Medical cannabis for inflammatory bowel disease: real-life experience of mode of consumption and assessment of side-effects

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Objective Use of medical cannabis for improving symptoms of inflammatory bowel disease is increasing. However, reports on long-term outcomes are lacking. This prospective, observational study assessed the effects of licensed cannabis use among patients with inflammatory bowel disease.

Methods Dose and mode of consumption, adverse events, use of other medications, and long-term effects were evaluated among 127 patients with inflammatory bowel disease using legalized medical cannabis. Blood count, albumin, and C-reactive protein were assessed before, 1 month, and at least 1 year after medical cannabis therapy was initiated. Questionnaires on disease activity, patient function, and signs of addiction were completed by patients and by a significant family member to assess its effects.

Results The average dose used was 31 ± 15 g/month. The average Harvey-Bradshaw index improved from 14 ± 6.7 to 7 ± 4.7 ($P < 0.001$) during a median follow-up of 44 months (interquartile range, 24–56 months). There was a slight, but statistically significant, average weight gain of 2 kg within 1 year of cannabis use. The need for other medications was significantly reduced. Employment among patients increased from 65 to 74% ($P < 0.05$). We conclude that the majority of inflammatory bowel disease patients using cannabis are satisfied with a dose of 30 g/month. We did not observe negative effects of cannabis use on the patients' social or occupational status.

Conclusions Cannabis use by inflammatory bowel disease patients can induce clinical improvement and is associated with reduced use of medication and slight weight gain. Most patients respond well to a dose of 30 g/month, or 21 mg Δ9-tetrahydrocannabinol (THC) and 170 mg Cannabidiol (CBD) per day. Eur J Gastroenterol Hepatol 31: 1376–1381

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic, debilitating, non-infectious, inflammatory diseases of the digestive tract. Treatment consists of various anti-inflammatory and immunomodulating drugs. However, the rate of response to currently available treatments is limited to 40–60% [1,2], and many patients remain symptomatic despite maximal medical treatment.

The beneficial effects of cannabinoids on human health have been postulated for centuries. Yet, the use of cannabinoids, particularly in the form of cannabis remains controversial and is subject to public debate [3]. Cannabinoids are often used to alleviate various health-related problems, including symptoms related to multiple sclerosis [4], chronic intractable pain, dystonic movement disorders, Tourette's syndrome [5], epilepsy [6], and anorexia among patients with AIDS or cancer [3,4]. In gastroenterology, cannabis has been used to treat anorexia, emesis, abdominal pain, gastroenteritis, diarrhea, intestinal inflammation, and diabetic gastroparesis [7].

Cannabinoids have an anti-inflammatory effect, mainly through the cannabinoid receptor type 2 [8]. Studies in-vitro and with laboratory animals showed that cannabinoids shift the balance of pro- and anti-inflammatory cytokines towards the T-helper cell type 2 profiles (Th2 phenotype) and suppress cell-mediated immunity; whereas humoral immunity might be enhanced [9]. Cannabinoids directly inhibited tumor necrosis factor (TNF)-alpha secretion [10,11]. Manipulation of the endocannabinoid system by phytocannabinoids, cannabinoid receptor type 1 and type 2 agonists and antagonists, endogenous cannabinoids and synthesizing and degrading enzymes of the endocannabinoid system would very likely be beneficial for patients with IBD [12].

Anecdotal reports of medical cannabis use by IBD patients are accumulating and many report pain relief, improved appetite, and weight gain [13]. Approximately 12 to 15% of IBD patients report using cannabis regularly as part of their IBD treatment [14,15]. However, concerns have been raised regarding the effects of prolonged use of cannabis on intellectual functioning and the possibility of addiction, accompanied by doubt as to whether the observed improvements reflect reduced inflammation or merely symptomatic improvement [16]. Cannabis is

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currently not approved by the United States Food and Drug Administration for any medicinal purposes; although several states have approved its use for various indications and others have legalized it for recreational use.

