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is known as a partial agonist of CB1 and CB2 receptors. By activating CB receptors, THC suppresses the production of pro-inflammatory cytokines and chemokines and induces T cell apoptosis [15, 20]. Δ9-tetrahydrocannabinolic acid (THCA), a precursor of THC, has anti-inflammatory activity on colon epithelial cell cultures, by inhibiting IL-8 secretion [19]. Animal models show that cannabidiol is capable of modulating the endocannabinoid system, through activation of CB1 by inhibiting FAAH [21]. However, because of the complex pathogenesis of IBD it remains uncertain whether these anti-inflammatory effects can be expected in humans as well.

3.0 Cannabis use among adult patients with IBD

The literature search identified 80 publications. Trials and surveys on cannabis treatment for IBD were included. Only one article focussed on adolescent and pediatric IBD patients. Studies performed in adults were included as well. By handsearching we finally included nine studies that evaluate cannabis treatment for adult patients with IBD [2-6, 22-25] and one for adolescent IBD patients (13 – 21 years of age) [8]. These studies are shown in Table 1. In summary, a high prevalence of cannabis use in adult and adolescent IBD patients is seen in various countries [2-6]. Many patients report beneficial

effects of cannabis on IBD-related symptoms, as well as improvement of quality of life. Only one study group presented their results between Crohn's disease and ulcerative colitis patients separately [22]. The ulcerative colitis-group consisted of 2 patients so these patients were precluded from statistical analysis. More objective measurements were obtained with the Crohn's Disease Activity Index (CDAI) and Harvey Bradshaw score, which significantly decreased after a period of cannabis use [22-24]. This effect was not seen with cannabidiol [25]. A few side effects (panic attack, drowsiness, poor diet, lethargy and addiction) of cannabis were reported by patients [3]. However the safety profile of cannabis and cannabidiol in the treatment of IBD is poorly examined. Until now, cannabis in the treatment of IBD seems promising.

Clear limitations of these studies were the low number of included patients and the lack of standardization of the used amount or the route of use of cannabis. No studies report endoscopic or histological evaluation of disease activity before and after cannabis use. Therefore, the occurrence of mucosal healing in human intestinal epithelium is unknown. Based on current research no distinction can be made between the effects of cannabis use on symptom relief in Crohn's disease or ulcerative colitis. Crohn's disease is caused by transmural inflammation instead of ulcerative colitis where the inflammation is limited to the mucosa, with the result that abdominal pain is more frequently seen in Crohn's disease. This distinction could be relevant in further research. The high prevalence rates of cannabis in IBD patients may be influenced by the recent approval of medical marijuana by various states in the US and Canada and also by increased attention in the press about the beneficial effects of cannabis use for medical purposes.

4.0 The endocannabinoid system and the brain

The endocannabinoid system is not only involved in the gastrointestinal tract. The CB1 receptors are also widely distributed in the brain [26], which explains psychotropic properties as described in cannabis use and abuse.

The endocannabinoid system is already present in early stages of brain development. During embryonal development of the central nervous system CB1 receptors and endogenous cannabinoids (AEA and 2-AG) were detectable from 14 weeks of gestation [27]. The endocannabinoid system is subject to constant change from childhood to adolescence [27-29]. Therefore, cannabis use may have an adverse effect on brain development, in case of early exposure, making cannabis a controversial treatment option in children. Studies show that adolescents who frequently use cannabis in high doses have a lower intelligence quotient (IQ) and reduced cognitive function [30]. These effects are dose-dependent. Cessation of cannabis use for 1 year does not result in full recovery of neurocognitive functioning, especially when cannabis abuse was started in adolescence [30, 31]. The precise extent to

which cannabis itself is responsible for these effects is unknown. Lower social-economic status and young age may influence the observed effect on cognitive function [32].

THC is the primary psychoactive component of cannabis and is able to affect brain function, by influencing cognitive functions (learning, working memory and attention). Also neurophysiologic effects can occur, symptoms are: anxiety, paranoia and psychiatric disorders (hallucinations, schizophrenia and schizophrenia-like psychotic disorders) [33, 34]. A dose-response relationship is seen for these side-effects [35]. Regular cannabis use in high dose before the age of 15 years is associated with psychiatric disease and cognitive impairment [36].

