COLLEGE OF PHARMACY
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SUMMARY OF A CHRONIC PAIN REVIEW:

Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain

An AHRQ review conducted by
the Pacific Northwest Evidence-based Practice Center

DRUG REGIMEN REVIEW CENTER,
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SEPTEMBER 13, 2022

I have no conflicts of interest to disclose

REVIEW METHODS[1,2]

- **Study Design:** living SR with random-effects meta-analysis as appropriate (last update 6-2022)

- **Literature search:** robust searches of multiple bibliographic databases
  - Included studies: RCTs, or high-quality controlled observational studies with **at least 4 weeks of follow-up**

- **Comparisons:** Cannabis or cannabinoids (including synthetic) vs. another CBP, active or inactive treatment, or no treatment
  - Classified by type of CBP (eg, whole-plant, plant extract or synthetic), and THC: CBD ratio

- **Population:** *adults* with chronic (pain > 12 weeks) pain

Abbreviations: SR, systematic review; CBD, cannabidiol; CBP, cannabinoid-based product; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol

REVIEW RESULTS[2]

- Overview of included studies (n = 29 as of 6-22 update)
  - RCTs (n = 21; total N = 1,912); Observational (n = 8; total N = 13,769)
  - **RCTs**
    - Mostly similar THC:CBD plant extract (n = 7) or synthetic high THC (n = 9)
    - Mostly placebo comparator; active comparator (n = 3)
    - Duration: 4 to 47 weeks (most 4 to 12 weeks)
    - Mean age ~50-65 years
    - Mostly female (~% female range: 3% to 89%)
    - Pain type:
      - Neuropathic (n = 15); fibromyalgia (n = 2); others (n = 4)
  - **Observational**
    - Most studies with participant choice of cannabis (n = 5)
    - Variable comparators including no cannabis (n=3), usual care (n=2), no medical cannabis card (n = 1), and active (n=2)
    - Duration: 12 to 208 weeks
    - Mean age ~46 to 61 years
    - Female % range ~55-59%
    - Pain type: mixed, including musculoskeletal or neuropathic

Abbreviations: SR, systematic review; CBD, cannabidiol; CBP, cannabinoid-based product; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol

REVIEW MAIN FINDINGS: CBP VS PLACEBO, SHORT-TERM EFFECTS[2]

CBP Group (n RCTs)	Benefit (n RCTs)	Selected Safety (n RCTs)
Comparable THC:CBD – whole plant extract, oromucosal spray • Pain type: neuropathic (n=6); inflammatory arthritis (n= 1)	*Moderate SOE* • Pain severity (n=7): small + • Function (n=6): small + *Low SOE* • Pain response (n=4): +?	*Low SOE* • SAE (n=3): -- • Dizziness (n= 6): large ↑ • Nausea (n=6): moderate ↑ • Sedation (n=6): large ↑
High THC– synthetic THC, oral • Pain type: neuropathic (n=6); visceral pain (n=1); fibromyalgia (n=1)	*Low SOE* • Pain severity (n= 6): moderate + • Function (n=3): -- • Pain response (n=4): moderate+	*Moderate SOE* • Dizziness (n= 2):): large ↑ *Low SOE* • WAE (n=4): +? • Nausea (n=2): +? • Sedation: moderate ↑

Abbreviations: AE, adverse event(s); CBD, cannabidiol; CBP, cannabinoid-based product; THC, tetrahydrocannabinol; SOE, strength of evidence; WAE, withdrawal from study due to AE

+ = Evidence from MA favors CBP vs comparator; +? = statistically insignificant effect, but point estimate shows possible small benefit; -- = no effect/statistically insignificant; ↑/↓ = increased or decreased risk for CBP vs comparator

REVIEW MAIN FINDINGS: CBP VS PLACEBO, SHORT-TERM EFFECTS[2]

CBP Group (n RCTs)	Benefit (n RCTs)	Selected Safety (n RCTs)
High THC:CBD – whole-plant-extract, oral • Pain type: neuropathic (n=1); fibromyalgia (n=1)	• Pain severity (n=2): insufficient evidence • Pain response (n=2): no evidence • Function (n=1): insufficient evidence	*Low SOE* • WAE (n=1): large ↑ • Dizziness (n= 1): large ↑

Abbreviations: AE, adverse event(s); CBD, cannabidiol; CBP, cannabinoid-based product; THC, tetrahydrocannabinol; SOE, strength of evidence; WAE, withdrawal from study due to AE

+ = Evidence from MA favors CBP vs comparator; +? = statistically insignificant effect, but point estimate shows possible small benefit; -- = no effect/statistically insignificant; ↑/↓ = increased or decreased risk for CBP vs comparator

- Insufficient or no evidence for benefits or risks:
  - Low THC (topical CBD, and oral CBD)
  - Other cannabinoids (oral cannabidivarin)
  - Whole-plant cannabis (12% THC)
  - All CBPs *vs* non-placebo comparators

