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ORIGINAL RESEARCH

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UK medical cannabis registry: an updated analysis of clinical outcomes of cannabis-based medicinal products for inflammatory bowel disease

Aashray Gupta[a], Simon Erridge[a,b], Vivian Graf[a], Monica Kelada[a], Lara Bapir[a], Naveen Jesuraj[a], John Warner-Levy[a], Evonne Clarke[b], Katy McLachlan[b], Ross Coomber[b,c], James J. Rucker[b,d,e], Michael W. Platt[b] and Mikael H. Sodergren[a,b]

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ABSTRACT

Background: Treatments for inflammatory bowel disease (IBD) remain limited, and cannabis-based medicinal products (CBMPs) provide promise in addressing inflammation and pain. However, long-term data on CBMP efficacy in IBD are scarce. This study examines health-related quality of life (HRQoL) changes in IBD patients treated with CBMPs.

Research design and methods: Patients with IBD were identified from the UK Medical Cannabis Registry. Primary outcomes were changes in the short IBD questionnaire (SIBDQ), EQ-5D-5L, single-item sleep quality scale (SQS), and generalized anxiety disorder-7 (GAD-7), from baseline to 18-months after CBMP treatment started. Secondary outcomes were adverse event prevalence.

Results: Analysis of 116 patients with IBD included 94 males (81.03%) with a mean age of 39.52 ± 9.12 years. There were improvements in the SIBDQ, GAD-7, SQS, and EQ-5D-5L Index ($p < 0.001$). At 18-months, 30 (25.86%) patients achieved a minimal clinically important difference (MCID) in the SIBDQ. Patients with severe baseline anxiety and above-median THC doses were more likely to achieve this MCID ($p < 0.050$). Twenty (17.24%) patients reported 155 (133.62%) adverse events.

Conclusions: CBMP treatment was associated with improvement in IBD-specific outcomes in patients and general HRQoL over 18-months. However, causation cannot be inferred. Hence, randomized controlled trials are still required.

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Cannabis; tetrahydrocannabinol; cannabidiol; Crohn's disease; ulcerative colitis; inflammatory bowel disease

1. Introduction

Inflammatory bowel disease (IBD) is a chronic disease characterized by repetitive inflammation of the gastrointestinal tract [1]. In 2019, it was estimated that 4.9 million people are living with IBD globally [2], with prevalence in the UK estimated to be 1 in 123 [3]. IBD encompasses Crohn's disease (CD) and ulcerative colitis (UC), each with distinct patterns of inflammation [4,5]. Common symptoms include abdominal pain, diarrhea, and bloody stools [6]. IBD can also cause extra-intestinal manifestations affecting the skin, mouth, eyes, and one or more joints [4,5]. IBD has a high impact on physical, mental, social, and financial health and wellbeing [7–9].

Current IBD treatments, both pharmaceutical and surgical, aim to manage symptoms, reduce inflammation, and promote healing [9,10]. While effective for many, these treatments have limitations [11,12]. Biological agents, such as anti-tumor necrosis factor (TNF) agents, offer an alternative for those unresponsive to first-line therapies [13,14]. However, up to 40% of patients are non-responsive to anti-TNF therapy initially, and a further 23–46% may lose response after 1 year [15].

Cannabis-based medicinal products (CBMPs) present another therapeutic option for IBD symptom relief [16]. CBMPs are derived from the cannabis plant, which contains greater than 100 potentially bioactive phytocannabinoids [17]. The most well studied are (–)-trans-Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [17]. These interact with the endocannabinoid system (ECS) [16]. The ECS consists of endogenous cannabinoids, anandamide and 2-arachindonoylglycerol (2-AG), and the G-protein coupled cannabinoid receptors 1 and 2 (CB1 and CB2) [16]. 2-AG is a nonselective agonist for CB1 and CB2 receptors, while anandamide is a partial cannabinoid receptor agonist with a stronger affinity for the CB1 receptor [16]. THC is a partial agonist for both CB1 and CB2 receptors [18]. CBD primarily acts by preventing the breakdown and subsequent reuptake of anandamide [19]. The ECS plays an important role in regulating the gastrointestinal system, with CB1 and CB2 receptors found in every layer of the intestinal section, including the myenteric and submucosal plexi [16,20]. Cannabinoids also have several other targets such as transient receptor potential vanilloid type 1 (TRPV1) channels, peroxisome proliferator-activated receptors, and

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serotonin (5-HT) receptors, all of which have been implicated in either inflammation or pain [21–23].

Pre-clinical studies have indicated the potential benefits of utilizing CBMPs to alter the ECS in IBD treatment [24]. In murine IBD models, ablation of CB1/2 receptors was associated with a higher risk of colitis [25], while treatment of mice with CB1/2 agonists prevented symptoms of colitis [26]. In several rodent models, CBD treatment reduced levels of pro-inflammatory cytokines, including TNF-α [27], an integral cytokine in IBD pathogenesis [28]. Furthermore, activation of the CB2 receptor inhibited the release of the pro-inflammatory cytokine IL-8 in human colonic epithelial cell lines [29] and suppressed the pro-inflammatory response of macrophages and inhibited neutrophil recruitment in other models [30,31]. CBD may also produce anti-inflammatory effects through the TRPV1 receptor [24,32–34].

In addition to inflammation, pre-clinical models show promise in addressing common symptoms experienced by IBD patients. CB1 receptors modulated the analgesic effects of cannabinoids in a rodent model of colorectal distension-induced visceral pain [35]. CBD may also have analgesic effects via action at 5-HT receptors and TRPV1 channels [23,34]. CBD also reduced intestinal hypermotility in a murine model [36], while both CB1 and CB2 receptor agonists inhibited diarrhea in experimentally induced colitis mice models [26]. Given the role of several cannabinoid receptors in modulating the gastrointestinal system, inflammation, and pain, the ECS is an attractive therapeutic target.

Although pre-clinical studies highlight the potential of CBMPs for the treatment of IBD, there are limited data available collected from randomized controlled trials (RCTs). The most recent meta-analysis of RCTs investigating CBMPs in IBD emphasized this problem, with only six RCTs meeting inclusion criteria [37]. The outcome of this meta-analysis concluded that cannabinoids were not shown to induce disease remission but were associated with improvements in health-related quality of life (HRQoL) of IBD patients [37]. However, this meta-analysis and others are limited by the paucity of trials available and the low sample size within each RCT [37,38].

At present, there is uncertainty around the effects of CBMPs in IBD. However, reported benefits in HRQoL, alongside high self-reported use of cannabis by IBD patients, highlight the need for further research [16,39]. Previously, our group has analyzed the effect of CBMPs on patient-reported outcome measures (PROMs) in IBD patients using data from the United Kingdom Medical Cannabis Registry (UKMCR) and demonstrated an improvement in IBD-specific, anxiety-related and general HRQoL outcomes up to 3 months [40]. However, conclusions from this study were limited by low patient numbers which prevented meaningful sub-group analysis. Further, changes in PROMs were measured over a period of only 3 months. This is in parallel to many of the randomized controlled trials which do not assess the long-term effects of CBMPs [37,38]. Short study periods have limited conclusions being drawn about the long-term impact of CBMPs in IBD patients as well as any related long-term adverse events [38,39,41]. Hence, this study primarily aimed to evaluate differences in PROMs for patients prescribed CBMPs for IBD over an 18-month period using data collected from the UKMCR. Secondary aims included analysis of prognostic factors associated with positive changes in IBD-specific outcomes and a longitudinal assessment of adverse events during CBMP treatment.