In Israel, medical cannabis is permitted and used for several disease-specific conditions, including IBD. The use of medical cannabis is regulated by the Ministry of Health. In order for a patient to receive a license to use medical cannabis, the treating physician has to submit a detailed request, including relevant medical information and justification for its use. However, physicians are not directly involved in the decision to approve the request. Following approval, the patient is granted a license and is referred to an authorized dispensary. Authorized dispensaries supply plant-derived cannabis, manufactured under strict quality control conditions, with precise data about the content of various cannabinoids in each product. Since recreational cannabis use in Israel is illegal, patients are expected to use it discreetly and refrain from use in public. Each patient's clinical condition is evaluated by the treating physician before the application is submitted and regularly thereafter when the license is renewed. This provides the treating physician with a detailed evaluation of the patient's medical condition before and after cannabis use. Dispensaries maintain data about purchased products, so they have a record of the patient's history of cannabis consumption. These procedures enable research regarding cannabis use in real-life.

The aim of this study was to investigate the patterns of use and patients' experiences with medical cannabis, and to assess safety and side-effects, as well as daily functioning among a cohort of patients with IBD.

Methods

Study population

The study population included IBD patients who received a license for use of medical cannabis from the Israeli Ministry of Health and were followed at Meir Medical Center from 2011 through 2016. Details regarding the formulation and specific commercial cannabis products purchased by the patients during the study period were obtained from the authorized dispensary, and the dose and mode of use were recorded.

Information on disease activity and results of medical tests before cannabis use were obtained from electronic medical records. Data after initiating cannabis use were obtained prospectively.

Mode and dose of cannabis use

We used the diagnostic and statistical manual of mental disorders (5th ed.) (DSM-V) criteria for cannabis abuse to detect signs of abuse or addiction [17]. The DSM-V defines a problematic, clinically significant pattern of cannabis use as manifested by the presence of at least two of five criteria. These are defined as tolerance (need for markedly increased amounts), withdrawal symptoms (characteristic withdrawal syndrome), impaired control (using larger amounts than intended), neglect of activities (important social, occupational, or recreational activities given up), and abuse (failure to fulfill major obligations at work, school, or home).

Some of these criteria (such as the need to dedicate a great deal of time to obtaining cannabis) are the result of illicit use and, therefore, were not applicable to our cohort. However, other criteria, such as consumption of larger amounts and failure to fulfill major role obligations at work, school, or home were applicable. Therefore, the patients were asked whether the amount of cannabis they used was enough or would they rather be supplied with more. Details about the amount of cannabis prescribed to the patients were extracted from the license (which specifies the monthly amount a patient may receive) and from actual purchase reports of the dispensary. Reports from the dispensary included amount of purchased cannabis, as well as strain and exact Δ9-tetra- hydrocannabinol (THC) and Cannabidiol (CBD) content of the purchased product.

Patient-reported outcomes of cannabis consumption

Patient-reported outcomes were evaluated using a questionnaire that included information on satisfaction, effect on disease symptoms, and overall harmful effects. Satisfaction varied on a scale from 1 (= very unsatisfied) to 8 (= very satisfied).The effect of cannabis on disease symptoms varied on a scale from 1 (= deteriorated) to 8 (= significant improvement) and perception of cannabis use as 'beneficial' or 'harmful.' Patients were also asked whether cannabis use interferes with any important activity, such as work, social functioning, or family interactions. Rate of employment before and after cannabis consumption was compared to that of the general population. Data about employment rates and working hours of the general population were extracted from the website of the Central Bureau of Statistics (http://www.cbs.gov.il/ publications 18) of Israel, which was last updated in October 2018.

Reported outcome from family members

To further assess the effect of cannabis on patient functioning, we also asked a close relative of the patient to answer a similar questionnaire regarding whether they were satisfied with the patient's use of cannabis, whether they thought it was harmful to the patient in any way, and whether they would prefer the patient to stop or reduce cannabis use. Patients' relatives completed this questionnaire separately in the absence of patients.

Side effects and effect on disease activity

Patients' experiences with the treatment were assessed using the Harvey-Bradshaw Index which records the effects of cannabis on disease activity, dose of cannabis at the beginning of treatment and at the end of follow-up, consumption of other medications before and after cannabis use, hospitalization before and during cannabis consumption, laboratory tests (including blood count, CRP, liver, and kidney function), and employment of the patient before and during cannabis use. Patients were also asked about side-effects resulting from cannabis use, including effect of cannabis on appetite, sleep, nausea, mood, concentration, and social interactions.

The study was approved by the Institutional Ethics Committee at Meir Medical Center, and all patients provided written informed consent before enrollment.

