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Cannabis-based medicines and medical cannabis for adults with cancer pain (Protocol).
Cochrane Database of Systematic Reviews 2022, Issue 2. Art. No.: CD014915.
DOI: [10.1002/14651858.CD014915](https://doi.org/10.1002/14651858.CD014915).

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[Intervention Protocol]

Cannabis-based medicines and medical cannabis for adults with cancer pain

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: New, published in Issue 2, 2022.

Citation: Häuser W, Welsch P, Radbruch L, Fisher E, Bell RF, Moore RA. Cannabis-based medicines and medical cannabis for adults with cancer pain (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 2. Art. No.: CD014915. DOI: [10.1002/14651858.CD014915](https://doi.org/10.1002/14651858.CD014915).

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the efficacy, tolerability and safety of cannabis-based medicines, including medical cannabis, for treating pain and other symptoms in adults with cancer.

BACKGROUND

Description of the condition

Cancer is the second leading cause of death globally, accounting in 2018 for an estimated 9.6 million deaths, or one in six deaths ([World Health Organization 2021](#)). Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancer are the most common among women ([World Health Organization 2021](#)). Pain is one of the most feared symptoms associated with cancers, and can occur at any time of the disease. The frequency and intensity of pain tend to increase as the cancer advances ([van den Beuken-van Everdingen 2016](#)). A systematic review has shown that approximately 40% of patients suffered pain after curative treatment, 55% during cancer treatment, and 66% in advanced disease ([van den Beuken-van Everdingen 2016](#)). Pain may be specifically related to the cancer (direct tumour effects, systemic tumour effects), the effects of cancer treatments (e.g. radiation or chemotherapy) or due to some other comorbid disease ([Swarm 2019](#)). In this review, we define cancer pain as pain arising as a direct consequence of the cancer and/or of cancer therapy, and not due to another condition.

The World Health Organization (WHO) analgesic ladder advocates a stepwise approach to analgesia for cancer pain. It recommends that opioids be used as first line treatment for moderate to severe cancer pain ([World Health Organization 2019](#)). An overview of Cochrane Reviews found the quantity and quality of evidence supporting the use of opioids for cancer pain to be low ([Wiffen 2017](#)). In clinical practice, however, most cancer patients will achieve adequate pain relief with opioids. However, wide inter-patient variability in the response to opioids has been reported and 20% to 30% of people with cancer pain are defined as opioid non-responders ([Corli 2016](#)). There is therefore a substantial need for new analgesics that can effectively and safely supplement or replace opioids in patients with insufficient relief of cancer pain.

Description of the intervention

The cannabinoid (CB) system is ubiquitous in the animal kingdom, with multiple functions that move the organism back to equilibrium. A large body of evidence currently supports the presence of CB receptors and ligands in the peripheral and central nervous system, but also in other tissues such as bone and in the immune system ([Owens 2015](#); [Soliman 2019](#)). The endocannabinoid system has three broad and overlapping functions in mammals. The first is a stress recovery role, operating in a feedback loop in which endocannabinoid signalling is activated by stress and functions to return endocrine, nervous, and behavioural systems to homeostatic balance. The second is to control energy balance through regulation of the intake, storage, and utilisation of food. The third involves immune regulation; endocannabinoid signalling is activated by tissue injury and modulates immune and inflammatory responses ([Hillard 2012](#)). Thus, the endocannabinoid neuromodulatory system is involved in multiple physiological functions, such as anti-nociception, cognition and memory, endocrine function, nausea and vomiting, inflammation, and immune recognition ([De Vries 2014](#); [Hillard 2012](#)).

Cannabis is a genus of the flowering plant in the family Cannabaceae. The number of species within the genus is disputed.

Three species are recognized, *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. These plants, commonly known as marijuana, have been used for pain relief for millennia, and have additional effects on appetite, sleep, and mood ([Kalant 2001](#)). Because of the multiple mechanisms of action of cannabis in the human organism, cannabis has the potential to modulate some of the most common and debilitating symptoms of cancer and its treatments, including nausea and vomiting, loss of appetite, and pain ([Kleckner 2019](#)).

