

# Guidance on the suggested use of medical cannabis

## Crohn's and ulcerative colitis

**About this document:** The following information on the use of medical cannabis serves as a suggested use guide for those participating in the Utah Medical Cannabis Program. The intended audience for this document includes, pharmacy medical providers, patients intending to use medical cannabis, and caregivers of patients intending to use medical cannabis.

This document details the guidance on the use of medical cannabis for Crohn's and ulcerative colitis. This document does not include general instructions on the use of medical cannabis, contraindications, warnings, precautions and adverse reactions to using cannabis and drug-to-drug interactions which could be found in the extended guidance document titled *Guidance on the Suggested Use of Medical Cannabis*. The extended guidance document can be found on the Department of Health and Human Services Center for Medical Cannabis website ([www.medicalcannabis.utah.gov](http://www.medicalcannabis.utah.gov)).

**About the authors:** This document was authored by the Utah Cannabis Research Review Board and Department of Health and Human Services staff.

**About the Utah Cannabis Research Review Board:** Under Utah Health Code 26-61-201, the Cannabis Research Review Board is a board of medical research professionals and physicians who meet on a voluntary basis to review and discuss any available scientific research related to the human use of cannabis, cannabinoid product or an expanded cannabinoid product that was conducted under a study approved by an Institutional Review Board (IRB) or was conducted and approved by the federal government.

**Guidance:** There is insufficient evidence to support or refute that short-term (8-10 week) cannabis treatment reduces inflammation or induces clinical or endoscopic response/remission in patients with active Crohn's disease or ulcerative colitis (trials for Crohn's disease: THC-predominant cannabis cigarettes or CBD-rich cannabis oil; trials for ulcerative colitis: CBD-predominant cannabis oral capsule or THC-predominant cannabis cigarettes)

There is limited evidence to support the conclusion that short-term (8-10 week) cannabis treatment may improve patient-reported quality-of-life in patients with active Crohn's disease or ulcerative colitis (trials for Crohn's disease: CBD-rich cannabis oil; trials for ulcerative colitis: CBD-predominant cannabis oral capsule or THC-predominant cannabis cigarettes).

<sup>a</sup> Developed using level of evidence categories from the 2017 National Academies of Sciences, Engineering, and Medicine report on cannabis (National Academies of Sciences, Engineering, and Medicine, 2017d).

**Important note:** In the event of significant adverse effects, stop use of medical cannabis until adverse effects have resolved, and then reduce to previous, best-tolerated dose. To avoid unwanted psychoactive adverse effects, "start low and go slow", especially when using cannabis products for the first time or using new dosages or types of products.

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The sections below on ulcerative colitis and Crohn's disease are adapted from published systematic reviews, or randomized controlled trials identified from the Cochrane organization database, or systematic searches of the Ovid-Medline and Embase databases. *All trials included patients with active ulcerative colitis or Crohn's disease.* Randomized controlled trials (RCT) evidence is primarily among people with mild-moderate Inflammatory Bowel Disease (IBD) severity. Most RCTs used cannabis-based treatments as an adjunctive therapy to standard IBD treatment. Many of the trials required that patients had an insufficient response to 1 or more standard IBD treatments.

Cannabis and cannabinoids are often promoted as treatments for many illnesses and are widely used among patients with ulcerative colitis (UC). Few studies have evaluated the use of these agents. Further, cannabis has potential for adverse events, and the long-term

consequences of cannabis and cannabinoid use in UC are unknown.

A review of 3 trials that measured quality of life (QoL) in UC patients indicated that there was significant improvement in the reported QoL for participants who consumed cannabinoids for a period of 8-10 weeks when compared to those participants on placebo (Irving, et al., 2018; Naftali, Bar-Lev, Schleider, Scklerovsky Benjaminov, et al., 2021; Tartakover, et al., 2021). Additionally, reported outcomes were significant for improving pain related to irritable bowel disease and had a lower risk of adverse events (AE) when compared to the placebo group (Irving, et al., 2018). Other measures, such as frequency of bowel movements, did not have any statistical significance in either the study or control groups, while another study reports a decline in frequency (Naftali, Bar-Lev, Schleider, Scklerovsky Benjaminov, et al., 2021).

Adverse Events that were reported for patients who received CBD were ranked as mild to moderate; however, 10% of these patients reported severe neurological events, including disturbed attention, dizziness, and dizziness with joint swelling/muscle twitching. The placebo group had 3 treatment-emergent severe AEs, including 1 event of chest pain (Irving, et al., 2018).