Statistical analysis

Categorical variables were described using frequency and percentage. Continuous variables, such as results of blood tests, were described as mean and SD and those that were not normally distributed, such as answers to questionnaires, were expressed as median and interquartile range. Student's *t*-test was employed to evaluate changes in paired variables in the study group before, 1 month, and 1 year after cannabis treatment was initiated. The McNemar test was used for paired nominal data. A *P*-value < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0(IBM Corp., Armonk, New York, USA).

Results

Study population

A total of 180 IBD patients holding, or applying for, a license to use medical cannabis from the Israel Ministry of Health were identified. Of these, 53 were excluded for the following reasons: could not be reached (n = 14), did not have IBD (n = 9), were not using medical cannabis (n = 10; either never started or discontinued use of cannabis), age < 18 (n = 2), death from an unrelated cause (n = 1), 17 patients did not have sufficient data for analysis. The final study population included 127 patients (Fig. 1). Eighty-one patients were already using cannabis at the time of study recruitment and 46 patients started using cannabis during the study period. However, since these two groups did not match we analyzed them together. Demographic details of the study population are presented in Table 1.

Median duration of IBD was 13 years, [interquartile range (IQR), 7.5–18], 45% had a previous surgery related to IBD and 6% had more than one operation in the past (Table 1). Forty-seven patients (37%) had additional comorbidities, including asthma, hypertension, diabetes, or ischemic heart disease.

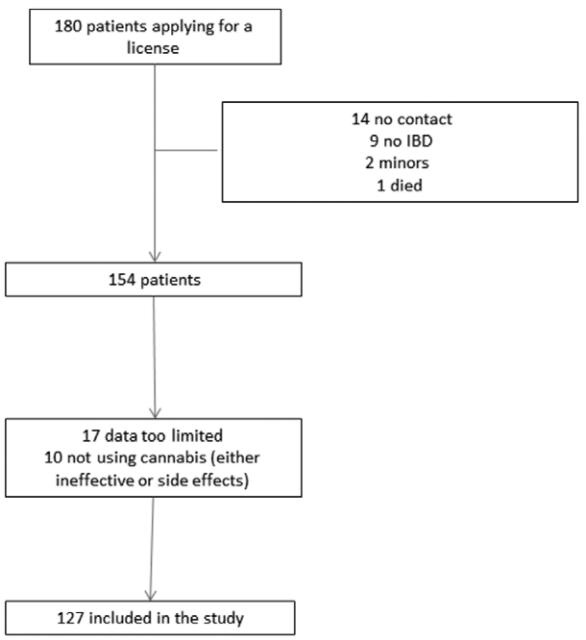

Fig. 1. Study population flow diagram

Mode and dose of cannabis use

The license for medical cannabis from the Israel Ministry of Health defines the monthly dose for each patient. However, the patient can apply for a change in dose over time. The initial average approved and consumed dose of cannabis was 28 ± 16 g/month, and after at least 1 year of follow-up, it was 31 g/month; this difference was not statistically significant. During the median 44-month follow-up period, 50% of patients remained on the same dose, while 32% increased the dose and 6% decreased it. Data were not available for 12% (Table 2).

Detailed data from the supplier on the composition of cannabis was available for 51 of the 127 (40%) patients. Twelve patients used a single strain and 36 used a combination of 2 or 3 strains in order to titrate the relative dose of THC and CBD. The average monthly dose of THC was 0.64 ± 1.1 g and of CBD 5.1 ± 2.9 g. This is an average of 21 mg THC and 170 mg CBD per day. The most common mode of consumption was smoking (56.7%), followed by oil (16.5%) and inhalation (12.6%) (Table 3). Of the 100 patients who answered the question regarding their satisfaction with the treatment dose, 56% responded that they were satisfied with the dose they received, while 44% stated that they would like to increase it.

Patient-reported outcomes of cannabis consumption

The median grade of patient satisfaction from treatment was 7 (IQR, 6–8). Most patients reported significant improvement in their symptoms, with a median of 8 (IQR, 7–8) (Table 4).