5.0 Alternative agents influencing the endocannabinoid system

Inhalation by smoking is the most frequently used mode of application for cannabis consumption. Various side-effects and risk for developing addiction to smoking are well-known. Therefore, other modes of application are urgently needed.

5.1 Cannabidiol oil

One of the treatment options is cannabidiol (CBD) oil. It is important to acknowledge that CBD has low affinity for the CB1 and CB2 receptors resulting in the absence of psychotropic effects [21, 37]. Therefore, CBD could be used safely in children with IBD. However, a low dose of 20 mg/day of CBD does not improve Crohn's Disease Activity Index (CDAI) of adults with IBD. This lack of effect on IBD symptoms can be explained by the fact that only a single compound of cannabis (only CBD) is used. The authors also suggested that the dose of CBD used might be too low to be effective [25].

CBD has successfully been used in children for therapy-resistant epilepsy (Dravet syndrome, Sturge-Weber syndrome and Lennox-Gastaut syndrome), resulting in a significant reduction in seizure frequency [38-40]. 120 children and young adults with Dravet syndrome were included in a double-blind, placebo-controlled trial that reported a decrease of median seizure frequency per month from 12.4 to 5.9 (95% CI -41.1 to -5.4; P=0.01) during the 14-week treatment period [38]. This reduction was also seen in a double-blind, placebo-controlled trial in 225 children and adults with Lennox-Gastaut syndrome after 14 weeks of CBD use (41.9% reduction in the 20 mg/kg CBD group (P=0.005) compared to 37.2% reduction in the 10 mg/kg CBD group (P=0.002)) [40]. 4 children with Sturge-Weber syndrome showed a significant drop in seizure frequency after 8 weeks of CBD treatment (average number of seizures per month dropped from 10.7 to 7.7) [39]. The dose used was between 5-25 mg/kg/day orally. Kaplan et al. [39] started with a low dose of CBD (5 mg/kg/day) and increased the dose by 5 mg/kg/day per week as tolerated up to a maximum of 25 mg/kg/day. Continuous doses of 10 mg/kg/day or 20 mg/kg/day were used by Devinsky et al. [38, 40]. More adverse effects were seen when higher doses (20 – 25 mg/kg/day) of CBD were used: somnolence, lethargy, behavioural

problems and increased seizure activity. In addition, gastro-intestinal adverse effects were reported (diarrhoea and vomiting) in 45% of patients with Dravet syndrome and in 16% - 26% of patients with Lennox-Gastaut syndrome. After dose reduction almost all adverse effects resolved completely. 0.05 – 0,13 % of patients who received CBD had to be withdrawn from the trial and discontinued CBD administration due to adverse effects. Laboratory values showed elevated liver enzymes in the CBD group [38, 40].

5.2 Sativex® (Nabiximols)

Sativex is an oromucosal plant-based cannabinoid spray. It is mainly used in patients with multiple sclerosis where it is able to relieve spasticity-related and neuropathic pain [41]. Also patients with chronic pain and post-operative pain experience beneficial effects of Sativex. A meta-analysis on the efficacy of cannabis-based medicines, including Sativex, for pain management showed a significant pain reduction in chronic pain -0.61 (-0.78 to -0.43, $P < 0.0001$) [42]. This spray contains both phytocannabinoids THC and CBD. Each spray delivers a dose of 100 µL, containing 2.7 mg THC and 2.5 mg CBD. Sativex is generally well tolerated in patients with multiple sclerosis-related spasticity, however adverse effects (such as anxiety, depression, constipation or diarrhoea, nausea, headache, dry mouth and somnolence) were commonly seen. These effects occurred in <10% of people and usually appear during the first 4 weeks of treatment. More serious effects (allergic phenomena, euphoria, psychosis, panic, hallucinations, paranoia, suicidal ideation, memory changes and cognitive decline) were seen in <1% of people [41]. No clinical trials have been performed on the efficacy and safety of Sativex in patients with IBD.

