INPLASY PROTOCOL

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None declared.

Cannabis medicines for symptom management in adults with chronic non-cancer conditions

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Review question / Objective: **To estimate the benefits and harms of cannabis medicines to manage symptoms in adults with chronic non-cancer conditions. We will conduct a systematic review with meta-analysis of randomised controlled trials.**
Condition being studied: **Chronic non-cancer conditions.**
Information sources: **We will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE accessed via Ovid (from 1966), EMBASE accessed via Ovid (from 1980), PschINFO accessed via Ovid (from inception) and LILACS (from inception). Appendix 1 shows the search strategy for Ovid MEDLINE.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 July 2022 and was last updated on 18 July 2022 (registration number INPLASY202270090).

INTRODUCTION

Review question / Objective: **To estimate the benefits and harms of cannabis medicines to manage symptoms in adults with chronic non-cancer conditions. We will conduct a systematic review with meta-analysis of randomised controlled trials.**

Rationale: **Description of the condition**
People with chronic health conditions such as organ failure (lung, heart, kidney) frequently experience symptoms including anxiety, pain, breathlessness, fatigue and anorexia or nausea.1 2 These symptoms may be incompletely treated with conventional medicines including pain relief, anti-sickness treatments or

anxiolytics, which can be ineffective for some people or cause side-effects that limit wellbeing and daily functioning.3-5

Patients are reported to use cannabis medicines to treat symptoms related to chronic conditions. In a large health system that conducts routine cannabis screening, 2% of patients in primary care had medical cannabis use documented in their electronic medical record.6 In adults with chronic, non-cancer pain prescribed opioids, 24% had used cannabis for pain during 4 years of assessment.7

Description of the intervention

Cannabis is a flowering plant genus that contains compounds (known as cannabinoids) that bind to specific cannabinoid receptors in the body.8 The human body also has an endocannabinoid system (known as ECS) that consists of endogenously produced cannabinoids, enzymes that metabolise cannabinoids, and receptors that bind cannabinoids to produce endogenous effects in several organ systems.9

Medicinal cannabis includes pharmaceutical grade cannabinoids manufactured synthetically or derived from the cannabis plant. Cannabis-derived compounds occur naturally in the plant and contain varying amounts of cannabinoids, the two most common of which are CBD and THC. These compounds can be extracted directly from the plant and used to manufacture drug products.

Synthetic cannabis-related compounds are manufactured in the laboratory and may (dronabinol) or may not (nabilone) also occur in the cannabis plant.

Synthetic formulation of THC (dronabinol) and synthetic THC analogue (nabilone) were approved by the US Food and Drug Administration in 1985 for treatment of nausea and vomiting associated with cancer chemotherapy and approved for management of weight loss in patients with acquired immunodeficiency syndrome.10 In 2018, the US Food and Drug Administration approved the only plant-derived medicine (cannabidiol) for treatment of seizures for two rare types of epilepsy.

How the intervention might work

Cannabinoids bind to cell-surface receptors, CB1R and CB2R, to exert pleiotropic effects on a range of tissues. CB1R is highly expressed in the central and peripheral nervous systems, and, to a lesser extent, peripheral tissues including the gastrointestinal tract, and cardiac and hepatic tissues. CB2R is expressed in immune cells as well as peripheral and central nervous systems. CB2R may modulate nociception, drug addiction and neuroinflammation. Cannabinoids can influence appetite, learning, memory, anxiety, addiction, and neurodegeneration in the central nervous system as well as peripheral tissue functions including pain, energy metabolism, inflammation, reproduction, and hepatic and musculoskeletal functions.11

Cannabinoids may assist with symptoms of long-term conditions such as nausea, pain, anorexia, anxiety, and gut disturbance, through their pleiotropic effects based on the known distribution and actions of the endogenous cannabinoid system and receptors.

Why this review is needed

Cannabis medicines are not currently approved for symptom management in long term conditions. A systematic review of the current evidence including effectiveness and safety of cannabis medicines could assist to understand the evidence base for their use in chronic conditions and evaluation research.

Condition being studied: Chronic non-cancer conditions.

METHODS

Search strategy:

1. Medical Marijuana/
2. Cannabis/
3. Exp Cannabinoids
4. cannabi*.mp.
5. mari?uan*.mp.
6. ganga.mp.
7. ganjas.mp.
8. nabilo*.mp.
9. CBD.mp.
10. DMH-11C.mp.
11. tetrahydrocannab*.mp.
12. THC.mp.
13. dexanabinol.mp.
14. ajulemic.mp.

15. dronabinol.mp.
16. nabiximol*.mp.
17. sativex.mp.
18. endocannabi*.mp.
19. levonantradol.mp.
20. (faah and (inhibitor or hydrolase)).mp.
21. PF-04457845.mp.
22. fatty acid am?d hydrolase.mp.
23. cannador.mp.
24. benzopyranoperidine.mp.
25. nabitan.mp.
26. nabutam.mp.
27. SP-106.mp.
28. marinol.mp.
29. Cesamet.mp.
30. Canemes.mp.
31. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. exp Neoplasms/
33. (cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*).tw.
34. 32 or 33
35. 31 not 34
36. ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
37. 35 and 36.