How the intervention might work

Cannabis contains over 450 compounds, with at least 120 classified as phytocannabinoids. Two are of particular medical interest. Delta 9-tetrahydrocannabinol (delta 9-THC) is the main active constituent, with psychoactive (e.g. reduction of anxiety) and pain-relieving properties. The second molecule of interest is cannabidiol (CBD), which has lower affinity for the cannabinoid (CB) receptors and the potential to counteract the negative effects of tetrahydrocannabinol (THC) on memory, mood, and cognition, but may also have an effect on pain modulation due to anti-inflammatory properties. The specific roles of currently identified cannabis-based medicines that act as ligands at CB-receptors within the nervous system (primarily but not exclusively CB1 receptors) and in the periphery (primarily but not exclusively CB-2 receptors) are only partially elucidated, but there are many pre-clinical data to support their influence on nociception ([Owens 2015](#); [Soliman 2019](#)). It is also hypothesised that cannabis reduces alterations in cognitive and autonomic processing in chronic pain states. The frontal-limbic distribution of CB receptors in the brain suggests that cannabis may preferentially target the affective qualities of pain ([Lee 2013](#)).

Terminology and definitions of cannabis-based medicines (CbMs) vary in the literature. A terminology based on the proposals of the task forces of the European Pain Federation (EFIC) ([Häuser 2018](#)), and the International Association for the Study of Pain (IASP) ([Soliman 2019](#)) is listed in [Appendix 1](#).

CbMs are available in different forms.

Licensed medical drugs or products currently being tested for medical use:

1. plant-derived cannabinoids: oromucosal THC and CBD (Nabiximols; Sativex) or oral CBD (Epidiolex). Nabiximols is approved in some countries for the treatment of refractory spasticity in patients with multiple sclerosis ([Krcevski-Skvarc 2018](#)). Oral CBD is approved by the European Medicines Agency for the management of Dravet Syndrome and Lennox-Gastaut Syndrome, two rare forms of epilepsy in children ([European Medicines Agency 2019](#));
2. synthetic cannabinoids: nabilone (Cesamet or Canemes), a synthetic THC, is approved in some countries for the management of refractory nausea/emesis in cancer patients ([Abuhasira 2018](#); [Krcevski-Skvarc 2018](#)). Dronabinol (Marinol or Syndros), a synthetic THC, is approved for similar therapeutic use in some countries ([Abuhasira 2018](#); [Krcevski-Skvarc 2018](#)). Levonantradol, a potent synthetic THC is used in research, but is not available as a licensed therapeutic drug in any country of the world.

Magistral preparations (i.e. any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient) of cannabis plant derivatives:

1. defined cannabinoids such as dronabinol;
2. herbal cannabis, resins and extracts, such as oil or tinctures with defined content of THC and/or CBD, together with other active ingredients (phytocannabinoids other than CBD/THC, terpenes and flavonoids).

The main forms of administration are:

- oromucosal: spray (nabiximols);
- oral: capsules (dronabinol, nabilone), oil (CBD), extracts (dronabinol, herbal cannabis);
- smoke or vapour inhalation: CBD, dronabinol, herbal cannabis, resins;
- topical or rectal: CBD, herbal cannabis, resins, extracts.

There is a great variability in European countries with regard to the availability of the different CbMs and medical cannabis and their reimbursement by health statutory companies (Krcevski-Skvarc 2018).

In addition, CBD and extracts of cannabis flowers (THC content of <0.2%) are available in many countries as nutritional supplements (Radbruch 2020).

Cannabinoid receptor antagonists and negative allosteric modulators (e.g. rimonabant (SR141716A)) and modulators that increase or enhance endocannabinoid system activity (e.g. fatty acid amide hydrolase inhibitors) are experimental medications which have been not yet been approved for use in pain therapy outside clinical studies (Ye 2019).

Why it is important to do this review

Contrary to the usual path of drug approval, CbMs in an increasing number of European countries have bypassed traditional approval by drug agencies and have been made available by legislative bodies as therapeutic products for pain management (Krcevski-Skvarc 2018). Propelled by public advocacy and the media, medical cannabis in particular has been promoted as an effective and safe treatment for cancer pain (Blake 2017). Other benefits that are quoted include the potential reduction of harm related to opioid use, and the purported benefits for sleep disturbance as well as mood disorders (Vyas 2018). The worldwide surge in use of cannabis in the management of cancer patients is illustrated by the prevalent use of medical cannabis and illegal cannabis by up to 40% of cancer patients in Canada and Israel, countries where legal access to medical cannabis is available (Bar-Lev Schneider 2018; Martell 2018).

