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BRIEF EVIDENCE REVIEW:

Randomized Control Trial Evidence for the Treatment of Inflammatory Bowel Diseases with Cannabis-based Products

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I have no conflicts of interest to disclose

BRIEF EVIDENCE REPORT OBJECTIVE & METHODS

- **Objective:**
  - Summarize recent clinical evidence for the treatment of Crohn's disease (CD) or ulcerative colitis (UC) with CBPs using a hierarchy-of-evidence approach
  - Assist the CRRB with updates to current guidance

- **Methods:**
  - Searched for SRs of RCTs or RCTs published since 2018* Cochrane reviews by Kafil et al[1,2]
    - Included SRs including at least 1 RCT, or RCT of any design
    - Patients with CD or UC
    - Treatment with cannabis-based product for any duration
  - Summarized major efficacy and safety outcomes – integrated results from Kafil et al with additional RCTs

*Narrowed RCT search dates to 2022-2023 based on the search dates of an SR by Vinci et al[3]

Abbreviations: CBP, cannabis- or cannabinoid-based product; CD, Crohn's disease; CRRB, Utah Cannabis Research Review Board; RCT, randomized controlled trial; SR, systematic review; UC, ulcerative colitis

KAFIL ET AL (2018) CONCLUSIONS

- **Crohn's Disease[1]**
  - Included 3 RCTs (n = 79-93 total) of adults with active disease
  - All efficacy and safety outcomes rated as very low or low certainty
  - Concluded effects of cannabis or cannabis oil are uncertain

- **Ulcerative Colitis[2]**
  - Included 2 RCTs (n = 92 total) of adults with active disease
  - All efficacy and safety outcomes rated as low certainty, except for QoL, changes in CRP, and AE event rate from 1 trial (moderate certainty)
  - Concluded effects of cannabis or cannabidiol are uncertain

Abbreviations: AE, adverse event; CBP, cannabinoid- or cannabis-based product; CRP, C-reactive protein; RCT, randomized controlled trial; QoL, quality of life;

OVERVIEW OF RCTS FOR UC TREATMENT

RCT	Participants (total n with UC)	Cannabis-based Treatment
Naftali et al 2013*[4]	Adults with UC who failed a prior therapy (n=10)	Cannabis cigarettes twice daily (11.5 mg THC/cigarette)
Irving et al 2018#[5]	Adults with **mild-mod** active UC (n=60)	CBD-rich botanical extract capsules (50 mg BID titrated to 250 mg twice daily; each capsule with 4.7% THC)
Naftali et al 2021#[6]	Adults with **mild-mod** active UC (n=32)	Cannabis cigarettes with up to 80 mg** THC twice daily
Tartakover et al 2021[7]	Adults with **mild-mod** active UC (n=19)	Cannabis cigarettes with 11.5 mg THC (and <0.5% CBD) per cigarette; unknown total # cigarettes

Included by Kafil et al 2018

**conflicting doses reported (may be 11.5 mg THC instead)

*Published as an abstract only.

- All 8-10 weeks of treatment vs placebo
- 3 of 4 trials with ROB ratings from an SR[2,3]
  - Low ROB (N=1)[5]
  - High ROB (N=2)[6,7]

Abbreviations: CBD, cannabidiol; mod, moderate; n, number; PBO, placebo; RCT, randomized controlled trial; ROB, risk of bias; THC, tetrahydrocannabinol; UC, ulcerative colitis;

RESULTS: CLINICAL RESPONSE OR REMISSION

Outcome(s)	CBP Intervention (N RCTs)	Select Result(s)
Change in disease activity scores	THC-predominant cigarettes (N=3); CBD-predominant capsules (N=1)	• 2 THC trials > PBO[#6,7] • 2 trials with numerical reductions vs PBO (1 trial**[5] and 1 trial*[4])
Clinical remission	CBD-predominant capsule	ITT: CBD (28%) vs PBO (26%)**[5] PPA: CBD (41%) vs PBO (30%)**[5]
	THC-predominant cigarette	*Described* as favoring cannabis*[6]
Clinical response	CBD-predominant capsule	CBD (31%) vs PBO (22%)**[2]
Endoscopic sub-score improvement, change or final score	CBD-predominant capsule	CBD (67%) vs PBO (39%), P=0.054**[5]
	THC-predominant cigarette	• Mean final scores: THC (1.25±2) vs PBO (1.69±1), P = 0.374**[6] • *Described* as improved by 1 trial*[7]

