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Cannabis for the Treatment of Crohn's Disease and Ulcerative Colitis: Evidence From Cochrane Reviews

Tahir S. Kafil, MD, FRCPC,* Tran M. Nguyen, MSc,† John K. MacDonald, MA,* and Nilesh Chande, MD, FRCPC‡,§

Background: We systematically reviewed the safety and effectiveness of cannabis and cannabinoids treatment for Crohn's disease (CD) and ulcerative colitis (UC).

Methods: MEDLINE, Embase, WHO ICTRP, AMED, PsychINFO, CENTRAL, ClinicalTrials.Gov, and the European Clinical Trials Register were searched for relevant studies.

Main Results: Five randomized controlled trials (3 CD and 2 UC studies, 185 participants) were included. One CD study (N = 21) showed 45% (5 of 11) of the cannabis cigarette group experienced clinical remission compared with 10% (1 of 10) of the placebo group (risk ratio [RR] 4.55; 95% CI, 0.63–32.56). Another CD study (N = 19) did not show significant rates of clinical remission. Forty percent (4 of 10) of participants in the cannabis oil group experienced remission compared with 33% (3 of 9) of the placebo group (RR 1.20; 95% CI, 0.36–3.97). A UC study (N = 60) did not have significant clinical remission rates. Twenty-four percent (7 of 29) of cannabis oil participants experienced remission compared with 26% (8 of 31) of placebo participants (RR 0.94; 95% CI, 0.39–2.25). A second UC study (N = 32) showed the effects on disease activity, C-reactive protein levels, and fecal calprotectin levels were uncertain. Adverse events were more prevalent in the cannabis groups for both CD and UC studies. GRADE analysis for the UC and CD studies ranged from very low to moderate.

Conclusions: In summary, no firm conclusions can be made regarding the safety and effectiveness of cannabis and cannabinoids in adults with CD and UC.

Key Words: cannabis, cannabinoids, Crohn's disease, ulcerative colitis, inflammatory bowel disease

INTRODUCTION

Cannabis and cannabinoids are used to treat many illnesses, with a high prevalence of use among patients with Crohn's disease (CD) and ulcerative colitis (UC).[1] However, there is limited evidence to support the use of cannabis in CD and UC, and there were no controlled trials evaluating its use in inflammatory bowel disease (IBD) patients until a prospective, placebo-controlled, randomized study was first published in 2013.[2] Cannabinoids have been shown to have anti-inflammatory properties in previous experimental animal models. It is postulated that cannabis modulates inflammation via the endocannabinoid system.[3]

Cannabinoids containing tetrahydrocannabinol (THC) may cause altered sensory perception and euphoria. However, some cannabinoids such as cannabidiol have no psychoactive effect. In addition, adverse events (AEs) and the long-term effects of cannabis and cannabinoid use in patients with CD and UC are unknown. Two Cochrane systematic reviews assessed the safety and effectiveness of the use of cannabis in patients with IBD.[4,5] This article is based on these 2 Cochrane reviews.

MATERIALS AND METHODS

Search Strategy

Literature searches were conducted from inception to January 2, 2018, for UC studies and from inception to October 17, 2018, for CD studies. MEDLINE, Embase, PsychINFO, AMED, CENTRAL, and the Cochrane IBD Group Specialized Register were searched. We searched ClinicalTrials.Gov, the European Clinical Trials Register, and the WHO clinical trials registry (ICTRP) for ongoing studies. In addition, conference abstracts and references were also searched, and industry leaders in the field were contacted for upcoming publications. The full search strategies are reported in Appendix 1 (see online supplementary material).

Eligibility

Randomized controlled trials (RCTs) that compared any formulation of cannabis or cannabinoid derivatives (natural or synthetic) to a placebo or an active comparator for the treatment of participants with CD or UC were considered for inclusion. Studies that assessed different doses of cannabis or cannabinoids were also included. Abstracts were included if the study authors could be reached for additional information.