At the time of writing this protocol, the amount and quality of evidence for CbMs for chronic pain has been low, with the evidence compromised by studies of short duration and small participant numbers (Fisher 2020; Stockings 2018). In addition, a systematic overview of systematic reviews has pointed out that non-Cochrane systematic reviews of cannabinoids for pain are of overwhelmingly low or very low quality (Moore 2020). A 2020 systematic review of randomised controlled trials (RCTs) of CbMs for chronic pain concluded that studies in this field have unclear or high risk of bias, and outcomes had GRADE ratings of low- or very low-quality

evidence, with little confidence in the estimates of effect (Fisher 2020). The systematic review found no benefit of nabiximols, compared to placebo, for at least 30% of pain relief (two RCTs delivering treatment of two to five weeks) and mean change of pain from baseline (four RCTs delivering treatment of two to five weeks). The review authors did not perform quantitative analysis for the outcomes of emotional functioning, sleep, and health-related quality of life. Another systematic review analysed the same RCTs as Fisher 2020 and did not find nabiximols were superior when compared to placebo for reducing pain and sleep problems (Häuser 2019). However, this review did find patient impression of change to be much or very much improved in the group receiving nabiximols (Häuser 2019).

Additional outcomes have gained importance to assess the efficacy and safety of CbMs for cancer pain. The US Food and Drug Administration (FDA) has suggested new combined responder outcomes for cancer pain trials: patients are only considered responders if they experience a clinically significant decrease in pain intensity compared with baseline at the primary analysis time point, and overall analgesic use is either decreased or stable compared with baseline (Basch 2014). Moreover, Cochrane Reviews of the use of opioids for cancer pain have favoured the primary outcome of mild or no pain at 14 days (Wiffen 2017). Our review will look for that outcome to allow comparability with opioids for cancer pain, as it was not an outcome reported in Fisher 2020.

Potential positive effects of CbMs for people with cancer have to be balanced against potential side effects. A systematic review with pooled analysis of studies of CbMs for chronic pain have emphasised the high rate of adverse effects with low (unfavourable) numbers needed to harm for central nervous system and psychiatric adverse effects (Stockings 2018). Fisher 2020 did not analyse these adverse effects.

In view of these considerable uncertainties we have seen the need to update the literature and to assess the efficacy, tolerability, and safety of CbMs compared to placebo or conventional medications for cancer pain. We will pay special attention to:

- additional patient-reported outcomes beyond pain, such as sleep problems and mood;
- opioid sparing effects;
- central nervous system and psychiatric adverse effects.

OBJECTIVES

To assess the efficacy, tolerability and safety of cannabis-based medicines, including medical cannabis, for treating pain and other symptoms in adults with cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials are the best design to minimise bias when evaluating the effectiveness of an intervention. We will consider randomised, double-blind (participants and physicians), controlled trials comparing cannabis-based medicines and medical cannabis with placebo or any other established analgesic for cancer pain, according to the ladder scheme of the WHO (World Health Organization 2019). Trials must include participant-reported pain

outcomes. We will include RCTs of any duration, though the emphasis of the review is on studies of a double-blinded duration of two weeks or longer. The clinical importance of experimental studies (one to three days) and very short-term studies (four to 13 days) in chronic pain is limited. In addition we will consider studies in which CbMs are used as add-on therapy to established analgesics, compared to these established analgesics without CbMs, and with participant-reported pain outcomes. Studies should include at least 20 participants per treatment arm. We will include RCTs reporting at least one of our primary outcomes.

Types of participants

Eligible studies will include adults (18 years of age and older) of any gender and race with cancer pain. We will include all types and stages of cancer, in all settings. We will include all types of cancer therapy-related pain. We will include studies with mixed pain conditions, if the results for patients with cancer-related pain are reported separately

Types of interventions

We will assess cannabis-based medicines (plant-based cannabinoids (cannabidiol, dronabinol, nabiximols)), or synthetic cannabinoids (nabilone) or medical cannabis (cannabis flowers or full spectrum cannabis extracts) at any dose or by any route that were administered for the relief of cancer pain, if compared with placebo or other established analgesic medication for cancer pain. We will not consider experimental and non-registered drugs such as cannabinoid receptor antagonists and negative allosteric modulators (e.g. rimonabant (SR141716A)) and modulators that increase or enhance endocannabinoid system activity (e.g. fatty acid amide hydrolase inhibitors) or synthetic cannabinoids (e.g. levonantradol).