[#] Statistical superiority to PBO *No statistical hypothesis test reported
** No statistical superiority (failed to show difference)

Abbreviations: CBD, cannabidiol; CBP, cannabis- or cannabinoid-based product; ITT, intention-to-treat analysis; N, number; PBO, placebo; PPA, per-protocol analysis; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol;

RESULTS: INFLAMMATORY MARKERS

Outcome(s)	CBP Intervention (N RCTs)	Select Result(s)	
Changes in various blood/plasma inflammatory markers[a] and fecal calprotectin levels[b]	CBD-predominant capsule (N=1)	• Greater reductions from BL with CBD vs PBO, but not statistically significant*[5]	
Change in fecal calprotectin levels	THC-rich cigarettes (N=1)	<u>Baseline</u> THC: **170**±33 PBO: **226**±34[6]	<u>Treatment end</u> THC: **134**±33 (P=0.072)[##] PBO: **218**±67 (P=0.9)[##6]
Change in CRP levels	THC-rich cigarettes (N=2)	Mixed results: • Increased from BL (both CBP and PBO) in 1 trial[##6] • Decreased from BL (both CBP and PBO) in 1 trial[#4]	

[a] Included CRP (from blood) and select cytokines (IL-2, IL-6, TNF-alpha) from plasma

[b] Differences may not have detected because ~62% of patients had values exceeding detection limits

** No statistical superiority to PBO (failed to show difference)

[#] Possible statistical superiority to PBO (comparison is unclear)

[##] No significant differences for *within-treatment arm change from baseline*

Abbreviations: BL, baseline; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based products; PBO, placebo; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol;

RESULTS: QUALITY OF LIFE

Outcome(s)	CBP Intervention (N RCTs)	Select Result(s)	
Change in mean IBDQ total and sub-domain scores	CBD-predominant capsule (N=1)	• Change in total IBDQ score favored cannabis over PBO in PPA# but not ITT analysis* • Numerical differences* favored cannabis for all sub-domains except systemic symptoms[5]	
Patient overall global impression of change		• Cannabis > PBO (both ITT and PPA)#[5]	
Change in SF-36 total[a] score	THC-rich cigarettes (N=2)	<u>Baseline</u> THC, trial 1[6]: **77** ± 4 THC, trial 2[7]: **72.7** ± 6.7	<u>8 weeks</u> **98** ± 20# **98.2** ± 7.3#
		PBO, trial 1[6]: **78** ±3 PBO, trial 2[7]: **77.1** ±3.7	**78** ± 17 **82** ± 4

[a] Inferred as the total survey score; investigators did not describe this detail

*No statistical superiority to PBO (failed to show difference) # Statistical superiority to PBO

Abbreviations: CBD, cannabidiol; IBDQ, inflammatory bowel disease questionnaire; ITT, intention-to-treat; PBO, placebo; PPA, per-protocol analysis; RCT, randomized controlled trial; SF-36, 36-item short form survey; THC, delta-9-tetrahydrocannabinol;

RESULTS: ADVERSE EVENTS

CBP Intervention (N RCTs)	Select AE Result(s)		
CBD-predominant capsule (N=1)[5]		**Cannabis**	**Placebo**
	Any AE	90%	48%
	D/c due to AE	45% (often dizziness)	23% (often GI symptoms)
	Common cannabis-associated AEs	Dizziness, somnolence, disturbed attention, nausea	
THC-rich cigarettes (N=1)[6]		**Cannabis**	**Placebo**
	Cough	41%	20%
	Dizziness	35%	6%
	Difficulty stopping use	29%	12%
	Confusion	29%	6%
	Behavioral change	23%	0%

- Most AEs (per information from 2 trials) mild-moderate severity[6,7]

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; GI, gastrointestinal; N, number; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol;

OVERVIEW OF RCTS FOR CD TREATMENT

RCT	Participants (total n)	Cannabis-based Treatment
Naftali et al 2013a[#4]	Adults with **mod** CD (n=20)	Cannabis cigarettes, 11.5 mg THC twice daily
Naftali et al 2013b*[8]	Adults with **mild to mod-severe** active CD (n=21)	Cannabis cigarettes, 115 mg THC twice daily
Naftali et al 2017a*[9]	Adults with **mild to mod-severe** active CD (n=19)	Cannabis oil (CBD 5%), about CBD 10 mg twice daily **sublingually**
Naftali et al 2017b*#[10]	Adults with active CD (n=50)	Cannabis oil (CBD 15% and THC 4%)
Naftali et al 2018[#11]	**Mod** active CD (n=46)	
Naftali et al 2021[12]	Adults with **mild-mod** CD (n=56)	Cannabis oil (16% CBD, 4% THC), started with CBD 16 mg and THC 4 mg orally, titrated to symptoms
Tartakover et al 2021[7]	Adults with **mild-mod** CD (n=30)	Cannabis oil (4:1 CBD to THC), titrated to symptoms. Max 16 mg CBD/4 mg THC

