BMJ Open

Cannabinoids versus placebo for pain. A systematic review with meta-analysis and Trial Sequential Analysis; Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031574
Article Type:	Protocol
Date Submitted by the Author:	11-May-2019
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Keywords:	PAIN MANAGEMENT, Herbal medicine < THERAPEUTICS, Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Cannabinoids versus placebo for pain: A protocol systematic review with meta-analysis and Trial Sequential Analysis

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Abstract

Introduction Pain is a frequent clinical symptom, and with significant impact on patient well-being. Therefore, sufficient pain management is of utmost importance. While cannabinoids have become a more popular alternative to traditional types of pain medication among patients, the quality of evidence supporting the use of cannabinoids has been questioned. The beneficial and harmful effects of cannabinoids in patients with pain is unknown. Accordingly, we aim to assess the efficacy, tolerability, and safety of cannabinoids (herbal, plant-derived extracts and synthetic) compared with placebo for any type of pain.

Methods and analysis We will conduct a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis to assess the beneficial and harmful effects of cannabinoids in any dose, formulation, and duration. We will accept placebo or no treatment as control interventions. We will include participants with any type of pain (acute and chronic pain, cancer-related pain, headache, neuropathic pain or any other types of pain). We will systematically search The Cochrane Library, MEDLINE, EMBASE, Science Citation Index, and BIOSIS for relevant literature. We will follow the recommendations by Cochrane and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The risk of systematic errors (bias) and random errors (play of chance) will be assessed. The overall certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination Ethical approval is not a requirement since no primary data will be collected. The findings of this systematic review will be submitted for peer-reviewed publication and disseminated in national and international conferences.

Discussion Although cannabinoids are now being used to manage different pain conditions, the evidence for the clinical effects are unclear. The present review will systematically assess the current evidence for the benefits and harms of cannabinoids to inform practice and future research.

Strengths and limitations of this study

- Our methodology is based on the Cochrane Handbook for Systematic Reviews of Interventions, the PRISMA guideline, and a systematic eight step procedure for valid assessments of statistical and clinical significance
- We systemically plan to assess risks of random errors ('play of chance) and systematic errors ('bias')
- We have systematically predefined minimal important differences for all outcomes
- The certainty of the evidence with be assessed using the GRADE approach

Description of pain

Pain is the most commonly reported symptom in the general population and in a medical setting [1-3]. Persistent pain is a major international health problem [4], prompting the World Health Organization (WHO) to endorse a global campaign against pain [5]. Pain is the leading reason for use of alternative medicines (e.g. acupuncture) [6]. Pain has been associated with a low degree of health-related quality of life and may lead to psychosocial distress, insomnia, and depressive symptoms [7-15]. Pain is also among the most common reasons for temporary or permanent work disability [16]. Pain is always subjective and may be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [17].

Pain may be caused by or be related to different clinical disorders and classified according to several different characteristics [18-21]. Below, we describe shortly some of these classifications.

Acute and chronic pain

Pain may be classified as 'acute pain' or 'chronic pain'.

- Acute pain usually has a well-defined onset and most often a readily identifiable cause (e.g. surgery). Acute pain is expected to run its course in a short time frame and management typically focuses on symptomatic relief until this happens [22]. Acute pain is a common symptom, affecting between 37% to 84% of hospitalised patients [23] .

- Chronic pain is often characterised by an ill-defined onset and a prolonged, fluctuating course [22]. Chronic pain often persists past normal healing time and hence lacks the acute warning function of

physiological nociception [24]. Pain is usually regarded as chronic when it lasts or recurs for more than three to six months [17, 25]. A chronic pain patient usually does not appear to be in pain, and the only definitive way to determine the presence of pain is to obtain a verbal report from the patient [22]. A recent systematic review has demonstrated considerable heterogeneity in the criteria for a diagnosis of chronic pain applied in large epidemiological studies [26]. Chronic pain is a frequent condition, affecting an estimated 20% of people worldwide [27-30] and accounting for 15% to 20% of physician visits according to European observational studies [31, 32].

Cancer-related pain

Pain may also be classified based on whether it is cancer-related or non-cancer-related. Cancer-related pain is pain caused by the cancer itself (primary tumour and metastases) or its treatment (e.g. radiation therapy) [22, 33].

Postoperative pain

Postoperative pain includes pain from inflammation caused by tissue trauma (i.e. surgical incision, dissection, burns) or direct nerve injury (i.e. nerve transection, stretching, or compression) [34]. Inflammation results in activation and sensitisation of nociceptive pain pathways, resulting in primary and secondary hyperalgesia and central sensitisation, which is characterized by clinically increased pain, allodynia, and increased sensitivity from surrounding non-damaged anatomical areas [35].

Headache

Up to 90% of all patients with headaches may be classified as suffering from either tension-type headache, migraine, or cluster headache. While episodic tension-type headache is the most frequent headache type in population-based studies, migraine is the most common diagnosis in patients presenting to primary care physicians with headache [36].

Other types of pain

Pain in one or more anatomic regions where the aetiology is unknown is defined as idiopathic pain [37]. Examples of idiopathic pain are chronic widespread pain, fibromyalgia, irritable bowel syndrome, and back pain that is not diagnosed as musculoskeletal or as neuropathic pain [33].

Pain types defined according to specific mechanism causing the pain

Somatic nociceptive pain

Nociceptive pain is the most frequent type of pain. It results from activity in neural pathways caused by actual tissue damage or potentially tissue-damaging stimuli [31, 38] originating from somatic nociceptors from skin, bone, joints, or muscles [39].

Visceral nociceptive pain

The visceral nociceptive pain is pain resulting from viscera in the thoracic, pelvis, or abdominal organs [40-42]. Visceral pain is diffuse, less distinctive, and difficult to localise [42]. It is often characterised by referred visceral pain and followed by symptoms from the autonomic nerve system (e.g. nausea, sweating, cardiovascular symptoms) [43].

Neuropathic pain

The 2011 International Association for the Study of Pain definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" [44]. Neuropathic pain leads to a heterogeneous group of symptoms, including unremitting and spontaneous burning or shooting sensations, abnormal pain sensation to normal and harmless stimuli (allodynia), or a raised sensitivity to noxious stimuli (hyperalgesia) [45].

Neuropathic pain may be classified as central neuropathic pain or peripheral neuropathic pain. Central neuropathic pain conditions are mainly attributed to multiple sclerosis and post-stroke pain [46], while peripheral neuropathic pain is largely due to post-herpetic neuralgia and diabetic neuropathy [47]. Persistent postoperative pain (incidence up to 10% of surgical patients) may mostly be considered as iatrogenic neuropathic pain [48].

Description of the intervention

Cannabis (also called marijuana) is the most common illegally used psychoactive substance worldwide [49]. Cannabis was used by an estimated 182 million people worldwide in 2014, this corresponds to approximately 3.8 percent of the global adult population [49]. Cannabinoids refer to a heteromorphic group of molecules that

demonstrate activity upon cannabinoid receptors [50]. Cannabinoids may be classified into three groups: 1) endocannabinoids, 2) phytocannabinoids, and 3) synthetic cannabinoids [50].

Endocannabinoids

Endocannabinoids are characterised by being the endogenously generated cannabinoids [51]. The primary types of endocannabinoids are the lipid endocannabinoid arachidonoyl ethanolamide (named anandamide) [52] and the endocannabinoid 2-arachidonoylglycerol (2-AG) [53, 54]. Arachidonoyl ethanolamide binds to the brain cannabinoid receptor with high affinity and mimics the behavioural actions of tetrahydrocannabinol when injected into rodents (e.g. block peripheral pain, inhibiting gastric emptying) [52, 55-57]. A number of other endocannabinoids have been discovered, but follow-up studies about biosynthesis, cellular transport, metabolism, and biological function have focused primarily on anandamide and 2-AG [58].

Phytocannabinoids

Phytocannabinoids are cannabinoids found in the cannabis plant [59]. The best characterised phytocannabinoids are the psychotropic tetrahydrocannabinol (THC) and the primarily anti-inflammatory cannabidiol (CBD) [60]. Nabiximols (marketed as Sativex®) is a sublingually administered oromucosal spray based on a mixture of tetrahydrocannabinol and cannabidiol [61].

Synthetic cannabinoids

Synthetic cannabinoids are analogues of the cannabinoids found in natural marijuana that are chemically synthesised. They may have been commercially available in Europe since 2004 and in the United States since 2008 [62]. The use of synthetic cannabinoids is increasing in Europe [63]. From 2005 to 2011, synthetic cannabinoids represented two-thirds of all new substances reported to the European Monitoring Centre for Drugs and Drug Addiction Early Warning System [63].

The most commonly prescribed cannabinoid-based medicines are the synthetic cannabinoids dronabinol (marketed as Marinol®) and nabilone (marketed as Cesamet®) [61].

Endocannabinoid system

All cannabinoids act on cannabinoid receptors. These cannabinoid receptors are located throughout the body but are mostly located in the brain [64]. The cannabinoid receptors and endocannabinoids (see paragraph above) are together named the endocannabinoid system [65].

The endocannabinoid system is thought to have three broad and overlapping functions in mammals [66]. The first function of the endocannabinoid system 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 [66]. The second function of the endocannabinoid system is to control energy balance through regulation of the intake, storage, and utilisation of food [66]. The third function of the endocannabinoid system involves immune regulation; endocannabinoid signalling is activated by tissue injury and modulates immune and inflammatory responses [66].

Cannabinoid receptors

There are two types of cannabinoid receptors, type I and type II [67]. Cannabinoid receptor type I are most abundant in the central nervous system, especially in areas promoting nociception, short-term memory, and in the basal ganglia, but are also found in the peripheral nerves, uterus, testis, and bones [67]. Tetrahydrocannabinol activates cannabinoid type I receptors in the dopaminergic mesolimbic brain circuit, resulting in enhanced release of dopamine [68]. Such activation of the so-called 'brain reward system' is hypothesised to mediate the positive reinforcing and rewarding effects of almost all drugs of abuse [58]. More than weekly use of cannabis downregulates brain cannabinoid type I receptors; abstinence results in receptor upregulation within several days [69] . These receptor changes are associated with an often uncomfortable or distressing cannabis withdrawal syndrome [70], which may serve as negative reinforcement to continue cannabis use in order to suppress the withdrawal symptoms.

In contrast, cannabinoid receptor type II, is mostly found in the periphery, often in conjunction with immune cells, but may appear in the central nervous system particularly under conditions of inflammation in association with microcytes [67]. The physiological responses that result from cannabinoid receptor activation are euphoria, psychosis, impaired memory and cognition, reduced locomotor function, increased appetite, as well as anti-emetic, pain-relieving, anti-spasticity, and sleep-promoting effects [71].

Applicability of cannabinoid-based medicines

Cannabis is most commonly consumed via smoked, inhaled vapor, or oral routes of administration [72]. Vaporising cannabis ('vaping') heats the material without burning which theoretically minimises potential carcinogens compared to smoking and may produce less respiratory irritation [73, 74]. Sublingual administration is used for some medical cannabis preparations (e.g. nabiximols).

In recent years, cannabinoid-based medicines have become increasingly available to patients in many countries [61]. Besides usage for treatment of different pain conditions [50], cannabinoid-based medicines are used for treatment of nausea and vomiting associated with cancer chemotherapy and the treatment of AIDS-associated anorexia [75]. Cannabinoid-based medicines are used to reduce seizure frequency in patients with drug-resistant epilepsy [76]. In Denmark, Sativex® (nabiximols) is approved for the treatment of moderate to severe spasticity due to multiple sclerosis in patients who have not responded adequately to other anti-spasticity medication [77]. An American survey indicated that 6% of adults (or 12 million) have utilised cannabis in attempts to treat chronic pain [78]. In pain clinics across Canada, the proportion of users of cannabinoid-based medicines is estimated to be between 12% to 15% [79].

Why it is important to do this review

We identified ten previous reviews with meta-analyses assessing the effects of cannabinoids on different types of pain [79-88]. Bearing in mind that some of the previous reviews investigated more than one type of pain, eight reviews assessed the effects of different cannabinoids on neuropathic pain [79-85, 88]; four reviews assessed the effects of different cannabinoids on nociceptive pain (e.g. rheumatoid arthritis) [79, 80, 83, 84]; three reviews assessed the effects of different cannabinoids on cancer-related pain [79, 83, 84]; four reviews assessed the effects of different cannabinoids on fibromyalgia-related pain [79, 80, 83, 87]; and three reviews assessed the effects of different cannabinoids on postoperative pain [79, 84, 86]. All the previous reviews included randomised clinical trials, but only two of the ten reviews systematically assessed the risk of bias in the trials [81, 88], and none of the previous reviews took into account the risks of random errors [79-88]. Only two out of the ten reviews used predefined Cochrane methodology [87, 88] and only four reviews used the GRADE approach [81, 86-88].

Most of the reviews concluded that the assessed cannabinoids were effective against pain [79-83, 85, 88]. In **Table 1** (**Additional file 1**)**,** we have summarised the results and conclusions of the previous reviews. Five of the reviews reported serious adverse events (e.g. agitation, impaired memory, abuse, dissociation, acute psychosis, and death) [79, 81-83, 88]. The reviews also showed that the most commonly reported adverse events were sedation, dizziness, dry mouth, increased appetite, somnolence, confusion, nausea, and disturbances in concentration [79-82, 84, 85, 87, 88].

A correlation between psychiatric disorders (e.g. schizophrenia and psychosis) and increased cannabinoid consumption have previously been hypothesised [89-95]. Di Forti et. al recently conducted a study indicating that daily cannabis use was associated with increased odds of psychotic disorder compared with never users (adjusted odds ratio [OR] 3.2, 95% CI 2.2–4.1), increasing to nearly five-times increased odds for daily use of high-potency (THC ≥10%) types of cannabis (adjusted odds ratio [OR] 4.8, 95% CI 2.5–6.3) [96].

Objective

The objective of our systematic review is to assess the beneficial and harmful effects of cannabinoids versus placebo or no intervention for any type of pain (acute and chronic pain, cancer-related pain, headache, neuropathic pain, or any other types of pain).

Methods

This systematic review protocol has been developed based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews evaluating healthcare interventions [97, 98]. A PRISMA-P checklist file is attached (**Additional file 2**).

Criteria for considering studies for this review

Type of studies

Randomised clinical trials irrespective of trial design, setting, publication status, publication year, and language. If we identify quasi-randomised studies and observational studies during our searches for randomised clinical trials, we will only include their reporting on harms in a narrative way. By not systematically searching for all observational studies on harm, we run the risk of putting more focus on benefit than harm. We are aware that this is a limitation of our review.

Types of participants

Participants with any type of pain, i.e. acute and chronic pain, cancer-related pain, headache, neuropathic pain, or any other types of pain (as defined by the trialists). Participants will be included irrespective of age, sex, and comorbidities.

Types of interventions

Experimental intervention

Any type of cannabinoids such as: herbal cannabis (hashish, marihuana), plant-based extracts (e.g. nabiximole), or synthetic cannabinoids (e.g. cannabidiol, dronabinol, levonantradol, nabilone). We will accept cannabinoids at any dose, by any route, administered for the relief of pain.

Control intervention

Placebo or no intervention.