Types of outcome measures

Primary outcomes

The proposed primary outcomes are the same as those used by [Wiffen 2017](#) in the overview review of opioids for cancer pain.

1. Proportion of participants reporting no worse than mild pain on treatment by 14 days after start of treatment (typically below 30/100 mm on a 100 mm visual analogue scale (VAS) or below 3 on an 11-point numeric rating scale) as an acceptable outcome when their pain is moderate or severe ([Moore 2013](#)).
2. Patient Global Impression of Change (PGIC) of much improved or very much improved.
3. Withdrawals due to adverse events.

Secondary outcomes

1. Withdrawals due to lack of efficacy.
2. Participants experiencing any serious adverse event.
3. Combined responder: number of participants who reported a pain relief of 30% or greater and overall opioid use reduced or stable compared to baseline for parallel and cross-over design studies and loss of this therapeutic response for studies with an enriched enrolment randomised withdrawal (EERW) design.
4. Number of participants who reported pain relief of 30% or greater.
5. Number of participants who reported pain relief of 50% or greater.

6. Main pain intensity: we will prefer numeric over visual pain scales.
7. Sleep problems: we will preferentially extract outcomes of multidimensional questionnaires over single-item questionnaires.
8. Depression: we will preferentially extract outcomes of multidimensional questionnaires over single-item questionnaires.
9. Anxiety: we will preferentially extract outcomes of multidimensional questionnaires over single-item questionnaires.
10. Daily maintenance opioid dosage (mg morphine equivalent).
11. Daily breakthrough opioid dosage (mg morphine equivalent).
12. All central nervous system adverse events according to the Medical Dictionary for Regulatory Activities ([International Council for Harmonization 2020](#)).
13. All psychiatric adverse events according to the Medical Dictionary for Regulatory Activities ([International Council for Harmonization 2020](#)).

Search methods for identification of studies

Electronic searches

We will search the following databases, without language or date restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library.
- MEDLINE (via Ovid) (1946 to present).
- Embase (via Ovid) (1974 to present).

The search strategy for MEDLINE is outlined in [Appendix 2](#). It will be modified where necessary to search the other databases.

Searching other resources

We will review the bibliographies of any RCTs identified. We will search the following clinical trials databases to identify additional published or unpublished data: the US National Institutes of Health clinical trials register (www.ClinicalTrials.gov), the European Union Clinical Trials Register (www.clinicaltrialsregister.eu), the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and the International Association for Cannabinoid Medicines (IACM) databank (www.cannabismed.org/studies/study.php). In addition, we will search grey literature, check reference lists of reviews and retrieved articles for additional studies, and perform citation searches on key articles. We will contact experts in the field for unpublished and ongoing trials. We will contact study authors for additional information where necessary.

Data collection and analysis

Selection of studies

Two review authors (WH, PW) will independently determine eligibility by reading the abstract of each study identified by the search. They will eliminate studies that clearly did not satisfy the inclusion criteria, and will obtain full copies of the remaining studies. Two review authors (WH, LR) will independently read these studies and reached agreement by discussion. In case of disagreement, agreement will be reached by consulting a third

review author (EF). We will not anonymise the studies before assessment. We will create a PRISMA flow chart (Moher 2009).

Data extraction and management

Two review authors (WH, PW) will extract data independently using a pre-piloted standard form and check for agreement before entering data into Review Manager 5.4 (RevMan 5 2020). Two review authors (WH, LR) will independently extract data, including information about the study funding sources and study author conflicts of interest, the cancer condition, number of participants treated, study setting, inclusion and exclusion criteria, demographic and clinical characteristics of the study samples (age, gender, race, pain baseline), prior recreational cannabis use, drug and dosing regimen, co-therapies allowed, rescue medication, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse event (AE) or serious AE). We will analyse the nature of all serious AEs. We will not analyse the nature of all AEs, but will concentrate on the ones which are regarded to be most relevant AEs of CbMs and MC, namely central nervous system and psychiatric AEs.

Assessment of risk of bias in included studies

Two review authors (WH, LR) will independently assess risk of bias for each study with the original version of Cochrane's 'Risk of bias' tool, using the criteria outlined in the 2011 edition of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will also use criteria adapted from those used by the Pain, Palliative and Supportive Care Review Group for reviews on medication therapy for cancer pain, with any disagreements resolved by discussion. In case of disagreement, agreement will be reached by consulting a third review author (EF).