2. Methods

2.1. Study design and participants

This was a prospective case series of patients from the UKMCR prescribed CBMPs following a primary diagnosis of either CD or UC. The UKMCR was the first prospective registry launched in the UK and has been collecting pseudonymized data since December 2019 [42]. It is managed by Curaleaf Clinic [42]. Every patient provided written and informed consent during registration, prior to baseline data collection. Following this, participants were enrolled consecutively. The UKMCR received approval from the Central Bristol Research Ethics Committee (22/SW/0145). This study has been performed in line with the Strengthening the Reporting of Observational Studies in Epidemiology guidance [43].

2.2. Data collection

This study analyzed patients who were treated with CBMPs for a primary indication of CD or UC and were enrolled in the UKMCR for 18 months or more on the date of data extraction, 13 December 2023. Participants were requested to electronically provide responses to PROMs at baseline and after 1-, 3-, 6-, 12-, and 18-months of treatment. Participants with incomplete baseline PROMs were excluded.

Patient demographic data was also collected and recorded by clinicians. These data consisted of age, gender, occupation, and body mass index (BMI). Any comorbidities were noted, and the Charlson co-morbidity index was calculated for every patient [44]. Information about alcohol, tobacco, and cannabis use was recorded which included average weekly alcohol consumption, smoking status, smoking pack years, cannabis use status, and method of administration. Cannabis gram years, a novel metric, was calculated to quantify previous cannabis use for participants prior to treatment initiation [42].

Records of CBMP prescriptions were maintained throughout treatment. This included information about cannabis strains, formulations, route of administration, and CBD and THC doses per day. Treatment options for patients included sublingual or oral preparations and vaporized dried flowers.

2.3. Patient related outcome measures

The primary outcomes of this study were the changes in self-reported PROMs from baseline at 1-, 3-, 6-, 12- and 18-months. This included the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) alongside three general HRQoL PROMs: the EQ-5D-5L, Generalized Anxiety Disorder-7 (GAD-7) and Single-Item Sleep Quality Scale (SQS). At each subsequent time-point from baseline, Patient Global Impression of Change (PGIC) values were also collected.

SIBDQ is an IBD-specific HRQoL instrument investigating the impact of IBD on four domains: bowel, systemic, emotion, and social [45–47]. It is a 10-question measure with each question scored on a 7-point Likert scale from 1 (severe problem) to 7 (no problem) [47]. Hence, total scores range from 10 to 70 with a lower SIBDQ score indicating a poor HRQoL, while scores close to 70 indicate health close to an optimal level and a 9-point change in the SIBDQ is considered a minimal clinically important difference (MCID) [45,46].

EQ-5D-5L is a generic health status measure to assess a patient's HRQoL and comprises five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [46,48]. Within each domain, patients rate across five levels of severity, ranging from 1 to 5 (1 = none, 2 = slight, 3 = moderate, 4 = severe, 5 = extreme) [46,48]. This response is mapped to country-specific EQ-5D-5L value sets to obtain an EQ-5D-5L index [48,49]. The highest possible index score is 1, while a score <0 depicts health states considered worse than death [48].

GAD-7 is utilized to screen for Generalized Anxiety Disorder (GAD) and evaluate its severity in a clinical or research setting [50]. The GAD-7 is a 7-item scale of generalized anxiety symptoms, with each item scored from 0 (not at all) to 3 (daily) [50,51]. With a total possible value of 21, scores of 5, 10, and 15 are considered as cutoffs for mild, moderate, and severe anxiety, respectively [50].

SQS is a self-reported measure of patients' sleep quality. It instructs patients to rate their quality of sleep over the last 7 days on a scale of 0 ('terrible') to 10 ('excellent') [52].

The PGIC assesses patients' perception of improvements in their symptoms following treatment induction [53]. Patients self-rate their perceived improvement in symptoms on a 7-point single-item scale from 1 ('no change') to 7 ('a great deal better) [53].

2.4. Adverse events (AEs)

Adverse events (AEs) were self-reported by patients alongside PROM completion, at the time of the AE or to clinicians during follow-ups. AEs were recorded in accordance with the common terminology criteria for adverse events version 4.0 [54].

2.5. Missing data

Baseline observation carried forward (BOCF) method was utilized to address missing PROM data; hence, any missing PROM data were replaced by the baseline value even if any post-baseline PROM values were recorded [55].

2.6. Statistical analysis

Descriptive statistics was used to analyze patient demographics, co-morbidities, previous alcohol and tobacco use, cannabis status, and AEs. Data were either presented as mean ± standard deviation (SD) or as median and interquartile range (IQR). Applying the central limit theorem, a repeated measures one-way analysis of variance (ANOVA) was utilized to investigate the mean differences between patients for each PROM at each timepoint [56]. Pairwise comparison with Bonferroni correction was conducted on values which were statistically significant on repeated measures ANOVA. Further, sub-group analysis was conducted based on the initial diagnosis of CD or UC.

An univariable logistic regression model was utilized to examine the effect of each independent variable on the possibility of achieving the MCID in the SIBDQ at 18-months. Following this, all variables were incorporated into a multivariable regression model, which adjusted for other included variables and assessed the impact of each variable on the likelihood of achieving the MCID. Data were presented as the odds ratio (OR) and 95% confidence interval (CI).

Statistical analysis was conducted using the Statistical Package for the Social Sciences [IBM Corp. Released 2022. IBM SPSS Statistics for Macintosh, Version 29. Armonk, NY] with statistical significance being defined as $p < 0.050$.

3. Results

3.1. Baseline demographic characteristics and cannabis exposure

After data extraction, 116 IBD (CD – 78; UC – 38) patients were included in this analysis (Table 1). The patients comprised 94 males (81.03%) and 22 females (18.97%), with a mean age of 39.52 ± 9.12 years and BMI of 25.25 ± 5.75 kg/m^2. In terms of employment, the most common category was professionals (n = 44; 37.93%), followed by unemployment (n = 24; 20.69%). Anxiety/depression (n = 27; 23.28%) was the most prevalent comorbidity (Supplementary Table S1). Secondary and tertiary indications for treatment are detailed in full in Supplementary Table S2. The most common secondary indication was chronic pain (n = 46; 39.66%).

Median weekly alcohol consumption amongst patients was 0.00 [0.00–4.00] units, while 66.38% (n = 77) of patients were either current or ex-smokers (Table 2). At the time of starting treatment, 78 patients (67.24%) were already utilizing cannabis and a further 17 (14.66%) had consumed cannabis in the past.

3.2. CBMP dosing

A large proportion of patients were prescribed both oils and dried flower at baseline (n = 52,44.83%) and 18-months (n = 56,48.28%, Table 3). The number of patients prescribed oils only decreased at 18-months, but the number of patients treated with dried flower only or both increased. Median CBD and THC doses of these patients at 18-months were 35.00 [21.88–75.00] and 195.00 [106.20–230.00] mg/day, respectively. At 18-months, median CBD and THC doses of those prescribed oils only were 45.00 [20.00–-68.75] and 10.00 [5.40–13.00] mg/day. Patients prescribed dried flower only, had median CBD and THC doses of 15.00 [10.00–60.00] and 210.00 [122.50–315.00] mg/day.