Co-interventions

We will accept any co-intervention but only if this co-intervention is planned to be delivered similarly in both intervention groups. If this plan is not followed, then these trials will be assessed as a subgroup due to potential confounding.

Patient and Public Involvement

We have had email correspondence with several relevant patient associations in Denmark to select the most patient relevant outcomes. The patient associations we have been in contact with include: The Danish Diabetes Association, Steno Diabetes Centre Copenhagen, The Danish Rheumatism Association, The Danish Multiple Sclerosis Society, and Danish Cancer Society. We are very thankful for their input.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Pain assessment on visual analogue scale (VAS) or numerical rating scale (NRS)

- Proportion of participants with a serious adverse event defined as any untoward medical occurrence that resulted in death; was life threatening; was persistent; or led to significant disability, nephrotoxicity, superinfection, need for respiratory support, need for circulatory support, or prolonged hospitalisation [99]. As we expect the trialists' reporting of serious adverse events to be heterogeneous and not strictly according to the ICH-GCP recommendations, we will include the event as a serious adverse if the trialists either: 1) use the term 'serious adverse event' but not refer to ICH-GCP, or 2) report the proportion of participants with an event we consider fulfils the ICH-GCP definition (e.g. myocardial infarction or hospitalisation). If several of such events are reported then we will choose the highest proportion reported in each trial.
- Quality of life measured on any valid continuous scale

Secondary outcomes

- Dependence (as defined by trialists)
- Psychosis (as defined by trialists)
- Proportion of participants with one or more adverse event not considered to be serious
- Sleep quality measured on any valid continuous scale

Exploratory outcomes

- Each serious adverse event separately
- Each adverse event not considered serious separately.
- Twenty-four-hour morphine consumption (as defined by trialists)
- Physical function (as defined by trialists)
- Depressive symptoms (e.g. Hamilton Depression Rating Scale)

We will for all outcomes use the trial results reported at maximal follow-up except for acute pain. For acute pain, we will use the trials' results reported at the time point closest to 24 hours after the intervention is given.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health

Sciences Literature (LILACS), Science Citation Index Expanded on Web of Science, and BIOSIS in order to identify relevant trials.

We will search all databases from their inception to the present.

Searching other resources

The reference lists of relevant publications will be checked for any unidentified randomised trials. We will contact authors of included studies, and major pharmaceutical companies, by email asking for unpublished randomised trials. Further, we will search for ongoing trials on:

- ClinicalTrials.gov (www.clinicaltrials.gov)
- Google Scholar (https://scholar.google.dk/)
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/)
- European Medicines Agency (EMA) (http:// www.ema.europa.eu/ema/)
- United States Food and Drug Administration (FDA) (www.fda.gov)
- China Food and Drug Administration (CFDA) (http://eng.sfda.gov.cn/WS03/CL0755/)
- Medicines and Healthcare products Regulatory Agency (https://www.gov.uk/government/organisations/ medicines-and-healthcare-products-regulatory-agency)
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/ trialsearch/)

We will also consider relevant for the review unpublished and grey literature trials, if we identify such trials.

Data collection and analysis

We will perform the review following the recommendations of Cochrane [100]. The analyses will be performed using Review Manager 5 [101] and Trial Sequential Analysis [102]. In case of Review Manager statistical software not being sufficient, we will use STATA 15 [103].

Selection of studies

Two authors (JB, SKK) will independently screen titles and abstracts. We will retrieve all relevant full-text study reports/publications, and four review authors (JB, SKK, JRF, MM) will independently screen the full text and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through

discussion or, if required, we will consult a fifth author (JCJ). Trial selection will be displayed in an adapted flow diagram as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [104].

Data extraction and management

Four authors (JB, SKK, JRF, MM) will in pairs extract data independently from included trials. Disagreements will be resolved by discussion with a fifth author (JCJ). We will assess duplicate publications and companion papers of a trial together to evaluate all available data simultaneously (maximise data extraction, correct bias assessment). We will contact the trial authors by email to specify any additional data, which may not have been reported sufficiently or at all in the publication.

Trial characteristics

Bias risk components (as defined below); trial design (parallel, factorial, or crossover); number of intervention arms; length of follow-up; estimation of sample size; inclusion and exclusion criteria.

Participant characteristics and diagnosis

Number of randomised participants; number of analysed participants; number of participants lost to follow-up/ withdrawals/crossover; compliance with medication; age range (mean or median) and sex ratio; type of pain (acute and chronic pain, cancer-related pain, headache, neuropathic pain or any other types of pain); baseline pain score; drug and dosing regimen; study design (placebo or active control); study duration and follow-up; analgesic outcome measures and results; adverse events (participants experiencing any adverse event, or serious adverse event).

Co-intervention characteristics

Type of co-intervention; dose of co-intervention; duration of co-intervention; and mode of administration.

Outcomes

All outcomes listed above will be extracted from each randomised clinical trial, and we will identify if outcomes are incomplete or selectively reported according to the criteria described later in 'incomplete outcome data' bias domain and 'selective outcome reporting' bias domain.

Notes

Funding of the trial and notable conflicts of interest of trial authors will be extracted, if available.

We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Four review authors (JB, SKK, JRF, MM) will independently transfer data into the Review Manager file [101]. Disagreements will be resolved through discussion or, if required, we will consult with a fifth author (JCJ).

Assessment of risk of bias in included studies

We will use the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions [100] in our evaluation of the methodology and hence the risk of bias of the included trials. We will evaluate the methodology in respect of:

- Random sequence generation
- Allocation concealment
- Blinding of participants and treatment providers
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- For-profit bias
- Overall risk of bias

These components enable classification of randomised trials as being at low risk of bias and at high risk of bias. The latter trials tend to overestimate positive intervention effects and underestimate negative effects [105-111].

We will classify the trials according to the following criteria.

Random sequence generation

- Low risk: If sequence generation was achieved using computer random number generator or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.
- Unclear risk: If the method of randomisation was not specified, but the trial was still presented as being randomised.

- High risk: If the method of sequence generation was inadequate i.e. alternate medical record numbers or other non-random sequence generation.

Allocation concealment

- Low risk: If the allocation of patients was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, drug bottles, or containers prepared by an independent pharmacist or investigator.
- Uncertain risk: If the trial was classified as randomised but the allocation concealment process was not described.
- High risk: If the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

- Low risk: If the participants and the treatment providers were blinded to intervention allocation and this was described.
- Uncertain risk: If the procedure of blinding was insufficiently described.
- High risk: If blinding of participants and the treatment providers was not performed.

Blinding of outcome assessment

- Low risk of bias: If it was mentioned that outcome assessors were blinded and this was described.
- Uncertain risk of bias: If it was not mentioned if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described.
- High risk of bias: If no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

- Low risk of bias: If missing data were unlikely to make treatment effects depart from plausible values. This could be either (1) there were no drop-outs or withdrawals for all outcomes or (2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups. Generally, the trial is judged as at a low risk of bias due to incomplete outcome data if drop-outs are less than 5%. However, the 5% cut-off is not definitive.
- Uncertain risk of bias: If there was insufficient information to assess whether missing data were likely to induce bias on the results.

- High risk of bias: If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

Selective outcome reporting

- Low risk of bias: If a protocol was published before or at the time the trial was begun, and the outcomes specified in the protocol were reported on. If there is no protocol or the protocol was published after the trial has begun, reporting pain assessment on VAS or NRS and serious adverse events will grant the trial a grade of low risk of bias.
- Uncertain risk of bias: If no protocol was published and the outcome pain assessment on VAS or NRS and serious adverse events were not reported on.
- High risk of bias: If the outcomes in the protocol were not reported on.

For-profit bias

- Low risk of bias: If the trial appeared to be free of other components of for-profit bias.
- Unclear risk of bias: If it was unclear whether the trial was free of for-profit bias.
- High risk of bias: If there was a high risk of for-profit bias.

Overall risk of bias

- Low risk of bias: The trial will be classified at overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified at 'low risk of bias'.
- High risk of bias: The trial will be classified at 'high risk of bias' if any of the bias risk domains described in the above are classified at 'unclear' or 'high risk of bias'.

We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective outcome reporting' for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of our primary outcome results at overall low risk of bias. Both our primary and secondary analyses will be presented in the summary of findings tables.

Differences between the protocol and the review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between the protocol and the review' section of the systematic review.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well as the Trial Sequential Analysis- adjusted CIs (see below).

Continuous outcomes

We will calculate the mean differences (MDs) and the standardised mean difference (SMD) with 95% CI for continuous outcomes, as well as the Trial Sequential Analysis-adjusted CIs (see below).

Dealing with missing data

We will, as first option, contact all trial authors to obtain any relevant missing data (i.e. for data extraction and for assessment of risk of bias, as specified above).

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

Continuous outcomes

We will primarily analyse scores assessed at single time points. If only changes from baseline scores are reported, we will analyse the results together with follow-up scores [100]. If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible. We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis (see paragraph below) for continuous outcomes, we will impute data.

Assessment of heterogeneity

We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by chi^2 test (threshold $P < 0.10$) and measure the quantities of

heterogeneity by the I^2 statistic [112, 113]. We will investigate for heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided [100].

Assessment of reporting biases

We will use a funnel plot to assess reporting bias if ten or more trials are included. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (i.e. a funnel plot assesses bias due to small sample size). From this information, we assess possible reporting bias. For dichotomous outcomes, we will test asymmetry with the Harbord test [114] if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test [115] and the adjusted rank correlation [116].

Unit of analysis issues

We will only include randomised clinical trials. For trials using crossover design, only data from the first period will be included [100, 117]. There will therefore not be any unit of analysis issues.

Minimal important difference

In clinical intervention research it is of utmost importance always to define minimal important differences (MID) and to define thresholds for clinical significance [118]. If a large number of trial participants are randomised, small and clinically irrelevant intervention effects may lead to statistically significant results and rejection of the null hypothesis [119]. Jaeschke et al. defined the minimal important difference as "the smallest difference in score in the domain of interest which patients perceive as beneficial" [120].

Estimations of minimal important differences should be used as arbitrary strict precise thresholds. However, to avoid erroneous conclusions minimal important differences need to be estimated and predefined when assessing the effects of interventions for pain. Olsen et al. have conducted two systematic reviews on this matter in order to gather the evidence and present an estimate of the minimal important difference [121, 122]. Olsen et al. conducted a systematic review on the minimal important difference in patients with acute pain and concluded that the median of the studies' results was 17 mm on VAS (IQR 14 mm to 23 mm) [121]. Another systematic review conducted by Olsen et al. was on the minimal important difference in patients with chronic pain and the results showed a median of 23 mm on VAS (IQR 12 mm to 39 mm) when using the within-patient anchor-based method, while the median in studies using the sensitivity- and specificity-based method was 20 mm on VAS (IQR

15 mm – 30 mm) [122]. We have described detailed considerations about minimal important differences in **Appendix 1**.

Based on the previously conducted systematic reviews we will choose at minimal important difference equivalent to 10 mm or 1 point on the visual analogue scale and the numerical rating scale, respectively, regarding a pain-relieving effect.

Data synthesis

Meta-analysis

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions [100], Keus et al. [123], and the eight-step assessment suggested by Jakobsen et al. [118]. We will use the statistical software Review Manager 5.3 [101] provided by Cochrane to analyse data. We will assess our intervention effects with both random-effects meta-analyses [124] and fixed-effect meta-analyses [125]. We will use the more conservative point estimate of the two [118]. The more conservative point estimate is the estimate closest to zero effect. If the two estimates are similar, we will use the estimate with the highest P value [118]. We use four primary and four secondary outcomes, and therefore, we will consider a P value of 0.02 as the threshold for statistical significance [118, 126]. We will investigate for heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided [100]. We will use the eight-step procedure to assess if the thresholds for statistical and clinical significance are crossed [118]. Our primary conclusion will be based on results with low risk of bias [118].

Where multiple trial intervention groups are reported in a single trial, we will include only the relevant groups. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting [100]. Trials with a factorial design will be included.

If quantitative synthesis is not appropriate, we will report the results in a narrative way.

Trial Sequential Analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We wish to control the risks of type I errors and type II errors. We will therefore perform Trial Sequential Analysis on the outcomes, in order to calculate the required information

size (that is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries [102, 127-135]. A more detailed description of Trial Sequential Analysis can be found in the Trial Sequential Analysis manual [128] and at http://www.ctu.dk/tsa/. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction of 20%, an alpha of 2.0% for our primary and secondary outcomes, a beta of 10%, and diversity as suggested by the trials in the meta-analysis. For the outcome "pain assessment on visual analogue scale (VAS) or numerical rating scale (NRS)", we will use a minimal important difference estimate based on previously conducted systematic reviews [121, 122]. We will accept a pain-relieving effect equivalent to 10 mm or 1 point on the visual analogue scale and the numerical rating scale, respectively, or a consumption of at least 5 mg morphine.

For all remaining continuous outcome, we will in the Trial Sequential Analysis use the observed SD, a mean difference of the observed SD/2, an alpha of 2.0% for our primary and secondary outcomes, and a beta of 10%.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis

We will perform the following subgroup analysis when analysing the primary outcomes (All-cause mortality, pain assessment on VAS or NRS, serious adverse event, and quality of life).

- Trials at high risk of bias compared to trails at low risk of bias
- Trials compared according to type of pain (acute pain, chronic pain and cancer pain)
- Trials compared according to type of chronic pain
- Trials compared according to type of cannabinoids used
- Trials compared according to dosage of cannabinoids used (below median compared to median and above)
- Trials compared according to duration of cannabinoids administration (below median compared to median and above)
- Age of participants: 0 to 59 years compared to 60 to 79 years compared to above 80 years
- Trials compared according to baseline pain score (below median compared to median and above)

We will use the formal test for subgroup interactions in Review Manager [101].

Sensitivity analysis

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on both the primary and secondary outcomes.

- 'Best-worst-case' scenario: We will assume that all participants lost to follow-up in the cannabinoid intervention group have survived and had no serious adverse event, and that all those participants lost to follow-up in the placebo group have not survived, and had a serious adverse event.
- 'Worst-best-case' scenario: We will assume that all participants lost to follow-up in the cannabinoid intervention group have not survived, and had a serious adverse event, and that all those participants lost to follow-up in the placebo group have survived, and had no serious adverse event.

We will present results of both scenarios in our review.

For all continuous outcome when analysing a 'beneficial outcome' will be the group mean plus two standard deviations (SDs) (we will secondly use one SD in another sensitivity analysis) of the group mean and a 'harmful outcome' will be the group mean minus two SDs (we will secondly use one SD in another sensitivity analysis) of the group mean [118].

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis.

- Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials.

We will present results of this scenario in our review. Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results [118].

Summary of Findings

We will create a Summary of Findings table using each of the primary outcomes (all-cause mortality, pain assessment on VAS or NRS, serious adverse event, and quality of life). We will use the five GRADE considerations (bias risk of the trials, consistency of effect, imprecision, indirectness, and publication bias) to

assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes [118, 136-138]. We will use methods and recommendations described in Chapter 8 (Section 8.5) and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions [100] using GRADEpro software. We will justify all decisions to downgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. Firstly, we will present our results in the Summary of Findings table based on the results from the trials with low risk of bias, and secondly, we will present the results based on all trials.