We will assess the following risks of bias for each study as follows.

1. Random sequence generation (checking for possible selection bias). We will assess the method used to generate the allocation sequence as: low risk of bias (i.e. any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (when the method used to generate the sequence was not clearly stated); high risk of bias (studies used a non-random process [e.g. odd or even date of birth; hospital or clinic record number]).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We will assess the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (when method was not clearly stated). We will exclude studies that did not conceal allocation and are therefore at a high risk of bias (e.g. open list).
3. Blinding of participants and personnel/treatment providers (systematic performance bias). We will assess the methods used to blind participants and personnel/treatment providers from knowledge of which intervention a participant received. We will assess the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an

adequate description of how it was achieved); high risk of bias (blinding of participants was not ensured, e.g. tablets different in form or taste).

4. Blinding of outcome assessment (checking for possible detection bias). We will assess the methods used to blind study outcome assessors from knowledge of which intervention a participant received. We will assess the methods as: low risk of bias (study stated that outcome assessors were blinded to the intervention or exposure status of participants); unclear risk of bias (study stated that the outcome assessors were blinded but did not provide an adequate description of how it was achieved); high risk of bias (outcome assessors knew the intervention or exposure status of participants).
5. Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We will assess the methods used to deal with incomplete data as: low risk of bias (i.e. less than 10% participant dropout or used 'baseline observation carried forward' (BOCF) analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); or high risk of bias (used 'completer' analysis).
6. Reporting bias due to selective outcome reporting (reporting bias). We will check if an a priori study protocol was available and if all outcomes of the study protocol were reported in the publications of the study. There is low risk of reporting bias if the study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review are reported in the pre-specified way, or if the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that are prespecified (convincing text of this nature may be uncommon). There is a high risk of reporting bias if not all of the study's prespecified primary outcomes are reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that are not pre-specified; one or more reported primary outcomes are not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report did not include results for a key outcome that would be expected to have been reported for such a study. There is unclear risk of bias if insufficient information is available to permit judgement of 'Low risk' or 'High risk'.
7. In addition to the original 'Risk of bias' criteria outlined in the 2011 edition of the *Cochrane Handbook* (Higgins 2011), we will assess 'Group similarity at baseline' (selection bias) as another risk of bias. We will assess similarity of the study groups at baseline for the most important prognostic clinical and demographic indicators. There is low risk of bias if groups are similar at baseline for demographic factors, value of main outcome measure(s), and important prognostic factors. There is an unclear risk of bias if important prognostic clinical and demographic indicators are not reported. There is high risk of bias if groups are not similar at baseline for demographic factors, value of main outcome measure(s), and important prognostic factors.

We will also assess overall risk of bias in each trial according to guidance in the current edition of the *Cochrane Handbook* (Higgins 2021).

- Low risk of bias: The trial is judged to be at low risk of bias for all domains for this result.
- Some concerns: The trial is judged to raise some concerns in at least one domain for this result, but not to be at high risk for any domain for this result.
- High risk of bias: The trial is judged to be at high risk of bias in at least one domain for this result or the judged to raise some concerns in multiple domains for this result in a way that substantially lowers confidence in the result.

Measures of treatment effect

We will calculate numbers needed to treat for an additional beneficial outcome (NNTB) as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner. We will use dichotomous data to calculate risk differences (RD) with 95% confidence intervals (CIs) using a fixed-effect model unless we find significant statistical or clinical heterogeneity (see below). We will set the threshold for a clinically relevant benefit or a clinically relevant harm for categorical variables by an NNTB or NNTH less than 10 (Moore 2008).

We will calculate standardized mean differences (SMD) with 95% CIs for continuous variables, using a random-effects model. We will use Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD, with Hedges' *g* value of 0.2 = small, 0.5 = medium, and 0.8 = large (Cohen 1988). We will label a *g* value less than 0.2 to be a 'not substantial' effect size. We will assume a minimally important difference if the Hedges' *g* value was 0.2 or greater (Fayers 2014). To increase interpretability, we will analyse the mean difference of mean pain intensity. If needed, we will convert 0-10 and 0-100 numerical rating scales (NRS) or VAS to a single scale.