3.3. Patient-reported outcome measures (PROMs)

Across each PROM, there was a significant difference across all time periods ($p < 0.050$, Supplementary Table S3). On pairwise

Table 1. Baseline demographic Information.

	CD (n = 78)	UC (n = 38)	Total (n = 116)
Age	39.37 ± 8.47	39.82 ± 10.44	39.52 ± 9.12
Body Mass Index (kg/m^2)	25.20 ± 6.01	25.35 ± 5.23	25.25 ± 5.75
Gender			
Male	61 (78.21%)	33 (86.84%)	94 (81.03%)
Female	17 (21.79%)	5 (13.16%)	22 (18.97%)
Occupation			
Crafts and Related TradesWorkers	3 (3.85%)	2 (5.26%)	5 (4.31%)
Elementary Occupations	0 (0.00%)	1 (2.63%)	1 (0.86%)
Managers	3 (3.85%)	2 (5.26%)	5 (4.31%)
Other Occupations	6 (7.69%)	5 (13.16%)	11 (9.48%)
Plant and MachineOperators, and Assemblers	2 (2.56%)	1 (2.63%)	3 (2.59%)
Professional	29 (37.18%)	15 (39.47%)	44 (37.93%)
Service and Sales Workers	6 (7.69%)	2 (5.26%)	8 (6.90%)
Skilled Agricultural, Forestryand Fishery Workers	0 (0.00%)	1 (2.63%)	1 (0.86%)
Technicians and AssociateProfessionals	9 (11.54%)	5 (13.16%)	14 (12.07%)
Unemployed	20 (25.64%)	4 (10.53%)	24 (20.69%)

Demographic data collected by clinicians of patients prescribed CBMPs for a primary diagnosis of CD or UC. Data are presented as either mean ± SD or n(%). $n = 116$. SD – standard deviation; CD – Crohn's disease; UC – ulcerative colitis.

Table 2. Tobacco, alcohol and cannabis Consumption.

	CD (n = 78)	UC (n = 38)	Total (n = 116)
Tobacco Status			
Current Smoker	17 (21.79%)	7 (18.42%)	24 (20.69%)
Ex-Smoker	38 (48.72%)	15 (39.47%)	53 (45.69%)
Never Smoked	23 (29.49%)	16 (42.11%)	39 (33.62%)
Tobacco Pack Years	5.00 [3.00–12.00]	4.50 [1.00–12.75]	5.00 [3.00–12.00]
Weekly Alcohol Consumption (units)	0.00 [0.00–4.00]	0.00 [0.00–5.75]	0.00 [0.00–4.00]
Cannabis Status			
Current User	59 (75.64%)	19 (50.00%)	78 (67.24%)
Ex-User	6 (7.69%)	11 (28.95%)	17 (14.66%)
Never Used	13 (16.67%)	8 (21.05%)	21 (18.10%)
Cannabis Gram Years	6.00 [2.75–12.00]	4.00 [1.75–10.00]	5 [2.00–10.00]

Clinicians collected information about patients' tobacco, alcohol and cannabis history at baseline. Data are presented as n(%) or median[iqr]. $n = 116$. IQR – interquartile range; CD – Crohn's disease; UC – ulcerative colitis.

Table 3. Cannabis-Based Medicinal Products (CBMPs) Prescription.

Prescription	Baseline	1-Month	3-Months	6-Months	12-Months	18-Months
Oils	**37 (31.90%)**	**31 (26.96%)**	**24 (20.87%)**	**20 (17.39%)**	**20 (17.39%)**	**18 (15.65%)**
CBD, mg/day	20.00 [20.00–40.00]	20.00 [20.00–50.00]	40.00 [20.00–50.00]	38.75 [20.00–81.25]	20.00 [18.75–42.50]	45.00 [20.00–68.75]
THC, mg/day	1.00 [1.00–1.50]	5.00 [5.00–10.00]	5.00 [5.00–10.00]	6.50 [5.00–10.75]	10.00 [5.00–10.23]	10.00 [5.40–13.00]
Dried Flower	**27 (23.28%)**	**21 (18.26%)**	**23 (20.00%)**	**24 (20.87%)**	**35 (30.43%)**	**41 (35.65%)**
CBD, mg/day	1.00 [0.00–12.00]	5.00 [0.00–70.00] 102.50	5.00 [0.00–65.00] 110.00	37.50 [5.00–63.75] 182.50	20.00 [10.00–77.50]	15.00 [10.00–60.00]
THC, mg/day	20.00 [19.25–20.75]	[95.00–180.00]	[100.00–187.50]	[110.00–228.13]	200.00 [146.25–272.50]	210.00 [122.50–315.00]
Both	**52 (44.83%)**	**63 (54.78%)**	**67 (58.26%)**	**70 (60.87%)**	**60 (52.17%)**	**56 (48.70%)**
CBD, mg/day	20.00 [15.50–21.00]	25.00 [20.00–50.00]	25.00 [20.00–55.00]	27.50 [20.00–70.00]	30.00 [19.38–78.88]	35.00 [21.88–75.00]
THC, mg/day	21.00 [20.00–21.00]	105.00 [100.00–110.00]	110.00 [105.00–174.00]	176.00 [106.04–209.38]	152.50 [105.00–212.75]	195.00 [106.20–230.00]
All Patients	**116**	**115**	**115**	**115**	**115**	**115**
CBD, mg/day	20.00 [8.00–20.00]	20.00 [20.00–50.00]	25.00 [20.00–52.50]	30.00 [20.00–72.50]	25.00 [11.88–75.88]	30.00 [13.75–70.00]
THC, mg/day	20.00 [1.50–21.00]	100.00 [12.00–105.00]	105.00 [30.00–151.25]	122.00 [100.00–203.75]	150.00 [85.00–210.00]	142.50 [97.50–247.05]

Patients were prescribed either oils, dried flower or a combination of both. Cannabidiol (CBD) and (–)-trans-δ9-tetrahydrocannabinol (THC) doses were calculated in mg/day and presented as median[iqr]. $n = 116$. IQR – interquartile range.

comparison at each follow-up compared to baseline, there were improvements in the SIBDQ, GAD-7, SQS, EQ-5D-5L index value, and pain and discomfort domain of the EQ-5D-5L ($p < 0.050$, Figure 1 and Table 4). There were improvements in the mobility, self-care, and usual activities domains at various time-points ($p < 0.050$, Table 4). Whilst there was a difference in the repeated measures one way ANOVA of the EQ-5D-5L anxiety and depression domain ($p = 0.032$), there was no difference in pairwise comparisons between any follow-ups after Bonferroni correction ($p > 0.050$). Furthermore, the mean PGIC value at the 1-month follow-up was 5.22 ± 1.55 and increased at each follow-up to a mean score of 5.62 ± 1.44 after 18-months. PROM completion rate decreased at each follow-up time-point and is shown in Supplementary Table S4.