AREAS WITH LIMITED EVIDENCE[1,2]

- Author-identified limitations of approach or evidence:
  - Limited evidence for many types of chronic pain:
    - Ex.: low back pain, OA, inflammatory arthritis, fibromyalgia
  - No or limited evidence for the following CBPs:
    - Whole-plant cannabis
    - Cannabis extracts (high THC:CBD)
    - Low THC: CBD
    - Rich in other cannabinoids
  - Little information about other important outcomes:
    - Measures of functionality
    - Use with opioids
    - Long-term benefit(s) and risk(s)
    - CBPs versus active comparators

Abbreviations: CBD, cannabidiol; CBP, cannabinoid-based product; OA, osteoarthritis; THC, delta-9-tetrahydrocannabinol

COMPARISON TO OTHER RECENT REVIEWS

- **Wang et al 2021 (32 RCTs of 5174 adults)[3]**
  - SR with similar population, interventions, and studies (ie, RCTs with ≥ 1 month follow-up)
  - Similar conclusions that non-inhaled CBPs show small improvement in pain, function (and sleep quality) versus placebo
  - Similar safety conclusions; additionally reported increased transient cognitive impairment and impaired attention
    - Rated evidence as moderate to high certainty

- **Sainsbury et al 2021 (17 RCTs of 861 adults)[4]**
  - SR with more focused population (chronic NP), slightly different studies (placebo-controlled RCTs of any duration), and similar interventions
  - Similar conclusions that THC and THC/CBD interventions improve pain intensity and pain response
    - Rated evidence as low to moderate quality

Abbreviations: CBD, cannabidiol; CBP, cannabinoid-based product; THC, delta-9-tetrahydrocannabinol; RCT, randomized controlled trial; SR, systematic review

COMPARISON TO CURRENT CRRB GUIDANCE

- CRRB "Persistent Pain" Guidance
  - Overall conclusion ("…moderate evidence to support the conclusion that medical cannabis and cannabinoids can have clinically significant effects in the management of chronic pain…particularly…neuropathy"[5]) is similar to recently published SRs

- Current review includes some trials (~6) published since the CRRB document was drafted

- The living review includes more information by type of cannabinoid or CBP, and safety outcomes

Abbreviations: CBD, cannabidiol; CBP, cannabinoid-based product; THC, delta-9-tetrahydrocannabinol; RCT, randomized controlled trial; SR, systematic review

REVIEW SUMMARY AND CONCLUSION

- CBPs, particularly those with high THC: CBD or equal THC: CBD, may improve some short-term pain outcomes, especially among people with neuropathic pain
  - Increased risk for AEs, especially with THC-containing CBPs
  - Limited high-quality evidence for other cannabinoids, and whole-plant cannabis
  - Limited evidence for other important outcomes
  - Based on low to moderate SOE

- Current CRRB guidance for persistent pain generally in agreement with McDonagh et al. conclusions
  - The CRRB may consider minor additions, for example:
    - Revisions to the level of evidence, if deemed applicable
    - Details about evidence for various CBPs and/or THC:CBD ratio
    - Possible AE information

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid-based product; THC, delta-9-tetrahydrocannabinol; SOE, strength of evidence

REFERENCES

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To access the review and check for updates:

https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review

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Extra slides

METHODS

- The living SR (McDonagh et al) and surveillance updates were located in a preliminary search, and used as the primary summary given the quality and recent search dates
- Recent SRs with a similar focus on RCTs of CBPs for chronic pain were searched for in Epistemonikos using search terms for cannabis or cannabinoids (or synonyms/related terms) published in 2021-2022 and "systematic reviews" filter in September 2022 (83 results)
  - Title and abstracts were screened, and 2 reviews with a similar focus were selected for comparison
- Results from the living SR were compared to evidence and recommendations from the CRRB guidance document on persistent pain

REVIEW: SOE AND EFFECT SIZE DEFINITION[1,2]

Effect Size			
	Small	Moderate	Large
Mean difference on 10-pt scale (x10 for 100 pt scale)	0.5 to 1.0 pts	>1 to 2 pts	>2 pts
Standardized mean difference	0.2 to 0.5	>0.5 to 0.8	>0.8
RR or OR	1.2 to 1.4	1.5 to 1.9	≥ 2.0

Strength of Evidence (SOE)
Grading of Evidence: Combined assessment of bias (limitations), and the measured effect in terms of consistency, directness, and precision
Assigned SOE: Classified as high, moderate, low, or insufficient based on level of confidence for how likely it is that the measured effect is the the true effect. For *moderate* SOE, overall the findings is considered stable but there is some doubt due to deficiencies. Whereas for *low* SOE, the author's concluded there is enough evidence to estimate an effect (unlike *insufficient evidence),* but it is not considered stable.

Abbreviations: OR, odds ratio; pt, point; pts, points; RR, risk ratio; SOE, strength of evidence