Unit of analysis issues

We will split the control treatment arm between active treatment arms in a single study if the active treatment arms are not able to be combined for analysis. We will include studies with a cross-over design where separate data from the two periods are reported, data are presented that exclude a statistically significant carry-over effect, or statistical adjustments are carried out in case of a significant carry-over effect. We do not anticipate cluster trials for this intervention.

Dealing with missing data

We will use intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. Where means or standard deviations (SDs) are missing, we will attempt to obtain these data through contacting trial authors. Where SDs are not available from trial authors, we will calculate them from *t*-values, *P* values, CIs, or standard errors, where reported by the studies (Higgins 2020a). Where rates of pain relief of 30% and of 50% or greater are not reported or provided on request, we will calculate them from means and SDs using a validated imputation method (Furukawa 2005).

Assessment of heterogeneity

We will deal with clinical heterogeneity by combining studies that examined similar conditions. We will assess statistical heterogeneity by using the *I*² statistic. Where the *I*² value is greater than 50%, we will consider possible reasons for this.

Assessment of reporting biases

We will assess publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNTB of 10 or higher (Moore 2008)).

Data synthesis

We will use a random-effects model, using the inverse variance method in Review Manager 5.4 for meta-analysis, because we expect clinical heterogeneity due to the different types of cancer pain conditions (RevMan 5 2020).

Subgroup analysis and investigation of heterogeneity

We intend to perform subgroup analyses for the primary outcomes according to the following, where there are at least two studies available:

- different types of cannabis-based medicines;
- different dosages of the same cannabis-based medicine and study duration. We will distinguish short-term (four to 12 weeks), intermediate-term (13 to 26 weeks), and long-term (more than 26 weeks) studies (Chaparro 2013) as well as experimental studies (one to three days) and very short-term (three to 13 days) studies;
- types of controls (placebo; established analgesic);
- types of cancer-related pain (pain directly caused by cancer, e.g. by bone metastases versus pain caused by cancer treatment, e.g. chemotherapy-induced polyneuropathy).

These subgroup analyses were predefined due to the many uncertainties about CbMs for chronic pain, such as the selection of the type of CbM (cannabis flowers versus cannabinoids), optimal dosage for efficacy, duration of efficacy and comparative efficacy and safety to established medications (Fisher 2020; Häuser 2018).

Sensitivity analysis

We will perform a sensitivity analysis by excluding studies with imputed rates of pain relief of 30% and of 50% or greater if the use of imputation methods has been necessary. We will perform a sensitivity analysis excluding studies with less than 14 days duration.

Summary of findings and assessment of the certainty of the evidence

Two review authors (WH, PW) will independently rate the certainty of the body of evidence for the outcomes. We will use the GRADE system to rank the certainty of the evidence using the guidelines provided in the *Cochrane Handbook* (Schünemann 2020) and the GRADE Handbook (Schünemann 2013).

The GRADE system considers study design as a marker of quality. It uses the following criteria for assigning a certainty level to the body of evidence for a given outcome:

1. high: randomised trials without downgrading; or double-upgraded observational studies;
2. moderate: downgraded randomised trials; or upgraded observational studies;
3. low: double-downgraded randomised trials; or observational studies without downgrading;
4. very low: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports;

Factors that may decrease the certainty level of a body of evidence are as follows.

1. Limitations in the design and implementation of available studies, suggesting high likelihood of bias. We will assume that there are limitations in study design if more than 50% of participants were from low-quality studies, as defined by the original Cochrane 'Risk of bias' tool (Higgins 2011).
2. Indirectness of evidence (indirect population, intervention, control, outcomes). We will assess if the study population is different from the population in routine clinical care by assessing if patients with relevant medical conditions (cardiovascular, hepatic, renal and endocrine system) have been excluded. If exclusion of participants with clinically relevant medical conditions resulted in 50% or more of the total number of participants, we will decrease the certainty of evidence.
3. Unexplained heterogeneity ($I^2 > 50%$) or inconsistency of results.
4. Imprecision of results (wide confidence intervals; confidence interval including zero; low number of events).
5. High probability of publication bias. We will assume a potential publication bias if all studies were initiated and funded by the manufacturer of the drug tested in the trial.

