COLLEGE OF PHARMACY
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RAPID LITERATURE REVIEW

CANNABIS OR CANNABINOID PRODUCTS FOR ACUTE PAIN

DRUG REGIMEN REVIEW CENTER, UNIVERSITY OF UTAH COLLEGE OF PHARMACY

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I have no conflicts of interest to disclose

PRESENTATION OUTLINE

- Evidence review approach
- Expert comments on human experimental models
- Overview of evidence for use of CBPs for people with acute pain
  - Systematic reviews of randomized controlled trials
  - Randomized controlled trials
- Summary

RAPID REVIEW METHODS

- **Objective:**
  - Identify and summarize relevant evidence to assist in decision-making by the CRRB

- **Relevant evidence:**
  - Systematic reviews (SRs) of randomized, controlled trials (RCTs) or RCTs
  - *Intervention*: cannabis, cannabis-derived products, or cannabinoids (abbreviated **CBPs**)
  - *Population:* people with acute pain
    - Pain no longer than about ~1 month
    - NOT human experimental models for acute pain

RAPID REVIEW METHODS

- Searched 2 major databases: Medline and Embase
  - SRs: no date restriction
  - RCTs: 2020 to present (April to May 2022)

- Focus on information reported in SRs
  - Primary: measures of pain intensity
  - Assessment of risk-of-bias (ROB)/quality of included RCTs

- Perform ROB assessment for RCTs not included in a SR using the Cochrane risk of bias 2 tool[1]

BACKGROUND

- Animal studies generally support potential effectiveness of CBPs for acute pain[2,3]

- **Mixed evidence** of efficacy of CBPs for acute pain in human experimental models
  - Neilsen et al. (5 trials): 3 with limited evidence of efficacy
    - Other 2 trials showed attenuation of opioid analgesia, and hyperalgesia[4]
  - Beaulieu et al.: "They are mostly negative and in 4 of them, more intense pain was reported at high doses"[5]
  - No benefit of oral CBD for pain intensity, allodynia or hyperalgesia in 2 additional trials[6,7]

RAPID REVIEW RESULTS

- Identified 11 SRs containing at least 1 relevant RCT

- Total of 11 RCTs published between 1981 and 2022
  - 10 RCTs were included in a SR
  - No SR included *all* identified RCTs

- Variable research question(s) across included SRs
  - Pain of any duration (N=3)[8-10]
  - 4 focused on acute pain (N=2)[11-12] or post-surgical pain (N=2)[13-14]
  - Pain associated with certain conditions (ie, orthopedics [N=2][15-16,] orofacial [N=1][17])
  - Potential opioid-sparing effects (N=1)[3]

RAPID REVIEW RESULTS

- **Conclusions from SRs** *addressing* acute pain evidence:
  - The majority concluded CBPs are *not* better than control for analgesia[8,12,13,17]
  - 2 SRs reported a *possible benefit* of CBPs for acute pain
    - Pooled effect (6 trials) for reduction in patient-reported scores pain scores for CBPs vs control[11]:
      - MD (95%CI): –0.90 (–1.69 to –0.10), I^2 = 65%
      - Heterogeneity related to route of administration

Select Abbreviations: CI, confidence interval; MD, mean difference

RAPID REVIEW RESULTS

- **Conclusions from SRs** addressing acute pain evidence:
  - Increased pain at rest post-surgery at 12 hours (but not 1-6 hours) for CBPs vs placebo, I^2 = 72%[16]
  - Limited evidence (3 SRs) does not support a reduction in opioid use with adjunctive CBP[4,13,15]
  - *Safety* per acute pain focused SR (6 RCTs)[11]:
    - Serious AE, CBP vs control: 3.7% vs 2.65%, OR = 1.44 (95%CI, 0.60 to 3.48)
    - Dizziness: OR = 1.96 (95%CI, 1.20 to 3.20)
    - Hypotension: OR = 3.61 (95%CI, 1.02 to 12.80)