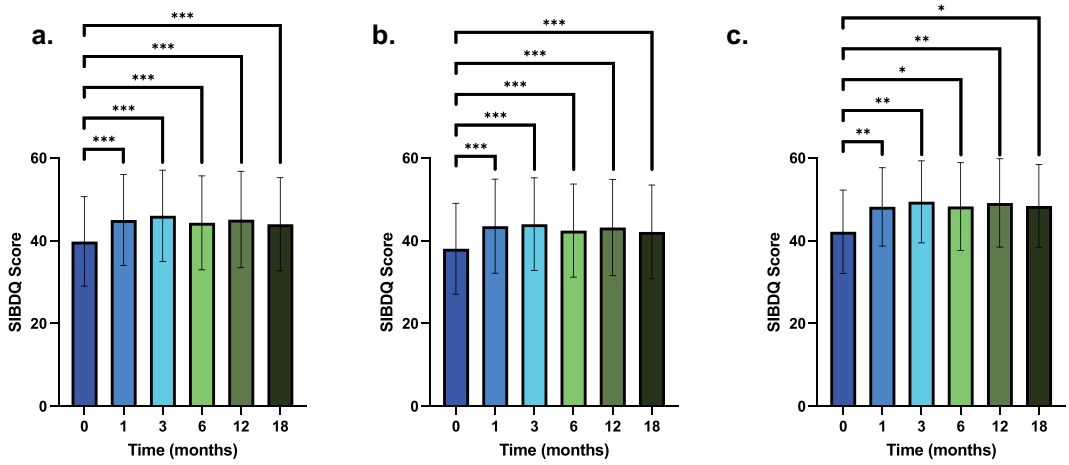

Figure 1. Repeated measures one way ANOVA with post-hoc pairwise comparison with Bonferroni correction comparing patient reported short inflammatory bowel disease questionnaire (SIBDQ) scores at baseline (0 months) to 1-month, 3-months, 6-months, 12-months, and 18-months of treatment with CBMPs to identify patient improvement in inflammatory bowel disease (IBD) symptoms. (a) All IBD patients: $n = 116$. (b) Crohn's disease patients: $n = 78$. (c) Ulcerative colitis patients: $n = 38$. Data is presented as mean ± standard deviation. ***$p < 0.001$, **$p < 0.010$, *$p < 0.050$.

Table 4. Repeated measures one way ANOVA.

PROM		Baseline	1–Month	3–Months	6–Months	12–Months	18–Months
SIBDQ	Score	39.38 ± 10.82	45.02 ± 10.99	45.77 ± 11.04	44.32 ± 11.34	45.11 ± 11.63	44.17 ± 11.27
	p-value	–	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
GAD-7	Score	5.95 ± 5.82	4.03 ± 4.60	3.89 ± 4.28	4.39 ± 4.78	4.62 ± 5.11	4.93 ± 5.09
	p-value	–	<0.001***	<0.001***	0.005**	0.023*	0.025*
SQS	Score	4.93 ± 2.48	5.99 ± 2.52	6.18 ± 2.35	6.09 ± 2.32	5.90 ± 2.45	5.86 ± 2.50
	p-value	–	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
EQ-5D-5L Index	Score	0.60 ± 0.28	0.68 ± 0.24	0.68 ± 0.24	0.65 ± 0.28	0.66 ± 0.28	0.66 ± 0.28
	p-value	–	<0.001***	<0.001***	0.004**	<0.001***	<0.001***
EQ-5D-5L Mobility	Score	1.77 ± 0.94	1.58 ± 0.78	1.54 ± 0.80	1.66 ± 0.92	1.61 ± 0.86	1.66 ± 0.94
	p-value	–	0.008**	<0.001***	0.783	0.047*	0.176
EQ-5D-5L Self-Care	Score	1.44 ± 0.78	1.24 ± 0.55	1.32 ± 0.69	1.41 ± 0.78	1.36 ± 0.74	1.41 ± 0.76
	p-value	–	0.016*	0.285	1.000	0.736	1.000
EQ-5D-5L Usual Activities	Score	2.13 ± 1.15	1.87 ± 1.04	1.87 ± 1.06	1.94 ± 1.07	1.88 ± 1.12	1.97 ± 1.10
	p-value	–	0.020*	0.003**	0.071	<0.001***	0.168
EQ-5D-5L Pain & Discomfort	Score	2.86 ± 1.04	2.46 ± 1.00	2.39 ± 0.97	2.50 ± 1.09	2.45 ± 1.07	2.55 ± 1.08
	p-value	–	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
EQ-5D-5L Anxiety Depression	Score	1.98. ± 1.12	1.78 ± 0.95	1.81 ± 0.96	1.82 ± 1.00	1.84 ± 1.03	1.79 ± 0.98
	p-value	–	0.081	0.198	0.092	0.474	0.052
PGIC	Score	–	5.22 ± 1.55	5.50 ± 1.39	5.56 ± 1.38	5.60 ± 1.44	5.62 ± 1.44

With post-hoc pairwise comparison with Bonferroni correction comparing patient-reported outcome measures (PROMs) at baseline to 1-month, 3-months, 6-months, 12-months, and 18-months of treatment with CBMPs to identify patient improvement. $n = 116$. Data is presented as mean ± standard deviation. SD – standard deviation; SIBDQ – short inflammatory bowel disease questionnaire; GAD-7 - generalized anxiety disorder-7; SQS – sleep quality scale; PGIC – patient global impression of change. For the GAD-7, a lower score indicated reduced anxiety, but for all other PROMs, a higher score signified an improved outcome. ***$p < 0.001$, **$p < 0.010$, *$p < 0.050$.

When PROM data was analyzed in CD or UC subgroups, improvements were seen in the SIBDQ score, GAD-7, SQS, and all the domains and index of the EQ-5D-5L in CD patients ($p < 0.050$; Supplementary Table S5A). In the UC patient cohort, improvements were seen in the SIBDQ, SQS, and EQ-5D-5L pain and discomfort domain ($p < 0.050$), but not in the GAD-7 and all other EQ-5D-5L parameters ($p > 0.050$) (Supplementary Table S5B).

3.4. Logistic regression

Univariable and multivariable logistic regression models assessed the effect of independent variables on achieving a MCID in the SIBDQ after 18-months of CBMP treatment. Thirty patients (25.86%) reported an improvement in SIBDQ score equal to or above the MCID (Supplementary Table S6).

In the univariable analysis, baseline sleep quality and baseline anxiety levels were associated with an increased likelihood of achieving the MCID in the SIBDQ at 18-months (Supplementary Table S7). 'Poor/Terrible' sleep (OR = 5.28, 95% CI = 1.57–17.75, $p = 0.007$) and severe anxiety (OR = 5.58, 95% CI = 1.60–19.39, $p = 0.007$) were associated with achieving the MCID in the SIBDQ. Additionally, patients treated with THC doses above the median were more likely to achieve the MCID in the SIBDQ (OR = 3.11, 95% CI = 1.27–7.60, $p = 0.013$).

When all variables were included in a multivariable regression model, severe baseline anxiety (OR = 6.78, 95% CI = 1.37–33.57, $p = 0.019$) and above median doses of THC (OR = 7.22, 95% CI = 1.58–33.00, $p = 0.011$) were associated with a greater likelihood of achieving the MCID, but this was no longer the case for baseline sleep quality ($p > 0.050$) (Table 5).

Table 5. Multivariable regression analysis examining impact of independent factors on achieving the minimal clinically important difference (MCID) in the short inflammatory bowel disease questionnaire (SIBDQ) at 18-months.