Outcomes

The primary outcomes included clinical remission for induction of remission studies (as defined by the studies) and clinical relapse at study endpoint for maintenance of remission studies (as defined by the studies). Secondary outcomes include: clinical response, endoscopic improvement, endoscopic remission, histological response, c-reactive protein (CRP), fecal calprotectin measurements (FCP), quality of life, AEs, serious AEs (SAEs), withdrawals due to AEs and cannabis dependence, and withdrawal effects. Validated scoring systems such as the Crohn's Disease Activity Index (CDAI) or Disease Activity Score were included.

Risk of Bias and Data Extraction

Two authors (TK and NC) independently assessed bias using the Cochrane risk of bias tool.[6] Random sequence generation, allocation sequence concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias were assessed for each study. Each category was given a rating of low, high, or unclear risk of bias and justification for judgment was provided. We contacted the study authors if further clarification was needed to assess the risk of bias. Two authors (TK and NC) independently extracted the prespecified outcomes from each study. Any conflicts involving data extraction or risk of bias were resolved through discussion and consensus or by consulting with a third author (JKM) as necessary. If data were unclear or missing, the corresponding authors were contacted for clarification.

The GRADE criteria were used to the evaluate the quality of evidence supporting the outcomes.[7,8] Outcomes were rated as high, moderate, low, or very low certainty evidence. Outcomes from RCTs start as high certainty evidence and can be downgraded based on several criteria including risk of bias, indirect evidence, inconsistency, imprecision, and publication bias.

Statistical Analysis

The Cochrane Review Manager software (RevMan 5.3.5, Denmark, Copenhagen) was used to analyze data on an intention-to-treat (ITT) basis. For dichotomous outcomes, missing data were treated as failures. We counted treatment failures as a failure to enter remission for induction studies and as a relapse for maintenance studies. We conducted an available case analysis for missing continuous outcomes. For continuous outcomes with missing standard deviations, the standard deviations were imputed when reasonably possible. A sensitivity analysis was performed to assess the impact of any imputation.

Statistical heterogeneity was assessed using the χ^2 test and I^2 statistic. For the χ^2 test, a *P* value of less than 0.1 was considered statistically significant. We used the I^2 statistic to assess the magnitude of statistical heterogeneity. Heterogeneity was assessed by doing a visual assessment to identify any outliers in the forest plot. If outliers were identified, a sensitivity analysis was performed to explore possible explanations for the heterogeneity. A random-effects model was used if significant heterogeneity was identified.

Data were not pooled if the heterogeneity was greater than 75% (eg, $I^2 > 75\%$). Data were combined when the interventions, participant groups, and outcomes were deemed sufficiently similar (determined by consensus). However, when we were unable to pool the data, we narratively summarized the results of individual trials.

RESULTS

Description of Studies

The literature search identified 210 studies. A total of 129 studies remained after duplicates were removed. Twelve reports of 5 studies (185 participants) (Table 1)[2, 9–12] and 1 ongoing study[13] were included in the review (Fig. 1). No studies assessing maintenance of remission in patients with quiescent CD or UC were identified.

Crohn's Disease

The study by Naftali et al in 2013 was a single-center, placebo-controlled, randomized, double-blind trial that assessed induction of remission in participants with active CD.[2] Participants were given either cannabis cigarettes (115 mg of THC) twice daily or placebo cigarettes composed of cannabis flowers with the THC extracted. Participants were treated for 8 weeks. Twenty-two participants were randomized, but only 21 participants were included in the final analysis (cannabis, n = 11; placebo, n = 10). Inclusion criteria included an established diagnosis of CD, at least 20 years of age, and active CD (defined as a CDAI score between 200 and 450 points) at study entry. All participants previously failed at least 1 form of medication for their CD, including corticosteroids, 5-aminosalicylates, methotrexate, azathioprine, 6-mercaptopurine, or antitumour necrosis factor-alpha (TNF-α). Participants receiving corticosteroids had to be receiving a stable dose for at least 1 month before study entry, and participants receiving azathioprine or 6-mercaptopurine had to be receiving a stable dose for at least 3 months before entry. Participants were followed at weeks 0, 2, 8, and 10. The primary outcome was induction of remission (defined as a CDAI score <150) after 8 weeks of cannabis