RAPID REVIEW RESULTS

- **Design and risk of bias** of RCTs
  - All randomized, controlled; 1 with unknown blinding[18]
  - Total number of participants: 20 to 340
  - All with placebo comparator, often (n=7) with other analgesics[19,21-24,27,28,]; 4 trials with active comparator[15,21,24,27,28]
  - All trials except for 2[19,20] were rated as having an *unclear* risk of bias (Cochrane tool) for 2+ measures[4,8,11-13,16]
- **Population** of RCTs:
  - Post-operative pain after various major surgeries (N=8)[18,20-22,24-26]
    - 1 knee arthroplasty – osteoarthritis at baseline[23]
  - Tooth extraction (N=2)[27,28]
  - Acute, non-traumatic lower back pain (N=1)[19]

RAPID REVIEW RESULTS

- **CBP intervention** was a single cannabinoid in all trials
- Most trials administered a single CBP dose

CBP Intervention	Number of trials	Population(s)
Levonantradol IM x 1 dose[18,25,26]	3	Unknown, trauma, or renal surgery
THC x 1 dose,[22] or **dronabinol** 5 mg orally x 8 doses within 48 hr[24]	2	Hysterectomy, or radical prostatectomy
Nabilone 0.5 x 1 dose,[20] or 1-2 mg orally x 3 doses within 24 hr[21]	2	Variable major surgery, or elective surgeries (pain: secondary outcome)
CBD 400 mg orally x 1 dose[19]	1	Non-traumatic acute LBP
CBD topically TID x 14 days[23]	1	Unilateral knee arthroplasty
GW842166[a] orally x 1 dose[27]	1	Tooth extraction
AZD1940[b] orally x 1 dose[28]	1	Tooth extraction

Abbreviations: CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; CBP, cannabinoid-based product; hr, hour; IM, intramuscularly; TID, three times daily;
[a] CB2 receptor agonist; [b] peripheral CB1 and CB2 receptor agonist

RAPID REVIEW RESULTS

- **Analgesic efficacy**
  - CBP not better than placebo for pain in most trials[19,20,22-24,27,28]
  - Two trials with some degree of analgesia for post-surgical pain:
    - Both of levonantradol IM vs placebo: 1 with a significant decrease in pain,[26] and other with numerical decrease[25]
      - Active comparator outperformed levonantradol and placebo in 3rd levonantradol trial[12,18]
  - Increased pain 9-24 hours post-operatively for highest dose of nabilone vs placebo and active comparator[21]
  - NSAIDs, but not experimental CBPs, reduced pain versus placebo after tooth extraction[27,28]

SUMMARY

- Review included 11 RCTs of 20-340 participants, primarily conducted in the acute post-operative period

- Available clinical trial evidence limited by:
  - Unclear risk of bias for 2 or more domains for most trials
  - Use of a single cannabinoid often for only 1 dose, and often administered at variable times relative to surgery
  - Other clinical and methodological heterogeneity

- The limited evidence is *inconclusive* regarding efficacy of CBPs for acute pain

Thank you

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Extra slides

ACUTE PAIN: NEW QUALIFYING CONDITION

- Utah Medical Cannabis Act, 26-61a-104[29]:
  - "Pain that is expected to last for two weeks or longer for an acute condition, including a surgical procedure, for which a medical professional may generally prescribe opioids for a limited duration…"

- Medical cannabis card expires 30 days from issue

EVIDENCE REVIEW APPROACH

- Searched Embase and Ovid-Medline
- Used filter for for systematic reviews
  - Reviewed title/abstract for 228 possible reviews
- Focus on SRs + updated search for RCTs from 2020 to present (based on Fisher 2021 SR)
  - Reviewed title/abstract for 125 possible clinical trials
- Criteria:
  - Systematic review or overview of systematic reviews of RCTs
  - Trial of cannabis, cannabis-derived products, or cannabinoids vs any comparator
  - Acute pain disorder (primarily per review author report; or ≤4 wk)
- Not reviewed:
  - Healthy volunteers (ie, experimental pain models)
  - Non-randomized in-human data
  - Pre-clinical data