Variable	n	OR [95% CI]	p-value
Age			
18–30	14	-1.16 [0.18–7.42]	Ref
31–40	55	1.20 [0.15–9.38]	0.877
31–50	28	1.46 [0.13–15.97]	0.863
51+	14		0.758
Gender			
Male	90	-0.50 [0.11–2.36]	Ref
Female	21		0.383
BMI (kg/m^2)			
≤ 20	16	0.52 [0.09–3.04]-0.22 [0.05–1.11]	0.470
20.01–25	47	1.37 [0.35–5.31]	Ref
25.01–30	28		0.067
> 30	20		0.652
Primary Diagnosis			
CD	75	-2.04 [0.59–7.14]	Ref
UC	36		0.263
Cannabis Status			
Naïve	20	-2.93 [0.39–21.99]	Ref
Ex-User	15	1.04 [0.18–6.06]	0.295
Current User	76		0.968
Treatment Type			
Oils	17	-1.06 [0.13–8.75]	Ref
Dried Flower	39	1.04 [0.14–7.70]	0.958
Both	55		0.970
CBD Dose			
≤ median (≤30.00 mg/day)	56	-2.61 [0.81–8.39]	Ref
> median (>30.00 mg/day)	55		0.108
THC Dose			
≤ median (≤136.25 mg/day)	55	-7.22 [1.58–33.00]	Ref
> median (>136.25 mg/day)	56		0.011*
Baseline Sleep Quality			
Good/Excellent	35	-4.58 [0.94–22.36]	Ref
Fair	36	2.22 [0.47–10.40]	0.060
Poor/Terrible	40		0.313
Baseline Anxiety			
Sub-clinical	56	-0.83 [0.19–3.64]	Ref
Mild	27	3.80 [0.70–20.48]	0.805
Moderate	14	6.78 [1.37–33.57]	0.121
Severe	14		0.019*

A multivariable regression model determined the effect of age, gender, BMI, primary diagnosis, cannabis status, treatment type, cannabidiol (CBD) dose, (−)-trans-δ9-tetrahydrocannabinol (THC) dose, baseline sleep quality, and baseline anxiety on the likelihood of achieving the MCID in the SIBDQ at 18-months. For baseline sleep quality, terrible/poor, fair, and good/excellent sleep were defined as scores of 0–3, 4–6, and 7–10 on the single-item sleep quality scale (SQS), respectively. For baseline anxiety, mild, moderate, and severe anxiety were defined as scores of ≥ 5, ≥10, and ≥15 on the generalized anxiety disorder-7 (GAD-7). $n = 111$. Results are presented as the odds ratio (OR) and the 95% confidence intervals (CI). *$p < 0.050$.

3.5. Adverse events

Figure 2 outlines the total incidence and severity of AEs experienced and recorded by patients during the CBMP treatment period. Twenty patients (17.24%) reported 155 (133.62%) AEs, which were largely mild ($n = 71$; 61.21%) or moderate ($n = 66$; 56.90%) in severity, and no life-threatening/disabling AEs were reported (Figure 2 & Supplementary Table S8). Fatigue ($n = 15$, 12.93%) and dry mouth ($n = 11$, 9.48%) were the AEs with the highest incidence (Supplementary Table S8).

4. Discussion

Results from this study suggest CBMP treatment was associated with improvements in IBD-specific, anxiety, sleep and general HRQoL PROMs. There were consistent improvements in symptoms perceived by patients over the 18-month period. Furthermore, patients treated with above median doses of THC and with severe baseline anxiety were more likely to achieve the MCID in the SIBDQ. Sub-group analysis based on primary diagnosis showed improvements in IBD-specific measures in both CD and UC patient groups, however, improvements in anxiety and general HRQoL were only seen in the CD group. Sleep quality improvements were seen at all time-points from baseline in the CD group and at 3-, 6- and 12-months in UC patients. CBMPs were tolerated well in this study with only 20 patients reporting a total of 155 adverse events.

CBMP treatment was associated with improvements in the SIBDQ at all time-points in both CD and UC patients. A similar trend was observed in a previous study by our group from the UKMCR, however the treatment period was only 3-months, the sample size was smaller, and after sub-group analysis UC patients did not see a statistically significant improvement [40]. A post-hoc power analysis was conducted, with β set at 0.1. This indicates that the study was adequately powered, as a

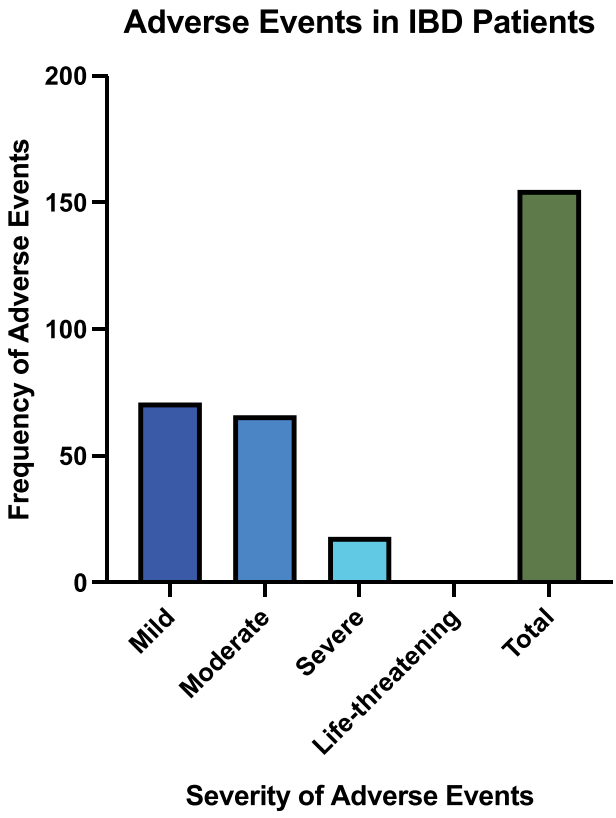

Figure 2. Frequency of adverse events categorized by severity of adverse events (AEs) during 18-month treatment and number of total adverse events. AEs were categorized as mild, moderate, severe, or life-threatening/disabling.

sample size of 56 was determined to be sufficient for detecting a statistically significant difference between baseline and 18-month SIBDQ scores. There is a lack of available data from similar long-term observational studies or RCTs on changes in IBD-specific measures; however, short-term benefits of CBMPs on HRQoL have been demonstrated in meta-analyses of RCTs [37,39]. However, there is heterogeneity between available RCTs with respect to CBMPs. In one recent RCT, the intervention was smoked cannabis, which is not an approved route of administration in the UK [39]. These results add to the growing evidence of CBMPs on IBD-specific HRQoL outcomes, however there is still a lack of evidence regarding its long-term impact on active inflammation. Previous RCTs have been conducted for short periods of time with a maximum study period of 10 weeks, showing no significant changes in inflammation; however, future studies should assess inflammatory changes using endoscopy over longer time periods [37,39,57]. Recent observational studies have attempted to study the effects of cannabis in IBD, which have failed to find any significant improvements and in some cases found that cannabis use was associated with worse outcomes [58–61]. However, these studies did not collect data prospectively. Consequently, these outcomes may be more reflective of cannabis use being more common in individuals with more severe disease attempting to provide symptomatic relief, rather than cannabis contributing to worsening of IBD [61].