TABLE 1. Characteristics of Included Studies

Study	No. Patients	UC or CD	Country, No. Centers	Interventions	Duration of Therapy	Methods
Naftali et al 2013[a]	21	CD	1 country	Cannabis cigarettes 115mg THC (n= 11)	8 wk	Randomized, Double-blind, Placebo-controlled
			1 center	Placebo (n = 10)		
Naftali et al 2017a[a]	29	CD	1 country	Cannabis oil 5% cannabidiol (n = 10)	8 wk	Randomized, Double-blind, Placebo-controlled
			1 center	Placebo (n = 9)		
Naftali et al 2017b[a]	50	CD	1 country	Cannabis oil 15% cannabidiol and 4% THC (n = 24)	8 wk	Randomized, Double-blind, Placebo-controlled
			1 center	Placebo (n = 26)		
Irving et al 2018[a]	60	UC	1 country	Cannabidiol 4.7% THC (n = 29)	10 wk	Randomized, Double-blind, Placebo-controlled
			9 centers	Placebo (n = 31)		
Naftali et al 2018[a]	32	UC	1 country	Cannabis cigarettes 11.5 mg THC (n = 17)	8 wk	Randomized, Double-blind, Placebo-controlled
			1 center	Placebo (n = 15)		

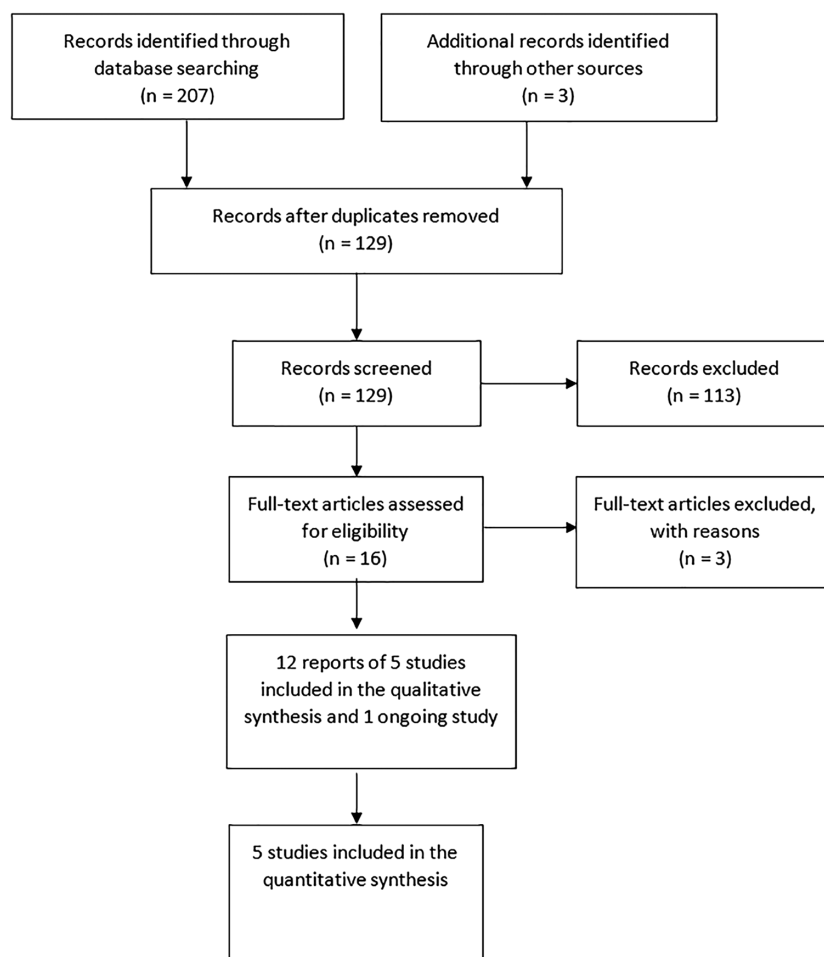[a]Induction of remission study

FIGURE 1. Flow diagram of studies

treatment. Secondary outcomes included response rate (defined as a 100-point CDAI reduction from baseline), a reduction of at least 0.5 mg in C-reactive protein (CRP), and an improvement in quality of life of at least 50 points from baseline, as measured by the Short-Form 36 (SF-36) health survey. Adverse events were assessed by questionnaire, and severity was assessed on a scale from 1 to 7, with 1 corresponding with no symptoms and 7 corresponding with severe symptoms.

