A systematic review and meta-analysis of randomised controlled trials:

Safety and efficacy of medicinal cannabis in management of pain, sleep, and fatigue in cancer survivors

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BACKGROUND

Pain, fatigue, and sleep disturbance commonly co-occur in people with cancer, which can greatly reduce quality of life.[1,2]

Treatment options for fatigue are limited, and those for pain and sleep have associated side effects and cost implications. [2]

Natural products and complementary and alternative medicines are thus of growing interest, such as medicinal cannabis.[3]

Up to **one third** of cancer survivors use medicinal cannabis, predominantly for symptom management during treatment.[4-6]

Given the high prevalence of medicinal cannabis use among cancer survivors and the rapidly developing area of research, an up-to-date and comprehensive quantitative synthesis of the literature is warranted to inform clinical practice and ensure safety of use.

REFERENCES: 1. Kwekkeboom KL, et al., The Role of Inflammation in the Pain, Fatigue, and Sleep Disturbance Symptom Cluster in Advanced Cancer. J Pain Symptom Manage, 2018. 55(5); **2.** Sheikh-Wu, S. et al., Interventions for managing a symptom cluster of pain, fatigue, and sleep disturbances during cancer survivorship: A systematic review. Onc Nurs Forum, 2021. 47(4); **3.** Satija, A. and S. Bhatnagar, Complementary Therapies for Symptom Management in Cancer Patients. Indian J Palliat Care, 2017. 23(4); **4.** Martell, K., et al., Rates of cannabis use in patients with cancer. Curr Oncol, 2018. 25(3); **5.** Macari, D.M., et al., Medical Cannabis in Cancer Patients: A Survey of a Community Hematology Oncology Population. Am J Clin Oncol, 2020. 43(9); **6.** Do, E.K., et al., Cannabis use among cancer survivors in the United States: Analysis of a nationally representative sample. Cancer, 2021. 127(21).

METHODS

RESEARCH AIM:

In cancer survivors of any age, this review aimed to examine existing evidence on the safety and efficacy of medicinal cannabis, compared to any control, on pain, sleep, and fatigue.

- Five databases were searched from inception to 25 October 2022.
- A snowballing search strategy was used up until 27 April 2023.
- Screening was conducted in duplicate using Covidence software.
- Data were pooled with meta-analysis (where ≥two studies reported the same outcome).
- Quality of evidence was appraised using RoB2.
- GRADE was applied to assess the certainty of the evidence. Four levels of certainty for the estimated effect of each outcome were possible: very low, low, moderate, or high.

STUDY INCLUSION CRITERIA:

- **Population:** Humans of any age with any active cancer type at any stage of their cancer journey.
- **Intervention:** Any medicinal cannabis intervention.
- **Comparator:** Any control (e.g., placebo, usual care).
- **Outcomes:** Measured incidence or severity of at least one primary outcome: pain, sleep, or fatigue.
- **Study design:** Randomised controlled trials with full text published in peer-reviewed journal.

RESULTS

STUDY AND POPULATION CHARACTERISTICS:

- Of 7936 records screened, **16 studies** of **20 interventions** (N=2225 total participants; 100% adults) were included.
- Most studies included participants with **mixed cancer types** (81%), who were undergoing **active cancer treatment** (63%).
- **Interventions:** whole plant extract (with THC and CBD [n=10], with THC [n=2]), synthetic THC (n=7), synthetic CBD (n=1).
- **Dose:** varied greatly.
- **Route:** oral (n=9 studies), oromucosal (n=7 studies).
- Most studies (67%) had **high or unclear risk of bias**.
- 13 studies (81%) measured **pain**, 11 (69%) measured **sleep**, 8 (50%) measured **fatigue** (mostly only as an adverse event), and five (31%) measured all three primary outcomes of interest.

FINDINGS:

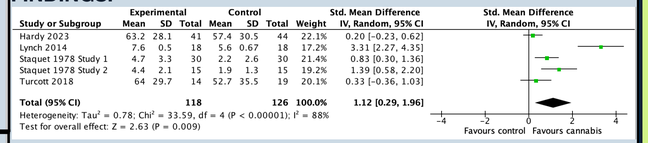

Figure 1. Pain severity was decreased in adults using medicinal cannabis compared to placebo (SMD:1.1, 95%CI:0.3-2.0; p=0.009; n=5 studies; I^2=88%; effect size: very large; GRADE: low).

The likelihood of somnolence was increased with medicinal cannabis compared to placebo (OR: 2.6; 95% CI: 1.6, 4.0; p<0.0001; I^2=0%; n=9 studies; n=1370 participants; GRADE: moderate), **but there was no effect on sleep disturbance, fatigue, or quality of life**.

FINDINGS: SAFETY

- There was a **60% increased likelihood of any gastrointestinal symptom** (nausea, vomiting, constipation, diarrhoea, abdominal discomfort, dry mouth) with medicinal cannabis compared to placebo (OR: 1.6; 95% CI: 1.1, 2.3; p=0.01; I^2=0%; n=12 studies; n=1920 participants; GRADE: moderate).
- There was a **60% increased likelihood of any adverse event** (headache, dizziness, asthenia, dyspnoea, oedema, or somnolence) with medicinal cannabis compared to placebo (OR: 1.6; 95% CI: 1.3, 2.1; p=0.0002; I^2=0%; n=11 studies; n=1993 participants; GRADE: moderate).

TAKE HOME MESSAGES:

- **Medicinal cannabis might benefit pain management in adult cancer survivors, but use should be closely monitored for increased side effects.**
- **The current studies provide insufficient support for medicinal cannabis as a therapeutic intervention for sleep or fatigue.**
- Confidence in findings was limited by most studies having high or unclear risk of bias, small samples, heterogenous interventions, unvalidated primary outcome measures, and inadequate data reported for meta-analysis.
- Future well-powered trials that assess pain in conjunction with sleep and fatigue, use validated outcome measures, and report data in full are needed to confirm efficacy and safety.

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