At the 18-month follow-up, there was an improvement in the EQ-5D-5L Index Value. This was mainly driven by improvements in the pain and discomfort domain which had the greatest mean change of 0.31 from baseline to 18-months. This was an important finding as IBD patients have previously reported worse health in this domain than the other domains [62]. These findings align with Wang et al.'s meta-analysis which demonstrated an increased likelihood of patients, with chronic pain reporting a MCID when treated with cannabinoids compared to placebo [63].

In the sub-group analysis based on primary diagnosis, there were no improvements in the GAD-7 or EQ-5D-5L Index Value in the UC group. Conversely, in the CD group there were improvements in the GAD-7 at 1-, 3-, and 6-months, and at all follow-up time points in the EQ-5D-5L index. These differences might be due to differences in baseline health between each cohort. The UC sub-group had lower baseline GAD-7 values and higher EQ-5D-5L index values (Supplementary Tables S4A & S4B). Since only 38 UC patients were part of the study compared to 78 CD patients, the size of the UC sub-group may have influenced the research outcomes and made it more sensitive to drop-outs [64]. It is important to note here that baseline observation carry forward (BOCF) was used to adjust for dropouts which biased analysis toward the null hypothesis. These outcomes, however, do align somewhat with a previous meta-analysis which concluded there were no benefits of cannabinoid therapy for UC patients for HRQoL versus placebo, but improvements were seen in CD patients [37].

Following univariable and multivariable analyses, severe baseline anxiety had a statistically significant association with achieving the MCID in the SIBDQ, while poor/terrible sleep was deemed significant in the univariable analysis only. This finding could be explained by the fact that CBMPs may cause larger improvements and have a greater efficacy in patients with moderate-to-severe symptoms, including anxiety, as shown by a retrospective observational study [65]. It was likely that patients with severe anxiety had worse scores on the SIDBQ initially. However, it is also possible that the main benefit to patients was in anxiety and sleep, and those people continued treatment to receive these benefits, while patients with good baseline sleep and anxiety dropped out due to a reduced clinical effect on IBD-specific symptoms. Since the SIBDQ also comprises an emotional domain, this effect may also be reflective of the effects on psychological symptoms [66]. Finally, patients treated with above median THC doses were more likely to achieve the MCID. This could result from higher THC doses producing greater psychotropic effects, leading to improved patient outcomes [67]. Further studies are needed to tease out the precise symptom burden CBMPs are most effective in addressing.

Only 20 patients (17.24%) reported a total of 155 adverse events (133.62%). The majority of AEs were mild or moderate in severity, and none were disabling/life-threatening. The most common AEs were fatigue and dry mouth, which was similar to other studies conducted on the UKMCR [40,68]. Further, these results were similar to the observational cross-sectional study of Australian IBD patients utilizing CBMPs, as well as an RCT conducted by Naftali et al., both of which reported low

number of patients affected by AEs as well as very few severe AEs [39,69].

This study does have significant limitations which must be considered. Firstly, this is a case series without a placebo control or comparator arm. Although associations between CBMP therapy and improved HRQoL outcomes can be seen, causality cannot be determined. The lack of blinding and randomization means the study is affected by other confounding variables. Only 16.67% of the patients were cannabis naïve, creating a selection bias as these patients could see improved HRQoL outcomes due to the expectation of success of CBMP therapy, given their experience utilizing illicit cannabis. Conversely, these patients may have built tolerance to cannabinoids, biasing the results to the null [70]. The majority of patients were males, again not representative of the general IBD population [71]. Furthermore, PROMs are subjective and open to recall bias from the patient and the responses over time are subject to attrition bias. These limitations restrict the generalizability of the study to a broader patient population.

Conversely, this study had a relatively large sample size and is the longest known longitudinal assessment of CBMP use in IBD patients. Due to the distinct aroma and taste of CBMPs and its vasoactive effects, it is difficult to conduct double-blinded RCTs, hence this study adds important real-world evidence [72]. The UKMCR consists of patients from across the UK and Channel Islands, making this a geographically diverse study [42]. Lastly, by utilizing BOCF, which is conservative in nature, to account for missing data, analysis was biased toward the null hypothesis, making any statistically significant finding more robust.

Future work assessing CBMP efficacy in IBD patients should focus on conducting double-blinded RCTs, utilizing innovative approaches to developing placebo. These should use objective measures to assess local and systemic inflammation, such as endoscopy, c-reactive protein, and a full blood count. This will help assess the anti- inflammatory effects of CBMPs in IBD. Limitations of this study should be used to inform these RCTs, especially to ensure study samples are representative of the IBD population. Continued longitudinal assessment through the UKMCR is integral to increase real-world evidence and complement findings from RCTs.

5. Conclusion

To conclude, the findings suggest an association between CBMP treatment and improved outcomes in both IBD-specific and general HRQoL measures. This highlights the potential of CBMPs as an alternative treatment for IBD patients, especially those non-responsive to traditional therapy and biologics. The effect of CBMPs seemed to vary slightly in CD patients versus UC patients, while baseline anxiety levels and THC dose affected the likelihood of achieving a minimal clinically important difference in an IBD-specific measure at 18-months. However, conclusions need to be treated with caution regardless of statistical significance due to limitations. There remains a lack of evidence of CBMP efficacy in IBD, especially on the underlying disease, hence, results from this study can inform future RCTs.