The study by Naftali et al in 2017 was a single-center, placebo-controlled, randomized, double-blind trial that assessed the effects of cannabidiol in participants with active CD.[9] Participants were given either 2 mL twice daily of cannabis oil at a concentration of 5 mg/mL (ie, 20 mg/day or approximately 5% cannabidiol) or placebo containing 2 mL of pure olive oil twice daily. Twenty-one participants were recruited, but 19 participants completed the study. Participants were at least 20 years of age, had active CD (defined as a CDAI score between 200 and 450 points), and had received at least 1 form of medication for CD with no effect. Previous treatments included corticosteroids, 5-aminosalicylates, methotrexate, azathioprine, 6-mercaptopurine, or anti-TNF-α. Participants receiving corticosteroids had to be on a stable dose for at least 1 month. Participants receiving thiopurines had to be on a stable dose for at least 3 months, and participants receiving anti-TNF-α had received at least 4 infusions before treatment failure was declared. Participants were visited at weeks 0, 2, 8, and 10. The primary outcome was a 70-point reduction in the CDAI score from week 0 to week 8. Secondary outcomes included any AEs, the ability to stop steroids in participants who were initially treated with steroids, and a reduction in at least 1 mg/dL in the CRP level. Adverse events were assessed by a questionnaire similar to the one described for the study by Naftali et al in 2013.

The second study by Naftali et al in 2017 was an abstract presented at the International Association of Cannabis Medicine Conference in September 2017 and was sent to us by the first author.[10] It is a placebo-controlled, randomized, double-blind trial looking at the effect of cannabis on CD. Participants were randomized to either cannabis oil (15% cannabidiol and 4% THC) or placebo oil for 8 weeks of treatment. The cannabis oil group had 24 participants, and the placebo oil group had 26 participants. Inclusion criteria were not specified. Outcomes included the CDAI, inflammatory markers, and quality of life as measured by the Short-Form 36 health survey. These outcomes were assessed before, during, and after treatment.

Ulcerative Colitis

The study by Irving et al in 2018 was a multicenter, placebo-controlled, randomized, double-blind study that compared cannabidiol capsules (up to 4.7% THC) (n = 29) with placebo (n = 31) over a 10-week period.[11] Cannabidiol was started at a dose of 50 mg twice daily which, if tolerated, was increased

to 250 mg twice daily. Participants who were previously diagnosed with mild to moderate UC and were on stable doses of 5-aminosalicylates for at least 2 weeks before screening for study entry were eligible for inclusion. Participants with severe UC or proctitis were excluded. The primary outcome was clinical remission (defined as a Mayo score ≤2 with no subscore >1) after 10 weeks of treatment. Secondary outcomes included inflammatory marker levels (CRP, plasma interleukin, and FCP), stool frequency, rectal bleeding, physician global assessment of illness severity score, and the inflammatory bowel disease questionnaire (IBDQ) score. The original study protocol only planned an ITT analysis, but 1 year after completion of the study they added a per protocol analysis set.

The study by Naftali et al in 2018 was an abstract publication of a randomized, placebo-controlled trial. The study enrolled participants with UC who were not responsive to conventional medical treatment (N = 32).[12] For 8 weeks, participants in the treatment group (n = 17) were given 2 cannabis cigarettes (11.5 mg THC; 23 mg THC/day) daily, and participants in the placebo group (n = 15) were given cigarettes with the THC extracted from the cannabis leaves.

Outcomes reported in the abstract included disease activity index (DAI), Mayo endoscopic score, endoscopic findings, and laboratory tests (CRP, FCP).

Risk of Bias

The methodological quality of the studies is summarized in Table 2. All studies were low risk of bias regarding sequence generation and generally low risk of bias regarding allocation concealment. There was a high risk of bias in 2 studies for blinding due to concerns that participants in the cannabis group discovered their allocation due to the psychotropic effects of cannabis.

EFFECTS OF INTERVENTIONS

Crohn's Disease

Cannabis cigarettes (115 mg THC) vs placebo cigarettes at 8 weeks.