Participant or population: Adults aged 18 years or over receiving symptom management for any type of chronic non-cancer long condition lasting 3 months or longer. We will exclude children and young people aged under 18 years, since treatment approaches are likely to be systematically different.

Intervention: We will include any licensed pharmacological interventions based on cannabinoids from the cannabis plant and synthetic products. We will include studies in which cannabis medicines are compared with active treatments, standard care, or placebo.

Comparator: Standard care or any comparative intervention.

Study designs to be included: Randomised controlled trials and quasi-randomised controlled trials.

Eligibility criteria: No additional criteria.

Information sources: We will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE accessed via Ovid (from 1966), EMBASE accessed via Ovid (from 1980), PschINFO accessed via Ovid (from inception) and LILACS (from inception). Appendix 1 shows the search strategy for Ovid MEDLINE.

Main outcome(s): Pain.

Additional outcome(s):
o Anxiety
o Depression
o Anorexia
o Nausea
o Vomiting
o Restless legs
o Breathlessness
o Constipation
o Fatigue
• Adverse effects
o 'Feeling high'
o Euphoria
o Sedation
o Dizziness
o Heightened sense of anxiety or agitation
o Depression
o Hallucinations
o Paranoia
o Hypotension
o Focal dystonia
o Extrapyramidal effects
o Oculogyric crisis
• Withdrawal from treatment due to adverse events
• Daily functioning/disability
• Health-related quality of life (any instrument).

Data management: We will download all the titles and abstracts retrieved by electronic searching to a reference management database. We will remove duplicates. Two review authors (IH, SP) will independently

examine the remaining references. We will exclude those studies that clearly did not meet the inclusion criteria and we obtain copies of the full text of potentially relevant references. The same two review authors will independently assess the eligibility of the retrieved papers. The review authors will not be blinded to the authors' names, institutions, and journals of publication. We will resolve disagreements by discussion and documented the reasons for exclusion.
For the included studies, two review authors (SP, IH) will independently abstract data on characteristics of study participants (inclusion criteria, age, gender, type of condition and stage of disease, co-morbidities, co-interventions); dose, frequency, route of administration and duration of experimental and control interventions; risk of bias; outcomes, and deviations from the protocol onto a data abstraction form specially designed for the review. We will resolve disagreements by discussion or by appeal.

Quality assessment / Risk of bias analysis: We will assess the risk of bias in included studies using the Cochrane 'Risk of bias' tool.12
This will include assessment of:
- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result
- Overall bias

Two review authors will independently apply the 'Risk of bias' tool and resolve differences by discussion. We will summarise results in both a 'Risk of bias' graph and a 'Risk of bias' summary.

Strategy of data synthesis: For dichotomous outcomes (withdrawal from treatment), we will calculate the relative risk (RR) and its respective 95% confidence interval (CI). We will incorporate cross-over trials in the meta-analyses using only the data for the first period for the meta-analysis. For continuous outcomes, we will calculate the mean difference (MD) and 95% CI or standardised mean difference (SMD) if endpoints are reported on different scales. Where we judge the trials sufficiently similar, we will summarise their results in a meta-analysis.
For dichotomous outcomes, we will combine the RR for each study. We will use random-effects models with inverse variance weighting for all meta-analyses due to the anticipated clinical and methodological diversity of the studies.
If trials have multiple treatment groups, we will divide the 'shared' comparison group into the number of treatment groups and treated comparisons between each treatment group and the split comparison group as independent comparisons.

Subgroup analysis: We will conduct the following subgroup analyses for the primary outcome if sufficient trials were available:
- history of cannabis use, naive users; prior users of cannabis
- type of cannabinoid agent
- reduced kidney function; normal kidney function.

Sensitivity analysis: We will carry out sensitivity analyses for the primary outcome, if sufficient trials are available, excluding trials at high risk of bias and trials with cross-over design.

Language restriction: None.

Country(ies) involved: New Zealand.

Keywords: medical cannabis; chronic conditions; symptoms; randomized controlled trials.

Dissemination plans: Publication in peer-reviewed journals; conference proceedings.

Contributions of each author:
Author 1 - Isabel Whybrow-Huppatz - Author 1 selected studies, extract data, adjudicate risk of bias, assist with analyses, provide intellectual contribution to the findings and manuscript.
Author 2 - Rachael Walker - Author 2 conceived the study; reviewed the protocol;

provided intellectual input into study design and manuscript.
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Author 3 - Jasjot Maggo - Author 3 reviewed the protocol, assisted with data collection and provided intellectual input into study design and manuscript.
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Author 5 - Suetonia Palmer - Author 5 conceived the study, wrote the protocol, extracted data and adjudicated risk of bias, did the statistical analysis, and wrote the first draft of the manuscript.
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