EXPERT COMMENTS ON IN-HUMAN EXPERIMENTAL PAIN MODELS

- Neilson et al. (2022) SR: focus on opioid-sparing effects[4]
  - 5 within-patient randomized trials (n = 82; moderate GRADE)
  - Interventions: 2.5-20 mg dronabinol orally; 1 trial of smoked cannabis (contained THC; CBD not stated)
  - Inconsistent: increased pain (2 trials), decreased pain (2 trials), decreased affective "unpleasantness" of pain (1 trial)
  - Possible opioid-sparing effect in 1 trial; potential hyperalgesic effect of dronabinal 20 mg in 1 trial
  - Possible increased abuse liability when given with opioids (3 trials)
- Beaulieu et al. (2021) expert opinion letter[5]:
  - 7 studies; study drugs not reported
  - "They are mostly negative and in 4 of them, more intense pain was reported at high doses"

ACUTE PAIN: GENERAL DEFINITION

- Pain resolving within ~4 weeks[30,31]

- Examples[32,33]:
  - Dental pain
  - Post-surgical pain
  - Musculoskeletal injuries

- General pharmacotherapy options[32,33]:
  - Acetaminophen
  - NSAIDs
  - Opioids
  - Gabapentinoids
  - Others per condition

Overview of acute pain randomized, controlled trials

Study	Population (n)	Intervention	Efficacy
Post-operative pain			
Kantor 1981*[25]	Unknown surgery (n=61)	Levonantradol (0.25, 0.5 or 1 mg) IM x 1 dose **vs** PBO; other: N/S	+ (unknown statistical sig)
Jain 1981*[26]	Acute trauma or fracture surgery (n=56)	Levonantradol (1.5, 2, 2.5, or 3 mg) IM x 1 dose **vs** PBO; other: N/S	+
Guillard 1983*[18]	Renal surgery (n=100)	Levonantradol (1 or 2 mg) IM x 1 dose **vs** meperidine IM or PBO IM; other: noramidopurine, camylofine	Meperidine > PBO and CBP
Buggy 2003[22]	Hysterectomy (n=20)	THC 5 mg orally x 1 dose **vs** PBO; other: morphine	+/-
Beaulieu 2006[21]	Variable major surgeries (n = 41)	Nabilone (1 or 2 mg) x 3 doses **vs** ketoprofen **vs** PBO; other: morphine	Increased pain with nabilone 2 mg vs PBO
Seeling* 2006[24]	Radical prostatectomy (n = 105)	Dronabinol 5 mg x 8 doses vs PBO; other: piritramide	+/-

Key: * lack of information about approval by an Institutional Review Board or similar body; +, efficacy favors CBP over comparator (numerically or statistically); +/-, efficacy favors neither CBP or PBO

Abbreviations: CBP, cannabinoid-based product; IM, intramuscular; PBO, placebo; THC, delta-9-tetrahydrocannabinol; vs, versus;

Overview of acute pain randomized, controlled trials

Study	Population (n)	Intervention	Efficacy
Post-operative pain			
Levin 2017[20]	Elective variable surgeries, all women (n=340)	Nabilone 0.5 mg orally x 1 dose pre-op **vs** placebo; other: N/S	+/-
Haffar 2021[23]	Primary knee OA post unilateral TKA (n=89)	Topical CBD stick (120 mg/oz) **vs** matched topical EO stick **vs** matched topical CBD stick + EO **vs** matched topical PBO stick, all topically TID x 14 days; other: APAP, gabapentin, meloxicam; prn opioid for mod-severe pain	+/-
Dental pain			
Ostenfeld 2011[27]	Tooth extraction (n=123)	GW842166 (100 mg or 800 mg) x 1 dose pre-op **vs** ibuprofen 800 mg **vs** PBO; other: codeine, APAP	+/-
Kallio-maki[28] 2013	Tooth extraction (n=151)	AZD1940 800 mcg orally x 1 dose pre-op **vs** naproxen 500 mg **vs** PBO; other: APAP	+/-
Other acute pain			
Bebee 2021[19]	Non-traumatic LBP < 30 days (n=100)	CBD 400 mg orally x 1 dose **vs** PBO Other treatments: oxycodone q6h, and as needed; ibuprofen and APAP for some	+/-

Key: +/-, efficacy favors neither CBP or PBO; Abbreviations: APAP, acetaminophen; CBD, cannabidiol; N/S, not specified; OA, osteoarthritis; PBO, placebo; THC, delta-9-tetrahydrocannabinol; vs, versus;