Clinical remission rates (defined as a CDAI score <150) at 8 weeks were reportedly higher in the cannabis group compared with placebo.[2] Clinical remission was reported in 45% (5 of 11) of participants in the cannabis group compared with 10% (1 of 10) of participants in the placebo group (risk ratio [RR] 4.55; 95% CI, 0.63–32.56; very low certainty evidence) (Fig. 2). Clinical response (defined as a 100-point CDAI reduction from baseline) at 8 weeks was reported in 91% (10 of 11) of participants in the treatment group in comparison with 40% (4 of 10) of participants in the placebo group (RR 2.27; 95% CI, 1.04–4.97; very low certainty evidence).

No differences in the serum CRP levels were detected. From week 0 to week 8, a decrease in CRP of more than 0.5 mg/dL was found in 27% (3 of 11) of participants in the treatment

group in comparison with 20% (2 of 10) of participants in the placebo group (RR 1.36; 95% CI, 0.28–6.56; low certainty evidence). Quality of life scores increased in the treatment group compared with the placebo group. The treatment group had an increase of 28 points from baseline to week eight, in comparison with a 5-point increase in the placebo group. None of the participants experienced any difficulty or withdrawal symptoms when they stopped the cannabis treatment after 8 weeks. Participants in the cannabis group also reported improvements in satisfaction, pain, and appetite. Endoscopic remission, endoscopic response, histological response, SAEs, and withdrawal due to AEs were not reported in this study.

Cannabis oil (5% cannabidiol sublingual oil) vs placebo oil at 8 weeks.

At 8 weeks, clinical remission rates in the cannabis (5% cannabidiol sublingual oil) and placebo groups were similar (Fig. 3).[9] Clinical remission was reported in 40% (4 of 10) of participants in the cannabis oil group in comparison with 33% (3 of 9) of participants in the placebo group (RR 1.20; 95% CI, 0.36–3.97; very low certainty evidence). Although the study protocol stated they were going to assess clinical response (defined as a 70-point CDAI reduction score) from week 0 to 8 as the primary outcome and reduction in CRP level, the final data for these outcomes were not reported. Additionally, endoscopic response, endoscopic remission, and histological response were not assessed in this study.

Cannabis oil (15% cannabidiol and 4% THC) vs placebo oil at 8 weeks.

Differences in CDAI and quality of life scores (SF-36) were found in a study (N = 39) comparing cannabis oil (15% cannabidiol and 4% THC) with placebo oil.[10] After 8 weeks of treatment, the mean quality of life score was 96.3 in the cannabis oil group compared with 79.9 in the placebo group (mean difference [MD] 16.40; 95% CI, 5.72–27.08, low certainty evidence). In addition, the mean CDAI score at 8 weeks was 118.6 in the cannabis oil group compared with 212.6 in the placebo group (MD −94.00; 95% CI, 148.86–39.14, low certainty evidence). The abstract did not report on any other outcomes.

Ulcerative Colitis

Cannabidiol capsules (100 mg to 500 mg/day with up to 4.7% THC) vs placebo capsules at 10 weeks.

There was no difference between the cannabidiol group and the placebo group in clinical remission rates at 10 weeks.[11] Clinical remission was reported in 24% (7 of 29) of participants in the treatment group in comparison with 26% (8 of 31) of participants in the placebo group (RR 0.94; 95% CI, 0.39–2.25)

TABLE 2. Methodological Quality of Included Studies

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting
Naftali et al 2013a	Low risk[a]	Unclear risk[b]	High risk[c]	Unclear risk[d]	Unclear risk[e]
Naftali et al 2017a	Low risk[a]	Low risk[f]	Low risk[g]	Low risk[h]	Unclear risk[i]
Naftali et 2017b	Low risk[a]	Low risk[f]	Low risk[g]	Low risk[h]	Unclear risk[i]
Irving et al 2018	Low risk[j]	Low risk[k]	Low risk[g]	Unclear risk[l]	Low risk[m]
Naftali et al 2018	Low risk[a]	Low risk[f]	High risk[c]	Low risk[h]	Unclear risk[n]

[a]Block method was used for randomization; [b]methods not described; [c]blinding was attempted but participants were able to correctly identify the group they belonged to; [d]higher drop-out rates in the placebo group; [e]difference in primary outcome reported between protocol and final manuscript; [f]fequentially numbered bottles; [g]double-blind; [h]No dropouts; [i]pre-specified outcomes not reported; [j]randomization schedule; [k]centralized randomization; [l]higher drop-outs rates in the treatment group; [m]all pre-specified outcomes were reported; [n]pre-specified outcomes not reported in abstract, but could still be reported in final manuscript
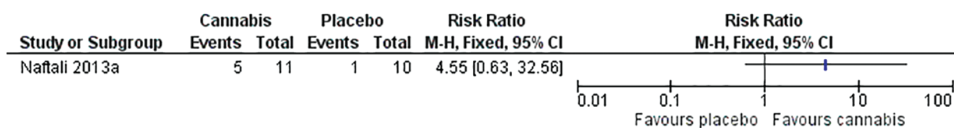

FIGURE 2. Clinical remission at 8 weeks (Crohn's disease): Cannabis cigarettes (115mg THC) vs placebo cigarettes
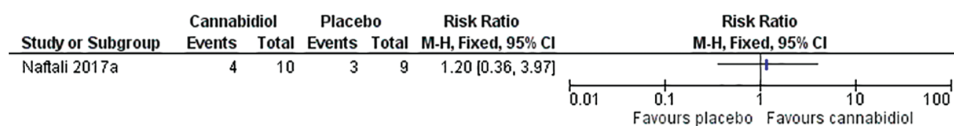

FIGURE 3. Clinical remission at 8 weeks (Crohn's disease): Cannabis oil (5% cannabidiol sublingual oil) vs placebo oil

([Fig. 4](#)). The GRADE rating for this outcome was low due to very sparse data (15 events). No difference in clinical response rates at 10 weeks was reported. Clinical response (defined as a decrease in total Mayo score of ≥3 points compared with baseline, with a reduction of at least 1 point in endoscopy findings subscore) was reported in 31% (9 of 29) of participants in the cannabidiol group compared with 23% (7 of 31) of participants in the placebo group (RR 1.37; 95% CI, 0.59–3.21). The GRADE rating for this outcome was low due to very sparse data (16 events).

C-reactive protein levels between the treatment and placebo groups were similar at 10 weeks. The mean CRP in the cannabidiol group was 9.428 mg/L ± 17.4 compared with 7.64 mg/L ± 10.7 in the placebo group (MD 1.79; 95% CI, 5.67–9.25). The GRADE rating for this outcome was moderate due to sparse data (60 participants).

The IBDQ scores between the treatment and placebo groups were similar at 10 weeks. The mean IBDQ score was 164.2 ± 29.1 in the cannabidiol group compared with 146.8 ± 47.5 in the placebo group (MD 17.40; 95% CI, 3.45–38.25). The GRADE rating for this outcome was moderate due to sparse data. In addition, the pain (MD 0.32; 95% CI, 0.51–1.15), stool frequency (MD 0.00; 95% CI, 0.35–0.35), and rectal bleeding (MD 0.09; 95% CI, 0.47–0.29) scores were similar at 10 weeks. Relapse, endoscopic remission, endoscopic response, histological response, and cannabis withdrawal effects were not reported in this study.

Cannabis cigarettes (23 mg THC/day) vs placebo cigarettes at 8 weeks.

A small study (N = 32) compared cannabis cigarettes with placebo.[12] Clinical remission and clinical response were not reported as outcomes in this study. Greater improvements were reported in DAI scores and the Mayo endoscopic score in the cannabis group in comparison with placebo. After 8 weeks of therapy, the DAI in the cannabis group was 4 ± 3.2 compared with 8 ± 2 in the placebo group (MD −4.00; 95% CI, 5.98–2.02; 28 participants). After 8 weeks of treatment, the Mayo endoscopic score decreased from a median of 2 (interquartile range [IQR] 2 to 2.5) to 1 (IQR 0 to 2) in the cannabis group and from 2 (IQR 2 to 2) to 2 (IQR 1.25 to 2) in placebo group. Mean serum CRP concentrations were similar at 8 weeks. The mean CRP in the cannabis group was 0.7 mg/L ± 1.2 compared with 1 mg/L ± 1.6 in the placebo group (MD 0.30; 95% CI, 1.35–0.75). The GRADE rating was low due to very sparse data (28 events). After 8

weeks of treatment, FCP levels were lower in the cannabis group than the placebo group. The mean FCP concentration was 115 µg/g ± 103 in the cannabis group compared with 229 µg/g ± 230 in the placebo group (MD 114.00; 95% CI, 246.01–18.01). The authors reported that no SAEs were observed. Relapse, endoscopic response, endoscopic remission, histological response, symptom improvement, quality of life, AE withdrawals due to AEs, and cannabis withdrawal effects were not reported in this study.