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Declarations of interest

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Data availability statement

Data were derived from the UK Medical Cannabis Registry (ukmedicalcannabisregistry.com) and restrictions apply. Please contact the corresponding author directly for further details.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Salim SY, Söderholm JD. Importance of disrupted intestinal barrier in inflammatory bowel diseases. Inflamm Bowel Dis. 2011;17(1):362–381. doi: 10.1002/ibd.21403
2. Wang R, Li Z, Liu S, et al. Global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: a systematic analysis based on the global burden of disease study 2019. BMJ Open. 2023;13(3):e065186. doi: 10.1136/bmjopen-2022-065186
   • **Outline of the international epidemiology of inflammatory bowel disease.**
3. Crohn's & Colitis UK. New research shows over 1 in 123 people in UK living with Crohn's or Colitis. 2022. Accessed 19 December 2024. Available from: https://crohnsandcolitis.org.uk/news-stories/news-items/new-research-shows-over-1-in-123-people-in-uk-living-with-crohn-s-or-colitis.
4. Roda G, Chien Ng S, Kotze PG, et al. Author correction: Crohn's disease. Nat Rev Dis Primers [Internet]. 2020;6(1):1–19. Available from: https://www.nature.com/articles/s41572-020-0156-2
5. Kobayashi T, Siegmund B, Le Berre C, et al. Ulcerative colitis. Nat Rev Dis Primers [Internet]. 2020;6(1):74. Available from: https://pubmed.ncbi.nlm.nih.gov/32913180/
6. Fakhoury M, Al-Salami H, Negrulj R, et al. Inflammatory bowel disease: clinical aspects and treatments. J Inflamm Res [Internet]. 2014;7:113. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4106026/
7. Johnston RD, Logan RFA. What is the peak age for onset of IBD? Inflamm Bowel Dis. 2008;14:S4–S5. doi: 10.1002/ibd.20545
8. Burisch J, Jess T, Martinato M, et al. The burden of inflammatory bowel disease in Europe. J Crohns Colitis. 2013;7(4):322–337. doi: 10.1016/j.crohns.2013.01.010
9. Peek-Kuijt NMS, Aantjes MJ, Verwey M, et al. Treatment goals in IBD: a perspective from patients and their partners. PEC Innov. 2022;1:100034. doi: 10.1016/j.pecinn.2022.100034
10. Cai Z, Wang S, Li J. Treatment of inflammatory bowel disease: a comprehensive review. Front Med (Lausanne). 2021;8. doi: 10.3389/fmed.2021.765474
11. Murray A, Nguyen TM, Parker CE, et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020;2020(8):8. doi: 10.1002/14651858.CD000543.pub5
12. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(4):590–599. doi: 10.1038/ajg.2011.70
13. Nielsen OH, Ainsworth MA, Jarcho JA. Tumor necrosis factor inhibitors for inflammatory bowel disease. Jarcho JA, editor. N Engl J Med. 2013;369(8):754–762. doi: 10.1056/NEJMct1209614
14. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology [Internet]. 2009;137(4):1250–1260. quiz 1520. Available from: https://pubmed.ncbi.nlm.nih.gov/19596014/
15. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-tnf treatments in inflammatory bowel disease. Autoimmun Rev. 2014;13(1):24–30. doi: 10.1016/j.autrev.2013.06.002
16. Ahmed W, Katz S. Therapeutic use of cannabis in inflammatory bowel disease. PubMed. 2016;12:668–679.
17. Keimpema E, Di Marzo V, Harkany T. Biological basis of cannabinoid medicines. Sci (1979). 2021;374(6574):1449–1450. doi: 10.1126/science.abf6099
18. Shahbazi F, Grandi V, Banerjee A, et al. Cannabinoids and cannabinoid receptors: the story so far. iScience. 2020;23(7):101301. doi: 10.1016/j.isci.2020.101301
19. Almeida DL, Devi LA. Diversity of molecular targets and signaling pathways for CBD. Pharmacol Res Perspect. 2020;8(6):8. doi: 10.1002/prp2.682
20. Katchan V, David P, Shoenfeld Y. Cannabinoids and autoimmune diseases: a systematic review. Autoimmun Rev. 2016;15(6):513–528. doi: 10.1016/j.autrev.2016.02.008
21. Muller C, Morales P, Reggio PH. Cannabinoid ligands targeting TRP channels. Front Mol Neurosci. 2019;11:11. doi: 10.3389/fnmol.2018.00487
22. Dubuquoy L. PPAR as a new therapeutic target in inflammatory bowel diseases. Gut. 2006;55(9):1341–1349. doi: 10.1136/gut.2006.093484
23. De Gregorio D, McLaughlin RJ, Posa L, et al. Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain. Pain [Internet]. 2019;160(1):136–150. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6319597/#!po=41.2500
24. Hryhorowicz S, Kaczmarek-Ryś M, Zielińska A, et al. Endocannabinoid system as a promising therapeutic target in inflammatory bowel disease – a systematic review. Front Immunol. 2021;12. doi: 10.3389/fimmu.2021.790803
25. Massa F, Marsicano G, Hermann H, et al. The endogenous cannabinoid system protects against colonic inflammation. J Clin Invest [Internet]. 2004;113(8):1202–1209. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC385396/
26. Kimball ES, Schneider CR, Wallace N, 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-Gastro Liver Physiol. 2006;291(2):G364–G371. doi: 10.1152/ajpgi.00407.2005
27. Henshaw FR, Dewsbury LS, Lim CK, et al. The effects of cannabinoids on pro- and Anti-inflammatory Cytokines: a systematic review of in vivo studies. Cannabis Cannabinoid Res. 2021;6(3):177–195. doi: 10.1089/can.2020.0105
28. Sands BE, Kaplan GG. The role of TNFα in ulcerative colitis. The J Clin Pharmacol. 2007;47(8):930–941. doi: 10.1177/0091270007301623
29. Ihenetu K, Molleman A, Parsons MJ, et al. Inhibition of interleukin-8 release in the human colonic epithelial cell line HT-29 by cannabinoids. Eur J Pharmacol. 2003;458(1–2):207–215. doi: 10.1016/S0014-2999(02)02698-5
30. Ashton J, Glass M. The Cannabinoid CB2 receptor as a target for inflammation-dependent neurodegeneration. Curr Neuropharmacol. 2007;5(2):73–80. doi: 10.2174/157015907780866884
31. Kapellos TS, Taylor L, Feuerborn A, et al. Cannabinoid receptor 2 deficiency exacerbates inflammation and neutrophil recruitment. The FASEB J. 2019;33(5):6154–6167. doi: 10.1096/fj.201802524R
32. Tsuji F, Aono H. Role of transient receptor potential vanilloid 1 in inflammation and autoimmune diseases. Pharmaceuticals. 2012;5(8):837–852. doi: 10.3390/ph5080837
33. Massa F, Sibaev A, Marsicano G, et al. Vanilloid receptor (TRPV1)-deficient mice show increased susceptibility to dinitrobenzene sulfonic acid induced colitis. J Mol Med. 2005;84(2):142–146. doi: 10.1007/s00109-005-0016-2
34. Anand U, Jones B, Korchev Y, et al. CBD effects on TRPV1 signaling pathways in cultured DRG neurons. J Pain Res. 2020;13:2269–2278. doi: 10.2147/JPR.S258433
35. Brusberg M, Arvidsson S, Kang D, et al. CB1 receptors mediate the analgesic effects of cannabinoids on colorectal distension-induced visceral pain in rodents. J Neurosci. 2009;29(5):1554–1564. doi: 10.1523/JNEUROSCI.5166-08.2009
36. Pagano E, Capasso R, Piscitelli F, et al. An orally active cannabis extract with high content in Cannabidiol attenuates chemically-induced intestinal inflammation and hypermotility in the mouse. Front Pharmacol. 2016;7. doi: 10.3389/fphar.2016.00341
37. Vinci A, Ingravalle F, Bardhi D, et al. Cannabinoid therapeutic effects in inflammatory bowel diseases: a systematic review and meta-analysis of randomized controlled trials. Biomedicines. 2022;10(10):2439. doi: 10.3390/biomedicines10102439
   •• **Systematic review and meta-analysis of the effects of cannabis-based medicinal products on inflammatory disease.**

38. Doeve BH, van de Meeberg MM, van Schaik FDM, et al. A systematic review with meta-analysis of the efficacy of cannabis and cannabinoids for inflammatory bowel disease. Journal Of Clinical Gastroenterology. 2020;55(9):798–809. doi: 10.1097/MCG.0000000000001393
•• **Systematic review and meta-analysis of the effects of cannabis-based medicinal products on inflammatory disease.**
39. Naftali T, Bar-Lev Schleider L, Sklerovsky Benjaminov F, et al. Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: a randomized controlled trial. Chuang W-L, editor. PLOS ONE. 2021;16(2):e0246871. doi: 10.1371/journal.pone.0246871
•• **Randomized controlled trial demonstrating in ulcerative colitis that cannabis-based medicinal products are not associated with clinical remission.**
40. Dalavaye N, Erridge S, Nicholas M, et al. The effect of medical cannabis in inflammatory bowel disease: analysis from the UK medical cannabis registry. Expert Rev Gastroenterol Hepatol. 2022;17(1):85–98. doi: 10.1080/17474124.2022.2161046
41. Nduma BN, Mofor KA, Tatang J, et al. The use of cannabinoids in the treatment of inflammatory bowel disease (IBD): a review of the literature. Cureus [Internet]. 2023;15. Available from: https://www.cureus.com/articles/141323-the-use-of-cannabinoids-in-the-treatment-of-inflammatory-bowel-disease-ibd-a-review-of-the-literature#
42. Erridge S, Salazar O, Kawka M, et al. An initial analysis of the UK medical cannabis registry: outcomes analysis of first 129 patients. Neuropsychopharmacol Rep. 2021;41(3):362–370. doi: 10.1002/npr2.12183
43. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies*. Bull World Health Organ. 2007;85(11):867–872. doi: 10.2471/BLT.07.045120
44. Brusselaers N, Lagergren J. The Charlson comorbidity index in registry-based research. Methods Inf Med. 2017;56(05):401–406. doi: 10.3414/ME17-01-0051
45. Lichtiger S, Binion DG, Wolf DC, et al. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. Aliment Pharmacol Ther. 2010;32(10):1228–1239. doi: 10.1111/j.1365-2036.2010.04466.x
46. Travis S, Feagan BG, Peyrin-Biroulet L, et al. Effect of Adalimumab on clinical outcomes and health-related quality of life among patients with ulcerative colitis in a clinical practice setting: results from InspirADA. J Crohns Colitis. 2017;11(11):1317–1325. doi: 10.1093/ecco-jcc/jjx093
47. Wilcox AR, Dragnev MCC, Darcey CJ, et al. A new tool to measure the burden of crohn's disease and its treatment. Inflamm Bowel Dis. 2010;16(4):645–650. doi: 10.1002/ibd.21094
48. Hernandez G, Garin O, Dima AL, et al. EuroQol (EQ-5D-5L) validity in assessing the quality of life in adults with asthma: cross-sectional study. J Med Internet Res. 2019;21(1):e10178. doi: 10.2196/10178
49. van Hout B, Janssen MF, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708–715. doi: 10.1016/j.jval.2012.02.008
50. Spitzer RL, Kroenke K, Williams JBW, et al. A brief measure for assessing generalized anxiety disorder. Arch Intern Med. 2006;166(10):1092. doi: 10.1001/archinte.166.10.1092
51. Sapra A, Bhandari P, Sharma S, et al. Using generalized anxiety disorder-2 (GAD-2) and GAD-7 in a primary care setting. Cureus. 2020:12. doi: 10.7759/cureus.8224
52. Snyder E, Cai B, DeMuro C, et al. A new single-item sleep quality scale: results of psychometric evaluation in patients with chronic primary insomnia and depression. J Clin Sleep Med. 2018;14(11):1849–1857. doi: 10.5664/jcsm.7478
53. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther. 2004;27(1):26–35. doi: 10.1016/j.jmpt.2003.11.003
54. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US national cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). JAMA Oncol. 2015;1(8):1051. doi: 10.1001/jamaoncol.2015.2639
55. Shao J, Jordan DC, Pritchett YL. Baseline observation carry forward: reasoning, properties, and practical issues. J Biopharm Stat. 2009;19(4):672–684. doi: 10.1080/10543400902964118
56. Kwak SG, Kim JH. Central limit theorem: the cornerstone of modern statistics. Korean J Anesthesiol. 2017;70(2):144. doi: 10.4097/kjae.2017.70.2.144
57. Naftali T, Bar-Lev Schleider L, Almog S, et al. Oral cbd-rich Cannabis induces clinical but not endoscopic response in patients with Crohn's disease, a Randomised controlled trial. J Crohns Colitis. 2021;15(11):1799–1806. doi: 10.1093/ecco-jcc/jjab069
58. Iablokov V, Gregor J, Chande N, et al. Cannabis use in patients with inflammatory bowel disease following legalization of cannabis in Canada. Crohns Colitis 360. 2024 May 9;6(2):otae031. doi: 10.1093/crocol/otae031 PMID: 38800569; PMCID: PMC11120235.
59. Noureldin M, Van T, Cohen-Mekelburg S, et al. Legalization of cannabis does not reduce opioid prescribing in patients with inflammatory bowel disease: a difference-in-difference analysis. Am J Gastroenterol. 2024 Oct 1;119(10):2130–2133. doi: 10.14309/ajg.0000000000002834 Epub 2024 Apr 29. PMID: 38767951; PMCID: PMC11452269.
60. Glickman D, Dalessio S, Raup-Konsavage WM, et al. The Impact of Cannabis use on clinical outcomes in inflammatory bowel disease: a population-based longitudinal cohort study. Inflamm Bowel Dis. 2024 Jul 3;30(7):1055–1061. doi: 10.1093/ibd/izad151 PMID: 37580878; PMCID: PMC11219477.
61. Erridge S, Sodergren MH. Cannabis use: a marker of clinical severity in inflammatory bowel disease? Inflamm Bowel Dis. 2024 Feb 1;30(2):322–323. doi: 10.1093/ibd/izad221
62. Gao Z, Wang P, Hong J, et al. Health-related quality of life among Chinese patients with Crohn's disease: a cross-sectional survey using the EQ-5D-5L. Health Qual Life Outcomes. 2022;20(1):62. doi: 10.1186/s12955-022-01969-z
63. Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. BMJ. 2021;n1034:n1034. doi: 10.1136/bmj.n1034
• **Meta-analysis of the outcomes of cannabinoids prescribed for chronic pain.**
64. Faber J, Fonseca LM. How sample size influences research outcomes. Dental Press J Orthod. 2014;19(4):27–29. doi: 10.1590/2176-9451.19.4.027-029.ebo
65. Rapin L, Gamaoun R, El Hage C, et al. Cannabidiol use and effectiveness: real-world evidence from a Canadian medical cannabis clinic. J Cannabis Res. 2021;3(1):19. doi: 10.1186/s42238-021-00078-w
66. Han S-W, Gregory W, Nylander D, et al. The SIBDQ: further validation in ulcerative colitis patients. Am J Gastroenterol. 2000;95(1):145–151. doi: 10.1111/j.1572-0241.2000.01676.x
67. Stith SS, Li X, Brockelman F, et al. Understanding feeling "high" and its role in medical cannabis patient outcomes. Front Pharmacol. 2023;14.
68. Tait J, Erridge S, Holvey C, et al. Clinical outcome data of chronic pain patients treated with cannabis-based oils and dried flower from the UK medical cannabis registry. Expert Rev Neurother. 2023;23(4):413–423. doi: 10.1080/14737175.2023.2195551
69. Benson MJ, Abelev SV, Connor SJ, et al. Medicinal cannabis for inflammatory bowel disease: a survey of perspectives, experiences, and current use in Australian patients. Crohns Colitis. 2020;2(2). doi: 10.1093/crocol/otaa015
70. Colizzi M, Bhattacharyya S. Cannabis use and the development of tolerance: a systematic review of human evidence. Neurosci Biobehav Rev. 2018;93:1–25. doi: 10.1016/j.neubiorev.2018.07.014
71. Shah SC, Khalili H, Gower-Rousseau C, et al. Sex-based differences in incidence of inflammatory bowel diseases—pooled analysis of population-based studies from western countries. Gastroenterology. 2018;155(4):1079–1089.e3. doi: 10.1053/j.gastro.2018.06.043
72. Banerjee R, Erridge S, Salazar O, et al. Real world evidence in medical cannabis research. Ther Innov Regul Sci. 2022;56(1):8–14. doi: 10.1007/s43441-021-00346-0