The use of other medications after 1 year of cannabis consumption was significantly reduced for all treatment options including 5 aminosalicylic acid, steroids, immunomodulators, and biologic (Table 4). New treatment was

Table 1. Demographic characteristics of the study cohort

Characteristics	Number (%)
No. of patients	127
Male/female	86/42 (67/33%)
Age	39.6 (range 18–75)
Tobacco smoking status (data from 117 patients)	
Never	52 (45%)
Past	33 (28%)
Current	32 (27%)
Crohn's disease/UC	107/20 (84/16%)
No other comorbidity	63%
IBD in family	37 (33%)
Median disease duration (years)	13 (IQR 7.5–18)
Past surgery	58 (45%)

IBD, inflammatory bowel disease; IQR, interquartile range; UC, ulcerative colitis.

Table 2. Disease parameters before and one year after cannabis use

Parameters	Before	After	*P*-value
HBI in prospective group (N = 46)	14 (IQR 9–18)	5 (IQR 3–8.5)	< 0.001
HBI retrospective group (N = 81)	10 (IQR 8–13)	5 (IQR 3–8)	< 0.001
HBI (all patients)	11 (IQR 8.5–15)	5 (IQR 3–8)	< 0.001
Weight (BMI < 24, standard; N = 122)	64 kg ± 11	66 kg ± 12	< 0.001
Weight (BMI > 27, obese; N = 5)	113.2 ± 12.6	103.2 ± 7.9	0.107
Hospitalization (data from 77 patients) a year before and a year after start of cannabis	51 (66%)	24 (31%)	< 0.001

BMI, body mass index; HBI, Harvey-Bradshaw Index; IQR, interquartile range.

started by 8 patients, of them 4 started new biologic treatment, whereas thiopurines, antibiotics, thalidomide, and ursodeoxycholic acid were each started by one patient. Of the 59 patients who stopped a medication, 18 did so without consulting their physician. The drugs they stopped included 5 aminosalicylic acid (7 patients), thiopurines (6 patients), biologics (3 patients), and steroids (3 patients).

To better estimate patients' daily functioning, we obtained data on employment before and 1 year after cannabis consumption from 99 patients. Full-time employment increased from 51 to 58% ($P < 0.005$) during the year of cannabis consumption and part-time employment status increased from 14 to 16% (P = NS). Of the 18% of patients who were not working after one year, 17% said they could not work due to disease activity. The employment rate among the general population in Israel is 76.8%, so the rate of employment observed in our patients was still low compared to the general population.

A total of 100 (78%) patients reported no harmful effects, 12 (9.4%) thought that cannabis caused certain side effects, but stated that the benefit of the treatment was greater than the harm and 15 (12%) did not respond. Only 10 patients (8%) stated that they refrain from an activity because of cannabis use. In the categories of neglect of activities and abuse, only 6 patients answered yes to both questions.

Reported outcomes by family members

A total of 47 relatives (35 spouses and 12 parents) answered that questionnaire. Most (87%) relatives reported that they thought cannabis use was beneficial. Only 6% and 8%, respectively thought the patient should stop or decrease use of medical cannabis.

Table 3. Details regarding cannabis use (N = 127)

Parameter	Value	Range
Age when started (years)	36 ± 13	17–72
Duration used (median; months)	44	IQR 24–56
Dose when started	28 ± 16 g/month	5–100 g/month
Current dose	31 ± 15 g/month	0–80 g/month
Mode of use		
Smoking	72 (56.7%)	
Inhalation	16 (12.6%)	
Oil	21 (16.5%)	
Cookies	8 (6.3%)	
No data	10 (7.9%)	
THC g/month (N = 51)	0.64 ± 1.1 g/month	0–4.8 g/month
CBD g/month (N = 51)	5.1 ± 2.9 g/month	0.2–13 g/month
Satisfied with the current dose	71 (56%)	
Want to increase cannabis dose	56 (44%)	
Overall satisfaction with cannabis use (scale from 1–7) (median)	7	IQR 6–7
Improvement in disease with cannabis use (scale from 1–8) (median)	8	IQR 7–8

IQR, interquartile range.

Side-effects and effect on disease activity

Side-effects described by the patients were minor. The most common was dry mouth (63%), followed by memory decline (34%), eye irritation (14%), dizziness (13%), confusion (9%), and restlessness (8%).

The median Harvey-Bradshaw Index was 11 (IQR, 8.5–15) before cannabis use. It decreased to 5 (IQR, 3–8) ($P < 0.001$) after a median of 44 months (IQR, 24–56 months) (data on 106 patients).The number of daily bowel movements decreased from 7 ± 2 to 3.4 ± 2 ($P < 0.01$) and the pain score decreased from 1.8 ± 0.7 to 0.6 ± 0.7 ($P < 0.01$). Steroid use decreased from 57 to 11.8%, immunomodulators from 63 to 33%, and TNF inhibitors from 51 to 30% (Table 4).