5.3 Synthetic cannabinoids

Nabilone and Dronabinol are synthetic cannabinoids, both can be administered orally. They mimic the effect of THC by acting like CB receptor agonists and alter endocannabinoid signalling. Both synthetic cannabinoids are approved for the treatment of nausea and vomiting caused by chemotherapy in cancer patients. Dronabinol is also approved as appetite stimulant in AIDS patients with weight loss. Nabilone was studied as an alternative antiemetic in children with chemotherapy for cancer. The authors conducted a double blind crossover study in 23 patients (aged from 1 to 17) with nabilone compared to domperidone. In the nabilone group adverse effects were more frequent, most commonly reported were drowsiness (55%), dizziness (36%) and mood changes (14%). One patient experienced hallucinations and withdrew from the trial. For the other participants adverse effects were thought to be acceptable, they continued the treatment [43]. The effect of nabilone and dronabinol on IBD symptoms and mucosal inflammation has not been studied.

5.4 FAAH and MAGL inhibitors

Another pharmacological strategy is to continue endocannabinoid signalling by inhibiting the metabolizing enzymes of anandamide (AEA) and 2-arachidonoylglycerol (2-AG), fatty acid amine hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively, instead of direct activation of the CB receptors [44]. Selective inhibition of FAAH or FAAH blockade reduced damage in experimental colitis models [14, 45]. Also MAGL inhibitors have potential to counteract colitis and related systemic inflammation [46]. So, both agents seem to have anti-inflammatory effects in murine colitis models. For the time being there are no studies in IBD patients with FAAH or MAGL inhibitors. Further research on this topic is highly recommended because of the potential immunomodulating mechanism.

6.0 Cannabis for medical purposes in children

Various effects of unintentional cannabis ingestion in children have been described such as lethargy, ataxia, hypotonia, mydriasis, tachycardia, hypoventilation and even respiratory insufficiency [47]. Despite these adverse effects, would cannabis be a potential treatment option in pediatric IBD?

A recent descriptive cross-sectional study in Colorado, described cannabis use in 99 pediatric patients (aged between 13 – 22 years) with IBD. As mentioned in the introduction, 32% of them used cannabis once during their lifetime while nine percent used cannabis daily or almost daily. Most frequently medical purposes for using cannabis were reported. Other reasons were to relax, to relieve tension, to feel good and to have a good time with friends. Participants used cannabis by smoking cigarettes or ingesting edibles. However, 37% reported problems with consuming cannabis like craving and need for higher doses to reach the same effect with the risk of developing addiction [8].

Pediatric IBD patients might benefit by relief in abdominal pain, nausea, cramping, diarrhoea and improvement in appetite and weight gain. These benefits are thought to be the result of the effect of cannabis on the endocannabinoid system and associated anti-inflammatory effect. However, the mechanism of action of THC and cannabidiol is not fully clarified, and well-designed clinical trials have not been performed. As a result of symptom reduction without actual decrease of inflammation the IBD disease activity may be underestimated by the patient, causing higher risks of serious complications. Side-effects remain a problem in children as well as concerns regarding brain development and cognition.

The mode of application is another important issue in children. Smoking cannabis clearly is an unacceptable option in children, because of the well-known negative effects of tobacco smoking on health. Therefore, oral cannabidiol (like the oral mucosal spray Sativex®) would be the preferred mode of application. However, no studies on the pharmacokinetics and pharmacodynamics of cannabidiol in children have been performed.

7.0 Conclusion

In summary, cannabis might potentially be a treatment option in pediatric IBD in addition to conventional treatment. However, to what extent cannabis acts as an immunomodulating agent or just enhances a general feeling of well-being is unclear currently. First, we support well-designed clinical trials to evaluate efficacy and safety of oral cannabidiol in children with IBD. These trials should include clinical response but also evaluate mucosal healing. For this specific age group extra focus has to be on the mode of application. Awaiting future research, cannabis should actively be discouraged as a treatment modality in pediatric IBD.

8.0 Expert opinion

During the last decade, IBD in children has a rising incidence and is accompanied by high disease burden. Since conventional therapies regularly are not sufficient, patients and parents are looking for alternative treatment options. Currently, cannabis is of high interest in this field. Evidence suggests that cannabis relieves IBD symptoms, improves quality of life and to a lesser extent induces immunomodulating effects. However, according to our literature research we advise against prescription of cannabis in pediatric IBD. There are still a lot of questions that need to be answered first.

