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\textsuperscript{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\textsuperscript{4}
  – Beaulieu et al.: “They are mostly negative and in 4 of them, more intense pain was reported at high doses”\textsuperscript{5}
  – No benefit of oral CBD for pain intensity, allodynia or hyperalgesia in 2 additional trials\textsuperscript{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)\textsuperscript{8-10}
  – 4 focused on acute pain (N=2)\textsuperscript{11-12} or post-surgical pain (N=2)\textsuperscript{13-14}
  – Pain associated with certain conditions (ie, orthopedics [N=2]\textsuperscript{15-16}, orofacial [N=1]\textsuperscript{17})
  – Potential opioid-sparing effects (N=1)\textsuperscript{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

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

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 3\(^{rd}\) 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
REFERENCES


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Extra slides
ACUTE PAIN: NEW QUALIFYING CONDITION

- Utah Medical Cannabis Act, 26-61a-104\textsuperscript{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 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
  – 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:
  – 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\textsuperscript{30,31}

• Examples\textsuperscript{32,33}:
  – Dental pain
  – Post-surgical pain
  – Musculoskeletal injuries

• General pharmacotherapy options\textsuperscript{32,33}:
  – Acetaminophen
  – NSAIDs
  – Opioids
  – Gabapentinoids
  – Others per condition
### Overview of acute pain randomized, controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population (n)</th>
<th>Intervention</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantor</td>
<td>Unknown surgery (n=61)</td>
<td>Levonantradol (0.25, 0.5 or 1 mg) IM x 1 dose vs PBO; other: N/S</td>
<td>+ (unknown statistical sig)</td>
</tr>
<tr>
<td>Jain</td>
<td>Acute trauma or fracture surgery (n=56)</td>
<td>Levonantradol (1.5, 2, 2.5, or 3 mg) IM x 1 dose vs PBO; other: N/S</td>
<td>+</td>
</tr>
<tr>
<td>Guillard</td>
<td>Renal surgery (n=100)</td>
<td>Levonantradol (1 or 2 mg) IM x 1 dose vs meperidine IM or PBO IM; other: noramidopurine, camylofine</td>
<td>Meperidine &gt; PBO and CBP</td>
</tr>
<tr>
<td>Buggy</td>
<td>Hysterectomy (n=20)</td>
<td>THC 5 mg orally x 1 dose vs PBO; other: morphine</td>
<td>+/-</td>
</tr>
<tr>
<td>Beaulieu</td>
<td>Variable major surgeries (n = 41)</td>
<td>Nabilone (1 or 2 mg) x 3 doses vs ketoprofen vs PBO; other: morphine</td>
<td>Increased pain with nabilone 2 mg vs PBO</td>
</tr>
<tr>
<td>Seeling</td>
<td>Radical prostatectomy (n = 105)</td>
<td>Dronabinol 5 mg x 8 doses vs PBO; other: piritramide</td>
<td>+/-</td>
</tr>
</tbody>
</table>

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

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<tr>
<th>Study</th>
<th>Population (n)</th>
<th>Intervention</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-operative pain</strong></td>
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<tr>
<td>Levin 2017&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Elective variable surgeries, all women (n=340)</td>
<td>Nabilone 0.5 mg orally x 1 dose pre-op vs placebo; other: N/S</td>
<td>+/-</td>
</tr>
<tr>
<td>Haffar 2021&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Primary knee OA post unilateral TKA (n=89)</td>
<td>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</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Dental pain</strong></td>
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<tr>
<td>Ostenfeld 2011&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Tooth extraction (n=123)</td>
<td>GW842166 (100 mg or 800 mg) x 1 dose pre-op vs ibuprofen 800 mg vs PBO; other: codeine, APAP</td>
<td>+/-</td>
</tr>
<tr>
<td>Kallio-maki 2013&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Tooth extraction (n=151)</td>
<td>AZD1940 800 mcg orally x 1 dose pre-op vs naproxen 500 mg vs PBO; other: APAP</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Other acute pain</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bebee 2021&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Non-traumatic LBP &lt; 30 days (n=100)</td>
<td>CBD 400 mg orally x 1 dose vs PBO Other treatments: oxycodone q6h, and as needed; ibuprofen and APAP for some</td>
<td>+/-</td>
</tr>
</tbody>
</table>

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;