Overall, patient weight did not change significantly during cannabis use. However, after excluding patients with body mass index > 27 (range, 27–38; n = 5), the average weight gain was 2 kg. Interestingly, an average weight loss of 10 kg was observed in the obese group (Table 2).

Platelet count decreased significantly, with no change in other laboratory tests, including hemoglobin, albumin, and CRP (Table 4).

Discussion

Cannabis use is prevalent among patients with IBD [13–15]. However, most of the published literature on this issue provides data on the prevalence and epidemiological aspects of cannabis use in these patients, but very limited information regarding the dose, mode of consumption, side-effects, and disease activity [18,19]. No information regarding development of drug dependency and patients' functioning has been collected. Cannabis use among IBD patients is increasing but evidence that will direct physicians how to manage this phenomenon is lacking; hence, the importance of characterizing these effects.

The current observational, real-life study takes advantage of the large clinical service at Meir Medical Center, where more than half of the IBD patients on medical cannabis in Israel are followed. We summarize our experience with patients with IBD using medical cannabis, focusing on their clinical experiences and information related to dose, mode of consumption, and side-effects.

For the current study, we retrieved the dose of crude cannabis along with the exact content of THC and CBD consumed by 51 patients. Interestingly, most patients

Table 4. Laboratory parameters and medications before and after cannabis use

Laboratory parameters (number of patients)	Before	1 month	*P*-value	1 year	*P*-value
Hemoglobin (112)	13.2	13.4	0.06	13.6	0.06
Albumin (99)	4.0	4.0	0.87	4.0	0.80
CRP (103)	1.92	1.8	0.72	1.6	0.90
Platelets(112)	324	305	< 0.01	287	< 0.01
Medications					
5 ASA	60 (59%)			20 (19.8%)	< 0.001
Steroids	57 (57%)			12 (11.8%)	< 0.001
Immunomodulators (thiopurines, methotrexate)	67 (63%)			35 (33%)	< 0.001
Biologics (TNF inhibitors/vedolizumab)	54 (51%)			32 (30%)	< 0.001

5 ASA, 5 aminosalicylic acid; CRP, C-reactive protein; TNF, tumor necrosis factor.

preferred to use higher doses of CBD, although this compound has no psychoactive effect. We found that the effective dose of cannabis was 30 g/month of crude cannabis, or 21 mg/day of THC and 170 mg/day of CBD. The cannabis used by our patients was plant-derived, and it was purchased from official dispensaries subject to strict quality control standards and analysis of contents. In our placebo-controlled studies of cannabis use in Crohn's disease [20,21], patients responded to 22 mg/day of THC, similar to the dose observed in this real-life cohort. In a study by Irving *et al.* [22] ulcerative colitis patients received 250 mg of CBD twice daily. The lower dose taken by our patients (who were free to titrate the dose according to their response) might explain why Irving *et al.* observed a very high number of major, compliance-related protocol deviations. As most of our patients reported that 30 g/month was effective, we suggest this should be regarded as the effective dose for IBD until more data are collected.

The most common mode of cannabis consumption (56% of the patients) was smoking. This form of consumption is obviously coupled with all the known harm of smoking and, therefore, cannot be recommended as a medical treatment [23]. If cannabis is proven in the future to have medical benefit, safer modes of consumption such as inhalation or oral ingestion should be developed. We found that most of the patients were satisfied with medical cannabis treatment and experienced prolonged improvement in disease-related symptoms, specifically abdominal pain and number of bowel movements per day. Improvement was also supported by the significant decrease in the clinically based Harvey-Bradshaw disease activity index. In addition, we found that these clinical effects were sustained during the relatively prolonged duration (median of 44 months)of our study. Furthermore, our findings of increased full-time employment and family satisfaction with the treatment demonstrate that the clinical improvement achieved with medical cannabis treatment was also associated with improvements in the patients' daily functioning.