The first key question is: what is the actual impact of cannabis on inflammation in IBD? Preclinical data in murine colitis models suggest that activation of CB receptors may lead to mucosal healing by inhibiting the inflammatory reaction [10, 15]. Direct activation of the CB receptors may be caused by inhalation of cannabis, using purified ingredients (such as CBD and Sativex®) or synthetic cannabinoids (Nabilone and Dronabinol). Moreover, continuous high levels of endogenous cannabinoids will lead to activation of the CB receptors as well. This effect can be achieved by inhibitors of the endocannabinoid-degrading enzymes, FAAH and MAGL. So far, these concepts are only tested in experimental trials. Whether activation of the CB receptors will realize mucosal healing in IBD patients as well, need to be further investigated. Therefore, it is important to evaluate disease activity endoscopically before and after treatment with one of these agents.

Second key question is which agent would be most applicable in pediatric patients. As mentioned earlier smoking cigarettes is no option in this category of patients. Purified ingredients of cannabis therefore are of special interest in children. Most experience exists with cannabidiol in children with therapy-resistant epilepsy syndromes [38-40]. A major benefit of cannabidiol is the lack of psychotropic side-effects. Furthermore, CBD seems well tolerated in this patient population, nevertheless adverse events on behaviour and gastro-intestinal tract are described as well. An anti-

inflammatory effect of CBD on IBD in humans is not proved yet. Experimental studies in animals have shown promising results of immunomodulating effects of CBD on colitis models [48]. An already available THC/CBD solution is the oromucosal spray, Sativex®, which appears to be easily suitable for pediatric IBD patients, though a serious doubt about sativex is the presence of THC in the solution. Due to the known effects of THC on the central nervous system, psychotropic adverse effect can be experienced by patients. More experience in children exists with Nabilone, a synthetic cannabinoid. Nabilone was used in children with chemotherapy related nausea as an antiemetic agent. However, serious side-effects like hallucinations were experienced by one of the patients [43]. Consequently, nabilone is likely not suitable for the treatment of pediatric IBD. Furthermore, long-term effects of cannabidiol and Sativex® are unknown. Chronic use of cannabis is associated with impaired neurodevelopment outcome and addiction. Whether these agents can cause these serious adverse effects as well is unclear. The same is probably true for synthetic cannabinoids through the equal mechanism of action in the endocannabinoid system.

Knowledge about the endocannabinoid system is rapidly expanding. With increasing availability of legal cannabis and medical marijuana around the world, the use of cannabis for medical purposes is of high interest. There still are many gaps in understanding these cannabinoid-based medicines before they can be administrated to children, so further research in this field is sorely needed. Currently the main benefit of cannabis for the treatment of IBD is improvement of quality of life which is most likely caused by a general well-being, a known effect of cannabis. To what extent this effect can be attributed to reduced inflammation is uncertain.

Nowadays, the endocannabinoid system serves as an encouraging therapeutic target for various abnormal conditions of the gastrointestinal tract. The focus for the next five years should be on the influence of the endocannabinoid system on inflammation of the bowel. To evaluate whether cannabis indeed can induce mucosal healing in the human gut, endoscopic examination before and after treatment is needed. The existing preclinical trials in murine colitis models report a major role for the endogenous cannabinoids and its inhibitory enzymes. However, before implementation of these agents in the treatment of IBD patients further preclinical research is required to better understand the mechanism of action of the FAAH and MAGL inhibitors on gastro-intestinal inflammation.

There is an urgent need for larger clinical trials. Especially elucidation of the efficacy and safety profile of cannabis and the purified ingredients is required. In our opinion, well-conducted trials on oral cannabidiol in pediatric IBD would be of high interest. The research in this field is well under way, but more time is needed before cannabis as part of IBD treatment in children can be recommended.

Funding

This paper was not funded.