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 the 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 (Irving, et al., 2018). 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 (Naftali, Bar-Lev, Schleider, Scklerovsky Benjaminov, et al., 2021). Another small trial using THC-predominant cannabis reported no serious AEs (Kafil, et al., 2018b).

A Cochrane meta-analysis was published in Issue 6, 2019. The primary outcomes were clinical remission and relapse. Secondary outcomes included endoscopic response, quality of life, adverse events, and cannabis dependence and withdrawal effects.

Two studies met the inclusion criteria. One study compared 10 weeks of cannabidiol capsules containing up to 4.7% delta-9-tetrahydrocannabinol (THC) with placebo capsules in participants with mild to moderate UC. The starting dose of cannabidiol was 50 mg twice daily, increasing to 250 mg twice daily if tolerated. Another study compared 8 weeks of therapy with two cannabis cigarettes per day containing 0.5 g of cannabis, corresponding to 23 mg THC/day, to placebo cigarettes in participants with UC who did not respond to conventional medical treatment. The effect of cannabidiol capsules (100 mg to 500 mg daily) compared to placebo on clinical remission and response is uncertain. Clinical remission at 10 weeks was achieved by 24% of the cannabidiol group compared to 26% in the placebo group. Clinical response and Serum CRP levels were similar in both groups after 10 weeks of therapy. There may be a clinically meaningful improvement in QoL at 10 weeks. Adverse events were more frequent in cannabidiol participants compared to placebo. One hundred percent of cannabidiol participants had an adverse event, compared to 77% of placebo participants. However, these adverse events were considered to be mild or moderate in severity. Common adverse events included dizziness, disturbance in attention, headache, nausea, and fatigue. More participants in the cannabidiol group withdrew due to an adverse event than placebo participants. Withdrawals in the cannabidiol group were mostly due to dizziness. Withdrawals in the placebo group were due to worsening UC. The effect of cannabis cigarettes (23 mg THC/day) compared to placebo on mean disease activity, CRP levels, and mean fecal calprotectin levels is uncertain. After 8 weeks, the mean disease activity index score in cannabis participants was 4 compared with 8 in placebo participants. After 8 weeks, the mean change in CRP levels was similar in both groups. No serious adverse events were observed. This study did not report on clinical remission, clinical response, quality of life, adverse events, or withdrawal due to adverse events.

*Conclusions. 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. Further studies with a larger number of patients are required to assess the effects of cannabis in UC patients with active and quiescent disease. Different doses of cannabis and routes of administration should be investigated. Lastly, follow-up is needed to assess the long-term safety outcomes of frequent cannabis use.*

Crohn's disease (CD) is a chronic immune-mediated condition of transmural inflammation in the gastrointestinal tract, associated with significant morbidity and decreased quality of life. The endocannabinoid system provides a potential therapeutic target for cannabis, cannabinoids, and animal models have shown benefits in decreasing inflammation. However, there is also evidence to suggest transient adverse events such as weakness, dizziness, diarrhea, and an increased risk of surgery in people with CD who use cannabis.

In the context of 7 trials, differences in the quality of life (QoL) were reported in 5 of them. The QoL was measured using the general QoL scale, the SF-36 scale, or an unknown scale (Naftali, Bar-Lev Schleider, Dotan, et al., 2013; Naftali, et al., 2017; Naftali, et al., 2018; Naftali, Bar-Lev Schleider, Almog, et al., 2021; Tartakover, et al., 2021). The findings of one trial measuring QoL were not reported (Naftali, et al., 2017). All trials that reported QoL results documented a significant improvement in QoL from baseline to 8 weeks in the cannabis arm compared to the placebo arm ((Naftali, Bar-Lev Schleider, Dotan, et al., 2013; Naftali, et al., 2017; Naftali, Bar-Lev Schleider, Almog, et al., 2021; Tartakover, et al., 2021). Similarly, the cannabis arm reported a higher QoL score at 8 weeks (Naftali, et al., 2018). Out of the five trials that observed an improvement in QoL, four utilized CBD-rich cannabis, while THC-rich cannabis was used in only one trial (Naftali, Bar-Lev Schleider, Dotan, et al., 2013; Naftali, et al., 2017; Naftali, et al., 2018; Naftali, Bar-Lev Schleider, Almog, et al., 2021; Tartakover, et al., 2021).

When looking at the researched effects of cannabis and cannabinoids on Crohn-related pain, we find that the evidence is limited. Significantly greater improvements in median pain scores were reported in one study when patients consumed THC-rich cannabis vs the placebo (Naftali, Bar-Lev Schleider, Dotan, et al., 2013). Bowel movement frequency was found to decrease in 2 studies that also utilized THC-rich cannabis, with no differences reported between the control and study groups (Naftali, Bar-Lev Schleider, Almog, et al., 2021; Tartakover, et al., 2021).

A review of 7 clinical trials conducted by Naftali et al. assessed changes in overall CD activity using the Crohn's Disease Activity Index (CDAI) (Merck & Co, Inc, 2023; Regueiro & Al Hashash, 2023) . The reports from all seven trials indicate a 71% improvement per the CDAI over 16 weeks in participants that received cannabis when compared to placebo groups (Kafil, et al., 2018a; Naftali, Bar-Lev Schleider, Dotan, et al., 2013; Naftali, Barlev, Gabay, et al., 2013; Naftali, et al., 2017; Naftali, et al., 2018; Naftali, Bar-Lev Schleider, Almog, et al., 2021). The 2 trials that did not support the improvement of the CDAI scores numerically improved from baseline to 8 weeks in both the cannabis and placebo arms, with differences from baseline non-significantly favoring cannabis (Naftali, et al., 2017; Tartakover, et al., 2021).

Symptom improvement included clinical remission as reported by 4 trials and indicated favorable support for treating with cannabis (Naftali, Bar-Lev Schleider, Dotan, et al., 2013; Naftali, et al., 2017). However, of the 4 trials, only 1 demonstrated statistical significance (Naftali, et al., 2018). One trial reported that there were no differences in the levels of inflammatory markers or C-reactive protein or calprotectin trial groups (Naftali, et al., 2017).

The studies that included trials of THC-rich cigarettes reported no serious AEs (Naftali, Bar-Lev Schleider, Dotan, et al., 2013; Naftali, Barlev, Gabay, et al., 2013). Nausea, sleepiness,

concentration, memory loss, confusion, and dizziness were reported by the cannabis arm and were rated as mild severity. The same findings were found in the placebo group (Naftali, Bar-Lev Schleider, Dotan, et al., 2013). However, 5 trials studying the effects of CBD-rich oils found that headache, sleepiness, nausea, and dizziness occurred at similar rates as the placebo group (Naftali, et al., 2017).

Cochrane meta-analysis was published in Issue 6, 2019. The primary outcomes were clinical remission and relapse. Secondary outcomes included endoscopic response, quality of life, adverse events, and cannabis dependence and withdrawal effects.

Three studies met the inclusion criteria. Participants in two of the studies were adults with active Crohn's disease who had failed at least one medical treatment. One small study compared eight weeks of treatment with cannabis cigarettes containing 115 mg of delta-9-tetrahydrocannabinol (THC) to placebo cigarettes containing cannabis with the THC removed in participants with active CD. The effects of cannabis on clinical remission were unclear. A difference was observed in clinical response rates. Ninety-one percent of the cannabis group achieved a clinical response compared to 40% of the placebo group. More AEs were observed in the cannabis cigarette group compared to placebo. These AEs were considered mild in nature and included sleepiness, nausea, difficulty with concentration, memory loss, confusion, and dizziness. One small study compared cannabis oil (5% cannabidiol) to placebo oil in people with active CD. There was no difference in clinical remission rates. Forty percent of cannabis oil participants achieved remission at 8 weeks compared to 33% of the placebo participants. There was no difference in the proportion of participants who had a serious adverse event. One small study compared cannabis oil (15% cannabidiol and 4% THC) to placebo in participants with active CD. Differences in QoL scores were observed. The mean QoL score after 8 weeks of treatment was 96.3 in the cannabis oil group compared to 79.9 in the placebo group. This study did not report on clinical remission, clinical response, CRP, or AEs.

*Conclusions. 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. Further studies with larger numbers of participants are required to assess the potential benefits and harms of cannabis in Crohn's disease. Future studies should assess the effects of cannabis in people with active and quiescent Crohn's disease. Different doses of cannabis and delivery modalities should be investigated.*

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This document is a summary of available peer-reviewed literature concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids. With the ongoing nature of cannabis and cannabinoid research, it is not meant to be complete or comprehensive and should be used as a limited complement to other reliable sources of information. This document is not a systematic review or meta-analysis of the literature and has not rigorously evaluated the quality and weight of the available evidence. There is a lack of controlled clinical trials yielding high level evidence of predictable therapeutic benefit for any given condition other than those for FDA approved formulations. This document includes warnings and risks related to the use of cannabis including cannabis use disorder, potentially irreversible brain damage/mental illness, and legal liability for DUI and potential for adverse work-related consequences.

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