In our cohort, the prevalence of immunomodulation treatment was 63%, as opposed to 13% in the general IBD population [24]. Treatment with TNF inhibitors was 51%, also higher than the reported prevalence of 23.4% for patients with CD [25]. This indicates that our study population included patients with more severe disease. This could be because in Israel, only patients who do not respond to conventional therapy are eligible for medical cannabis. These findings may further support potential benefits for medical cannabis in IBD because the patient-reported improvement in our study was found in a cohort of patients with more severe, treatment-refractory disease.

The reduction in the use of IBD-specific medication may seem encouraging, but 18 (14%) of our patients stopped treatment without consulting their physicians, 6 of them stopped thiopurines, and 3 stopped biologics. This observation raises a concern that the euphoria induced by cannabis may mask disease symptoms and temped patients to avoid necessary treatment.

When evaluating cannabis use in IBD, a major question is whether the observed improvement reflects reduction of inflammation, or whether it is the result of the tranquilizing effect of cannabis. Interestingly, despite the patient-reported symptomatic improvement with the use of medical cannabis, we were not able to demonstrate parallel improvement in inflammatory markers. Although platelets, which often act as acute phase reactants, were reduced, there were no significant changes in more specific inflammatory markers such as white blood cells and C reactive protein (CRP). However, the reduction in platelet count cannot be attributed to a direct effect of cannabis use [26], so it could reflect reduction in inflammation. On the other hand, we did observe a decrease in the use of IBD-specific medications, particularly steroids. Nevertheless, because this was an observational study, we cannot conclude whether this reduction was due to decreased disease activity or symptom severity.

In this study, we also addressed the concern of developing drug dependency or abuse in patients receiving medical cannabis. As our patients were using cannabis legally, only some of the DSM-V parameters for addiction applied [17]. Most of our patients used a stable dose of cannabis and their employment status improved. Since patients self reporting of drug abuse may be inaccurate [27], we questioned family members regarding patients function and observed that the functional improvement was also reported by the patients' relatives, so we can conclude that most patients did not present signs of addiction. However, 32% of the patients did increase the cannabis dose and 8 patients actually doubled it. Six of the 127 patients (5%) fulfilled 2 of the DSM criteria [17]. These patients did not present any functional impairment, but it seems that a subpopulation of cannabis users needs to be monitored more carefully and that effective doses of cannabis should be strictly defined.

Unemployment among IBD patients is a common and severe problem, contributing to patient distress. Leong *et al.*[28] reported an unemployment rate of 39% among patients with Crohn's disease and 44% with ulcerative colitis, whereas another study reported 34% [29]. These rates are comparable to the 27% unemployment rate in our cohort before cannabis use. However, the 18% unemployment rate after initiating cannabis use was significantly improved, indicating a beneficial effect on patient function.

Side-effects of prolonged cannabis use are not negligible. In a meta-analysis of 79 trials including 6462 participants (but none for the indication of IBD), Whiting *et al.* noted a hazard ratio of 3.03 (95% confidence interval, 2.42–3.80) for any side-effect. The most common side-effect was dizziness, but more serious side-effects, such as confusion (13/1160 patients) and hallucinations (10/898 patients) were also noted [30]. Doses varied widely from 5 to 60 mg per day. The rate of mild side-effects in our study was similar; however, we did not observe any of the more severe side-effects. This could be attributed either to our smaller cohort or to a lower dose of cannabis used by our patients.

This observational study is limited by the lack of a placebo arm. Therefore, we cannot draw definite conclusions regarding the anti-inflammatory efficacy of cannabis. However, in view of the limited number of well-designed, prospective, placebo-controlled studies in this area, our study provides important information about the effective dose range, clinical benefit, and safety of cannabis treatment for IBD.

Another limit of the study is that 22% of the patients were using cannabis orally, whereas 68% were either smoking or inhaling it. These different modes of consumption result in different pharmacokinetics of the drug, but we do not have data comparing the response in these two groups. Despite the lack of randomized controlled studies, cannabis is used by many IBD patients, and our real-life data provide us with important information which can guide the management of these patients until more information is available.

In summary, this study presents a real-life cohort of long-term cannabis users with IBD. In this cohort, cannabis resulted in improvement in symptoms and general functioning. Long-term side-effects were mild, and optimal doses were defined. Larger, randomized, placebo-controlled studies are needed.

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Conflicts of interest

L.S. is an employee of Tikun Olam company for medical cannabis. otherwise there are no conflicts of interest.

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