Declaration of Interest

L de Ridder discloses that for the last 3 years they have received consultation fee, research grant, or honorarium from ZonMw (national health institute), Janssen, Pfizer, Mundipharma, Shire and Abbvie. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Table 1. Evaluation of cannabis treatment among adult and adolescent IBD patients

First author, year, country	Participants	Design	Substance studied	Mode of application, dose	Main results	Limitations
Lal S, 2011, Canada [2]	N=291	Cross-sectional survey	Cannabis	Inhalation or oral ingestion, dosage unknown.	Lifetime cannabis use is common in patients with IBD. 33% of UC patients and 50% of CD patients used cannabis to relief IBD-related symptoms.	No evaluation of effectiveness of cannabis on IBD symptoms.
Naftali T, 2011, Israel [25]	N=30	Retrospective observational study	Cannabis	Mainly by inhalation, average of 2.4 joints/day containing 0.5 mg THC per joint.	Significant decrease in disease activity (Harvey Bradshaw index, (14 ± 6.7 to 7 ± 4.7, P < 0.001)). No dose-response relationship was reported.	Small sample size, lack of endoscopic or histological evaluation of disease activity.
Lahat A, 2012, Israel [23]	N=13	Prospective single arm trial	Cannabis	Inhalation, whenever the participants felt pain 3 inhalations of prepared cigarettes were advised.	Significant improvement in quality of life measurements, weight gain (4.3 ± 2 kg; P = 0.0002) and decreased Harvey Bradshaw index (11.36 ± 3.17 to 5.72 ± 2.68; P = 0.001) after 3 months of cannabis use.	Small number of participants, lack of standardization of used amount of cannabis per day.
Ravikoff Allegreti J, 2013, US [4]	N=292	Prospective cohort survey	Cannabis	Mainly inhalation, dosage unknown.	51% of patients with IBD reported ever having used cannabis. 16% of them used it for relief of IBD symptoms and the majority of them found it 'very helpful'.	No objective measures of disease activity before and after cannabis use.
Naftali T, 2013, Israel [24]	N=21	Double-blind placebo-controlled study	Cannabis	Inhalation, study group received twice daily a cigarette containing 115 mg of THC.	Significant lower CDAI score in the cannabis group after treatment with cannabis (from 330 ± 105 to 152 ± 109, P = 0.028). Reaching complete remission was not significant in the cannabis group (P=0.43).	Small sample size, short duration of cannabis use (8 weeks).
Storr M, 2014, Germany [6]	N=313	Population based survey	Cannabis	Inhalation and oral ingestion.	18% of respondents used cannabis to relief IBD-related symptoms. Cannabis use for more than 6 months was a strong predictor for requiring surgery (OR = 5.03, 95% CI = 1.45 – 17.46).	Lack of objective measures of disease activity before and after cannabis use.
Weiss A, 2015, US [5]	N=4098,796	Population based survey	Cannabis	Inhalation, dosage unknown.	Higher incidence of cannabis use in subjects with IBD (67.3% vs. 60.0%; univariate odds ratio 1.37, 95% CI (1.37–1.38)) and earlier age of onset of cannabis use, compared to non IBD-patients (15.7 years vs. 19.6 years; mean difference −3.97, 95% CI (3.96–3.98)).	No evaluation of effectiveness of cannabis on IBD symptoms.
Phatak UP, 2017, US [3]	N=53	Prospective questionnaire survey	Cannabis	Inhalation, dosage unknown	70% of participants had been using or were still using cannabis. 45% (24/53) used cannabis for medical reasons. 19% (7/37) were having adverse effects.	Unclear if attributed symptom relief is due to cannabis use or medical therapy. Lack of objective measures of disease activity.
Naftali T,	N=21	Randomized	Cannabidiol	Oral, 10 mg twice	No significant changes in	Small sample size,

2017, Israel [26]		controlled trial		a day	CDAI score before and after treatment in the cannabidiol group (337 ± 108 to 220 ± 122; P=*NS*), no difference in side-effects.	lack of endoscopic or histological evaluation of disease activity.
Hoffenberg EJ, 2018, US [8]	N=99, (13-21 years of age)	Descriptive cross-sectional study	Cannabis	Inhalation and oral ingestion, dosage unknown	32% of the participants ever used cannabis. Daily or almost daily was reported in 9% of the participants. 57% of participants reported one medical reason for cannabis use.	No evaluation of safety and benefit of frequent cannabis use, no standardization of route of use of cannabis.

*Abbreviations: UC= Ulcerative Colitis; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; OR = Odds Ratio; 95% CI = 95% Confidence interval, NS = not significant