* Included by Kafil et al 2018 #Published as an abstract only

- All 8 weeks of treatment vs placebo
- ROB per SR[1,3] (for 5 of 7 RCTs):
  - low (N=1)[10], some concerns (N=1)[11], high (N=3)[7,8,9]

Abbreviations: CBD, cannabidiol; CD, Crohn's disease; mod, moderate; RCT, randomized controlled trial; SR, systematic review; THC, delta-9-tetrahydrocannabinol;

RESULTS: CLINICAL RESPONSE OR REMISSION

Outcome(s)	CBP Intervention (N RCTs)	Select Result(s)
Change in disease activity scores[a]	THC-predominant cigarettes (N=2); CBD-rich oil (N=5)	• Cannabis change > PBO, or score at 8 weeks favored cannabis (5 of 7 RCTs)[#4,8, 10-12] • Non-significant change favoring cannabis to PBO (2 of 7 RCTs)*[7, 9]
Clinical remission[a]	THC-rich cigarette (N=2)	Cannabis (45%) vs PBO (10%)[*8]; descriptive improvements in 2nd trial**[4]
	CBD-rich oil (N=2)	Cannabis (40%) vs PBO (33.3%)[* 9]; and cannabis (65%) vs PBO (35%)[#11]
Clinical response[a]	High-dose THC-rich cigarette (N=1)	Cannabis (91%) vs PBO (40%)[#8]
Endoscopic score on SES-CD	CBD-rich oil (N=2)	No differences versus PBO at 8 weeks[#11.12]
		Median (IQR) at BL and 8 weeks: • Cannabis: 10 (7–14) → 7 (4–14) • PBO: 11 (7–14) → 8 (4–12)[12]

[a] Assessed on the Crohn's Disease Activity Index (CDAI)

[#] Statistical superiority to PBO

* No statistical superiority (failed to show difference)

**No statistical hypothesis test reported

Abbreviations: BL, baseline; CBD, cannabidiol; IQR, interquartile range; PBO, placebo; THC, delta-9-tetrahydrocannabinol;

RESULTS: INFLAMMATORY MARKERS

Outcome(s)	CBP Intervention (N RCTs)	Select Result(s)
Change in CRP or calprotectin levels[8, 11, 12] or level at 8 weeks[9]	CBD-rich oil (N=3) THC-rich cigarette (N=1)	• No significant differences from PBO* • Numerical observations: • CRP levels unchanged or declined slightly (N=3)[8,11, 12] • CRP levels increased (N=1)[9] • Calprotectin levels declined slightly (N=2)[11.12]

* No statistical superiority (failed to show difference) for CRP and/or calprotectin

Largest CBD-rich oil trial (final median dose, 80 mg CBD and 20 mg THC daily[12]):

Outcome(s), median [IQR]	Baseline		8 weeks	
	Cannabis	PBO	Cannabis	PBO
CRP levels (mg/dL)	1.4 (0.4-2.7)	1.7 (0.4-3.8)	1.3 (0.2-2.2)	1.5 (0.5-3)
Calprotectin levels (µg/g)	139 (64-300)	112 (50-185)	112 (65-300)	117 (50-300)

Abbreviations: CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; CRP, C-reactive protein; IQR, interquartile range; PBO, placebo; RCT, randomized controlled trial;

RESULTS: QUALITY OF LIFE

Outcome(s)	CBP Intervention (N RCTs)	Select Result(s)
Change in SF-36 score[a] or unknown QoL scale score	THC-rich cigarettes (N=1) CBD-rich oil (N=4)	• Improvements favoring cannabis, **or s**core at 8 weeks greater with cannabis > PBO[#7, 8, 10-12]

[a] Inferred as the total survey score; investigators did not describe this detail

[#] Statistical superiority to PBO, or within cannabis-arm superiority

Largest CBD-rich oil trial (final median dose, 80 mg CBD and 20 mg THC daily)[12]:

SF-36 total score, median (IQR)	Baseline		8 weeks	
	Cannabis	PBO	Cannabis	PBO
QoL survey score	74 (65-87)	74 (57-82)	91 (85-102)	75 (69-88)

Abbreviations: CBD, cannabidiol; CBP, CBP, cannabinoid- or cannabis-based product ; PBO, placebo; RCT, randomized controlled trial; SF-36, 36-item short form survey; THC, delta-9-tetrahydrocannabinol; QoL, quality of life;

RESULTS: ADVERSE EVENTS

CBP Intervention (N RCTs)	Select AE Result(s)
THC-rich cigarettes (N=2)	• No serious AEs[4,8]
	• AEs (with 115 mg THC twice daily), not > PBO: sleepiness, nausea, concentration, memory loss, confusion, dizziness[8]
CBD-rich oil (N=2)	Low-dose CBD, AEs similar to PBO: headache, sleepiness, nausea, dizziness[9]
	CBD oil, AEs with incidence ≥ 5% more than PBO: visual distortion, behavioral change, confusion, decreased memory, dizziness[12]

- AE information underreported by trials
- No data from 3 trials

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; N, number; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol;

EVIDENCE REVIEW SUMMARY

- Nine RCTs, including 4 for UC (n= 121) and 7 for CD (n=242)
- Four of seven RCTs with ROB ratings by SRs rated as *high risk*
- RCT evidence limited to short-term treatment of *active* IBD in adults using heterogenous cannabis formulations

Based on available RCT evidence in patients with UC or CD:

- Cannabis *may* improve some UC and CD symptoms in the short-term compared to placebo
  - Limited, uncertain evidence for clinical remission and response
- Cannabis *may* improve patient-reported quality of life versus placebo, in the short-term
- Effects of short-term cannabis on inflammatory markers and lesions in the GI tract are uncertain
- Short-term cannabis use appears to be associated with primarily mild-moderate severity events
  - AEs information is underreported by trials

Abbreviations: AE, adverse event; CBP, cannabinoid- or cannabis-based product; GI, gastrointestinal; RCT, randomized controlled trial;

INTERNATIONAL ORGANIZATION FOR IBD STUDY 2022 CONSENSUS PANEL CONCLUSION

- Consensus regarding lifestyle, behavioral, and environmental changes for people with IBD:
  - "Cannabis or cannabinoid use is not recommended as a treatment for IBD" (76% agreement from 41 panelists)
  - Stated rationale:

"…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 treatment of IBD" (page 669)[13]

Abbreviations: IBD, inflammatory bowel disease;

CURRENT CRRB GUIDANCE

Current graded recommendations for CD and UC:

"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)[14]

Abbreviations: CD, Crohn's Disease; CRRB, Utah Cannabis Research Review Board; UC, Ulcerative colitis;

CONSIDERATIONS FOR CRRB IBD GUIDANCE

- The CRRB may consider grading conclusions separately for conditions and outcomes, as appropriate

- Considerations for *graded* conclusions
  - Insufficient evidence: inflammation, clinical and endoscopic remission/response
  - Limited *or* insufficient evidence: improvement in patient-reported quality of life
  - May consider additional outcomes

- For each graded conclusion, consider:
  - Describing evidence is among patients with active disease, or consider adding a conclusion of no evidence among patients with quiescent (inactive) disease
  - Describing type(s) of cannabis studied
  - Stating conclusions are from short-term treatment

Abbreviations: CD, Crohn's Disease; CRRB, Utah Cannabis Research Review Board; IBD, inflammatory bowel disease; UC, Ulcerative Colitis;

CONSIDERATIONS FOR CRRB IBD GUIDANCE

- Additional considerations for elaboration in guidance:
  - All trials included patients with active UC or CD
  - RCT evidence is primarily among people with mild-moderate IBD severity
  - Most RCTs used cannabis-based treatments as an adjunctive therapy to standard IBD treatment
  - Many trials required that patients had an insufficient response to 1 or more standard IBD treatments
  - RCT evidence is limited to short-term treatment

Abbreviations: CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; CRRB, Utah Cannabis Research Review Board; IBD, inflammatory bowel disease; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol;

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Extra slides

NATIONAL ACADEMIES LOE RATINGS*[15]

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).
"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).
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).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[15]

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).
"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).
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).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[15]

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).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report.

Abbreviations: LOE, level of evidence;