Adverse Events

Two CD studies reported on AEs. Only 1 study reported on withdrawal symptoms from cannabis use. The prevalence of AEs was acquired from the authors for the Naftali 2013 study. Higher rates of AEs were reported in the cannabis group in comparison with the placebo group.[2] Eighty-two percent (9 of 11) of participants in the cannabis group experienced an AE in comparison with 20% (2 of 10) of placebo participants (RR 4.09; 95% CI, 1.15–14.57) ([Supplemental Fig. 1](#)). However, these AEs were mild and included nausea, confusion, dizziness, difficulty with concentration, memory loss, and sleepiness. The GRADE rating was very low due to high risk of bias and sparse data (11 events).

The AEs in the first study by Naftali in 2017 were rated on a scale from 1 to 7 and included headache, sleepiness, nausea, and dizziness.[9] The AE and SAE rates were similar between the cannabis oil and placebo groups.[9] Ten percent (1 of 10) of participants in the cannabis oil group experienced an SAE compared with 11% (1 of 9) of placebo participants (RR 0.90; 95% CI, 0.07–12.38). The GRADE rating was very low due to high risk of bias and sparse data (2 events; [Supplemental Fig. 2](#)). In both cases, the SAE was worsening CD, which required rescue intervention. The participants did not report any withdrawal symptoms when the treatment was stopped. The second study by Naftali in 2017 did not report on AEs.[10]

For UC, the Irving 2018 study reported AEs in detail.[11] This study reported that AEs were more frequent in the cannabidiol group in comparison with the placebo group.[11] All the participants in the cannabis group (29 of 29) experienced an AE compared with 77% (24 of 31) of participants in the placebo group (RR 1.28; 95% CI, 1.05–1.56) ([Supplemental Fig. 3](#)). The GRADE rating for this outcome was moderate due to sparse data (53 events). The AEs were categorized as mild or moderate in severity. Commonly reported AEs in the cannabidiol group included dizziness, somnolence, disturbance in attention, headache, memory impairment, nausea, dry mouth, vomiting,

Study or Subgroup	Cannabidiol Events	Total	Control Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Irving 2018	7	29	8	31	0.94 [0.39, 2.25]	

0.01 0.1 1 10 100
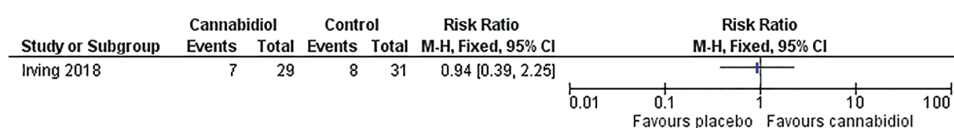Favours placebo   Favours cannabidiol

FIGURE 4. Clinical remission at 10 weeks (ulcerative colitis): Cannabidiol (100 to 500 mg/day with up to 4.7% THC) vs placebo

lower respiratory tract infection, disorientation, and fatigue. Common AEs reported in the placebo group include dizziness, headache, nausea, abdominal pain, worsening UC, abdominal distention, constipation, fatigue, back pain, and rash. There was no significant difference in SAE rates. None of the participants (0 of 29) in the cannabidiol group had a SAE compared with 10% (3 of 31) of participants in the placebo group (RR 0.12; 95% CI, 0.01–2.11) (Supplemental Fig. 4). The GRADE rating for SAEs was low due to very sparse data (3 events). Serious AEs in the placebo group were related to worsening of disease and 1 complicated pregnancy. None of the SAEs were thought to be treatment related. Study withdrawal due to AEs was more frequent in the cannabidiol group. In the cannabidiol group, 34% (10 of 29) participants withdrew compared with 16% (5 of 31) of placebo participants (RR 2.14; 95% CI, 0.83–5.51). The GRADE rating for this outcome was low due to very sparse data (15 events). Study withdrawals in the cannabidiol group were mostly due to dizziness, and study withdrawals in the placebo group were due to worsening UC. The Naftali 2018 study did not report details of AEs but mentioned no SAEs were observed.[12]

Quality of Evidence

The quality of evidence supporting the outcomes was assessed using the GRADE criteria. In CD participants, all the outcomes ranged from very low–quality to low-quality evidence mainly due to sparse data and high risk of bias (see supplemental Tables 1, 2 and 3). Similarly in UC participants, the evidence supporting the primary outcome (clinical remission at 10 weeks) was low quality due to sparse data. The quality of the evidence supporting secondary outcomes assessed in UC participants ranged from low to moderate quality mainly due to sparse data (see supplemental Tables 4 and 5).

DISCUSSION

The results of this review demonstrate that the effects of cannabis and cannabinoids on CD and UC are uncertain. There were only a few small studies looking at the use of cannabis or cannabinoids in active CD and UC. No studies evaluated maintenance treatment and relapse in quiescent CD or UC. Each study used different doses, formulations, and routes of administration of cannabis or cannabinoid, so this precluded meta-analysis. GRADE analyses of the CD data found that the certainty of the evidence supporting the outcomes was low to very low. GRADE analyses of the UC data showed that the overall certainty of evidence supporting the outcomes ranged from low to moderate. Overall, we are uncertain about the benefits and harms of cannabis and cannabidiol in people with active CD or UC.

There was a paucity of reported data on AEs (short and long term), so the safety of these agents is uncertain. For CD, the Naftali 2013 study reported a higher number of AEs in the cannabis group in comparison with the placebo group.[2]

However, the first study by Naftali in 2017 did not find a difference in the proportion of participants with AEs.[9] For UC, the study by Irving in 2015 reported a significantly higher rate of SAEs in the cannabidiol group compared with placebo but no significant difference in AEs.[11] The Naftali 2018 study did not report details of AEs but mentioned no SAEs were observed.[12] GRADE analysis indicated that the overall certainty of evidence for the AEs and SAEs outcomes was low to very low due to very sparse data.

There were concerns regarding the risk of bias in all the studies included in this review. For CD, in the Naftali 2013 study, blinding of participants and other bias was rated as high risk of bias because participants in the cannabis group were older than participants in the placebo group.[2] Although the authors randomly assigned participants, most participants were able to figure out which group they were assigned to due to the psychotropic effects of cannabis. The first study by Naftali in 2017 was rated as high risk of bias due to other bias.[9] Sixty percent of cannabis participants were smokers compared with none of the placebo participants. The second study by Naftali in 2017 was rated a low risk of bias.[10] For UC, the overall risk of bias for the Irving 2018 study was low.[11] Although the Naftali 2018 study was only a published abstract, we were able to obtain further information from the principal investigator to inform our risk of bias assessment.[12] The Naftali 2018 study was rated as high risk of bias for blinding of participants and personnel.[12] This was similar to Naftali 2013 because the unmasking of treatment assignment was very likely given the psychotropic nature of cannabis.

We must weigh the possibility of the small theoretical benefit of cannabis and cannabinoids in CD and UC against the well-established harms of cannabis, including mental health–related concerns.[14] Even if cannabis is not particularly effective to treat inflammation in IBD, there is a possibility it may have an adjunctive role for symptom management of pain, anorexia, or nausea. Further research into this area is warranted.

In conclusion, the effects of cannabis and cannabidiol on CD and UC are uncertain. No firm conclusions can be made regarding the effectiveness and safety of cannabis or cannabidiol in adults with active CD or UC. Studies with higher methodological quality and a larger number of participants are required to allow for more definitive conclusions on the effectiveness and safety of cannabis in CD and UC. Further data are needed on AEs, so future RCTs should more clearly assess and report on AEs. Long-term follow-up is required to assess withdrawal effects, safety outcomes, consequences in terms of cognitive function, and capacity to function in activities of daily living while using cannabis.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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