We will use the GRADE system criteria for assigning the grade of evidence (Schünemann 2013):

- high certainty: we are very confident that the true effect lies close to that of the estimate of the effect
- moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
- low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
- very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We plan to include one 'Summary of findings' table to present in a transparent and simple tabular format the main findings for comparisons of CbMs and medical cannabis with placebo or any established analgesic. In particular, we will include key information concerning the certainty of evidence, the magnitude of effect of the interventions examined, and the sum of available data on these outcomes:

- proportion of participants reporting no worse than mild pain on treatment by 14 days after start of treatment;
- proportion of participants reporting to be much or very much improved in the Patient Global Impression of Change (PGIC);
- proportion of participants dropping out due to adverse events;
- proportion of participants with serious adverse events;
- proportion of participants reporting a pain relief of 30% or greater and overall opioid use reduced or stable compared to baseline;
- daily maintenance opioid dosage (mg morphine equivalent);
- daily breakthrough opioid dosage (mg morphine equivalent).

ACKNOWLEDGEMENTS

We thank Joanne Abbott, PaPaS Information Specialist, for conducting the searches.

Cochrane Review Group funding acknowledgement: this project was funded by the National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Editorial and peer-reviewer contributions

The Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS) supported the authors in the development of this review.

The following people conducted the editorial process for this article.

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APPENDICES
Appendix 1. Terminology

Term	Definition	Examples/typical products
(Herbal) Cannabis, marijuana	The whole plant or parts or material from the plant (e.g. flowers, buds, resin, leaves)	<i>Cannabis sativa</i> , hashish
Medical or medicinal cannabis	The terms 'medical/medicinal cannabis' (or 'medical/medicinal marijuana') is used for cannabis plants, plant material, or full plant extracts used for medical purposes.	Bedrocan®, Bedrobinol®, Tilray 10THC/10CBD®
Cannabinoids	Cannabinoids are biologically active constituents of cannabis, or synthetic compounds, usually having affinity for and activity at cannabinoid receptors.	THC, CBD, CP55,940, WIN55,212-2, HU210
Phytocannabinoid	A cannabinoid found in the cannabis plant or purified/extracted from plant material	THC, CBD
Endocannabinoid	An endogenous ligand found in the body of humans and other animals and which has affinity for, and activity at, cannabinoid receptors	Anandamide, 2-AG
Endocannabinoid system modulators	In addition to individual phytocannabinoids, cannabis-derived or cannabis-based medicines, and cannabis extracts, other pharmacological approaches under development for manipulation of the endocannabinoid system include selective synthetic cannabinoid receptor agonists or antagonists, and inhibitors of the catabolism (e.g. fatty acid amide hydrolase [FAAH] inhibitors) or reuptake of endocannabinoids.	PF-04457845, URB597, rimonabant
Cannabis-based (or cannabis-derived) medicines	Registered, regulatory body approved medicinal cannabis extracts with defined and standardized phytocannabinoid content, particularly THC and CBD.	Nabiximols (Sativex®), dronabinol, marinol, Epidiolex®

Soliman 2019, adapted from Häuser 2018

Appendix 2. Search strategy for MEDLINE

Ovid MEDLINE(R)

1 Cannabis/

2 (cannabis or hemp or marijuana or ganja or hashish or marihuana or bhang or cannabinoid*).tw.

3 exp Cannabinoids

4 (dronabinol or marinol or nabilone or cesamet or "HU 211" or dexanabinol or nabiximols or sativex or tetrahydrocannabinol).tw.

5 CANNABIDIOL.tw.

6 cannabitol.tw.

7 1 or 2 or 3 or 4 or 5 or 6

8 exp Neoplasms/

9 (cancer* or neoplas* or tumor* 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.

10 8 or 9

11 exp Pain/

12 pain.tw.

13 11 or 12

14 7 and 10 and 13

15 randomized controlled trial.pt.

16 controlled clinical trial.pt.

17 randomized.ab.

18 placebo.ab.

19 drug therapy.fs.

20 randomly.ab.

21 trial.ab.

22 or/15-21

23 exp animals/ not humans.sh.

24 22 not 23

25 14 and 24

CONTRIBUTIONS OF AUTHORS

All authors participated in writing the protocol.

DECLARATIONS OF INTEREST

WH: none known. WH is a member of the PaPaS Editorial Board and had no input into the editorial decisions or processes for this protocol.

PW: none known.

LR: none known.

RF: none known.

RFB: none known.

RAM: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- National Institute for Health Research (NIHR), UK

Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS)