COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

CANNABIS, CANNABIS-BASED PRODUCTS, OR CANNABINOIDS BRIEF EVIDENCE REPORT:

EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS ON THE TREATMENT OF CROHN'S DISEASE OR ULCERATIVE COLITIS

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Drug Regimen Review Center

Lauren Heath, PharmD, MS, BCACP, Pharmacist
Joanne LaFleur, PharmD, MSPH, Director and Associate Professor

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ABBREVIATIONS

AE	Adverse event
BL	Baseline
CBD	Cannabidiol
CBP	Cannabinoid- or cannabis-based product
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CNS	Central nervous system
CRRB	Cannabis Research Review Board
F/u	Follow up
GI	Gastrointestinal
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
IL	Interleukin
ITT	Intention to treat
IQR	Interquartile range
LCAI	Lichtiger Colitis Activity Index
LOE	Level of Evidence
MA	Meta-analysis
MD	Mean difference
NRS	Numeric rating scale
OR	Odds ratio
PBO	Placebo
RCT	Randomized controlled trial
ROB	Risk of bias
RR	Risk ratio
UC	Ulcerative colitis
SAE	Serious adverse event
SMD	Standardized mean difference
SR	Systematic review
THC	(delta-9-)tetrahydrocannabinol
TNF	Tumor necrosis factor
QoL	Quality of life

1.0 OBJECTIVE

This brief report summarizes clinical evidence for the treatment of patients with Crohn's disease (CD) or ulcerative colitis (UC), types of inflammatory bowel disease (IBD), with cannabis- or cannabinoid-based products (CBPs) using a hierarchy-of-evidence approach. Refer to section 6 for details about methods used in this review.

Information from this report may be considered for updates to the Cannabis Research Review Board (CRRB) guidance for the use of cannabis to treat CD and UC (see section 5 for recommendations).

Current CRRB guidance concludes:

- "There is insufficient evidence to support that medical cannabis or cannabinoids are effective or ineffective for the general treatment of Ulcerative Colitis and Crohn's Disease" (page 4).[1]

To support this conclusion, CRRB guidance for treatment for CD or UC with cannabis cites 2 Cochrane systematic reviews (SRs) by Kafil et al, published in 2018. Randomized controlled trials (RCTs) included by Kafil TS et al 2018 were published between 2013 and 2018, and included evidence published in full text or as abstracts only with additional details provided by the study author.[2,3] Refer to **Appendix A** for a summary of results from Kafil et al SRs.

2.0 BACKGROUND

UC and CD are immune-mediated, chronic, relapsing-remitting, inflammatory bowel diseases (IBD). The colon mucosal layer is inflamed for patients with UC, leading to frequent diarrhea and bloody stools. With severe UC, patients typically exhibit systemic toxicity (eg, fever, tachycardia, anemia).[4] Patients with CD exhibit transmural inflammation that can affect any part of the gastrointestinal tract and report symptoms such as diarrhea, fatigue, and abdominal pain.[5] Treatment for IBD is selected based on disease severity and disease location in the GI tract (for CD) with the goal of inducing and maintaining clinical and endoscopic remission.[6-9] Disease-modifying anti-inflammatory medications are available for both UC and CD[6-9]; however, many patients do not fully respond to standard therapies.[10]

Cannabinoid receptors (CB1 and CB2) are present in the colon and there is evidence of changes in cannabinoid receptor and/or endocannabinoid-modulating enzyme expression in inflamed versus healthy colon or ileum tissue.[11] Pre-clinical studies of cannabinoids in mice and rat colitis models have generally demonstrated reduced inflammation and/or reduced disease activity.[12] Surveillance of patients with IBD suggests cannabis use is relatively common, with many patients endorsing symptomatic improvement (eg, improved abdominal pain, cramping, and/or diarrhea) with use.[13,14]

3.0 RESULTS

Our search identified 4 recent (2019-2022) IBD-focused SRs. Only 1 SR with direct meta-analysis (MA) by Vinci et al 2022[15] included at least 1 RCT not included by SRs used by prior CRRB guidance.[2,3] See **Appendix B** for a comparison of RCTs included by recent SRs. **Appendix C** summarizes results from the SR by Vinci et al 2022. Because no SR included all identified RCTs of cannabis for the treatment of IBD,

we summarized results of all RCTs (including those newly identified and those previously included by Kafil et al 2018) of cannabinoid- or cannabis-based products (CBPs) for UC and/or CD.

To the best of our knowledge, all RCTs of CBP treatment for IBD except for 1 have been conducted by the same research group from Israel (Naftali T and colleagues). Several RCTs from Naftali T et al are similar in the study authors and study design. Additionally, since SRs included published abstracts, it is possible that some studies published in full text match studies published as an abstract. **Authors of this report attempted to compare RCTs across publications, summarizing unique RCTs only; however, due to a lack of clarity in reporting, it is possible that results from the same patient/trial are reported more than once.**

3.1 Ulcerative Colitis Evidence

Below is a summary of RCT evidence for the treatment of UC with cannabis/cannabinoids, which includes results from 2 trials previously addressed in CRRB guidance,[16,17] including more details about a trial now published in full text that was previously addressed only in abstract form,[17] and results from 2 other smaller trials.[18,19] Refer to **Appendix D** for a summary of results from RCTs not addressed by prior CRRB guidance.

3.1.1 Summary of UC RCT Results

Four short-term (8-10 week treatment) RCTs compared cannabis to placebo (PBO) among adults (n=121 total) with active, mild to moderate UC.[16-19] Details of anti-inflammatory or disease-modifying UC med use were not reported by all trials (one trial is also only published as an abstract[18]). In 2 RCTs, patients were allowed to continue stable doses of UC medications (eg, ASA, glucocorticoids, biologic agents)[17,19] and another trial required patients to be on a stable dose of ASA or to have failed a prior UC treatment to participate.[16] Studied CBPs included oral CBD-rich (between 100-500 mg CBD daily) botanical extract capsules (1 trial),[16] or smoked THC-rich cannabis with approximately 23 mg THC daily* (3 trials).[17-19] Trials were very small (10 to 60 patients per trial). One trial did not report performing a power/sample size calculation,[19] and this information was lacking for an additional study published as an abstract.[18] Lack of power to detect differences between study arms is a potential concern. Risk of bias (ROB) ratings are not available for 1 study published as an abstract only[18]; the other trials were rated as having a low (1 trial)[15] or high† (2 trials)[17,19] ROB by SRs.[3,15] Three trials were conducted by the same research group (Naftali T and colleagues)[17-19] in Israel and the fourth trial was conducted as a pilot trial at 9 centers in the United Kingdom.[16]

* The approximate daily THC dose from one trial is uncertain as different sources report conflicting doses; in one trial, the dose could have been as high as 80 mg THC twice daily.

† One trial (Naftali 2018/Naftali 2021a) was rated as high ROB for blinding (due to potential unblinding from cannabis psychotropic effects) by Kafil 2018 et al and rated as low ROB overall by Vinci et al 2022; we include it as having a high ROB.

3.1.1.1 Clinical response or remission

UC disease activity was determined by a UC disease activity index in each trial. Two trials[17,19] used the Lichtiger Colitis Activity Index (Lichtiger score; LCAI)[‡] score,[20] 1 trial[16] used the Mayo score,[§21] and the last trial used the Ulcerative Colitis Activity Index (UCAI[**]).[18]

Short-term treatment with oral CBD-predominant cannabis extract or smoked THC-predominant cannabis (CBPs) may improve UC disease activity scores compared to baseline in patients with mild-moderate UC. Only 3 trials formally tested (ie, with a statistical hypothesis test) for a difference in changes in UC disease activity scores from baseline between the CBP and PBO, or for a difference in final score at the end of treatment. Two small trials of THC-predominant cannabis demonstrated superiority to PBO,[17,19] whereas the largest trial of CBD-predominant cannabis did not demonstrate superiority to PBO in the primary intention-to-treat (ITT) analysis.[16] In the 4th trial, treatment with THC-predominant cannabis numerically reduced patient UCAI scores compared to PBO, but no formal statistical analysis was reported.[18]

Few trials reported clinical remission or response per clinical disease activity criteria. **Clinical remission** (Mayo score ≤ 2 with no sub-score >1) rates were similar between oral CBD-predominant for cannabis- (28%) and PBO-treated patients (26%) at 10 weeks when assessed in all patients (ITT analysis); though, a non-significant benefit favoring CBD emerged when analyzed among patients who completed the trial according to protocol, with 41% of patients in the CBD arm compared to 30% of PBO achieving remission per the Mayo score.[16] Notably, many patients in the CBD arm of this trial dropped out due to adverse events.[16] **Clinical response** (Mayo score decreased by ≥3 with endoscopy sub-score improved by ≥1) was not significantly better after treatment with CBD-predominant cannabis (31%) compared to placebo (22%).[3] In 1 trial of THC-predominant cannabis, author's described clinical remission being achieved by more patients treated with cannabis than PBO; however, the proportion of patients achieving clinical remission at the end of the study was not reported formally.[17]

Three trials reported information on the secondary outcome of **endoscopic sub-scale scores**. Endoscopic scores numerically improved after CBD-predominant treatment (67% of patients with improvement) compared to placebo (39%), P=0.054 for the 10-week comparison.[16] Mean endoscopic scores were not different after THC-predominant treatment (final score 1.25±2) compared to PBO (final score 1.69±1), P=0.374 for the 8-week comparison.[17] Another trial with THC-predominant cannabis qualitatively described improved endoscopic activity in the cannabis arm, but details were not provided.[19]

[‡‡] LCAI is an Index of UC activity containing 8-items with scores ranging of 0 (no activity) to 21 (most disease activity; a score <10 is considered responsive to treatment. The index addresses symptoms of daily stool frequency, nocturnal diarrhea, blood in stool, fecal incontinence, abdominal pain/cramping, general well-being, and use of an anti-diarrheal.

[§] Mayo scores range from 0 (least severe) to 12 (most severe); the score ranks subcategories (each scored from 0 to 3) of stool frequency, rectal bleeding, endoscopic findings, and global medical assessment.

[**] We are not certain which scale was used.

3.1.1.2 Inflammatory markers

Levels of Inflammatory markers, including circulating C-reactive protein (CRP) and cytokines, interleukin (IL)-2, IL-6, and tumor necrosis factor(TNF)-alpha, were reduced after 10 weeks of treatment with both CBD-rich cannabis and PBO; although reductions tended to be numerically greater with CBD, the difference in the change in levels between treatment arms was not statistically significant.[16] Fecal calprotectin levels also decreased after treatment with CBD-rich cannabis and PBO without significant differences between the groups.[16] Although, authors pointed out that 62% of measured fecal calprotectin levels exceeded the detection limit of the assay (with a similar proportion of samples exceeding the limit in both arms),[16] which could have impacted the accuracy of the results.

Treatment with THC-rich smoked cannabis for 8 weeks also did not significantly change assessed inflammatory makers (white blood cell count, CRP, fecal calprotectin) compared to PBO. In the cannabis and PBO arms, CRP slightly increased from baseline. Fecal calprotectin levels improved numerically more in the cannabis arm (from 170±33 at baseline to 134±33 at treatment end; P=0.072 for within-group comparison) relative to PBO (from 226±34 at baseline to 218±67 at treatment end; P = 0.9 for within-group comparison).[22] In contrast, a second small trial of THC-rich cannabis published as an abstract only reported significantly decreased mean CRP levels from baseline to 8 weeks in both the cannabis and PBO arm.[18]

3.1.1.3 Quality of Life

All 3 trials reporting quality of life (QoL) measures found significantly improved QoL after 8-10 weeks of treatment with the CBP compared to PBO.[16,17,19]

Using the non-disease-specific short-form 36 survey, THC-rich cannabis significantly increased QoL from baseline to 8 weeks (trial 1: change from 77±4 to 98±20; trial 2: change 72.7±6.7 to 98.2±7.3) compared to PBO (trial 1: change from 78±3 to 78±17; trial 2: change from 77.1 ±3.7 at baseline to 82±4); P=0.007 for trial 1 and P<0.05 for trial 2.[17,19]

Total score and subdomain scores for bowel symptoms, systemic symptoms, emotional status, and social functioning on the IBD-specific patient-reported QoL scale (IBDQ; inflammatory bowel disease questionnaire) numerically improved at 10 weeks compared to baseline after treatment with both CBD-rich cannabis and PBO. Numerical increases from baseline in all domains except systemic symptoms tended to be greater in the cannabis arm; authors reported a lack of statistical difference in the ITT analysis but found a significant difference in the total IBDQ score favoring cannabis in the per-protocol analysis. Significantly more patient's endorsed generally feeling better (on the subject global impression of change scale) after cannabis treatment compared to PBO; significance was established in both the ITT and per-protocol analysis.[16]

3.1.1.4 Other outcomes or symptoms

Other reported outcomes or symptoms varied by trial. Below is a description of select other outcomes.

Regarding **pain,** treatment with CBD-rich cannabis did not significantly improve pain at 10 weeks compared to placebo.[3] Authors described that pain-related adverse events (AEs) tended to be more frequent in the PBO arm than cannabis arm. For example, the rate of abdominal pain in the PBO arm

was 16% compared to 3% for the cannabis arm.[16] Change in the proportion of patients endorsing an abdominal pain score ≥2 from baseline to 8 weeks significantly favored THC-rich cannabis to PBO (59% to 6% for cannabis vs 60% to 55% for PB0, P=0.006) in another trial.[17]

The **frequency of bowel movements** did not significantly differ after treatment with CBD-rich cannabis or PBO.[3] Median daily bowel movement frequency was significantly reduced from baseline to 8 weeks among patients who received THC-rich cannabis compared to PBO in one trial.[17] Yet, in another smaller trial, the frequency of bowel movements declined among both THC-rich cannabis- and placebo-treated patients from baseline to 8 weeks, with no difference between groups.[19]

Rectal bleeding subscale scores were similarly improved after 10 weeks of treatment with CBD-rich cannabis or PBO,[16] and after 8 weeks of THC-rich cannabis or PBO.[17]

The focus of 1 trial was the **correlations between endocannabinoid levels and changes in UC clinical symptoms** after treatment with THC-rich cannabis or PBO. In the PBO arm, select endocannabinoid levels declined over 8 weeks of treatment, whereas changes in endocannabinoid levels were not detected in the cannabis arm. Authors concluded "…the percent reduction in the levels of BM [bowel movements] was negatively correlated with changes in the circulating AEA [anandamide] and OEA [oleoylethanolamine], whereas changes in the QOL were positively correlated with the levels of 2-AG [arachidonylglycerol]" (page 7).[19]

3.1.1.5 Adverse events

A numerically greater proportion of patients with mild-moderate UC who received oral cannabis extract containing with CBD started at 50 mg twice daily and titrated up to 250 mg twice daily (with each capsule containing 4.7% THC) endorse any AE (90%) compared to patients who received PBO (48%). Most AEs among patients who received CBD were of mild to moderate in severity, but 10% (n=3 patients) of AEs were severe neurological events, including disturbed attention (n=1), dizziness (n=1), and dizziness with joint swelling/muscle twitching (n=1). Three treatment-emergent severe AEs were reported in the PBO arm, including 2 events associated with worsened UC and 1 event of chest pain. The most common treatment-related AEs were nervous system disorders (CBD 83% vs 26% PBO), gastrointestinal disorders (CBD 38% vs PBO 16%), and psychiatric disorders (CBD 24% vs PBO 3%); dizziness, somnolence, disturbed attention, and nausea were the most frequent CBD-associated AEs. Infections/infestations were numerically more frequent with CBD (31%) than PBO (10%), with 3 patients receiving CBD versus none on PBO reporting a lower respiratory infection, but authors did not consider these events to be treatment related. Tolerability was poor in the CBD arm, 45% (n=13) of patients stopped treatment due to AEs versus 23% (n=7) in the PBO arm; in the CBD arm, dizziness was the AE most likely to cause discontinuation, whereas worsened UC caused discontinuation in the PBO arm.[16]

Among the 3 trials of smoked THC-predominant cannabis, details of AEs were reported by only 1 trial. Of 32 total patients, AEs that were primarily of mild severity were as follows (% cannabis vs % PBO): cough (41% vs 20%), dizziness (35% vs 6%), confusion (29% vs 6%), difficulty stopping use (29% vs 12%), behavioral change (23% vs 0%), restlessness (11% vs 0%), shortness of breath (6% vs 0%), decreased memory (0% vs 40%). No hallucinations occurred, and no AE resulted in treatment discontinuation.[17] Another small trial using THC-predominant cannabis reported no serious AEs.[3]

3.2 Crohn's Disease Evidence

Below is a summary of RCT evidence for the treatment of CD with CBPs, which includes results from 3 trials previously addressed in CRRB guidance,[23-25] and 4 additional trials.[18,19,22,26] Several trials are published as an abstract only.[18,25,26] One of the trials not previously included is the largest published trial.[22] Refer to **Appendix D** for a summary of results from RCTs not addressed in prior guidance.

3.2.1 Summary of CD RCT Results

Seven short-term 8-week RCTs compared cannabis to placebo among adults (n= 242 total) with active, mild to moderate CD.[18,19,22-26] In most trials, patients were allowed to continue chronic CD treatment at a stable dose.[19,22-24,26] Details of prior treatments were not reported by each trial; in at least 3 trials, patients failed at least 1 prior treatment (eg, mesalamine, corticosteroids, thiopurines, methotrexate or anti-TNF-alpha).[18,23,24] Studied CBPs include THC-predominant cannabis cigarettes (n=2 trials; 115 mg THC BID or 11.5 mg THC BID),[18,23] or CBD-rich cannabis oil (n=5).[19,22,24-26] Most studies of the CBD-rich oil reported using an approximately 4:1 mixture of CBD to THC.[19,22,25,26] In 2 trials, the total allowed dose is unclear.[25,26] CBD was limited to a low dose (20 mg daily),[24] and cannabis oil was titrated to effect, with a maximal dose of about 16 mg CBD/4 mg THC or 320 mg CBD/80 mg THC among trials with detailed doses reported.[19,22] Individual studies were very small with total sample sizes ranging from 19 to 56 patients. Only 2 trials reported a formal sample size calculation,[22,23] and only 1 of those trials met the target sample size.[22] ROB ratings from a SR are available for 5 of 7 RCTs. Trials were rated as having a low ROB (n=1),[25] some concerns (n=1),[26] or high ROB (n=3).[2,15,19,23,24] All trials were conducted by the same research group in Israel (Naftali T and colleagues).

3.2.1.1 Clinical response or remission

All 7 trials assessed changes in overall CD disease activity using the Crohn's Disease Activity Index (CDAI).[8,27††] Overall, 5 of 7 trials reported significantly greater improvements on the CDAI from baseline to 8 weeks or significantly lower CDAI at 8 weeks among people who received cannabis relative to PBO.[2,18,22,23,25,26] In the 2 trials that failed to demonstrate statistical significance, CDAI scores numerically improved from baseline to 8 weeks in both the cannabis and placebo arms, with differences from baseline non-significantly favoring cannabis.[19,24] In the largest trial using CBD-rich cannabis oil (titrated per response to a maximum of 320 mg CBD and 80 mg THC daily), median (interquartile range [IQR]) CDAI scores declined from 282 (243–342) and 264 (234–320) at baseline to 166 (82–226) and 237 (121–271) at 8 weeks in the cannabis and placebo groups, respectively (uncontrolled P=0.038; P = 0.072 when controlled for age, gender and illness duration). Authors of this trial noted that improvements in CD disease activity per the CDAI favoring cannabis "…can be attributed mostly to improvement in general well-being and abdominal pain, as the change in the number of bowel movements was not significant" (page 1802).[22]

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†† CDAI is an CD severity index. Scores range from 0 points (least severe, asymptomatic) to 1100 points (severely active disease); scores of 150-222 indicate mildly to moderately active disease and scores of 221 to 450 indicate moderately to severely active disease. The total score accounts for stool frequency, abdominal pain, general well-being, use of medications for diarrhea, presence of an abdominal mass, anemia, relative difference in weight from the standard.

Clinical remission per the CDAI was reported by 4 trials. Each of these trials reported numeric results favoring cannabis,[23,24] however, statistical significance was only reached by 1 trial (another trial did not perform a statistical test).[26] High-dose THC-rich cannabis induced clinical remission (achievement of CDAI <150) in 45% of cannabis patients versus 10% of placebo patients, a non-statistically significant difference (P=0.43).[23] Remission (CDAI <150) was reached by 40% of patients using low-dose CBD oil compared to 33.3% of PBO patients.[24] One trial using CBD-rich oil reported a significantly greater percentage of patients achieving remission (CDAI<150) in the cannabis arm (65%) compared to the placebo arm (35%).[26] Descriptively, numerically more patients achieved remission with a CDAI score <100 (n=5) who used low-dose THC-rich cannabis compared to those who used PBO (n=1); 4 patients in the cannabis arm also successfully stopped steroid use during the trial.[18]

One trial using high-dose THC-rich cannabis reported **clinical response** per the CDAI (CDAI score decrease by ≥100 from baseline). A significantly higher proportion of patients in the cannabis arm (91%) responded to treatment compared to placebo (40%), P=0.028 (RR 2.27; 95%CI 1.04 to 4.97).[23]

Regarding **CD disease activity measured by endoscopy**, only 2 trials using CBD-rich cannabis oil reported secondary outcomes of the Simple Endoscopic Score for Crohn's Disease (SES-CD). In both trials, mean or median SES-CD scores improved in both cannabis and PBO groups, with no significant between group differences in endoscopic scores at 8 weeks.[22,26] Median (IQR) SES-CD declined from 10 (7–14) and 11 (7–14) at baseline to 7 (4–14) and 8 (4–12) at 8 weeks, for the cannabis versus placebo groups, respectively, in the largest trial (P=0.185 after controlling for age, gender and illness duration).[22] In both trials, the lack of significant difference in endoscopic disease severity contrasted with significant differences in overall disease activity per the CDAI, showing a benefit favoring cannabis.[22,26]

3.2.1.2 Inflammatory markers

Information about levels of inflammatory markers was not reported by 3 trials.[18,19,25] In other trials, including 1 trial using THC-rich cannabis and 3 trials using CBD-rich cannabis, there were no differences in the levels of inflammatory markers of CRP or calprotectin between study groups.[22-24,26] Numerical changes in CRP levels from baseline to 8 weeks varied slightly between trials. CRP levels remained the same or slightly declined after cannabis treatment in 3 trials,[19,23,26] whereas CRP levels increased from baseline after low-dose CBD-rich cannabis in another trial.[24] Calprotectin levels numerically declined slightly after CBD-rich cannabis treatment, in 2 trials.[22,26]

3.2.1.3 Quality of Life

Differences in QoL on the general QoL scale, SF-36, or an unknown scale (1 trial) were reported by 5 of 7 trials.[19,22,23,25,26] One trial described measuring QoL but did not report the result.[24] All trials reporting QoL results described either significantly greater improvement in QoL from baseline to 8 weeks favoring the cannabis arm to PBO arm,[19,22,23,25] or a higher QoL score at 8 weeks in the cannabis arm.[26] Improvements in QoL were seen in 1 trial using THC-rich cannabis and 4 trials using CBD-rich cannabis.[19,22,23,25,26] In the largest trial of CBD-rich cannabis (n=56 participants), median QoL score increased from 74 at baseline (both arms) to 91 in the cannabis arm and 75 in the PBO arm. Nonetheless, the magnitude of improvement in QoL in the cannabis arm over the PBO arm failed to reach the pre-specified secondary outcome threshold of 30 points, and the between-group difference in QoL was no longer statistically significant when corrected for age, gender, and duration of CD illness.[22]

3.2.1.4 Other outcomes or symptoms

Other reported outcomes or symptoms varied by trial. Below is a description of select other outcomes.

Few trials reported details about **pain.** One trial reported significantly greater improvements in median pain satisfaction scores (on a 1-to-7-point Likert scale, with scores of 1 indicating very satisfied) after THC-rich cannabis treatment compared to placebo. Median pain satisfaction ratings were 1 (range 1 to 2) in the cannabis arm compared to 4 (range 3 to 4) in the PBO arm (P=0.001).[23] In a trial of CBD-rich cannabis, abdominal pain significantly improved from baseline to 8 weeks in the cannabis arm but not the placebo arm; however, the difference in improvement between groups did not significantly differ when controlling for age, gender, and duration of illness.[22]

Bowel movement frequency was reported by 2 trials using CBD-rich cannabis. In both trials, bowel movement frequency significantly declined from baseline to 8 weeks in both the cannabis and PBO arms, without any between-group difference.[19,22]

Two trials, one using THC-rich cannabis and the other using CBD-rich cannabis, provided general descriptions of satisfaction or well-being. End of treatment median patient-reported **appetite** and **satisfaction** scores (on a 1-to-7-point Likert scale, with scores of 1 indicating very satisfied) were significantly lower in the THC-rich cannabis arm than the PBO arm.[23] Regarding the CBD-rich cannabis arm, Naftali et al described that **"**Patients in the extract group [cannabis arm] reported significant improvements in sleep, pain, abdominal swelling, appetite, general well-being, and general satisfaction with the treatment" (page 1803).[22]

The focus of 1 trial was the **correlations between endocannabinoid levels and changes in CD clinical symptoms** after treatment with CBD-rich cannabis or PBO. Endocannabinoids (OEA, AEA, 2-AG, PEA [palmitoylethanolamine], and AA [arachidonic acid]) did not change significantly from baseline to 8 weeks in either the cannabis or PBO arm.[19]

3.2.1.5 Adverse events

Among trials of THC-rich cigarettes, both trials reported no serious AEs.[18,23] AEs reported by patients in the cannabis arm (using THC 115 mg BID) included nausea, sleepiness, concentration, memory loss, confusion, and dizziness; the rate of these mild severity events did not significantly differ from PBO.[23]

Of 5 trials using CBD-rich oil, 3 did not provide information about AEs.[19,25,26] Patients receiving low-dose oral CBD reported AEs of headache, sleepiness, nausea, and dizziness, which occurred at similar rates as patients who received PBO.[24] AEs with an incidence ≥ 5% more in the CBD-rich oil arm compared to PBO arm include visual distortion, behavioral change, confusion, decreased memory, and dizziness.[22] No cannabis-treated patient in either trial endorsed withdrawal symptoms upon discontinuation after 8 weeks of treatment.[22,24]

4.0 SUMMARY AND COMPARISON TO PRIOR SR CONCLUSIONS

SRs by Kafil et al 2018 used in prior CRRB guidance concluded cannabis-based treatments have uncertain benefits for treatment of active mild to moderate severity UC and CD (see Appendix A).[2,3] For treatment of CD, the certainty of evidence from 3 small trials was rated as low or very low.[2] Similarly, for treatment of UC, the certainty of evidence for most outcomes was considered low, except for CRP, QoL, and AEs that were assessed as moderate certainty.[3] A newer SR by Vinci et al included 2 trials among CD patients and 1 trial among UC patients that were not included by Kafil et al (see Appendix C). Vinci et al did not use the same approach for evaluating the evidence as Kafil et al (ie, rating certainty of evidence for each outcome). Generally, Vinci et al concluded there is mixed evidence for adjunctive treatment with cannabinoids for IBD. Like Kafil et al, Vinci et al felt that current evidence does not suggest that cannabis is helpful adjunctively in patients with UC.[15] However, somewhat unlike Kafil et al,[2] Vinci et al concluded adjunctive treatment with cannabinoids might improve CD treatment success in the short-term.[15]

A 2022 consensus panel from the International Organization for the Study of Inflammatory Bowel Diseases concluded (with 76% agreement from 41 panelists) that "Cannabis or cannabinoid use is not recommended as treatment for IBD" (page 668). They describe that "…given the lack of robust clinical or endoscopic benefit with short-term use of tetrahydrocannabinol or cannabidiol in IBD, we do not recommend the use of cannabinoids for the treatment of IBD" (page 669).[28]

RCT evidence reviewed by this report included 4 studies (5 if counting 1 trial previously included in abstract form only) not assessed by prior CRRB guidance. Generally, cumulative RCT evidence suggests that adjunctive, short-term (8-10 week) treatment with CBPs may improve some symptoms of mild to moderate active UC or CD without significantly improving inflammation or lesions in the GI tract. However, few trials formally reported whether symptomatic improvements with cannabis over PBO achieved the threshold for clinical remission or response; when reported, the impact of CBPs compared to PBO on clinical remission is mixed. Nearly all trials reporting a QoL outcome found greater improvements in QoL among IBD patients who used cannabis compared to PBO. Information about AEs was not reported by each trial; cannabis was associated with primarily mild to moderate severity AEs. CBD-predominant oral cannabis was poorly tolerated by patients with UC in 1 trial; many patients discontinued treatment, primarily due to dizziness.[16] Notably, RCT evidence is limited to very small trials using heterogenous cannabis formulations, routes of administration, and doses.

While it is hypothesized that cannabinoids could improve UC and CD disease activity by reducing inflammation, it is also possible that cannabinoids improve symptoms through non-inflammatory effects. Naftali et al 2021 described that "…cannabis also affects GI physiology including reducing intestinal motility, increasing fluid absorption, and inducing analgesia" (page 10).[17]

5.0 CONSIDERATIONS FOR UPDATES TO THE CRRB GUIDANCE DOCUMENT

5.1 Considerations for graded statements

The CRRB may consider the following:

- Reviewing new RCT evidence not addressed in the prior guidance to determine whether changes to the current evidence rating for use of cannabis/cannabinoids for IBD is appropriate. See **Appendix F** for details of each level of evidence.
    - Current guidance states there is insufficient evidence for the general treatment of UC and CD with cannabis, which is appropriate if the CRRB considers overall findings to be mixed.
- Evaluating the level of evidence for UC and CD separately, and if appropriate, creating separate graded evidence statements for each condition.
- Evaluating the certainty of the evidence for certain outcomes separately.

5.2 Additional considerations

The CRRB may also consider:

- Including additional information in updated guidance about the body of RCT evidence, for example:
    - Address that all trials included patients with active UC or CD. There is a lack of RCT evidence for the effects of cannabis or cannabinoids on the maintenance of disease remission.
    - RCT evidence is primarily among people with mild to moderate IBD severity.
    - Most RCTs studied cannabis-based treatments as an adjunct to standard therapies. Additionally, many trials required that patients had an insufficient response to 1 or more standard treatments for UC or CD.
    - Available RCT evidence is limited to short-term treatment for 8-10 weeks.

6.0 METHODS

This brief evidence report searched for and evaluated relevant SRs of RCTs or RCTs published after the SRs by Kafil et al 2018[2,3] to identify potential updates to CRRB guidance. Two major bibliographic databases (Ovid-Medline and Embase) were searched for relevant SRs published between 2018 and June 8, 2023. Based the SR search results that identified a relevant SR published in 2022 (Vinci et al 2022),[15] an additional search in Ovid-Medline and Embase was performed for relevant RCTs published during 2022 or 2023. One RCT published in 2021 and not included by Vinci 2022 was incidentally discovered by searching for publications published by an author (Naftali T) in Ovid-Medline. Search strategies used free text and controlled vocabulary terms for cannabinoids or cannabis, inflammatory bowel disease, ulcerative colitis, and Crohn's disease. Search results were filtered for SRs and RCTs using a broadened SR filter developed by McMaster University for Ovid-Medline,[29] an independently-derived SR filter for Embase, and RCT filters from the Cochrane Organization for both databases.[30] Refer to **Appendix F** for a copy of the search strategies.

Literature search results were reviewed by a single author for inclusion. SRs including at least 1 RCT, or RCTs, for the treatment of IBD (UC or CD) with any type of cannabis or cannabinoid (plant-based or synthetic) were included. SRs lacking details of their search strategy, lacking a quality/ROB assessment for included studies, and/or otherwise not using a systematic process were excluded. For feasibility, we limited results to SRs focused on therapeutic efficacy/safety in people with IBD. (Some SRs asked broader or different questions). Since multiple relevant SRs of primary studies were identified, SRs exclusively including systematic reviews were excluded.

RCTs included by the SRs used in prior CRRB guidance were compared to RCTs included by newly identified SRs. For feasibility, results were extracted only from SRs that included at least 1 RCT not addressed in the prior CRRB guidance. Results from RCTs included by SRs used in prior guidance and any 'new' RCTs not previously addressed were extracted also.

Because no single SR included all RCTs identified from SRs or the RCT search, this evidence review primarily summarizes results from individual RCTs, including 'new' RCTs and RCTs previously addressed by CRRB guidance.

REFERENCES

1. Cannabis Research Review Board. *Guidance on the Suggested Use of Medical Cannabis Crohn's and Ulcerative Colitis*. Utah Department of Health and Human Services: 8 pages. Accessed August 18, 2023. Available at https://medicalcannabis.utah.gov/wp-content/uploads/Crohns-UC_v1_FINAL.pdf

2. Kafil TS, Nguyen TM, Macdonald JK, Chande N. Cannabis for the treatment of Crohn's disease. *Cochrane Database of Systematic Reviews*. 2018;2018(11)doi:10.1002/14651858.CD012853.pub2

3. Kafil TS, Nguyen TM, Macdonald JK, Chande N. Cannabis for the treatment of ulcerative colitis. *Cochrane Database of Systematic Reviews*. 2018;2018(2)doi:10.1002/14651858.CD012954

4. Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults. In: Lamont JT, ed. UpToDate; 2023. Accessed August 10, 2023. Available at https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-ulcerative-colitis-in-adults

5. Peppercorn MA, Kane SV. Clinical manifestations, diaganosis, and prognosis of Crohn disease in adults. In: JT L, ed. UpToDate; 2023. Accessed August 10, 2023. Available at https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-crohn-disease-in-adults

6. Hashash JA, Regueiro M. Medical management of low-risk adult patients with mild to moderate ulcerative colitis In: Kane SV, ed. UpToDate; 2023. Accessed August 10, 2023. Available at https://www.uptodate.com/contents/medical-management-of-low-risk-adult-patients-with-mild-to-moderate-ulcerative-colitis

7. Cohen RD, Stein AC. Management of moderate to severe ulcerative colitis in adults. In: Kane SV, ed. UpToDate; 2023. Accessed August 10, 2023. Available at https://www.uptodate.com/contents/management-of-moderate-to-severe-ulcerative-colitis-in-adults

8. Regueiro M, Hashash JI. Overview of the medical management of mild (low risk) Crohn disease in adults. In: Kane SV, ed. UpToDate; 2023. Accessed August 10, 2023. Available at https://www.uptodate.com/contents/overview-of-the-medical-management-of-mild-low-risk-crohn-disease-in-adults

9. Hashash JI, Regueiro M. Medical management of moderate to severe Crohn disease in adults. In: Kane SV, ed. UpToDate; 2023. Accessed August 10, 2023. Available at https://www.uptodate.com/contents/medical-management-of-moderate-to-severe-crohn-disease-in-adults

10. Moss AC. Approach to Treatment Failure in Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)*. 2022;18(6):360-363.

11. Gotfried J, Naftali T, Schey R. Role of Cannabis and Its Derivatives in Gastrointestinal and Hepatic Disease. *Gastroenterology*. 2020;159(1):62-80. doi:10.1053/j.gastro.2020.03.087

12. Couch DG, Maudslay H, Doleman B, Lund JN, O'Sullivan SE. The Use of Cannabinoids in Colitis: A Systematic Review and Meta-Analysis. *Inflamm Bowel Dis*. 2018;24(4):680-697. doi:10.1093/ibd/izy014

13. Velez-Santiago A, Alvarez-Torres E, Martinez-Rodriguez R, et al. A Survey of Cannabis Use among Patients with Inflammatory Bowel Disease (IBD). *Int J Environ Res Public Health*. 2023;20(6)doi:10.3390/ijerph20065129

14. Lal S, Prasad N, Ryan M, et al. Cannabis use amongst patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2011;23(10):891-896. doi:10.1097/MEG.0b013e328349bb4c

15. 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)doi:https://dx.doi.org/10.3390/biomedicines10102439

16. Irving PM, Iqbal T, Nwokolo C, et al. A Randomized, Double-blind, Placebo-controlled, Parallel-group, Pilot Study of Cannabidiol-rich Botanical Extract in the Symptomatic Treatment of Ulcerative Colitis. *Inflamm Bowel Dis*. 2018;24(4):714-724. doi:10.1093/ibd/izy002

17. Naftali T, Bar-Lev Schleider L, Scklerovsky Benjaminov F, Konikoff FM, Matalon ST, Ringel Y. Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: A randomized controlled trial. *PloS one*. 2021;16(2):e0246871. doi:https://dx.doi.org/10.1371/journal.pone.0246871

18. Naftali T, Barlev L, Gabay G, Chowers Y, Dotan I, Stein A. Tetrahydrocannabinol (THC) induces clinical and biochemical improvement with a steroid sparing efffect in active inflammatory bowel disease *Journal of Crohn's and Colitis*. 2013;7(Supplement 1):S153.

19. Tartakover Matalon S, Azar S, Meiri D, et al. Endocannabinoid Levels in Ulcerative Colitis Patients Correlate With Clinical Parameters and Are Affected by Cannabis Consumption. *Frontiers in endocrinology*. 2021;12:685289. doi:https://dx.doi.org/10.3389/fendo.2021.685289

20. Gray WN, Denson LA, Baldassano RN, Hommel KA. Disease activity, behavioral dysfunction, and health-related quality of life in adolescents with inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(7):1581-1586. doi:10.1002/ibd.21520

21. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317(26):1625-1629. doi:10.1056/nejm198712243172603

22. Naftali T, Bar-Lev Schleider L, Almog S, Meiri D, Konikoff FM. Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial. *Journal of Crohn's & colitis*. 2021;15(11):1799-1806. doi:https://dx.doi.org/10.1093/ecco-jcc/jjab069

23. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol*. 2013;11(10):1276-1280.e1271. doi:10.1016/j.cgh.2013.04.034

24. Naftali T, Mechulam R, Marii A, et al. Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial. *Dig Dis Sci*. 2017;62(6):1615-1620. doi:10.1007/s10620-017-4540-z

25. Naftali T, Schlieder LB, Konikoff F. The effect of canabis on Crohn's Disease Patients. *International Association of Cannabis Medicine (IACM)*. 2017,

26. Naftali T, Schlieder Bar-Lev L, Konikoff F, et al. UEG Week 2018 Oral Presentations. *United European Gastroenterology Journal*. 2018;6(S8):A75. doi:https://doi.org/10.1177/2050640618792817

27. Version MMP. Crohn's disease activity index (CDAI). 2023. Accessed August 20, 2023. Available at https://www.merckmanuals.com/professional/multimedia/clinical-calculator/crohn-disease-activity-index-cdai

28. Ananthakrishnan AN, Kaplan GG, Bernstein CN, et al. Lifestyle, behaviour, and environmental modification for the management of patients with inflammatory bowel diseases: an International Organization for Study of Inflammatory Bowel Diseases consensus. *The Lancet Gastroenterology and Hepatology*. 2022;7(7):666-678. doi:10.1016/S2468-1253(22)00021-8

29. McMaster University Health Information Research Unit. Search filters for Medline in Ovid syntax and the PubMed translation. hiru.mcmaster.ca; 2016. Last Updated February 9, 2016. Accessed November 7, 2022. Available at https://hiru.mcmaster.ca/hiru/hiru_hedges_medline_strategies.aspx

30. Lefebvre C, Manheimer E, Glanville J. Searching for studies. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0*. The Cochrane Collaboration; 2011:chap 6. Accessed November 7, 2022. Available at https://handbook-5-1.cochrane.org/

31. Naftali T, Lev L, Benjaminov F, Lish I, Hirsch J, Konikoff F. Cannabis induces clinical endoscopic improvement and endoscopic improvement in moderately active ulcerative colitis. . *ECCO - European Crohn's and Colitis Organization* 2018,

32. Desmarais A, Smiddy S, Reddy S, El-Dallal M, Erlich J, Feuerstein JD. Evidence supporting the benefits of marijuana for crohn's disease and ulcerative colitis is extremely limited: A meta-analysis of the literature. *Annals of Gastroenterology*. 2020;33(5):495-499. doi:10.20524/aog.2020.0516

33. Doeve BH, Van De Meeberg MM, Van Schaik FDM, Fidder HH. A Systematic Review with Meta-Analysis of the Efficacy of Cannabis and Cannabinoids for Inflammatory Bowel Disease: What Can We Learn from Randomized and Nonrandomized Studies? *Journal of Clinical Gastroenterology*. 2021;55(9):798-809. doi:10.1097/MCG.0000000000001393

34. Mack DR, Benchimol EI, Critch J, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for the Medical Management of Pediatric Luminal Crohn's Disease. *Journal of the Canadian Association of Gastroenterology*. 2019;2(3):E35-E63. doi:10.1093/jcag/gwz018

35. National Academies of Sciences Engineering a, Medicine. *The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research*. 2017: 487 pages. doi:10.17226/24625 Accessed April 2, 2023. Available at

hXps://nap.na9onalacademies.org/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-thecurrent-state

APPENDIX A – BRIEF SUMMARY OF EVIDENCE INCLUDED IN PRIOR CRRB GUIDANCE

Prior CRRB guidance for treatment of Crohn's and ulcerative colitis with medical cannabis cited 2 SRs by Kafil et al 2018[2,3] from the Cochrane organization. Evidence from those reviews is summarized in the table below.

Table A1. Overview of Methodology and Results from Systematic Reviews of RCTs of Patients with Crohn's Disease or Ulcerative Colitis Treated with a Cannabis- or Cannabinoid-based Product Included by Prior CRRB Guidance

Author, Publication Year N included studies n included participants	Study Design Databases Searched Date of Last Literature Search	Objective/PICOS and Methods	Results and Comments
Kafil TS et al 2018a[2] N = 3 RCTs (published in 5 reports) n = 79-93[a] people total	SR Medline, Embase, Allied and Alternative Medicine, PsycINFO, Cochrane IBD Group Specialized Register, CENTRAL, ClinicalTrials.Gov, European Clinical Trials Register, abstracts published at major meetings for relevant organizations. SR authors also contacted experts in the field. October 2018	**P:** Adults (≥18 years) with active (CSAI>150) or quiescent (CDAI ≤ 150) **Crohn's disease** **I:** Cannabis or cannabinoids (any type, including synthetic) **C:** Placebo or active comparator; or studies comparing different cannabis/cannabinoid doses **O:** Primary–disease remission (induction studies) or relapse (maintenance studies) on a validated CD scale **S:** RCTs published in full-text, or in abstract form only if authors were reachable and provided sufficient information. Studies of any duration were allowed. LOE assessed per GRADE criteria ROB assessed using Cochrane ROB tool	Three RCTs included. Authors did not perform MA due to heterogeneity in the type of cannabis used. Two trials were conducted among adults with active CD who failed at least 1 prior treatment (1st and 2nd trials below), and excluded people with comorbid mental illness or history of cannabis use: • Multi-center, DB RCT (n=21) comparing cannabis cigarettes (115 mg THC BID) vs PBO x 8 weeks; rated as high ROB (for blinding, other concerns), some concerns for 3 other domains, and low ROB for 2 domains ○ Clinical remission on CDAI (cannabis vs PBO): 45% (5/11) vs 10% (1/10); RR 4.55, 95%CI 0.63 to 32.56 (very low LOE) ○ Clinical response (CDAI decrease by >100; cannabis vs PBO): 91% (10/11) vs 40% (4/10), RR 2.27, 95%CI 1.04 to 4.97 (very low LOE) ○ CRP decrease by ≥ 0.5 mg/dL from BL to week 8 (cannabis vs PBO): 27% (3/11) vs 20% (2/10); RR 1.36, 95%CI 0.28 to 6.56 (low LOE) ○ Symptoms with patient-reported improvement in cannabis arm: pain, appetite, satisfaction ○ AEs: sleepiness, nausea, concentration difficulty, and memory loss, confusion, dizziness reported in cannabis arm. All considered mild. No withdrawal symptoms on cannabis discontinuation. AEs were more frequent with cannabis vs PBO (82% vs 20%; RR 4.09, 95%CI 1.15 to 14.57, very low LOE). • Single-center, DB RCT (n=19) comparing cannabis oil (CBD 5%, about 10 mg BID) vs PBO x 8 weeks; rated as high ROB (for difference in smoking rate), some concerns for 1 domain, and low ROB for 5 domains: ○ Clinical remission (cannabis vs PBO): 40% (4/10) vs 33% (3/9); RR 1.20, 95%CI 0.36 to 3.97 (very low LOE) ○ Serious AE (cannabis vs PBO); 10% (1/10) vs 11% (1/9); RR 0.90, 95%CI 0.07 to 12.38 (very low LOE) • DB RCT (n=50) comparing cannabis oil (CBD 15% and THC 4%) vs PBO x 8 weeks; rated as low ROB for all domains except for selective reporting bias (rated as some concerns) and published as an abstract ○ QoL score on SF-36 at study end (cannabis vs PBO): 96.3 vs 79.9 (MD 16.40, 95%CI 5.72 to 27.08, low LOE) ○ Mean CDAI score at study end (cannabis vs PBO): 118.6 vs 212.6 (MD –94, 95%CI –148.9 to –39.14, low LOE) ○ No AE information SR author's overall conclusion: "The effects of cannabis and cannabis oil on Crohn's disease are uncertain. Thus no firm conclusions regarding the efficacy and safety of cannabis and cannabis oil in adults with active Crohn's disease can be drawn. The effects of cannabis or cannabis oil in quiescent Crohn's disease have not been investigated" (page 2).[2] Authors expressed uncertainty about the efficacy of cannabis/cannabinoids for CD due to evidence being rated as low or very low certainty. All 3 included RCTs were conducted by the same lead author (Naftali T).
Kafil TS et al 2018b[3] N = 2 RCTs (published in 7 reports) n = 92 people total	SR Medline, Embase, WHO International Clinical Trials Registry, Allied and Alternative Medicine, PsycINFO, Cochrane IBD Group Specialized Register, CENTRAL, ClinicalTrials.Gov, European Clinical Trials Register, abstracts published at major	**P:** Adults (≥18 years) with active or quiescent **ulcerative colitis** **I:** Cannabis or cannabinoids (any type, including synthetic) and any route of administration **C:** Placebo or active comparator **O:** Primary–disease remission (induction studies) or relapse (maintenance studies)	Two RCTs included. Both trials were among people with active UC. • Multi-center, DB RCT (n=60) comparing CBD capsules (50 mg BID titrated up to 250 mg BID; each capsule contained 4.7% THC) vs PBO x 10 weeks among people with mild-mod UC; rated as low ROB on all domains except for attrition bias (rated as some concerns) • Clinical remission on Mayo score[b] (CBD vs PBO): 24% (7/29) vs 26% (8/31); RR 0.94, 95%CI 0.39 to 2.25 (low LOE) • Clinical response on Mayo score[b] (CBD vs PBO): 31% (9/29) vs 22% (7/31); RR 1.37, 95%CI 0.59 to 3.21 (low LOE) • Mean CRP level at 10 weeks (CBD vs PBO): 9.4 mg/L vs 7.6 mg/L; MD 1.79, 95%CI –5.67 to 9.25 (moderate LOE) • Mean IBDQ QoL score at 10 weeks (CBD vs PBO): 164.2 vs 146.8; MD 17.4, 95%CI –3.45 to 38.25 (moderate LOE)

	meetings for relevant organizations. SR authors also contacted experts in the field. January 2018	**S:** RCTs published in full-text, or in abstract form only if authors were reachable and provided sufficient information. Studies of any duration were allowed. LOE determined per GRADE criteria ROB assessed using Cochrane ROB tool	• Similar frequency of pain, stool frequency, and rectal bleeding between CBD and PBO arms • AE rate (CBD vs PBO): 100% (29/29) vs 77% (24/31); RR 1.28, 95%CI 1.05 to 1.56 (moderate LOE). Most AEs considered mild-moderate and were AEs associated with CBD (eg, dizziness, headache, nausea). Worsened UC occurred in the PBO arm. • Serious AE (CBD vs PBO): 0% (0/29) vs 10% (3/31, worsened UC & pregnancy), (low LOE) • Withdrawals from AE (CBD vs PBO): 34% (10/29) vs 16% (5/31); RR 2.14, 95%CI 0.83 to 5.51 (low LOE). • RCT (n=32) comparing cannabis cigarettes (0.5 g=23 mg THC/day) vs PBO x 8 weeks among people with UC who did not respond to standard medical therapy. Published as an abstract. Rated as low ROB on all domains except for blinding (rated high risk) and selective reporting (rated some concerns). • Mean disease activity on DAI at 8 weeks (cannabis vs PBO): 4 vs 8; MD –4, 95% CI –5.98 to –2.02 (no LOE) • Within study arm changes in median Mayo endoscopic score from BL to 8 weeks (cannabis vs PBO): 2 to 1 vs 2 to 2 • Mean CRP at 8 weeks (cannabis vs PBO): 0.7 mg/L vs 1 mg/L; MD –0.30, 95%CI –1.35 to 0.75 (low LOE) • Mean fecal calprotectin at 8 weeks (cannabis vs PBO): 115 mg/dL vs 229 mg/dL; MD –114, 95% CI –246.01 to 18.01) • AEs: no serious AEs SR author's overall conclusion: "The effects of cannabis and cannabidiol on UC are uncertain, thus no firm conclusions regarding the efficacy and safety of cannabis or cannabidiol in adults with active UC can be drawn. There is no evidence for cannabis or cannabinoid use for maintenance of remission in UC" (page 3).[3]

[a] *SR authors reported discrepant numbers of patients in each trial. The true total could be as low as 79 or as high as 93.*

[b] *Clinical remission was defined as achievement of a Mayo score ≤ 2 (and no sub-score on the scale >1), and clinical response was achievement of a Mayo score increase of ≥ 3 versus baseline (and endoscopy sub-score reduced by ≥1 point)*

Abbreviations: AE, adverse event; BID, twice daily; C, comparator; CBD, cannabidiol; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; DAI, Disease Activity Index; DB, double blind; I, experimental intervention; IBD, inflammatory bowel disease; CDAI, Crohn's Disease Activity Index; HBI, Harvey-Bradshaw Index; IBDQ, Inflammatory Bowel Disease Questionnaire; LOE, level of evidence per GRADE criteria; MA, meta-analysis; MD, mean difference; O, outcome(s); P, population; PBO, placebo; RCT, randomized controlled trial; ROB, risk of bias; RR, risk ratio; S, study design; SF-36, Short Form Health Survey-36 item; SR, systematic review; THC, tetrahydrocannabinol; UC, ulcerative colitis; QoL, quality of life;

APPENDIX B – COMPARISON OF EXPERIMENTAL TRIALS INCLUDED BY RECENT SYSTEMATIC REVIEWS

Table B2. Comparison of Experimental Studies of Cannabinoids in Patients with Crohn's Disease or Ulcerative Colitis Included by Recent SRs[a]

Author, Publication Year; IBD condition(s)	Naftali 2013a[18] CD and UC	Naftali 2013b[23] CD	Naftali 2017a[24] CD	Naftali 2017b[b25] CD	Irving 2018[16] UC	Naftali 2018a[b31]/ Naftali 2021a[17] UC	Naftali 2018b[26] CD	Matalon 2021[19] CD and UC	Naftali 2021b[22] CD
Vinci A, 2022[15]; CD and UC		X	X		X	X	X (abstract)	X	
Desmarais A, 2020[32]; CD and UC		X	X		X				
Doeve BH, 2019[33]; CD and UC		X	X		X	X (abstract)[c]	X (abstract)		
Mack DR, 2019[34]; CD		X	X						
SRs Included by Prior CRRB Guidance Document[d]									
Kafil TS, 2018[3]; UC	--Excl (abstract)--[d]				X	X (abstract)			
Kafil TS, 2018[2]; CD	--Excl (abstract)--[d]	X	X	X (abstract)					

[a] *'X' indicates that experimental study was included by the SR. Primary studies were classified as experimental based on the description by SRs, which could be inaccurate.*
[b] *Published as an abstract only. Kafil et al also included supplementary unpublished data provided by the study authors*
[c] *We are uncertain whether this abstract-only trial is identical to trial cited by Vinci 2022 and Kafil 2018, but due to matching titles and authors, and highly similar interventions and number of patients, the authors of this report guess that it is the same trial.*
[d] *These are SRs published by the Cochrane Organization, which were the only evidence reviewed for the Current CRRB CD and UC guidance document. Both Kafil TS et al reviews excluded an RCT by Naftali T et al 2013a which studied THC for patients with both CD and UC but it was excluded from these reviews for not reporting separate results among people with UC versus CD.*

Abbreviations: CD, Crohn's disease; CRRB, Cannabis Research Review Board; Excl, excluded; IBD, inflammatory bowel disease; SR, systematic review; THC, tetrahydrocannabinol, UC, ulcerative colitis;

APPENDIX C – RESULTS FROM RECENT SYSTEMATIC REVIEWS INCLUDING AT LEAST 1 TRIAL NOT PREVIOUSLY ADDRESSED

Table C1. Overview of Methodology and Results from Recent[a] Systematic Reviews of Studies of Patients with Crohn's Disease or Ulcerative Colitis Treated with a Cannabis- or Cannabinoid-based Product

Author, Publication Year N studies n participants	Study Design Databases Searched Date of Last Literature Search	Objective/PICOS	Included CBP Interventions N studies	Comments
Vinci A et al 2022[15] N = 6 RCTs (2 UC, 3 CD, and 1 mixed UC and CD) n= 227 people (208 included in the MA), all from the UK or Israel	SRMA Medline, Scopus, ClinicalTrials.Gov May 2022 (bibliographic databases) and August 2022 (ClinicalTrials.Gov)	**P:** Patients with IBD (UC or CD) **I:** Cannabinoids (inhaled or oral) **C:** Standard treatment **O:** Clinical improvement via standard scale or validated clinical measure **S:** RCT or prospective case-control study	CD RCTs • Smoked cannabis 0.5 g (11.5 mg THC) twice daily (N=2) • Cannabinoid oil 5 mg/mL (0.3 mg/kg) (N=1) • Cannabis oil 15% CBD + 4% THC (N=1) UC RCTs • Smoked cannabis 0.5 g (11.5 mg THC) twice daily (N=1) • CBD-rich extract, up to 500 mg/day (N=1) • Smoked cannabis (0.25 g steps up to 1g/day flower [23 mg THC]) Duration: 8-10 weeks	Log RR (95%CI) for therapeutic success[b] by random-effects MA, **CD RCTs** (4 RCTs of 116 patients total): • 0.42 (–0.04 to 0.89); I^2 = 0.00% Log RR (95%CI) for therapeutic success[b] by random-effects MA, **UC RCTs** (2 RCTs of 92 patients total): • 0.32 (–0.57 to 1.22); I^2 = 37.26% Mean difference (95%CI) in CDAI score change by random-effects MA, **CD RCTs** (3 RCTs of 70 patients total): • 36.73 (12.3 to 61.2); I^2 = 0.0% No safety outcome information reported *ROB assessment by Cochrane 2.0 tool:* trials rated overall as high risk (n=1), low risk (n=2), or some concerns (n=3). Matalon 2021 was rated as high risk due to missing outcome data. Trials rated as some concerns were primary due to concerns for deviations from the intended deviation. Two trials were rated as having some concerns due to selection of the reported results, and 1 trial additionally due to how the outcome was measured. *Author's conclusions*: Overall RCT evidence is mixed. Short-term adjunctive treatment with cannabinoids might improve clinical outcomes for people with CD, but not for people with UC. Conclusions are limited by the general paucity of trials, the fact that nearly all evidence is from the same research group from a single center, and small sample sizes. There is not information about use of cannabinoids during the maintenance treatment period.

[a] *For feasibility, we only extracted results from the SRs listed in Appendix B that included at least 1 study not addressed at all or only addressed as an abstract by Kafil et al SRs.*

[b] *Vinci et al 2022 did not clearly label the primary outcome assessed. It likely is 'therapeutic success,' defined as either disease relapse (by objective findings) or 'improved' disease activity on a standard rating scale*

Abbreviations: CBD, cannabidiol; CBP, cannabis- or cannabinoid-based product; CD, Crohn's disease; IBD, inflammatory bowel disease; C, comparator; CDAI, Crohn's Disease Activity Index; HBI, Harvey-Bradshaw Index; I, experimental intervention(s); *MA, meta-analysis; O, outcome(s);* P, population; *RCT, randomized controlled trial; ROB, risk of bias; SR, systematic review; THC, tetrahydrocannabinol UC, ulcerative colitis; QoL, quality of life;*

APPENDIX D – RANDOMIZED CONTROLLED TRIAL EVIDENCE NOT ADDRESSED OR ONLY ADDRESSED AS AN ABSTRACT IN PRIOR GUIDANCE

Table D1. Summary of Randomized Controlled Trial Evidence Not Addressed in Prior CRRB Guidance

Author, Publication Year NCT Country Study Design	Population (total n; randomization ratio)	CBP Intervention Co-intervention	Control Co-intervention	Primary Efficacy Measure	Treatment Duration Follow-up	Select Result(s)	ROB Rating on Cochrane ROB 2.0 per SR

Naftali T et al, 2021a[17a]
NCT01040910
Israel
R, DB (pts & providers), PC, SC trial
	Mild-mod UC
	(n=32; 1:1)
	Enrolled ages 26-40
	43% female
	No current cannabis use
	No psychiatric diagnosis or addiction traits
		Cannabis cigarettes (using batches of dried *C. Sativa* flower with 16% [80 mg] THC, 0.5% CBG, 0.1% CBD, and traces of other cannabinoids; contained terpenes: Myrcene, beta-caryophyllene, Selina-3,7(11)-diene, gamma-Selinene, 10-epie-gamma-eudesmol, beta-eudesmol, guaiol, and alpha-pinene) twice daily. Patients started with 0.25 g dried cannabis daily and gradually increased to 0.5 g twice daily.[b]
		
		Stable doses of UC medications
			Matched placebo cigarettes
			
			(they soaked cannabis in ethanol and mixed it with herbal spirits and yeast; final products contained <0.4% THC and other cannabinoids were not detected).
			
			Stable doses of UC medications
				Lichtiger score	8 weeks
					Two weeks
						<u>Primary</u>
						Significantly greater improvement in Lichtiger scores between baseline and 8 weeks in the cannabis arm compared to the placebo arm (P between groups = 0.006; P<0.001 for within-group change for cannabis arm and p=0.37 for within-group change for PBO arm)
						• Median? [not specified] (IQR) baseline Lichtiger score (cannabis vs PBO): 10.9 (9-14) vs 11 (9-13)
						• Median? [not specified] (IQR) 8-week Lichtiger score (cannabis vs PBO): 5 (1-7) vs 8 (7-10)
						<u>Other</u>
						• No significant between-group difference (P=0.374) in improvement in the Mayo endoscopic score [MES] (measured using colonoscopy in 90% of participants) after 8 weeks
						  ○ Cannabis arm: MES decreased from 2.13±1 to 1.25±2 (P=0.015)
						  ○ PBO arm: MES decreased from 2.15±1 to 1.69±1 (P=0.367)
						• Significantly reduced bowel movements (P=0.006) and increased proportion of patients with an abdominal pain score ≥ 2 (P=0.04) after 8 weeks for cannabis vs PBO
						• No significant differences between study arms in the change in hemoglobin level, WBC count, CRP, calprotectin, and weight
						• Significantly increased QoL score (by SF-36 scale) from baseline to 8 weeks in the cannabis arm vs PBO arm (P=0.026)
						• Patients receiving cannabis reported higher treatment satisfaction, and improved general health, libido, concentration, and pain
						• Reported AEs (% cannabis vs % PBO): cough (41% vs 20%), dizziness (35% vs 6%), confusion (29% vs 6%), difficulty stopping use (29% vs 12%), behavioral change (23% vs 0%), restlessness (11% vs 0%), SOB (6% vs 0%), decreased memory (0% vs 40%), hallucinations (0% both). No treatment discontinuations due to AE.
							Low risk overall
							
							Low risk on all 5 domains[15]

Naftali T et al, 2021b[22] NCT01826188 Israel R, DB, PC, SC trial	**Mild-mod CD** (n=56; 1:1) Enrolled ages 24-43 years 46% female No psychiatric history No current cannabis use	Oral cannabis oil (4:1 CBD:THC); titrated to symptoms, starting with 16 mg CBD and 4 mg THC daily. Final median dose was 80 mg CBD (IQR 52-108) and 20 mg THC (IQR 13-27). Stable doses of CD medications	Matched olive oil with chlorophyll (PBO) Stable doses of CD medications	CDAI score	8 weeks None	<u>Primary</u> Lower CDAI scores at 8 weeks in cannabis arm vs control (P=0.038, uncontrolled; P=0.072, controlling for age, sex, illness length) • Median (IQR) baseline CDAI (cannabis vs PBO): 282 (243-342) vs 264 (234-320) • Median (IQR) 8-week CDAI (cannabis vs PBO): 166 (82-226) vs 237 (121-271) <u>Other</u> • No differences in measures of inflammation (CRP, calprotectin) between groups • No significant difference in endoscopic disease (measured by SES-CD) between groups	NA, not assessed by SRs

Table D1. Summary of Randomized Controlled Trial Evidence Not Addressed in Prior CRRB Guidance

Author, Publication Year NCT Country Study Design	Population (total n; randomization ratio)	CBP Intervention Co-intervention	Control Co-intervention	Primary Efficacy Measure	Treatment Duration Follow-up	Select Result(s)		ROB Rating on Cochrane ROB 2.0 per SR
						• Significantly (P<0.05) improved patient-reported mood, sleep, pain, bloating, appetite, general well-being, and general satisfaction with cannabis vs PBO • AE with incidence ≥ 5% higher for cannabis vs PBO[c]: visual distortion, behavioral change, confusion, decreased memory, dizziness. No reported difficulty stopping cannabis.		
Matalon ST et al, 2021[19] Not provided Israel R, DB (pts & providers), PC trial	**Mild-mod CD** (n=30; ~1:1) & **Mild-Mod UC** (n=19; 1:1) 20-80 years old No psychiatric history No current cannabis use	*CD pts*: oral cannabis oil (4:1 CBD:THC); titrated to symptoms. Maximum daily allowed dose: 16 mg CBD and 4 mg THC.[d] *UC pts:* inhaled cannabis cigarettes (0.5 grams dried flower with 23% [11.5 mg] THC and <0.5% CBD). Unknown number of cigarettes daily. Stables doses of IBD medications	*CD pts:* PBO, no description *UC pts:* matched PBO cigarettes with <0.4% THC and undetectable other cannabinoids Stable doses of IBD medications	Not specified	8 weeks None	*CD patients* <u>Clinical parameters at 8 weeks</u> *(*cannabis vs PBO) • No significant difference in CDAI score • Significantly higher QoL score (SF-36) <u>Endocannabinoid (eCB) serum levels</u> (within-group analysis) • PBO arm and cannabis arm: no changes in the level of any eCB at 8 wks vs BL	*UC patients* <u>Clinical parameters at 8 weeks</u> (cannabis vs PBO) • Significantly lower Lichtiger score • Significantly higher QoL score (SF-36) <u>Endocannabinoid (eCB) serum levels</u> (within study group analysis) • PBO arm: significantly lower PEA, AA and AEA at 8 wks vs BL • Cannabis arm: no changes in the eCB levels at 8 wks vs BL <u>Correlation of eCBs with clinical parameters</u> "We found that the percent reduction in the levels of BM [bowel movements] was negatively correlated with changes in the circulating AEA and OEA, whereas changes in the QOL were positively correlated with the levels of 2-AG" (page 7)[19]	High risk overall[15] High risk on domain 3 (missing outcome data); Some concerns domain 2 (deviation from intended interventions); Low risk other domains[15]
Naftali T et al, 2018b[26] Not provided Israel R, DB, PC trial	**Mod active CD** (n=46, 1:1)	Cannabis oil (15% CBD and 4% THC) Stables doses of other medications	Placebo	Not specified	8 weeks Unknown	<u>Clinical parameters at 8 weeks</u> • Mean? [not specified] baseline CDAI (cannabis vs PBO): 288.4± 78.0 vs 298.5± 112.2 (P=0.71) • Mean? [not specified] 8-week CDAI (cannabis vs PBO): 143.1 ± 96.0 vs 209.5± 113.0 (P<0.05; unclear if the P value is for the change in scores or for comparison of scores at 8-weeks) • Remission by CDAI score <150 (cannabis vs PBO): 65% vs 35% (P<0.05) <u>Quality of Life</u> • Median (IQR) QoL on unknown scale at 8 weeks (cannabis vs PBO): 90.1 (83 to 102) vs 76 (68 to 92), P<0.05 <u>Laboratory parameters</u> • No significant differences in CRP or calprotectin levels at 8 weeks <u>Endoscopic parameters</u> • No significant differences in SES-CD score at 8 weeks		Some concerns overall[15] Rated as some concerns on 4 out of 5 domains (including bias from the randomization process, deviation from intended interventions, outcome measurement, outcome selection reporting)[15] Published as an abstract only

Table D1. Summary of Randomized Controlled Trial Evidence Not Addressed in Prior CRRB Guidance

Author, Publication Year NCT Country Study Design	Population (total n; randomization ratio)	CBP Intervention Co-intervention	Control Co-intervention	Primary Efficacy Measure	Treatment Duration Follow-up	Select Result(s)		ROB Rating on Cochrane ROB 2.0 per SR
Naftali T et al, 2013a[18] Not provided Israel R, PC trial	**Mod CD** (n = 20; randomization ratio not reported) & **Mod UC** (n = 10; randomization ratio not reported) 18-75 years old Failed prior therapy (steroid, immunomodulator, or TNF antagonist)	*CD and UC patients: 2* Cannabis cigarettes daily (0.5 g cannabis and 11.5 mg THC per cigarette) Stables does of other medications	Placebo Stables does of other medications	Not specified	8 weeks Two weeks	*CD patients*[e] <u>Clinical parameters at 8 weeks</u> (cannabis vs PBO) • Mean CDAI at BL cannabis: 358±99 • Mean CDAI at BL PBO: 373±94 Significant improvement at 8 weeks in the cannabis group (CDAI 139±111 relative to PBO (306±143); P<0.05). CDAI increased in the THC arm 2 weeks after cessation. No serious AE	*UC patients*[e] <u>Clinical parameters at 8 weeks</u> (cannabis vs PBO) • Mean UCAI, cannabis: 11±2 (BL) and 4±3 (8 weeks) • Mean UCAI, PBO 11±1.5 (BL) and 8±3 (8 weeks) No statistical test reported. No serious AE	NA, not assessed by SRs Published as an abstract only, so there is limited information to assess bias

[a] *This study was included by the 2018 Cochrane review (Kafil et al) as Naftali 2018 (abstract only); confirmed based on identical registered trial numbers (NCT01040910).*

[b] *The dose of THC/amount of cannabis studied is unclear; we reported the dose as described in the full text publication by Naftali et al 2021. However, SRs including this study described the approximate dose as being much lower (approximately 11.5 mg THC twice daily) compared to the dose of 80 mg THC twice daily described by the article.*

[c] *The number of patients with AE data is fewer than the total number of patients in the study for both study arms, so the true incidence of AE is unclear. Study authors described that all patients completed the trial.*

[d] *Daily CBD and THC calculated per information from the publication. The author of this report noted that the oil used by Matalon ST et al seems to be identical to the oil used by Natfali T et al 2021b ("Avidekel" from Tikun Olam Ltd.); however, the amount of THC & CBD per drop is discrepant between Matalon ST and Naftali T et al. If the true dosage is identical to what was reported by Naftali T et al 2021b, the maximum allowed daily dosage in the Matalon et al trial was about 320 mg CBD and 80 mg THC.*

[e] *Whether the data is presented as UC and CD patients combined, or separately by condition is unclear. Because the UCAI scores were described as "the UC group," the authors of this report interpreted the CDAI scores as being among CD patients only. However, the SR that identified this study considered the data to be combined for patients with both conditions.*

Abbreviations: 2-AG, 2-arachidonylglycerol; AA, arachidonic acid; AE, adverse event; AEA, anadamide; BL, baseline; BM, bowel movement; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRRB, Cannabis Research Review Board; CRP, C-reactive protein; DB, double blind; eCB, endocannabinoid; IBD, inflammatory bowel disease (includes CD and UC); Mod, moderate; NA, not applicable; NCT, National Clinical Trial registry number; OEA, oleoylethanolamine; PBO, placebo; PC, placebo-controlled; PEA, palmitoylethanolamine; pts, patients; QoL, quality of life; R, randomized; SC, single center; SES-CD, simple endoscopic score for CD; SR, systematic review; THC, tetrahydrocannabinol; TNF, Tumor necrosis factor; UC, ulcerative colitis; wks, weeks;

APPENDIX E – NATIONAL ACADEMIES LEVEL OF EVIDENCE CATEGORIES

Previously the CRRB used level of evidence (LOE) categories from the 2017 National Academies of Sciences, Engineering, and Medicine (NASEM) report for therapeutic recommendations in guidance documents.[35] Refer to Table E1 for details about these evidence categories.

Table E1. Levels of Evidence for Therapeutic Effects from the 2017 NASEM Cannabis Report

Conclusive Evidence
• "There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).[35] • "For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitation of the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence" (page 7).[35]
Substantial Evidence
• "There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).[35] • "For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence" (page 7).[35]
Moderate Evidence
• "There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[35] • "For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence." (page 8).[35]
Limited Evidence
• "There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[35] • "For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors" (page 8).[35]
No or Insufficient Evidence
• "There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[35] • "For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors" (page 8).[35]

Abbreviations: NASEM, The National Academies of Sciences, Engineering, and Medicine

APPENDIX F – LITERATURE SEARCHES

Searches for Systematic Reviews in Ovid-Medline and Embase

SR search 2018-present in Ovid-Medline, conducted on June 8, 2023:

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily** 1946 to June 07, 2023

Search Strategy:

#	Searches	Results
1	exp Crohn Disease/	44237
2	exp Colitis, Ulcerative/	40556
3	ulcerative colitis*.mp.	48976
4	crohn*.mp.	65613
5	inflammatory bowel disease*.mp.	68619
6	(UC or IBD).mp.	55174
7	1 or 2 or 3 or 4 or 5 or 6	148743
8	exp Cannabis/ or exp cannabinoids/ or exp Medical Marijuana/ or exp "Marijuana Use"/ or exp Marijuana Abuse/	37627
9	(mari?uana or pot or hash* or bhang* or gan?a* or weed* or hemp*).ti,ab,kw,kf.	84695
10	(Tetrahydrocannab* or cannabi* or THC or CBD or CBN or CBG or CBC, or THCV or CBDV or CBCV or CBGV or THCA or CBDA or CBGA or CBNA).ti,ab,kw,kf.	65192
11	(THC and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	629
12	(nabilone or dronabinol or marinol or syndros or cesamet or epid#olex or nabiximol* or Sativex or bedrocan or bedrobinol or bedica or bediol or bedrolite or dexanbinol).ti,ab,kw,kf.	1213
13	8 or 9 or 10 or 11 or 12	146445
14	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "systematic review"/ or ((sytematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	472503
15	(MEDLINE or Embase or Pubmed or systematic review).tw. or meta analysis.pt.	488156
16	14 or 15	588089
17	7 and 13 and 16	45
18	limit 17 to yr="2018 -Current"	31

SR search 2018-present in Embase, conducted on June 8, 2023:

#	Searches	Results
1	**'inflammatory bowel disease'**/exp OR **'crohn disease'**/exp OR **'ulcerative colitis'**/exp	**200,159**
2	**crohn***:ti,ab,kw	**100,699**
3	**'inflammatory bowel disease*'**:ti,ab,kw	**107,912**
4	**uc**:ti,ab,kw OR **ibd**:ti,ab,kw	**108,000**
5	**'cannabinoid'**/exp OR **'cannabis use'**/exp OR **'cannabis smoking'**/exp OR **'cannabis addiction'**/exp	**100,278**
6	**mari?uana**:ti,ab,kw OR **pot**:ti,ab,kw OR **hash***:ti,ab,kw OR **bhang***:ti,ab,kw OR **gan?a***:ti,ab,kw OR **weed***:ti,ab,kw OR **hemp***:ti,ab,kw	**106,129**
7	**tetrahydrocannab***:ti,ab,kw OR **cannabi***:ti,ab,kw OR **thc**:ti,ab,kw OR **cbd**:ti,ab,kw OR **cbn**:ti,ab,kw OR **cbg**:ti,ab,kw OR **cbc**:ti,ab,kw OR **thcv**:ti,ab,kw OR **cbdv**:ti,ab,kw OR **cbcv**:ti,ab,kw OR **cbgv**:ti,ab,kw OR **thca**:ti,ab,kw OR **cbda**:ti,ab,kw OR **cbga**:ti,ab,kw OR **cbna**:ti,ab,kw	**99,370**
8	**thc**:ti,ab,kw AND (**analog***:ti,ab,kw OR **enantiomer***:ti,ab,kw OR **isomer***:ti,ab,kw)	**823**
9	**cannabi***:ti,ab,kw AND (**analog***:ti,ab,kw OR **enantiomer***:ti,ab,kw OR **isomer***:ti,ab,kw)	**2,576**
10	**nabilone**:ti,ab,kw OR **dronabinol**:ti,ab,kw OR **marinol**:ti,ab,kw OR **syndros**:ti,ab,kw OR **cesamet**:ti,ab,kw OR **epid?olex**:ti,ab,kw OR **nabiximol***:ti,ab,kw OR **sativex**:ti,ab,kw OR **bedrocan**:ti,ab,kw OR **bedrobinol**:ti,ab,kw OR **bedica**:ti,ab,kw OR **bediol**:ti,ab,kw OR **bedrolite**:ti,ab,kw OR **dexanabinol**:ti,ab,kw	**1,925**
11	**#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10**	**225,279**
12	**cochrane***:jt OR **'systematic review*'**:jt OR **'meta analysis'**/exp OR **'systematic review'**/exp OR ((**systematic*** NEAR/3 **review***):ti,ab,kw) OR ((**systematic*** NEAR/2 **search***):ti,ab,kw) OR **'meta analys*'**:ti,ab,kw OR **metaanalys***:ti,ab,kw OR ((**overview** NEAR/4 (**review** OR **reviews**)):ti)	**702,172**
13	**#1** OR **#2** OR **#3** OR **#4**	**258,288**
14	**#11** AND **#12** AND **#13**	**76**
15	**#11** AND **#12** AND **#13** AND [2018-2023]/py	**51**

Searches for Randomized Controlled Trials in Ovid-Medline and Embase

RCT search 2022-present in Ovid-Medline, conducted on June 22, 2023:

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily** 1946 to June 21, 2023

Search Strategy:

#	Searches	Results
1	exp Crohn Disease/	44281
2	exp Colitis, Ulcerative/	40629
3	ulcerative colitis*.mp.	49096
4	crohn*.mp.	65706
5	inflammatory bowel disease*.mp.	68803
6	(UC or IBD).mp.	55372
7	1 or 2 or 3 or 4 or 5 or 6	149067
8	exp Cannabis/ or exp cannabinoids/ or exp Medical Marijuana/ or exp "Marijuana Use"/ or exp Marijuana Abuse/	37750
9	(mari?uana or pot or hash* or bhang* or gan?a* or weed* or hemp*).ti,ab,kw,kf.	84983
10	(Tetrahydrocannab* or cannabi* or THC or CBD or CBN or CBG or CBC, or THCV or CBDV or CBCV or CBGV or THCA or CBDA or CBGA or CBNA).ti,ab,kw,kf.	65425
11	(THC and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	632
12	(nabilone or dronabinol or marinol or syndros or cesamet or epid#olex or nabiximol* or Sativex or bedrocan or bedrobinol or bedica or bediol or bedrolite or dexanbinol).ti,ab,kw,kf.	1218
13	8 or 9 or 10 or 11 or 12	146924
14	(randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1575523
15	7 and 13 and 14	63
16	limit 15 to yr="2022 -Current"	4
17	limit 15 to yr="2021"	12

RCT search 2022-present in Embase, conducted on June 22, 2023:

#	Searches	Results

1	**'inflammatory bowel disease'**/exp OR **'crohn disease'**/exp OR **'ulcerative colitis'**/exp	**200,729**
2	**crohn***:ti,ab,kw	**100,913**
3	**'inflammatory bowel disease*'**:ti,ab,kw	**108,246**
4	**uc**:ti,ab,kw OR **ibd**:ti,ab,kw	**108,325**
5	**'cannabinoid'**/exp OR **'cannabis use'**/exp OR **'cannabis smoking'**/exp OR **'cannabis addiction'**/exp	**100,594**
6	**mari?uana**:ti,ab,kw OR **pot**:ti,ab,kw OR **hash***:ti,ab,kw OR **bhang***:ti,ab,kw OR **gan?a***:ti,ab,kw OR **weed***:ti,ab,kw OR **hemp***:ti,ab,kw	**106,423**
7	**tetrahydrocannab***:ti,ab,kw OR **cannabi***:ti,ab,kw OR **thc**:ti,ab,kw OR **cbd**:ti,ab,kw OR **cbn**:ti,ab,kw OR **cbg**:ti,ab,kw OR **cbc**:ti,ab,kw OR **thcv**:ti,ab,kw OR **cbdv**:ti,ab,kw OR **cbcv**:ti,ab,kw OR **cbgv**:ti,ab,kw OR **thca**:ti,ab,kw OR **cbda**:ti,ab,kw OR **cbga**:ti,ab,kw OR **cbna**:ti,ab,kw	**99,694**
8	**thc**:ti,ab,kw AND (**analog***:ti,ab,kw OR **enantiomer***:ti,ab,kw OR **isomer***:ti,ab,kw)	**830**
9	**cannabi***:ti,ab,kw AND (**analog***:ti,ab,kw OR **enantiomer***:ti,ab,kw OR **isomer***:ti,ab,kw)	**2,585**
10	**nabilone**:ti,ab,kw OR **dronabinol**:ti,ab,kw OR **marinol**:ti,ab,kw OR **syndros**:ti,ab,kw OR **cesamet**:ti,ab,kw OR **epid?olex**:ti,ab,kw OR **nabiximol***:ti,ab,kw OR **sativex**:ti,ab,kw OR **bedrocan**:ti,ab,kw OR **bedrobinol**:ti,ab,kw OR **bedica**:ti,ab,kw OR **bediol**:ti,ab,kw OR **bedrolite**:ti,ab,kw OR **dexanabinol**:ti,ab,kw	**1,936**
11	**#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10**	**225,963**
12	**'crossover procedure'**:de OR **'double-blind procedure'**:de OR **'randomized controlled trial'**:de OR **'single-blind procedure'**:de OR **random***:de,ab,ti OR **factorial***:de,ab,ti OR **crossover***:de,ab,ti OR ((**cross** NEXT/1 **over***):de,ab,ti) OR **placebo***:de,ab,ti OR ((**doubl*** NEAR/1 **blind***):de,ab,ti) OR ((**singl*** NEAR/1 **blind***):de,ab,ti) OR **assign***:de,ab,ti OR **allocat***:de,ab,ti OR **volunteer***:de,ab,ti	**3,152,616**
13	**#1** OR **#2** OR **#3** OR **#4**	**258,968**
14	**#11** AND **#12** AND **#13**	**215**
15	**#11** AND **#12** AND **#13** AND [2022-2023]/py	**23**