Ethics and Dissemination

Ethical approval is not a requirement since no primary data will be collected. The findings of this systematic review will be submitted for peer-reviewed publication and disseminated in national and international conferences and is expected to inform healthcare workers and providers about the occurrence of serious and non-serious adverse events following cannabinoid consumption. It is expected that the findings of this systematic review will identify some research gaps for future trials.

Discussion

This protocol aims at investigating the beneficial and harmful effects of cannabinoids in patients with any type of pain condition. The outcomes will be all-cause mortality, pain assessment on VAS or NRS, serious adverse events, quality of life, dependence, psychosis, non-serious adverse events, and sleep quality.

This protocol has several strengths. The predefined methodology is based on the Cochrane Handbook for Systematic Reviews of Interventions [100], the eight-step assessment suggested by Jakobsen et al. [118], Trial Sequential Analysis [84], and GRADE assessment [136-138]. Hence, this protocol takes into account both the risk of random error and the risk of systematic error. We predefined evidence-based estimations of minimal important differences which will limit the risk of focusing on statistically significant results with questionable clinical importance. This threshold of minimal important difference is based on the estimations of several previously conducted studies and reviews [121, 122]. Moreover, we are including all types of cannabinoids and all types of pain which will increase the statistical power and make it possible to perform essential subgroup analyses. We have been in contact with several relevant patient associations which has assisted us in choosing the most clinically relevant outcomes.

Our protocol also has several limitations. One of the potential limitations is that we include participants with all types of pain; cannabinoids might have different effects on different types of pain. It might e.g. be problematic to combine trials assessing the effects of cannabinoids on acute pain and chronic pain because of different underlying pathophysiological mechanisms [139]. On the other hand, the effects of cannabinoids on acute pain and chronic pain might be comparable and hence it might be valid to combine trials assessing the effects of cannabinoids on acute pain and chronic pain in meta-analysis, which would increase the statistical power. The results of the subgroup analysis comparing trials including participants with acute pain to participants with chronic pain will therefore be highlighted when reporting our review results. Moreover, we only intend to assess cannabinoids versus placebo or no intervention. Further systematic reviews with meta-analyses and Trial Sequential Analyses need to assess the benefits and harms of cannabinoids versus other pain killers, provided that cannabinoids show more benefit than harm in the present systematic review.

Furthermore, more than one active cannabinoid agent is often combined in the different intervention options provided to the patients with a pain condition, thereby making difficult to explore the analgesic effect and adverse event associated with a single cannabinoid agent. Hence, if we show a difference between the intervention options, it will be difficult to conclude what exactly caused the difference in effect. To minimise these limitations, we have planned a careful assessment of statistical and clinical heterogeneity as well as several subgroup analyses and sensitivity analyses. Another limitation is the large number of comparisons which increase the risk of type 1 error. We have adjusted our thresholds for significance according to the number of primary outcomes, but, as mentioned, we have also included multiple subgroup analyses. This large risk of type 1 error will be taken into account when interpreting the review results.

Acknowledgements

We hugely appreciate the contribution of The Danish Diabetes Association, Steno Diabetes Centre Copenhagen, The Danish Rheumatism Association, The Danish Multiple Sclerosis Society, and Danish Cancer Society in selecting the most patient relevant outcomes.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

JB drafted the protocol. JCJ, SKK, OM, CG, JRF and MM amended the protocol. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests

Ethics approval and consent to participate

Not applicable.

Word Count

10835 words, including the full references.

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Appendix

Minimal important difference

For the determination of minimal important differences in clinical trials two types of methods are available; anchor-based methods and distributional-based methods [1].

Anchor-based methods

Anchor-based methods relate the change in on a person reported outcome score, (e.g. a score on the visual analog scale (VAS)) to a subjective global assessment rating (e.g. scores from the Clinical Global Impressions-Improvement (CGI-I)) which is used as an 'anchor' [1]. Ideally, there needs to be an established association between the person reported outcome score and the 'anchor' to make any meaningful inference about a minimal important difference [2].

There are two subtypes of anchor-based methods, i.e., the '*within-patient score'* and the *'between-patients score'* [1].

- Within-patient score defines minimal important difference as the average minimal change in a given person's reported outcome score that leads to a clinically observable change in the subjective global assessment rating (the latter is used as an anchor) [1]. For example, to ascertain the minimal important difference regarding depression management, Moncrieff et. al describes the linking of within-patient scores (change from baseline) scores on the Hamilton Depression Rating Scale (the most commonly used depression rating scale) to scores on the Clinical Global Impressions-Improvement (CGI-I) scale, a scale which rates improvement on a scale of 1 (very much improved from baseline) through 4 (no change from baseline) to 7 (very much worse from baseline) [3]. Moncrieff et. al conclude that seven points on the Hamilton Depression Rating Scale correspond to a minimal important difference when using within-patient scores [3].
- The between-patients score method, also known as 'the group difference' method, compare the reported outcome scores between a group of people with no clinically observable change (based on a subjective global assessment rating (used as an anchor)) to a group of people with clinically observable change (based on a subjective global assessment rating (used as an anchor)). The minimal important difference is then estimated as the mean difference between these two groups [4]. For example, Musoro et. al defines the minimal important difference (MID) as the group difference in terms of quality of life assessed by HRQOL scores [5]. Participants were assigned to distinct subgroups reflecting various levels of change (e.g. no change, small positive changes, large positive changes, small negative changes or large negative changes). The group difference was identified by the

comparison of the average of the HRQOL scores of the group of participants with at 'small change' to the HRQOL scores of the group of participants with 'no change' [5].

There are also other anchor-based methods (e.g. the sensitivity- and specificity-based method and the social comparison method) [1]. The sensitivity- and specificity-based method aims to identify the minimal important difference that allows for the best discrimination between groups of patients (i.e., the score that produces the greatest sensitivity and specificity) [1]. For example, an outcome measure (e.g. NRS score) is considered a 'diagnostic test' and the anchor (e.g. Global Perceived Effect) is used as gold standard and hence standard methods may be used to estimate sensitivity and specificity. Sensitivity is the proportion of patients who report an improvement on the external criterion (anchor) and whose person reported outcome scores are above the threshold minimal important difference value [1]. Specificity is the proportion of patients who do not report an improvement on the external criterion (anchor) and whose person reported outcome scores are below the threshold minimal important difference value [1]. Receiver operating characteristic (ROC) curves are then used to identify the person reported outcome score with the greatest sensitivity and specificity [6-8].

The distributional-based methods

Distribution-based methods are based on the statistical characteristics of the obtained sample [9]. Crosby et. al [9] have identified two general types of distribution-based methods for estimations of minimal important differences:

- The first type of distribution-based method evaluate change in relation to sample variation [9]. Different types of variation can be used: effect size, standardised response mean, and responsiveness statistic [9]. The effect size represents individual change in relation to the number of pre-test standard deviations (SDs) [9]. Cohen et. al has suggested benchmarks to better interpret the effect sizes: .20 for ''small'' effects, .50 for ''moderate'' effects, and .80 for ''large'' effects [10]. Whereas the effect size is the ratio of individual change to the baseline standard deviation of the sample, standardised response mean is the ratio of individual change to the standard deviation of that change [11]. A large standardised response mean indicates that the change is large in comparison to the background variability in the measurements [9]. Guyatt et. al has proposed a responsiveness statistic as a variation of standardised response mean; calculated by dividing the difference between pre-test and post-test by the standard deviation of change observed for a group of stable participants [12].

- The second type distribution-based method is based on the measurement precision of the instrument [9]. This method include the standard error of the mean (SEM) and evaluate the change in relation to variation of the instrument as opposed to variation in the sample [9]. Standard error of the mean (SEM) is a measure of the precision of a test instrument and considered an attribute of the measure and not a characteristic of the sample per se [13]. The standard error of the mean (SEM) for a given measure is likely to vary across samples depending upon the method used to estimate reliability and the presence of extreme scores [9]. Different thresholds for a minimal important difference have been suggested, i.e., values of 1 SEM [14], 1.96 SEM [15], and 2.77 SEM [13, 15].

In conclusion, different methods for estimating minimal important differences exist, but no single method has been shown to be the optimal method. The question of whether to use anchor-based or distribution-based methods for determining clinically meaningful change has received considerable attention and debate [9]. Dworkin et. al defined the clinical importance of patient improvement as the clinically important changes in individuals that can be identified using either within-patient anchor-based method or distributional-based method [16, 17], while the clinical importance of group differences could be the clinical difference between a treatment group and a placebo group or between two different treatment groups [18]. Dworkin et. al claim that the clinical important difference identified in individuals cannot be directly extrapolated to the evaluation of group differences [17, 19-22]. The U.S. Food and Drug Administration also states in their web site “When defining meaningful change on an individual patient basis, that definition is generally larger than the minimum important difference for application to group mean comparisons” [22].

While it is claimed that the within-patient differences are larger than the between-group difference [22], based on the studies included in our review we are not able to find a significant difference between the minimal important difference estimated by the two different methods.

Previously conducted reviews on this subject

- Lynch & Campbell and Boychuk et. al both concluded that cannabinoids are a modestly effective and a safe treatment option for neuropathic pain [23, 24]. Lynch & Campbell and Boychuk et. al did not publish a protocol on beforehand [23, 24].
- Meng et. al concluded that there is moderate quality evidence to suggest that nabiximols (phytocannabinoid mixture) is effective in reducing neuropathic pain [25].

- Mücke et. al concluded that there is no high-quality evidence for the efficacy of any cannabis-based medicine in any condition with chronic neuropathic pain [26]. Mücke et. al further concluded that some adverse events may limit the clinical usefulness of cannabis-based medicines [26].
- Deshpande et. al concluded that current evidence suggests that very low-dose medical marijuana (< 34 mg/d) is associated with an improvement in refractory neuropathic pain of moderate severity in adults using concurrent analgesics. Deshpande et. al did not publish a protocol on beforehand [27].
- Martín-Sánchez et. al concluded that treatment of chronic pain based on cannabinoid compounds would entail more risk of adverse events than benefit [28]. Martín-Sánchez et. al included trials randomising participants with either neuropathic pain, cancer pain, fibromyalgia related pain and nociceptive pain [28]. Martín-Sánchez et. al did not publish a protocol on beforehand [28].
- Aviram et. al concluded that cannabinoid-based medicines were not effective for postoperative pain, however further investigation is advised [29]. Aviram et. al also concluded that evidence suggests a moderate to good treatment effect on neuropathic pain [29]. Furthermore, neuropathic pain patients should be advised that the inhalation of cannabinoids showed relatively better pain reduction effects than other routes of administration [29]. Aviram et. al stated that the total number of adverse events that were accumulated in the meta-analysis indicated that cannabinoid-based medicines should be used with caution [29]. Aviram et. al did not publish a protocol on beforehand [29].
- Campbell et. al concluded that levonantradol (synthetic cannabinoid analogue) was superior to placebo on postoperative pain but no more effective than codeine [30]. Campbell et. al also stated that there are suggestions of efficacy in spasticity and in neuropathic pain and that increasing the cannabinoid dose to increase the analgesia will increase adverse effects [30]. Campbell et. al did not publish a protocol on beforehand [30].
- Stevens et. al concluded that cannabinoids have no role in the management of acute pain, but cannabinoids were found to be well-tolerated, with most reported adverse effects only mild to moderate in severity [31].
- Walitt et. al concluded that no convincing, unbiased evidence suggests that nabilone (synthetic cannabinoid analog) is of value in treating people with fibromyalgia [32]. The tolerability of nabilone was low and adverse events (particularly somnolence, dizziness, vertigo) may limit its clinical usefulness [32].

TABEL 1

First author	Title	Year of publication	Design	Type of cannabinoid	Types of participants	Information sources	No. of trials	No. of participants	Published protocol	Outcomes	Assessment of adverse events	Assessment of risk of bias	Accounts for random error	Use of the GRADE	Conclusion
Lynch & Campbell [23]	Cannabinoids for treatment of chronic non-cancer pain; a systematic review of rando	2011	Systematic Review	**Phytocannabinoids;** Smoked cannabis, oromucosal extracts of cannabis-based medicine, and **synthetic cannabinoids**; nabilone, dronabin	Neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.	PubMed, EMBASE, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library, ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search	18 trials comparing the intervention with placebo	766	No	The primary outcome was pain in subjects with chronic non-cancer pain. The secondary outcomes were sleep, function, and quality of life.	Yes	Yes, except for reporting bias, publication bias and for-profit bias	No	No	Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy

	mized trials			ol and a novel THC analogue.		Premier (EBSCO), ClinicalTrials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline, OAIster (OCLC) and Google Scholar.									in fibromyalgia and rheumatoid arthritis. Did not pool data for meta-analysis but data was described qualitatively.
Meng et. al [25]	Selective Cannabinoids for Chro	2017	Systematic Review and Meta-	Dronabinol, nabilone and nabiximols	Neuropathic pain	Medline, Embase, Cochrane Library, PROSPERO, clinical	11 (10 trials comparing th	1219	No	The primary outcome was intensity of pain recorded	Yes	Yes	Bonferroni adjustment for multiple testi	Yes	Selective cannabinoids provide a small analgesic bene

	nic Neuropathic Pain: A Systematic Review and Meta-analysis		analysis			trials.gov, and Google Scholar. Pain societies (American Society of Anesthesiologists, European Society of Anaesthesiology, International Association for the Study of Pain, American Society of Regional Anesthesia and Pain Medicine, European	e intervention with placebo)			after a minimum of 2 weeks following initiation of selective cannabinoid and placebo/comparator administration, expressed on an NRS (0—no pain to 10—worst possible pain). Secondary outcomes were presence or absence of analgesia defined as			ng was not performed as per recommendations in the Cochrane Handbook.		fit in patients with chronic neuropathic pain.

						Society of Regional Anesthesia and Pain Therapy, and World Institute of Pain) in the last 2 years were also searched.				reduction in pain scores (NRS/VAS) by ≥30% at 2 weeks or more after initiation of intervention, quality of life (QoL), physical function, psychological function, sleep, overall patient satisfaction, and the incidence of adverse effects of selective cannabinoids.					

Martín-Sánchez et. al [28]	Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain	2009	Meta-analysis	**Phytocannabinoids** and **synthetic derivates of THC**, such as dronabinol, nabilone, or benzopyranoperidine (a synthetic nitrogen analog of THC)	Chronic pain of a pathological or traumatic origin	Medline/Pubmed, Embase, and The Cochrane Controlled Trials Register (CENTRAL)	18	?	No	The primary outcome was intensity of pain as scored by numerical rang scales. The Secondary outcomes were CNS related events	Yes	Yes, except for reporting bias, detection bias and for-profit bias	No	No	Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serio

															us harms.
Boychuk et. al [24]	The Effectiveness of Cannabinoids in the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Re	2015	Systematic Review	**Phytocannabinoids;** smoked cannabis, cannabis-based medicinal extracts (CBME) in the form of oromucosal sprays (nabiximols), vaporized cannabis, and **synthetic cannabinoids;** dron	Neuropathic pain	PubMed, Embase, Web of Science, and all evidence-based medicine reviews and databases (Cochrane Database of Systematic Reviews, ASP Journal Club, Database of Abstracts of Reviews of Effects [DARE], and Cochrane Controlled	13	771	No	Outcomes considered were reduction in pain intensity and adverse events.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabis-based medicinal extracts used in different populations of chronic non-malignant neuropathic pain patients may provide effective analgesia in conditions that are refractory

	view			abinol, nabilone, and CT-3		Trials Register [CCTR])									to other treatments.
Mücke et. al [26]	Cannabis products for adults with chronic neuropathic pain	2018	Cochrane Review	**Phytocannabinoids;** oromucosal spray containing THC or THC/CBD mix, smoked cannabis containing THC, THC and CBD as extract of cannabis sativa L., and **synt**	Neuropathic pain	Cochrane Library, MEDLINE and EMBASE. Following clinical trials databases were searched for additional data including unpublished data**:** US National Institutes of Health clinical trial register (www. Clinical	16 (15 of the trials comparing the intervention with placebo)	1750	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. We preferred composite neuropathic pain scores over single-scale generic pain scores if both measures were used by studies;	Yes	Yes	No	Yes	The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be

				hetic cann abin oids; nabil one, dron abin ol		Trials.gov), European Union Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and International Association for Cannabinoid Medicines (IACM) databank				PGIC (Patient Global Impression of Change) much or very much improved; Withdrawals due to adverse events (tolerability); Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence					outweighed by their potential harms.

						(www.cannabis-med.org/studies/study.php)				or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medica					

										l event' that may jeopardise the person, or may require an intervention to prevent one of the above characteristics/consequences.					
Aviram et. al [29]	Efficacy of Cannabis-Based Medicines for Pain Manage	2017	Meta-Analysis	**Phytocannabinoids;** Sativex/nabiximol, cannabidiol, cannabinoid cigarettes/vaporizer,	Chronic (cancer and non-cancer) pain and acute posto	MEDLINE/Pubmed and in Google Scholar using Medical Subject Heading (MeSH) terms	43 trials comparing the intervention with both 'activ	2437	No	The outcome measure that was chosen was the variable "pain intensity", as scored by the numerical rating scale (NRS-11),	Yes	Yes, except for, reporting bias, publication bias an	No	No	The current systematic review suggests that cannabinoid-based medicines might be effec

	ment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials			and **synthetic cannabinoids**; dronabinol and nabilone, CT-3, ajulemic acid, synthetic nitrogen analog of tetrahydrocannabinol (NIB), fatty acid amide hydrolase-1 (FAAH1) inhibitor (PF-04457845) (bloc	perative pain		edrugs' and placebo			numerical 11-point box (BS-11), visual analog scale (VAS), and the VAS section of the questionnaire short form McGill Pain Questionnaire.		dfor-profit bias			tive for chronic pain treatment, based on limited evidence, primarily for neuropathic pain patients.

				king degradation of endocannabinoids), benzopyranoperidine (BPP), and levonantradol											
Campbell et. al [30]	Are cannabinoids an effective and safe treatment option in the mana	2001	Systematic Review	Oral THC, an oral synthetic nitrogen analogue of THC (NIB), oral benzopyranoperidine (BPP), and intramuscular	Acute, chronic non-malignant pain, and cancer pain	MEDLINE, EMBASE, Oxford Pain Database, and Cochrane Library	9	222	No	Outcome measures for pain intensity; pain relief; the use of supplementary analgesia; patients' preferences; and adverse effects.	Yes	Yes, except for, reporting bias, publication bias and for-pr	No	No	Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the centr

	gement of pain? A qualitative systematic review			levonantradol								ofit bias			al nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used.
Deshpa	Efficac	2015	Syste	Cigarettes	Neur	MEDLINE,	6 tri	226	No	For outco	Yes	Yes,	No	No	There is

nde et. al [27]	y and adverse effects of medical marijuana for chronic noncancer pain		matic Review	or vaporizer containing delta-9-THC	opathic pain	EMBASE, and the International Pharmaceutical Abstracts	als comparing intervention with placebo. Placebo being cigarettes or vaporizer containing 0% delta-9-THC or with ca			mes, pain scores were extracted using the visual analogue scale (VAS) or an alternative numerical pain rating tool. If pain scores were not reported, surrogate measures of effectiveness were included (sleep, function, and quality of life). Frequency of serious and		except for, reporting bias, publication bias and for-profit bias			evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and

							nn abi no id re m ov al			most comm only report ed adver se effects was collect ed.					stren gth of delta -9- tetra hydr ocan nabi nol, and lack of funct ional outc ome s. Altho ugh well toler ated in the short term , the long- term effec ts of psyc hoac tive and neur ocog nitiv e effec ts of medi cal marij

															uana remain unknown.
Stevens et. al [31]	A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain	2017	Systematic Review	Levonantradol, nabilone, AZD1940, GW842166, dronabinol, ▵-9-THC	Acute postoperative pain	MEDLINE, EMBASE, Cochrane Library, and the World Health Organization International Clinical Trials Registry Platform	7 trials comparing intervention with placebo, Ketoprofen, Pethidine, Naproxen, and Ibup	611	Yes	The primary outcome was the qualitative analysis of the analgesic efficacy of cannabinoids in the management of acute pain compared to placebo or active comparator. The secondary outcome was the qualitative	Yes	Yes, except for, publication bias and for-profit bias	No	Yes	Based on the available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain.

							rofen			analysis of the reported adverse effects.					
Walitt et. al [32]	Cannabinoids for fibromyalgia	2016	Cochrane Review	Nabilone	Fibromyalgia	Cochrane Library, MEDLINE and EMBASE	2 trials comparing the intervention with either (1) placebo or (1) amitriptyline	72 (40)	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. PGIC (Patient Global Impression of Change) much or very much improved. Withdrawal due to adverse events	Yes	Yes, except for publication bias.	No	Yes	We found no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone

										(tolerability). Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of					was low in people with fibromyalgia.

										existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the person, or may require an intervention to prevent one of the above					

										characteristics/consequences.					

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First author	Title	Year of publication	Design	Type of cannabinoid	Types of participants	Information sources	No. of trials	No. of participants	Published protocol	Outcomes	Assessment of adverse events	Assessment of risk of bias	Accounts for random error	Use of the GRADE	Conclusion
Lynch & Campbell	Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials	2011	Systematic Review	**Phytocannabinoids;** Smoked cannabis, oromucosal extracts of cannabis-based medicine, and **synthetic cannabinoids;** nabilone, dronabinol and a novel THC analogue.	Neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.	PubMed, EMBASE, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library, ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search Premier (EBSCO), Clinical Trials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline, OAIster (OCLC) and Google Scholar.	18	1750	Yes	The primary outcome was pain in subjects with chronic non-cancer pain. The secondary outcomes were sleep, function, and quality of life.	Yes	Yes, except for reporting bias, publication bias and for-profit bias	No	No	Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis. Did not pool data for meta-analysis but data was described qualitatively.
Meng et. al	Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis	2017	Systematic Review and Meta-analysis	Dronabinol, nabilone and nabiximols	Neuropathic pain	Medline, Embase, Cochrane Library, PROSPERO, clinicaltrials.gov, and Google Scholar. Pain societies (American Society of Anesthesiologists, European Society of Anaesthesiology, International Association for the Study of Pain, American Society of Regional Anesthesia and Pain Medicine, European Society of Regional Anesthesia and Pain Therapy, and World Institute of Pain) in the last 2 years were also searched.	11 (10 trials comparing the intervention with placebo)	1219	No	The primary outcome was Intensity of pain recorded after a minimum of 2 weeks following initiation of selective cannabinoid and placebo/comparator administration, expressed on an NRS (0—no pain to 10—worst possible pain). Secondary outcomes were presence or absence of analgesia defined as reduction in pain scores (NRS/VAS) by ≥30% at 2 weeks or more after initiation of intervention, quality of life (QoL), physical function, psychological function, sleep, overall patient satisfaction, and the incidence of adverse effects of selective cannabinoids.	Yes	Yes	Bonferroni adjustment for multiple testing was not performed as per recommendations in the Cochrane Handbook.	Yes	Selective cannabinoids provide a small analgesic benefit in patients with chronic neuropathic pain.
Martín-Sánchez et. al	Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain	2009	Meta-analysis	**Phytocannabinoids** and synthetic derivates of THC, such as dronabinol, nabilone, or benzopyranoperidine (a synthetic nitrogen analog of THC)	Chronic pain of a pathologic al or traumatic origin	Medline/Pubmed, Embase, and The Cochrane Controlled Trials Register (CENTRAL)	18	?	No	The primary outcome was Intensity of pain as scored by numerical rang scales. The Secondary outcomes were CNS related events	Yes	Yes, except for reporting bias, detection bias and for-profit bias	No	No	Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms.
Boychuk et. al	The Effectiveness of Cannabinoids In the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Review	2015	Systematic Review	**Phytocannabinoids;** smoked cannabis, cannabis-based medicinal extracts (CBME) in the form of oromucosal sprays (nabiximols), vaporized cannabis, and **synthetic cannabinoids;** dronabinol, nabilone, and CT-3	Neuropathic pain	PubMed, Embase, Web of Science, and all evidence-based medicine reviews and databases (Cochrane Database of Systematic Reviews, ASP Journal Club, Database of Abstracts of Reviews of Effects [DARE], and Cochrane Controlled Trials Register [CCTR])	13	771	No	Outcomes considered were reduction in pain intensity and adverse events.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabis-based medicinal extracts used in different populations of chronic non-malignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments.
Mücke et. al	Cannabis products for adults with chronic neuropathic pain	2018	Cochrane Review	**Phytocannabinoids:** oromucosal spray containing THC or THC/CBD mix, smoked cannabis containing THC, THC and CBD as extract of cannabis sativa L., and **synthetic cannabinoids;** nabilone, dronabinol	Neuropathic pain	Cochrane Library, MEDLINE and EMBASE. Following clinical trials databases were searched for additional data including unpublished data: US National Institutes of Health clinical trial register (www.ClinicalTrials.gov), European Union Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and International Association for Cannabinoid Medicines (IACM) databank (www.cannabis-	16 (15 of the trials comparing the intervention with placebo)	1750	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. We preferred composite neuropathic pain scores over single-scale generic pain scores if both measures were used by studies; PGIC (Patient Global Impression of Change) much or very much improved; Withdrawals due to adverse events (tolerability); Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in	Yes	Yes	No	Yes	The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms.
Aviram et. al	Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials	2017	Meta-Analysis	**Phytocannabinoids:** Sativex/nabiximol, cannabidiol, cannabinoid cigarettes/vaporizer, and **synthetic cannabinoids:** dronabinol and nabilone, CT-3, ajulemic acid, synthetic nitrogen analog of tetrahydrocannabinol (NIB), fatty	Chronic (cancer and non-cancer) pain and acute postoperative pain	MEDLINE/Pubmed and in Google Scholar using Medical Subject Heading (MeSH) terms	43 trials comparing the intervention with both 'active drugs' and placebo	2437	No	The outcome measure that was chosen was the variable "pain intensity", as scored by the numerical rating scale (NRS-11), numerical 11-point box (BS-11), visual analog scale (VAS), and the VAS section of the questionnaire short form McGill Pain Questionnaire	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	The current systematic review suggests that cannabinoid-based medicines might be effective for chronic pain treatment, based on limited evidence, primarily for neuropathic pain patients.
Campbell et. al	Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review	2001	Systematic Review	Oral THC, an oral synthetic nitrogen analogue of THC (NIB), oral benzopyranoperidine (BPP), and Intramuscular levonantradol	Acute, chronic non-malignant pain, and cancer pain	MEDLINE, EMBASE, Oxford Pain Database, and Cochrane Library	9	222	No	Outcome measures for pain intensity; pain relief; the use of supplementary analgesia; patients' preferences; and adverse effects.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used.
Deshpande et. al	Efficacy and adverse effects of medical marijuana for chronic noncancer pain	2015	Systematic Review	Cigarettes or vaporizer containing delta-9-THC	Neuropathic pain	MEDLINE, EMBASE, and the International Pharmaceutical Abstracts	6 trials comparing interventions with placebo. Placebo being cigarettes or vaporizer containing 0% delta-9-THC or with cannabinoid removal	226	No	For outcomes, pain scores were extracted using the visual analogue scale (VAS) or an alternative numerical pain rating tool. If pain scores were not reported, surrogate measures of effectiveness were included (sleep, function, and quality of life). Frequency of serious and most commonly reported adverse effects was collected.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and strength of delta-9-tetrahydrocannabinol, and lack of functional outcomes. Although well tolerated in the short term, the long-term effects of psychoactive and neurocognitive effects of medical marijuana remain unknown.
Stevens et. al	A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain	2017	Systematic Review	Levonantradol, nabilone, AZD1940, GW842166, dronabinol, Δ-9-THC	Acute postoperative pain	MEDLINE, EMBASE, Cochrane Library, and the World Health Organization International Clinical Trials Registry Platform	7 trials comparing interventions with placebo, Ketoprofen, Pethidine, Naproxen, and Ibuprofen	611	Yes	The primary outcome was the qualitative analysis of the analgesic efficacy of cannabinoids in the management of acute pain compared to placebo or active comparator. The secondary outcome was the qualitative analysis of the reported adverse effects	Yes	Yes, except for, publication bias and for-profit bias	No	Yes	Based on the available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain.
Wallitt et. al	Cannabinoids for fibromyalgia	2016	Cochrane Review	Nabilone	Fibromyalgia	Cochrane Library, MEDLINE and EMBASE	2 trials comparing the intervention with either (1) placebo or (1) amitriptyline	72 (40)	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. PGIC (Patient Global Impression of Change) much or very much improved. Withdrawal due to adverse events (tolerability). Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or	Yes	Yes, except for publication bias.	No	Yes	We found no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone was low in people with fibromyalgia.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	25-26
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	25
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-9
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	10-12
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	12-13
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13-14
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	13
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	13-14
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	14
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	15-17
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	16
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	19-21
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	22-23
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	21
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	17
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	21

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Cannabinoids versus placebo for pain. Protocol for a systematic review with meta-analysis and Trial Sequential Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031574.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Jul-2019
Complete List of Authors:	Barakji, Jehad; The Copenhagen Trial Unit, Rigshospitalet Dept. 7812 Korang, Steven Kwasi; Rigshospitalet, Copenhagen Trial Unit; Holbaek Sygehus, Pediatric Dept. Feinberg, Joshua; Copenhagen Univ Hosp Maagard, Mathias; The Copenhagen Trial Unit, Rigshospitalet Dept. 7812 Gluud, Christian; Copenhagen Trial Unit (CTU), Center for Clinical Intervention Research Mathiesen, Ole; University of Copenhagen Jakobsen, Janus; Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Anaesthesia, Evidence based practice, Complementary medicine
Keywords:	PAIN MANAGEMENT, Herbal medicine < THERAPEUTICS, Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Cannabinoids versus placebo for pain: Protocol for a systematic review with meta-analysis and Trial Sequential Analysis

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Abstract

Introduction Pain is a frequent clinical symptom, and with significant impact on patient well-being. Therefore, sufficient pain management is of utmost importance. While cannabinoids have become a more popular alternative to traditional types of pain medication among patients, the quality of evidence supporting the use of cannabinoids has been questioned. The beneficial and harmful effects of cannabinoids in patients with pain is unknown. Accordingly, we aim to assess the efficacy, tolerability, and safety of cannabinoids (herbal, plant-derived extracts and synthetic) compared with placebo for any type of pain.

Methods and analysis We will conduct a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis to assess the beneficial and harmful effects of cannabinoids in any dose, formulation, and duration. We will accept placebo or no treatment as control interventions. We will include participants with any type of pain (acute and chronic pain, cancer-related pain, headache, neuropathic pain or any other types of pain). We will systematically search The Cochrane Library, MEDLINE, EMBASE, Science Citation Index, and BIOSIS for relevant literature. We will follow the recommendations by Cochrane and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The risk of systematic errors (bias) and random errors (play of chance) will be assessed. The overall certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination Ethical approval is not a requirement since no primary data will be collected. The findings of this systematic review will be submitted for peer-reviewed publication and disseminated in national and international conferences.

Discussion Although cannabinoids are now being used to manage different pain conditions, the evidence for the clinical effects are unclear. The present review will systematically assess the current evidence for the benefits and harms of cannabinoids to inform practice and future research.

Strengths and limitations of this study

- Our methodology is based on the Cochrane Handbook for Systematic Reviews of Interventions, the PRISMA guideline, and a systematic eight step procedure for valid assessments of statistical and clinical significance
- We systemically plan to assess risks of random errors ('play of chance) and systematic errors ('bias')
- We have systematically predefined minimal important differences for all outcomes
- The certainty of the evidence with be assessed using the GRADE approach

Pain is the most commonly reported symptom in the general population and in a medical setting [1-3]. Persistent pain is a major international health problem [4], prompting the World Health Organization (WHO) to endorse a global campaign against pain [5]. Pain is the leading reason for use of alternative medicines (i.e. acupuncture, etc.) [6]. Pain has been associated with a low degree of health-related quality of life and may lead to psychosocial distress, insomnia, and depressive symptoms [7-15]. Pain is also among the most common reasons for temporary or permanent work disability [16]. Pain is always subjective and may be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [17].

Cannabinoids have emerged as a potential alternative for the treatment of intractable pain [18]. Before the healthcare systems globally can endorse the applicability of cannabinoids for pain, the potential short-time and long-term adverse events encumbered with long-term use of cannabinoids must be investigated. This is of utmost importance because patients who consume cannabinoids to alleviate their chronic pain will most likely need to consume cannabinoids for the rest of their lifespan.

Description of pain

Pain may be caused by or be related to different clinical disorders and classified according to several different characteristics [19-22]. Below, we describe shortly some of these classifications.

Acute and chronic pain

Pain may be classified as 'acute pain' or 'chronic pain'.

- Acute pain usually has a well-defined onset and most often a readily identifiable cause (i.e. surgery, etc.). Acute pain is expected to run its course in a short time frame and management typically focuses on

symptomatic relief until this happens [23]. Acute pain is a common symptom, affecting between 37% to 84% of hospitalised patients [24] .

- Chronic pain is often characterised by an ill-defined onset and a prolonged, fluctuating course [23]. Chronic pain often persists past normal healing time and hence lacks the acute warning function of physiological nociception [25]. Pain is usually regarded as chronic when it lasts or recurs for more than three to six months [17, 26]. Chronic pain is a frequent condition, affecting an estimated 20% of people worldwide [27-30] and accounting for 15% to 20% of physician visits according to European observational studies [31, 32].

Cancer-related pain

Pain may also be classified based on whether it is cancer-related or non-cancer-related. Cancer-related pain is pain caused by the cancer itself (primary tumour and metastases) or its treatment (i.e. radiation therapy, etc.) [23, 33].

Postoperative pain

Postoperative pain includes pain from inflammation caused by tissue trauma (i.e. surgical incision, dissection, burns, etc.) or direct nerve injury (e.g. nerve transection, stretching, or compression) [34]. Inflammation results in activation and sensitisation of nociceptive pain pathways, resulting in primary and secondary hyperalgesia and central sensitisation, which is characterized by clinically increased pain, allodynia, and increased sensitivity from surrounding non-damaged anatomical areas [35].

Other types of pain

Pain in one or more anatomic regions where the aetiology is unknown is defined as idiopathic pain [36]. Examples of idiopathic pain are chronic widespread pain, fibromyalgia, irritable bowel syndrome, and back pain that is not diagnosed as musculoskeletal or as neuropathic pain [33].

Pain types defined according to specific mechanism causing the pain

Somatic nociceptive pain

Nociceptive pain is the most frequent type of pain. It results from activity in neural pathways caused by actual tissue damage or potentially tissue-damaging stimuli [31, 37] originating from somatic nociceptors from skin, bone, joints, or muscles [38].

Visceral nociceptive pain

The visceral nociceptive pain is pain resulting from viscera in the thoracic, pelvis, or abdominal organs [39-41]. Visceral pain is diffuse, less distinctive, and difficult to localise [41] and is often characterised by referred visceral pain [42].

Neuropathic pain

The 2011 International Association for the Study of Pain definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" [43].

Neuropathic pain may be classified as central neuropathic pain or peripheral neuropathic pain. Central neuropathic pain conditions are mainly attributed to multiple sclerosis and post-stroke pain [44], while peripheral neuropathic pain is largely due to post-herpetic neuralgia and diabetic neuropathy [45].

Description of the intervention

Cannabis (also called marijuana) is the most common illegally used psychoactive substance worldwide [46]. Cannabinoids refer to a heteromorphic group of molecules that demonstrate activity upon cannabinoid receptors [47]. Cannabinoids may be classified into three groups: 1) endocannabinoids, 2) phytocannabinoids, and 3) synthetic cannabinoids [47].

Endocannabinoids

Endocannabinoids are characterised by being the endogenously generated cannabinoids [48]. The primary types of endocannabinoids are the lipid endocannabinoid arachidonoyl ethanolamide (named anandamide) [49] and the endocannabinoid 2-arachidonoylglycerol (2-AG) [50, 51].

Phytocannabinoids

Phytocannabinoids are cannabinoids found in the cannabis plant [52]. The best characterised phytocannabinoids are the psychotropic tetrahydrocannabinol (THC) and the primarily anti-inflammatory cannabidiol (CBD) [53]. Nabiximols (marketed as Sativex®) is a sublingually administered oromucosal spray based on a mixture of tetrahydrocannabinol and cannabidiol [54].

Synthetic cannabinoids

Synthetic cannabinoids are analogues of the cannabinoids found in natural marijuana that are chemically synthesised. The most commonly prescribed cannabinoid-based medicines are the synthetic cannabinoids dronabinol (marketed as Marinol®) and nabilone (marketed as Cesamet®) [54].

Endocannabinoid system

All cannabinoids act on cannabinoid receptors. These cannabinoid receptors are located throughout the body but are mostly located in the brain [55]. The cannabinoid receptors and endocannabinoids (see paragraph above) are together named the endocannabinoid system [56].

Cannabinoid receptors

There are two types of cannabinoid receptors, type I and type II [57]. Cannabinoid receptor type I are most abundant in the central nervous system, especially in areas promoting nociception, short-term memory, and in the basal ganglia, but are also found in the peripheral nerves, uterus, testis, and bones [57]. Tetrahydrocannabinol activates cannabinoid type I receptors in the dopaminergic mesolimbic brain circuit, resulting in enhanced release of dopamine [58]. Such activation of the so-called 'brain reward system' is hypothesised to mediate the positive reinforcing and rewarding effects of almost all drugs of abuse [58].

In contrast, cannabinoid receptor type II, is mostly found in the periphery, often in conjunction with immune cells, but may appear in the central nervous system particularly under conditions of inflammation in association with microcytes [57]. The physiological responses that result from cannabinoid receptor activation are euphoria, psychosis, impaired memory and cognition, reduced locomotor function, increased appetite, as well as anti-emetic, pain-relieving, anti-spasticity, and sleep-promoting effects [59].

Administration of cannabinoids

Cannabis is most commonly consumed via smoked, inhaled vapor, or oral routes of administration [60]. Vaporising cannabis ('vaping') heats the material without burning which theoretically minimises potential carcinogens compared to smoking and may produce less respiratory irritation [61, 62]. Sublingual administration is used for some medical cannabis preparations (i.e. nabiximols, etc.).

Why it is important to do this review

We identified ten previous reviews with meta-analyses assessing the effects of cannabinoids on different types of pain [63-72]. Bearing in mind that some of the previous reviews investigated more than one type of pain, eight reviews assessed the effects of different cannabinoids on neuropathic pain [63-69, 72]; four reviews assessed the effects of different cannabinoids on nociceptive pain (i.e. rheumatoid arthritis, etc.) [63, 64, 67, 68]; three reviews assessed the effects of different cannabinoids on cancer-related pain [63, 67, 68]; four reviews assessed the effects of different cannabinoids on fibromyalgia-related pain [63, 64, 67, 71]; and three reviews assessed the effects of different cannabinoids on postoperative pain [63, 68, 70]. All the previous reviews included randomised clinical trials, but only two of the ten reviews systematically assessed the risk of bias in the trials [65, 72], and none of the previous reviews took into account the risks of random errors [63-72]. Only two out of the ten reviews used predefined Cochrane methodology [71, 72] and only four reviews used the GRADE approach [65, 70-72].

Most of the reviews concluded that the assessed cannabinoids were effective against pain [63-67, 69, 72]. In **Table 1** (**Additional file 1**)**,** we have summarised the results and conclusions of the previous reviews. Five of the reviews reported serious adverse events (i.e. agitation, impaired memory, abuse, dissociation, acute psychosis, death, etc.) [63, 65-67, 72]. The reviews also showed that the most commonly reported adverse events were sedation, dizziness, dry mouth, increased appetite, somnolence, confusion, nausea, and disturbances in concentration [63-66, 68, 69, 71, 72].

A correlation between psychiatric disorders (i.e. schizophrenia and psychosis etc.) and increased cannabinoid consumption have previously been hypothesised [73-79]. Di Forti et. al recently conducted a study indicating that daily cannabis use was associated with increased odds of psychotic disorder compared with never users (adjusted odds ratio [OR] 3.2, 95% CI 2.2–4.1), increasing to nearly five-times increased odds for daily use of high-potency (THC ≥10%) types of cannabis (adjusted odds ratio [OR] 4.8, 95% CI 2.5–6.3) [80].

Compared to previous systematic reviews on cannabinoids, we want to assess the effects of all types of cannabinoid versus placebo or no intervention for all different forms of pain. This increases the power and precision over the overall analysis and make it possible to conduct subgroup analyses and sensitivity analyses that may identify pain areas where cannabinoid could be especially beneficial and cause the least harms. In addition, we will implement a minimal clinically important threshold regarding analgesic efficacy based on previously conducted methodological studies which ensures that analgesic efficacy is of a firm significance before acceptance. Finally, by instigating all types of cannabinoids treated for any type of pain this systematic review will aid trialist in optimising the design of future randomised clinical trials by illuminating any research pitfalls of all previously conducted randomised clinical trials on this topic.

Objective

The objective of our systematic review is to assess the analgesic efficacy and adverse events encumbered with the use of cannabinoids compared to placebo or no intervention in participants with any type of pain (acute and chronic pain, cancer-related pain, headache, neuropathic pain, or any other types of pain). A secondary objective of this systematic review is to assess the impact of cannabinoid use on the quality of sleep and quality of life which is especially decreased in participants with chronic pain.

Methods

This systematic review protocol has been developed based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews evaluating healthcare interventions [81, 82]. A PRISMA-P checklist file is attached (**Additional file 2**).

Criteria for considering studies for this review

Type of studies

Randomised clinical trials irrespective of trial design, setting, publication status, publication year, and language. If we identify quasi-randomised studies and observational studies during our searches for randomised clinical trials, we will only include their reporting on harms in a narrative way. By not systematically searching for all observational studies on harm, we run the risk of putting more focus on benefit than harm. We are aware that this is a limitation of our review.

Types of participants

Participants with any type of pain, i.e. acute and chronic pain, cancer-related pain, headache, neuropathic pain, or any other types of pain (as defined by the trialists). Participants will be included irrespective of age, sex, and comorbidities.

Types of interventions

Experimental intervention

Any type of cannabinoids such as: herbal cannabis (hashish, marihuana), plant-based extracts (i.e. nabiximole, etc.), or synthetic cannabinoids (i.e. cannabidiol, dronabinol, levonantradol, nabilone, etc.). We will accept cannabinoids at any dose, by any route, administered for the relief of pain.

Control intervention

Placebo or no intervention.

Co-interventions

We will accept any co-intervention but only if this co-intervention is planned to be delivered similarly in both intervention groups. If this plan is not followed, then these trials will be assessed as a subgroup due to potential confounding.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Pain assessment on visual analogue scale (VAS) or numerical rating scale (NRS)
- Proportion of participants with a serious adverse event defined as any untoward medical occurrence that resulted in death; was life threatening; was persistent; or led to significant disability, nephrotoxicity, superinfection, need for respiratory support, need for circulatory support, or prolonged hospitalisation [83]. As we expect the trialists' reporting of serious adverse events to be heterogeneous and not strictly according to the ICH-GCP recommendations, we will include the event as a serious adverse if the trialists either: 1) use the term 'serious adverse event' but not refer to ICH-GCP, or 2) report the proportion of

participants with an event we consider fulfils the ICH-GCP definition. If several of such events are reported then we will choose the highest proportion reported in each trial.

- Quality of life measured on any valid continuous scale

Secondary outcomes

- Dependence (as defined by trialists)
- Psychosis (as defined by trialists)
- Proportion of participants with one or more adverse event not considered to be serious
- Quality of sleep measured on any valid continuous scale

Exploratory outcomes

- Each serious adverse event separately
- Each adverse event not considered serious separately.
- Twenty-four-hour morphine consumption (as defined by trialists)
- Physical function (as defined by trialists)
- Depressive symptoms (e.g. Hamilton Depression Rating Scale)

We will for all outcomes use the trial results reported at maximal follow-up except for acute pain. For acute pain, we will use the trials' results reported at the time point closest to 24 hours after the intervention is given.

Patient and Public Involvement

We have had email correspondence with several relevant patient associations in Denmark to select the most patient relevant outcomes. The patient associations we have been in contact with include: The Danish Diabetes Association, Steno Diabetes Centre Copenhagen, The Danish Rheumatism Association, The Danish Multiple Sclerosis Society, and Danish Cancer Society. Initially we presented our potential outcomes for the aforementioned patient associations and requested for their opinion. Initially we had not included quality of sleep as an outcome however this was mentioned by almost all patient associations and it was included as a crucial secondary outcome. All-cause mortality was questioned by one of the patient associations however we have chosen to keep this outcome because of potential increased risk of both acute coronary syndrome and chronic cardiovascular disease associated with cannabis use [84]. We are very thankful for their input.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), Science Citation Index Expanded on Web of Science, and BIOSIS in order to identify relevant trials. The preliminary search strategy for CENTRAL, MEDLINE (Ovid), Embase (Ovid), LILACS, Web of Science and BIOSIS is given in **Additional file 3**.

We will search all databases from their inception to the 1st of October 2019.

Searching other resources

The reference lists of relevant publications will be checked for any unidentified randomised trials. We will contact authors of included studies, and major pharmaceutical companies, by email asking for unpublished randomised trials. Further, we will search for ongoing trials on:

- ClinicalTrials.gov (www.clinicaltrials.gov)
- Google Scholar (https://scholar.google.dk/)
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/)
- European Medicines Agency (EMA) (http:// www.ema.europa.eu/ema/)
- United States Food and Drug Administration (FDA) (www.fda.gov)
- China Food and Drug Administration (CFDA) (http://eng.sfda.gov.cn/WS03/CL0755/)
- Medicines and Healthcare products Regulatory Agency (https://www.gov.uk/government/organisations/ medicines-and-healthcare-products-regulatory-agency)
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/ trialsearch/)

We will also consider relevant for the review unpublished and grey literature trials, if we identify such trials.

Data collection and analysis

We will perform the review following the recommendations of Cochrane [85]. The analyses will be performed using Review Manager 5 [86] and Trial Sequential Analysis [87]. In case of Review Manager statistical software not being sufficient, we will use STATA 15 [88].

Selection of studies

Two authors (JB, SKK) will independently screen titles and abstracts. We will retrieve all relevant full-text study reports/publications, and four review authors (JB, SKK, JRF, MM) will independently screen the full text and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a fifth author (JCJ). Trial selection will be displayed in an adapted flow diagram as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [89].

Data extraction and management

Four authors (JB, SKK, JRF, MM) will in pairs extract data independently from included trials. Disagreements will be resolved by discussion with a fifth author (JCJ). We will assess duplicate publications and companion papers of a trial together to evaluate all available data simultaneously (maximise data extraction, correct bias assessment). We will contact the trial authors by email to specify any additional data, which may not have been reported sufficiently or at all in the publication.

Trial characteristics

Bias risk components (as defined below); trial design (parallel, factorial, or crossover); number of intervention arms; length of follow-up; estimation of sample size; inclusion and exclusion criteria.

Participant characteristics and diagnosis

Number of randomised participants; number of analysed participants; number of participants lost to follow-up/ withdrawals/crossover; compliance with medication; age range (mean or median) and sex ratio; type of pain (acute and chronic pain, cancer-related pain, headache, neuropathic pain or any other types of pain); baseline pain score; drug and dosing regimen; study design (placebo or active control); study duration and follow-up; analgesic outcome measures and results; adverse events (participants experiencing any adverse event, or serious adverse event).

Co-intervention characteristics

Type of co-intervention; dose of co-intervention; duration of co-intervention; and mode of administration.

Outcomes

All outcomes listed above will be extracted from each randomised clinical trial, and we will identify if outcomes are incomplete or selectively reported according to the criteria described later in 'incomplete outcome data' bias domain and 'selective outcome reporting' bias domain.

Notes

Funding of the trial and notable conflicts of interest of trial authors will be extracted, if available.

We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Four review authors (JB, SKK, JRF, MM) will independently transfer data into the Review Manager file [86]. Disagreements will be resolved through discussion or, if required, we will consult with a fifth author (JCJ).

Assessment of risk of bias in included studies

We will use the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions [85] in our evaluation of the methodology and hence the risk of bias of the included trials. We will evaluate the methodology in respect of:

- Random sequence generation
- Allocation concealment
- Blinding of participants and treatment providers
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- For-profit bias
- Overall risk of bias

These components enable classification of randomised trials as being at low risk of bias and at high risk of bias. The latter trials tend to overestimate positive intervention effects and underestimate negative effects [90-96]. We will classify the trials according to the following criteria.

Random sequence generation

- Low risk: If sequence generation was achieved using computer random number generator or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.
- Unclear risk: If the method of randomisation was not specified, but the trial was still presented as being randomised.
- High risk: If the method of sequence generation was inadequate e.g. alternate medical record numbers or other non-random sequence generation.

Allocation concealment

- Low risk: If the allocation of patients was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, drug bottles, or containers prepared by an independent pharmacist or investigator.
- Uncertain risk: If the trial was classified as randomised but the allocation concealment process was not described.
- High risk: If the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

- Low risk: If the participants and the treatment providers were blinded to intervention allocation and this was described.
- Uncertain risk: If the procedure of blinding was insufficiently described.
- High risk: If blinding of participants and the treatment providers was not performed.

Blinding of outcome assessment

- Low risk of bias: If it was mentioned that outcome assessors were blinded and this was described.
- Uncertain risk of bias: If it was not mentioned if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described.
- High risk of bias: If no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

- Low risk of bias: If missing data were unlikely to make treatment effects depart from plausible values. This could be either (1) there were no drop-outs or withdrawals for all outcomes or (2) the numbers

and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups. Generally, the trial is judged as at a low risk of bias due to incomplete outcome data if drop-outs are less than 5%. However, the 5% cut-off is not definitive.

- Uncertain risk of bias: If there was insufficient information to assess whether missing data were likely to induce bias on the results.
- High risk of bias: If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (i.e. last observation carried forward, etc.).

Selective outcome reporting

- Low risk of bias: If a protocol was published before or at the time the trial was begun, and the outcomes specified in the protocol were reported on. If there is no protocol or the protocol was published after the trial has begun, reporting pain assessment on VAS or NRS and serious adverse events will grant the trial a grade of low risk of bias.
- Uncertain risk of bias: If no protocol was published and the outcome pain assessment on VAS or NRS and serious adverse events were not reported on.
- High risk of bias: If the outcomes in the protocol were not reported on.

For-profit bias

- Low risk of bias: If the trial appeared to be free of other components of for-profit bias.
- Unclear risk of bias: If it was unclear whether the trial was free of for-profit bias.
- High risk of bias: If there was a high risk of for-profit bias.

Overall risk of bias

- Low risk of bias: The trial will be classified at overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified at 'low risk of bias'.
- High risk of bias: The trial will be classified at 'high risk of bias' if any of the bias risk domains described in the above are classified at 'unclear' or 'high risk of bias'.

We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective outcome reporting' for each outcome result. Thus, we can assess the bias risk for each outcome assessed in

addition to each trial. Our primary conclusions will be based on the results of our primary outcome results at overall low risk of bias. Both our primary and secondary analyses will be presented in the summary of findings tables.

Differences between the protocol and the review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between the protocol and the review' section of the systematic review.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well as the Trial Sequential Analysis- adjusted CIs (see below).

Continuous outcomes

We will calculate the mean differences (MDs) and the standardised mean difference (SMD) with 95% CI for continuous outcomes, as well as the Trial Sequential Analysis-adjusted CIs (see below).

Dealing with missing data

We will, as first option, contact all trial authors to obtain any relevant missing data (i.e. for data extraction and for assessment of risk of bias, as specified above).

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

Continuous outcomes

We will primarily analyse scores assessed at single time points. If only changes from baseline scores are reported, we will analyse the results together with follow-up scores [85]. If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible. We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis (see paragraph below) for continuous outcomes, we will impute data.

Assessment of heterogeneity

We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by chi^2 test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the I^2 statistic [97, 98]. We will investigate for heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided [85].

Assessment of reporting biases

We will use a funnel plot to assess reporting bias if ten or more trials are included. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (i.e. a funnel plot assesses bias due to small sample size, etc.). From this information, we assess possible reporting bias. For dichotomous outcomes, we will test asymmetry with the Harbord test [99] if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test [100] and the adjusted rank correlation [101].

Unit of analysis issues

We will only include randomised clinical trials. For trials using crossover design, only data from the first period will be included [85, 102]. There will therefore not be any unit of analysis issues.

Minimal important difference

In clinical intervention research it is of utmost importance always to define minimal important differences (MID) and to define thresholds for clinical significance [103]. If a large number of trial participants are randomised, small and clinically irrelevant intervention effects may lead to statistically significant results and rejection of the null hypothesis [104]. Jaeschke et al. defined the minimal important difference as “the smallest difference in score in the domain of interest which patients perceive as beneficial” [105].

Estimations of minimal important differences should be used as arbitrary strict precise thresholds. However, to avoid erroneous conclusions minimal important differences need to be estimated and predefined when assessing the effects of interventions for pain. Olsen et al. have conducted two systematic reviews on this matter in order to gather the evidence and present an estimate of the minimal important difference [106, 107]. Olsen et al. conducted a systematic review on the minimal important difference in patients with acute pain and concluded

that the median of the studies' results was 17 mm on VAS (IQR 14 mm to 23 mm) [106]. Another systematic review conducted by Olsen et al. was on the minimal important difference in patients with chronic pain and the results showed a median of 23 mm on VAS (IQR 12 mm to 39 mm) when using the within-patient anchor-based method, while the median in studies using the sensitivity- and specificity-based method was 20 mm on VAS (IQR 15 mm – 30 mm) [107]. We have described detailed considerations about minimal important differences in **Appendix 1**.

Based on the previously conducted systematic reviews we will choose at minimal important difference equivalent to 10 mm or 1 point on the visual analogue scale and the numerical rating scale, respectively, regarding an analgesic effect.

Data synthesis

Meta-analysis

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions [85], Keus et al. [108], and the eight-step assessment suggested by Jakobsen et al. [103]. We will use the statistical software Review Manager 5.3 [86] provided by Cochrane to analyse data. We will assess our intervention effects with both random-effects meta-analyses [109] and fixed-effect meta-analyses [110]. We will use the more conservative point estimate of the two [103]. The more conservative point estimate is the estimate closest to zero effect. If the two estimates are similar, we will use the estimate with the highest P value [103]. We use four primary and four secondary outcomes, and therefore, we will consider a P value of 0.02 as the threshold for statistical significance [103, 111]. We will investigate for heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided [85]. We will use the eight-step procedure to assess if the thresholds for statistical and clinical significance are crossed [103]. Our primary conclusion will be based on results with low risk of bias [103].

Where multiple trial intervention groups are reported in a single trial, we will include only the relevant groups. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting [85]. Trials with a factorial design will be included.

If quantitative synthesis is not appropriate, we will report the results in a narrative way.

Trial Sequential Analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We wish to control the risks of type I errors and type II errors. We will therefore perform Trial Sequential Analysis on the outcomes, in order to calculate the required information size (that is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries [87, 112-120]. A more detailed description of Trial Sequential Analysis can be found in the Trial Sequential Analysis manual [113] and at http://www.ctu.dk/tsa/. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction of 20%, an alpha of 2.0% for our primary and secondary outcomes, a beta of 10%, and diversity as suggested by the trials in the meta-analysis. For the outcome "pain assessment on visual analogue scale (VAS) or numerical rating scale (NRS)", we will use a minimal important difference estimate based on previously conducted systematic reviews [106, 107]. We will accept an analgesic effect equivalent to 10 mm or 1 point on the visual analogue scale and the numerical rating scale, respectively, or a consumption of at least 5 mg morphine.

For all remaining continuous outcome, we will in the Trial Sequential Analysis use the observed SD, a mean difference of the observed SD/2, an alpha of 2.0% for our primary and secondary outcomes, and a beta of 10%.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis

We will perform the following subgroup analysis when analysing the primary outcomes (All-cause mortality, pain assessment on VAS or NRS, serious adverse event, and quality of life).

- Trials at high risk of bias compared to trails at low risk of bias
- Trials compared according to type of pain (acute pain, chronic pain and cancer pain)
- Trials compared according to type of chronic pain
- Trials compared according to type of cannabinoids used

We will use the formal test for subgroup interactions in Review Manager [86].

Sensitivity analysis

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on both the primary and secondary outcomes.

- 'Best-worst-case' scenario: We will assume that all participants lost to follow-up in the cannabinoid intervention group have survived and had no serious adverse event, and that all those participants lost to follow-up in the placebo group have not survived, and had a serious adverse event.
- 'Worst-best-case' scenario: We will assume that all participants lost to follow-up in the cannabinoid intervention group have not survived, and had a serious adverse event, and that all those participants lost to follow-up in the placebo group have survived, and had no serious adverse event.

We will present results of both scenarios in our review.

For all continuous outcome when analysing a 'beneficial outcome' will be the group mean plus two standard deviations (SDs) (we will secondly use one SD in another sensitivity analysis) of the group mean and a 'harmful outcome' will be the group mean minus two SDs (we will secondly use one SD in another sensitivity analysis) of the group mean [103].

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis.

- Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials.

We will present results of this scenario in our review. Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results [103].

Summary of Findings

We will create a Summary of Findings table using each of the primary outcomes (all-cause mortality, pain assessment on VAS or NRS, serious adverse event, and quality of life). We will use the five GRADE considerations (bias risk of the trials, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes [103, 121-123]. We will use methods and recommendations described in Chapter 8 (Section 8.5) and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions [85]

using GRADEpro software. We will justify all decisions to downgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. Firstly, we will present our results in the Summary of Findings table based on the results from the trials with low risk of bias, and secondly, we will present the results based on all trials.

Ethics and Dissemination

Ethical approval is not a requirement since no primary data will be collected. The findings of this systematic review will be submitted for peer-reviewed publication and disseminated in national and international conferences and is expected to inform healthcare workers and providers about the occurrence of serious and non-serious adverse events following cannabinoid consumption. It is expected that the findings of this systematic review will identify some research gaps for future trials.

Discussion

This protocol aims at investigating the beneficial and harmful effects of cannabinoids in patients with any type of pain condition. The outcomes will be all-cause mortality, pain assessment on VAS or NRS, serious adverse events, quality of life, dependence, psychosis, non-serious adverse events, and sleep quality.

This protocol has several strengths. The predefined methodology is based on the Cochrane Handbook for Systematic Reviews of Interventions [85], the eight-step assessment suggested by Jakobsen et al. [103], Trial Sequential Analysis [84], and GRADE assessment [121-123]. Hence, this protocol takes into account both the risk of random error and the risk of systematic error. We predefined evidence-based estimations of minimal important differences which will limit the risk of focusing on statistically significant results with questionable clinical importance. This threshold of minimal important difference is based on the estimations of several previously conducted studies and reviews [106, 107]. Moreover, we are including all types of cannabinoids and all types of pain which will increase the statistical power and make it possible to perform essential subgroup analyses. We have been in contact with several relevant patient associations which has assisted us in choosing the most clinically relevant outcomes.

Our protocol also has several limitations. One of the potential limitations is that we include participants with all types of pain; cannabinoids might have different effects on different types of pain. It might e.g. be problematic

to combine trials assessing the effects of cannabinoids on acute pain and chronic pain because of different underlying pathophysiological mechanisms [124]. On the other hand, the effects of cannabinoids on acute pain and chronic pain might be comparable and hence it might be valid to combine trials assessing the effects of cannabinoids on acute pain and chronic pain in meta-analysis, which would increase the statistical power. The results of the subgroup analysis comparing trials including participants with acute pain to participants with chronic pain will therefore be highlighted when reporting our review results. Moreover, we only intend to assess cannabinoids versus placebo or no intervention. Further systematic reviews with meta-analyses and Trial Sequential Analyses need to assess the benefits and harms of cannabinoids versus other pain killers, provided that cannabinoids show more benefit than harm in the present systematic review.

Furthermore, more than one active cannabinoid agent is often combined in the different intervention options provided to the patients with a pain condition, thereby making difficult to explore the analgesic effect and adverse event associated with a single cannabinoid agent. Hence, if we show a difference between the intervention options, it will be difficult to conclude what exactly caused the difference in effect. To minimise these limitations, we have planned a careful assessment of statistical and clinical heterogeneity as well as several subgroup analyses and sensitivity analyses. Another limitation is the large number of comparisons which increase the risk of type 1 error. We have adjusted our thresholds for significance according to the number of primary outcomes, but, as mentioned, we have also included multiple subgroup analyses. This large risk of type 1 error will be taken into account when interpreting the review results.

Acknowledgements

We hugely appreciate the contribution of The Danish Diabetes Association, Steno Diabetes Centre Copenhagen, The Danish Rheumatism Association, The Danish Multiple Sclerosis Society, and Danish Cancer Society in guiding us to select the most patient relevant outcomes.

The expert help from Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Copenhagen, Denmark) in making the search strategy is hugely appreciated.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

JB drafted the protocol. JCJ, SKK, OM, CG, JRF and MM amended the protocol. All authors read and approved the final manuscript.

Competing interests

None declared

Ethics approval and consent to participate

Not applicable.

Word Count

10835 words, including the full references.

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Appendix

Minimal important difference

For the determination of minimal important differences in clinical trials two types of methods are available; anchor-based methods and distributional-based methods [1].

Anchor-based methods

Anchor-based methods relate the change in on a person reported outcome score, (e.g. a score on the visual analog scale (VAS)) to a subjective global assessment rating (e.g. scores from the Clinical Global Impressions-Improvement (CGI-I)) which is used as an 'anchor' [1]. Ideally, there needs to be an established association between the person reported outcome score and the 'anchor' to make any meaningful inference about a minimal important difference [2].

There are two subtypes of anchor-based methods, i.e., the '*within-patient score'* and the *'between-patients score'* [1].

- Within-patient score defines minimal important difference as the average minimal change in a given person's reported outcome score that leads to a clinically observable change in the subjective global assessment rating (the latter is used as an anchor) [1]. For example, to ascertain the minimal important difference regarding depression management, Moncrieff et. al describes the linking of within-patient scores (change from baseline) scores on the Hamilton Depression Rating Scale (the most commonly used depression rating scale) to scores on the Clinical Global Impressions-Improvement (CGI-I) scale, a scale which rates improvement on a scale of 1 (very much improved from baseline) through 4 (no change from baseline) to 7 (very much worse from baseline) [3]. Moncrieff et. al conclude that seven points on the Hamilton Depression Rating Scale correspond to a minimal important difference when using within-patient scores [3].
- The between-patients score method, also known as 'the group difference' method, compare the reported outcome scores between a group of people with no clinically observable change (based on a subjective global assessment rating (used as an anchor)) to a group of people with clinically observable change (based on a subjective global assessment rating (used as an anchor)). The minimal important difference is then estimated as the mean difference between these two groups [4]. For example, Musoro et. al defines the minimal important difference (MID) as the group difference in terms of quality of life assessed by HRQOL scores [5]. Participants were assigned to distinct subgroups reflecting various levels of change (e.g. no change, small positive changes, large positive changes, small negative changes or large negative changes). The group difference was identified by the

comparison of the average of the HRQOL scores of the group of participants with at 'small change' to the HRQOL scores of the group of participants with 'no change' [5].

There are also other anchor-based methods (e.g. the sensitivity- and specificity-based method and the social comparison method) [1]. The sensitivity- and specificity-based method aims to identify the minimal important difference that allows for the best discrimination between groups of patients (i.e., the score that produces the greatest sensitivity and specificity) [1]. For example, an outcome measure (e.g. NRS score) is considered a 'diagnostic test' and the anchor (e.g. Global Perceived Effect) is used as gold standard and hence standard methods may be used to estimate sensitivity and specificity. Sensitivity is the proportion of patients who report an improvement on the external criterion (anchor) and whose person reported outcome scores are above the threshold minimal important difference value [1]. Specificity is the proportion of patients who do not report an improvement on the external criterion (anchor) and whose person reported outcome scores are below the threshold minimal important difference value [1]. Receiver operating characteristic (ROC) curves are then used to identify the person reported outcome score with the greatest sensitivity and specificity [6-8].

The distributional-based methods

Distribution-based methods are based on the statistical characteristics of the obtained sample [9]. Crosby et. al [9] have identified two general types of distribution-based methods for estimations of minimal important differences:

- The first type of distribution-based method evaluate change in relation to sample variation [9]. Different types of variation can be used: effect size, standardised response mean, and responsiveness statistic [9]. The effect size represents individual change in relation to the number of pre-test standard deviations (SDs) [9]. Cohen et. al has suggested benchmarks to better interpret the effect sizes: .20 for ''small'' effects, .50 for ''moderate'' effects, and .80 for ''large'' effects [10]. Whereas the effect size is the ratio of individual change to the baseline standard deviation of the sample, standardised response mean is the ratio of individual change to the standard deviation of that change [11]. A large standardised response mean indicates that the change is large in comparison to the background variability in the measurements [9]. Guyatt et. al has proposed a responsiveness statistic as a variation of standardised response mean; calculated by dividing the difference between pre-test and post-test by the standard deviation of change observed for a group of stable participants [12].

- The second type distribution-based method is based on the measurement precision of the instrument [9]. This method include the standard error of the mean (SEM) and evaluate the change in relation to variation of the instrument as opposed to variation in the sample [9]. Standard error of the mean (SEM) is a measure of the precision of a test instrument and considered an attribute of the measure and not a characteristic of the sample per se [13]. The standard error of the mean (SEM) for a given measure is likely to vary across samples depending upon the method used to estimate reliability and the presence of extreme scores [9]. Different thresholds for a minimal important difference have been suggested, i.e., values of 1 SEM [14], 1.96 SEM [15], and 2.77 SEM [13, 15].

In conclusion, different methods for estimating minimal important differences exist, but no single method has been shown to be the optimal method. The question of whether to use anchor-based or distribution-based methods for determining clinically meaningful change has received considerable attention and debate [9]. Dworkin et. al defined the clinical importance of patient improvement as the clinically important changes in individuals that can be identified using either within-patient anchor-based method or distributional-based method [16, 17], while the clinical importance of group differences could be the clinical difference between a treatment group and a placebo group or between two different treatment groups [18]. Dworkin et. al claim that the clinical important difference identified in individuals cannot be directly extrapolated to the evaluation of group differences [17, 19-22]. The U.S. Food and Drug Administration also states in their web site “When defining meaningful change on an individual patient basis, that definition is generally larger than the minimum important difference for application to group mean comparisons” [22].

While it is claimed that the within-patient differences are larger than the between-group difference [22], based on the studies included in our review we are not able to find a significant difference between the minimal important difference estimated by the two different methods.

Previously conducted reviews on this subject

- Lynch & Campbell and Boychuk et. al both concluded that cannabinoids are a modestly effective and a safe treatment option for neuropathic pain [23, 24]. Lynch & Campbell and Boychuk et. al did not publish a protocol on beforehand [23, 24].
- Meng et. al concluded that there is moderate quality evidence to suggest that nabiximols (phytocannabinoid mixture) is effective in reducing neuropathic pain [25].

- Mücke et. al concluded that there is no high-quality evidence for the efficacy of any cannabis-based medicine in any condition with chronic neuropathic pain [26]. Mücke et. al further concluded that some adverse events may limit the clinical usefulness of cannabis-based medicines [26].
- Deshpande et. al concluded that current evidence suggests that very low-dose medical marijuana (< 34 mg/d) is associated with an improvement in refractory neuropathic pain of moderate severity in adults using concurrent analgesics. Deshpande et. al did not publish a protocol on beforehand [27].
- Martín-Sánchez et. al concluded that treatment of chronic pain based on cannabinoid compounds would entail more risk of adverse events than benefit [28]. Martín-Sánchez et. al included trials randomising participants with either neuropathic pain, cancer pain, fibromyalgia related pain and nociceptive pain [28]. Martín-Sánchez et. al did not publish a protocol on beforehand [28].
- Aviram et. al concluded that cannabinoid-based medicines were not effective for postoperative pain, however further investigation is advised [29]. Aviram et. al also concluded that evidence suggests a moderate to good treatment effect on neuropathic pain [29]. Furthermore, neuropathic pain patients should be advised that the inhalation of cannabinoids showed relatively better pain reduction effects than other routes of administration [29]. Aviram et. al stated that the total number of adverse events that were accumulated in the meta-analysis indicated that cannabinoid-based medicines should be used with caution [29]. Aviram et. al did not publish a protocol on beforehand [29].
- Campbell et. al concluded that levonantradol (synthetic cannabinoid analogue) was superior to placebo on postoperative pain but no more effective than codeine [30]. Campbell et. al also stated that there are suggestions of efficacy in spasticity and in neuropathic pain and that increasing the cannabinoid dose to increase the analgesia will increase adverse effects [30]. Campbell et. al did not publish a protocol on beforehand [30].
- Stevens et. al concluded that cannabinoids have no role in the management of acute pain, but cannabinoids were found to be well-tolerated, with most reported adverse effects only mild to moderate in severity [31].
- Walitt et. al concluded that no convincing, unbiased evidence suggests that nabilone (synthetic cannabinoid analog) is of value in treating people with fibromyalgia [32]. The tolerability of nabilone was low and adverse events (particularly somnolence, dizziness, vertigo) may limit its clinical usefulness [32].

TABEL 1

First author	Title	Year of publication	Design	Type of cannabinoid	Types of participants	Information sources	No. of trials	No. of participants	Published protocol	Outcomes	Assessment of adverse events	Assessment of risk of bias	Accounts for random error	Use of the GRADE	Conclusion
Lynch & Campbell [23]	Cannabinoids for treatment of chronic non-cancer pain; a systematic review of rando	2011	Systematic Review	**Phytocannabinoids;** Smoked cannabis, oromucosal extracts of cannabis-based medicine, and **synthetic cannabinoids**; nabilone, dronabin	Neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.	PubMed, EMBASE, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library, ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search	18 trials comparing the intervention with placebo	766	No	The primary outcome was pain in subjects with chronic non-cancer pain. The secondary outcomes were sleep, function, and quality of life.	Yes	Yes, except for reporting bias, publication bias and for-profit bias	No	No	Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy

	mized trials			ol and a novel THC analogue.		Premier (EBSCO), ClinicalTrials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline, OAIster (OCLC) and Google Scholar.									in fibromyalgia and rheumatoid arthritis. Did not pool data for meta-analysis but data was described qualitatively.
Meng et. al [25]	Selective Cannabinoids for Chro	2017	Systematic Review and Meta-	Dronabinol, nabilone and nabiximols	Neuropathic pain	Medline, Embase, Cochrane Library, PROSPERO, clinical	11 (10 trials comparing th	1219	No	The primary outcome was intensity of pain recorded	Yes	Yes	Bonferroni adjustment for multiple testi	Yes	Selective cannabinoids provide a small analgesic bene

	nic Neuropathic Pain: A Systematic Review and Meta-analysis		analysis			trials.gov, and Google Scholar. Pain societies (American Society of Anesthesiologists, European Society of Anaesthesiology, International Association for the Study of Pain, American Society of Regional Anesthesia and Pain Medicine, European	e intervention with placebo)			after a minimum of 2 weeks following initiation of selective cannabinoid and placebo/comparator administration, expressed on an NRS (0—no pain to 10—worst possible pain). Secondary outcomes were presence or absence of analgesia defined as			ng was not performed as per recommendations in the Cochrane Handbook.		fit in patients with chronic neuropathic pain.

						Society of Regional Anesthesia and Pain Therapy, and World Institute of Pain) in the last 2 years were also searched.				reduction in pain scores (NRS/VAS) by ≥30% at 2 weeks or more after initiation of intervention, quality of life (QoL), physical function, psychological function, sleep, overall patient satisfaction, and the incidence of adverse effects of selective cannabinoids.					

Martín-Sánchez et. al [28]	Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain	2009	Meta-analysis	**Phytocannabinoids** and **synthetic derivates of THC**, such as dronabinol, nabilone, or benzopyranopyridine (a synthetic nitrogen analog of THC)	Chronic pain of a pathological or traumatic origin	Medline/Pubmed, Embase, and The Cochrane Controlled Trials Register (CENTRAL)	18	?	No	The primary outcome was intensity of pain as scored by numerical rang scales. The Secondary outcomes were CNS related events	Yes	Yes, except for reporting bias, detection bias and for-profit bias	No	No	Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serio

															us harms.
Boychuk et. al [24]	The Effectiveness of Cannabinoids in the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Re	2015	Systematic Review	**Phytocannabinoids;** smoked cannabis, cannabis-based medicinal extracts (CBME) in the form of oromucosal sprays (nabiximols), vaporized cannabis, and **synthetic cannabinoids;** dron	Neuropathic pain	PubMed, Embase, Web of Science, and all evidence-based medicine reviews and databases (Cochrane Database of Systematic Reviews, ASP Journal Club, Database of Abstracts of Reviews of Effects [DARE], and Cochrane Controlled	13	771	No	Outcomes considered were reduction in pain intensity and adverse events.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabis-based medicinal extracts used in different populations of chronic non-malignant neuropathic pain patients may provide effective analgesia in conditions that are refractory

	view			abinol, nabilone, and CT-3		Trials Register [CCTR])									to other treatments.
Mücke et. al [26]	Cannabis products for adults with chronic neuropathic pain	2018	Cochrane Review	**Phytocannabinoids;** oromucosal spray containing THC or THC/CBD mix, smoked cannabis containing THC, THC and CBD as extract of cannabis sativa L., and **synt**	Neuropathic pain	Cochrane Library, MEDLINE and EMBASE. Following clinical trials databases were searched for additional data including unpublished data**:** US National Institutes of Health clinical trial register (www. Clinical	16 (15 of the trials comparing the intervention with placebo)	1750	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. We preferred composite neuropathic pain scores over single-scale generic pain scores if both measures were used by studies;	Yes	Yes	No	Yes	The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be

				hetic cann abin oids; nabil one, dron abin ol		Trials.gov), European Union Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and International Association for Cannabinoid Medicines (IACM) databank				PGIC (Patient Global Impression of Change) much or very much improved; Withdrawals due to adverse events (tolerability); Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence					outweighed by their potential harms.

						(www.cannabis-med.org/studies/study.php)				or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medica					

										l event' that may jeopardise the person, or may require an intervention to prevent one of the above characteristics/consequences.					
Aviram et. al [29]	Efficacy of Cannabis-Based Medicines for Pain Manage	2017	Meta-Analysis	**Phytocannabinoids;** Sativex/nabiximol, cannabidiol, cannabinoid cigarettes/vaporizer,	Chronic (cancer and non-cancer) pain and acute posto	MEDLINE/Pubmed and in Google Scholar using Medical Subject Heading (MeSH) terms	43 trials comparing the intervention with both 'activ	2437	No	The outcome measure that was chosen was the variable "pain intensity", as scored by the numerical rating scale (NRS-11),	Yes	Yes, except for, reporting bias, publication bias an	No	No	The current systematic review suggests that cannabinoid-based medicines might be effec

	ment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials			and **synthetic cannabinoids**; dronabinol and nabilone, CT-3, ajulemic acid, synthetic nitrogen analog of tetrahydrocannabinol (NIB), fatty acid amide hydrolase-1 (FAAH1) inhibitor (PF-04457845) (bloc	perative pain		edrugs' and placebo			numerical 11-point box (BS-11), visual analog scale (VAS), and the VAS section of the questionnaire short form McGill Pain Questionnaire.		dfor-profit bias			tive for chronic pain treatment, based on limited evidence, primarily for neuropathic pain patients.

				king degradation of endocannabinoids), benzopyranoperidine (BPP), and levonantradol											
Campbell et. al [30]	Are cannabinoids an effective and safe treatment option in the mana	2001	Systematic Review	Oral THC, an oral synthetic nitrogen analogue of THC (NIB), oral benzopyranoperidine (BPP), and intramuscular	Acute, chronic non-malignant pain, and cancer pain	MEDLINE, EMBASE, Oxford Pain Database, and Cochrane Library	9	222	No	Outcome measures for pain intensity; pain relief; the use of supplementary analgesia; patients' preferences; and adverse effects.	Yes	Yes, except for, reporting bias, publication bias and for-pr	No	No	Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the centr

	gement of pain? A qualitative systematic review			levonantradol								ofit bias			al nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used.
Deshpa	Efficac	2015	Syste	Cigarettes	Neur	MEDLINE,	6 tri	226	No	For outco	Yes	Yes,	No	No	There is

nde et. al [27]	y and adverse effects of medical marijuana for chronic noncancer pain		matic Review	or vaporizer containing delta-9-THC	opathic pain	EMBASE, and the International Pharmaceutical Abstracts	als comparing intervention with placebo. Placebo being cigarettes or vaporizer containing 0% delta-9-THC or with ca			mes, pain scores were extracted using the visual analogue scale (VAS) or an alternative numerical pain rating tool. If pain scores were not reported, surrogate measures of effectiveness were included (sleep, function, and quality of life). Frequency of serious and		except for, reporting bias, publication bias and for-profit bias			evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and

							nn abi no id re m ov al			most comm only report ed adver se effects was collect ed.					stren gth of delta -9- tetra hydr ocan nabi nol, and lack of funct ional outc ome s. Altho ugh well toler ated in the short term , the long- term effec ts of psyc hoac tive and neur ocog nitiv e effec ts of medi cal marij

															uana remain unknown.
Stevens et. al [31]	A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain	2017	Systematic Review	Levonantradol, nabilone, AZD1940, GW842166, dronabinol, ▵-9-THC	Acute postoperative pain	MEDLINE, EMBASE, Cochrane Library, and the World Health Organization International Clinical Trials Registry Platform	7 trials comparing intervention with placebo, Ketoprofen, Pethidine, Naproxen, and Ibup	611	Yes	The primary outcome was the qualitative analysis of the analgesic efficacy of cannabinoids in the management of acute pain compared to placebo or active comparator. The secondary outcome was the qualitative	Yes	Yes, except for, publication bias and for-profit bias	No	Yes	Based on the available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain.

							rofen			analysis of the reported adverse effects.					
Walitt et. al [32]	Cannabinoids for fibromyalgia	2016	Cochrane Review	Nabilone	Fibromyalgia	Cochrane Library, MEDLINE and EMBASE	2 trials comparing the intervention with either (1) placebo or (1) amitriptyline	72 (40)	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. PGIC (Patient Global Impression of Change) much or very much improved. Withdrawal due to adverse events	Yes	Yes, except for publication bias.	No	Yes	We found no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone

										(tolerability). Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of					was low in people with fibromyalgia.

										existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the person, or may require an intervention to prevent one of the above					

										characteristics/consequences.					

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First author	Title	Year of publication	Design	Type of cannabinoid	Types of participants	Information sources	No. of trials	No. of participants	Published protocol	Outcomes	Assessment of adverse events	Assessment of risk of bias	Accounts for random error	Use of the GRADE	Conclusion
Lynch & Campbell	Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials	2011	Systematic Review	**Phytocannabinoids;** Smoked cannabis, oromucosal extracts of cannabis-based medicine, and **synthetic cannabinoids:** nabilone, dronabinol and a novel THC analogue.	Neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.	PubMed, EMBASE, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library, ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search Premier (EBSCO), Clinical Trials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline, OAIster (OCLC) and Google Scholar.	18	1750	Yes	The primary outcome was pain in subjects with chronic non-cancer pain. The secondary outcomes were sleep, function, and quality of life.	Yes	Yes, except for reporting bias, publication bias and for-profit bias	No	No	Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis. Did not pool data for meta-analysis but data was described qualitatively.
Meng et. al	Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis	2017	Systematic Review and Meta-analysis	Dronabinol, nabilone and nabiximols	Neuropathic pain	Medline, Embase, Cochrane Library, PROSPERO, clinicaltrials.gov, and Google Scholar. Pain societies (American Society of Anesthesiologists, European Society of Anaesthesiology, International Association for the Study of Pain, American Society of Regional Anesthesia and Pain Medicine, European Society of Regional Anesthesia and Pain Therapy, and World Institute of Pain) in the last 2 years were also searched.	11 (10 trials comparing the intervention with placebo)	1219	No	The primary outcome was intensity of pain recorded after a minimum of 2 weeks following initiation of selective cannabinoid and placebo/comparator administration, expressed on an NRS (0—no pain to 10—worst possible pain). Secondary outcomes were presence or absence of analgesia defined as reduction in pain scores (NRS/VAS) by ≥30% at 2 weeks or more after initiation of intervention, quality of life (QoL), physical function, psychological function, sleep, overall patient satisfaction, and the incidence of adverse effects of selective cannabinoids.	Yes	Yes	Bonferroni adjustment for multiple testing was not performed as per recommendations in the Cochrane Handbook.	Yes	Selective cannabinoids provide a small analgesic benefit in patients with chronic neuropathic pain.
Martín-Sánchez et. al	Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain	2009	Meta-analysis	**Phytocannabinoids** and synthetic derivates of THC, such as dronabinol, nabilone, or benzopyranoperidine (a synthetic nitrogen analog of THC)	Chronic pain of a pathologic al or traumatic origin	Medline/Pubmed, Embase, and The Cochrane Controlled Trials Register (CENTRAL)	18	?	No	The primary outcome was Intensity of pain as scored by numerical rang scales. The Secondary outcomes were CNS related events	Yes	Yes, except for reporting bias, detection bias and for-profit bias	No	No	Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms.
Boychuk et. al	The Effectiveness of Cannabinoids In the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Review	2015	Systematic Review	**Phytocannabinoids;** smoked cannabis, cannabis-based medicinal extracts (CBME) in the form of oromucosal sprays (nabiximols), vaporized cannabis, and **synthetic cannabinoids;** dronabinol, nabilone, and CT-3	Neuropathic pain	PubMed, Embase, Web of Science, and all evidence-based medicine reviews and databases (Cochrane Database of Systematic Reviews, ASP Journal Club, Database of Abstracts of Reviews of Effects [DARE], and Cochrane Controlled Trials Register [CCTR])	13	771	No	Outcomes considered were reduction in pain intensity and adverse events.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabis-based medicinal extracts used in different populations of chronic non-malignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments.
Mücke et. al	Cannabis products for adults with chronic neuropathic pain	2018	Cochrane Review	**Phytocannabinoids:** oromucosal spray containing THC or THC/CBD mix, smoked cannabis containing THC, THC and CBD as extract of cannabis sativa L., and **synthetic cannabinoids:** nabilone, dronabinol	Neuropathic pain	Cochrane Library, MEDLINE and EMBASE. Following clinical trials databases were searched for additional data including unpublished data: US National Institutes of Health clinical trial register (www.ClinicalTrials.gov), European Union Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and International Association for Cannabinoid Medicines (IACM) databank (www.cannabis-	16 (15 of the trials comparing the intervention with placebo)	1750	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. We preferred composite neuropathic pain scores over single-scale generic pain scores if both measures were used by studies; PGIC (Patient Global Impression of Change) much or very much improved; Withdrawals due to adverse events (tolerability); Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in	Yes	Yes	No	Yes	The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms.
Aviram et. al	Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials	2017	Meta-Analysis	**Phytocannabinoids:** Sativex/nabiximol, cannabidiol, cannabinoid cigarettes/vaporizer, and **synthetic cannabinoids:** dronabinol and nabilone, CT-3, ajulemic acid, synthetic nitrogen analog of tetrahydrocannabinol (NIB), fatty	Chronic (cancer and non-cancer) pain and acute postoperative pain	MEDLINE/Pubmed and in Google Scholar using Medical Subject Heading (MeSH) terms	43 trials comparing the intervention with both 'active drugs' and placebo	2437	No	The outcome measure that was chosen was the variable "pain intensity", as scored by the numerical rating scale (NRS-11), numerical 11-point box (BS-11), visual analog scale (VAS), and the VAS section of the questionnaire short form McGill Pain Questionnaire	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	The current systematic review suggests that cannabinoid-based medicines might be effective for chronic pain treatment, based on limited evidence, primarily for neuropathic pain patients.
Campbell et. al	Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review	2001	Systematic Review	Oral THC, an oral synthetic nitrogen analogue of THC (NIB), oral benzopyranoperidine (BPP), and Intramuscular levonantradol	Acute, chronic non-malignant pain, and cancer pain	MEDLINE, EMBASE, Oxford Pain Database, and Cochrane Library	9	222	No	Outcome measures for pain intensity; pain relief; the use of supplementary analgesia; patients' preferences; and adverse effects.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used.
Deshpande et. al	Efficacy and adverse effects of medical marijuana for chronic noncancer pain	2015	Systematic Review	Cigarettes or vaporizer containing delta-9-THC	Neuropathic pain	MEDLINE, EMBASE, and the International Pharmaceutical Abstracts	6 trials comparing interventio n with placebo. Placebo being cigarettes or vaporizer containing 0% delta-9-THC or with cannabinoid removal	226	No	For outcomes, pain scores were extracted using the visual analogue scale (VAS) or an alternative numerical pain rating tool. If pain scores were not reported, surrogate measures of effectiveness were included (sleep, function, and quality of life). Frequency of serious and most commonly reported adverse effects was collected.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and strength of delta-9-tetrahydrocannabinol, and lack of functional outcomes. Although well tolerated in the short term, the long-term effects of psychoactive and neurocognitive effects of medical marijuana remain unknown.
Stevens et. al	A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain	2017	Systematic Review	Levonantradol, nabilone, AZD1940, GW842166, dronabinol, ∆-9-THC	Acute postoperative pain	MEDLINE, EMBASE, Cochrane Library, and the World Health Organization International Clinical Trials Registry Platform	7 trials comparing interventio n with placebo, Ketoprofen, Pethidine, Naproxen, and Ibuprofen	611	Yes	The primary outcome was the qualitative analysis of the analgesic efficacy of cannabinoids in the management of acute pain compared to placebo or active comparator. The secondary outcome was the qualitative analysis of the reported adverse effects	Yes	Yes, except for, publication bias and for-profit bias	No	Yes	Based on the available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain.
Wallitt et. al	Cannabinoids for fibromyalgia	2016	Cochrane Review	Nabilone	Fibromyalgia	Cochrane Library, MEDLINE and EMBASE	2 trials comparing the intervention with either (1) placebo or (1) amitriptyline	72 (40)	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. PGIC (Patient Global Impression of Change) much or very much improved. Withdrawal due to adverse events (tolerability). Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or	Yes	Yes, except for publication bias.	No	Yes	We found no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone was low in people with fibromyalgia.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	25-26
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	25
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-9
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	10-12
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	12-13
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13-14
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	13
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	13-14
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	14
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	15-17
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	16
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	19-21
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	22-23
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	21
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	17
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	21

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Search strategies for
'Cannabinoids versus placebo for pain'
(J Barakji)
Preliminary searches performed 1 July 2019

Total number of records identified	**4106 records**
Number of duplicates removed	**1079 records**
Number of records in final list	**3027 records**

The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2019, Issue 6) (961 hits)

#1 MeSH descriptor: [Cannabis] explode all trees
#2 MeSH descriptor: [Cannabinoids] explode all trees
#3 (cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid*)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Pain] explode all trees
#6 (pain* or ache* or migraine*)
#7 #5 or #6
#8 #4 and #7

MEDLINE Ovid (1946 to July 2019) (465 hits)

1. exp Cannabis/
2. exp Cannabinoids/
3. (cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid* or 2-AG).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. 1 or 2 or 3
5. exp Pain/
6. (pain* or ache* or migraine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 5 or 6
8. 4 and 7
9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 8 and 9

Embase Ovid (1974 to July 2019) (1829 hits)

1. exp cannabis/
2. exp cannabinoid/
3. (cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid* or 2-AG).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4. 1 or 2 or 3
5. exp pain/
6. (pain* or ache* or migraine*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. 5 or 6
8. 4 and 7
9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. 8 and 9

LILACS (Bireme; 1982 to July 2019) (51 hits)

(cannabi$ or mari$uana or nabixmol$ or dronabinol$ or marinol$ or nabilon$ or cesamet$ or hash$ or hemp$ or levonantradol$ or anandamid$ or 2-AG) [Words] and (pain$ or ache$ or migraine$) [Words]

Science Citation Index Expanded (1900 to July 2019) and Conference Proceedings Citation Index – Science (1990 to July 2019) (Web of Science) (623 hits)
#5 #4 AND #3
#4 TS=(random* or blind* or placebo* or meta-analys*)
#3 #2 AND #1
#2 TS=(pain* or ache* or migraine*)
#1 TS=(cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid* or 2-AG)

BIOSIS (1969 to July 2019; Web of Science) (177 hits)
#5 #4 AND #3
#4 TS=(random* or blind* or placebo* or meta-analys*)
#3 #2 AND #1
#2 TS=(pain* or ache* or migraine*)
#1 TS=(cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid* or 2-AG)

BMJ Open

Cannabinoids versus placebo or no intervention for pain. Protocol for a systematic review with meta-analysis and Trial Sequential Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031574.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Sep-2019
Complete List of Authors:	Barakji, Jehad; The Copenhagen Trial Unit, Rigshospitalet Dept. 7812 Korang, Steven Kwasi; Rigshospitalet, Copenhagen Trial Unit; Holbaek Sygehus, Pediatric Dept. Feinberg, Joshua; Copenhagen Univ Hosp Maagard, Mathias; The Copenhagen Trial Unit, Rigshospitalet Dept. 7812 Gluud, Christian; Copenhagen Trial Unit (CTU), Center for Clinical Intervention Research Mathiesen, Ole; University of Copenhagen Jakobsen, Janus; Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Anaesthesia, Evidence based practice, Complementary medicine
Keywords:	PAIN MANAGEMENT, Herbal medicine < THERAPEUTICS, Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Cannabinoids versus placebo or no intervention for pain: Protocol for a systematic review with meta-analysis and Trial Sequential Analysis

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Abstract

Introduction Pain is a frequent clinical symptom with significant impact on the patient's well-being. Therefore, adequate pain management is of utmost importance. While cannabinoids have become a more popular alternative to traditional types of pain medication among patients, the quality of evidence supporting the use of cannabinoids has been questioned. The beneficial and harmful effects of cannabinoids in patients with pain is unknown. Accordingly, we aim to assess the efficacy, tolerability, and safety of cannabinoids (herbal, plant-derived extracts and synthetic) compared with placebo or no intervention for any type of pain.

Methods and analyses We will conduct a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis to assess the beneficial and harmful effects of cannabinoids in any dose, formulation, and duration. We will accept placebo or no treatment as control interventions. We will include participants with any type of pain (acute and chronic pain, cancer-related pain, headache, neuropathic pain, or any other types of pain). We will systematically search The Cochrane Library, MEDLINE, EMBASE, Science Citation Index, and BIOSIS for relevant literature. We will follow the recommendations by Cochrane and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The risk of systematic errors (bias) and random errors (play of chance) will be assessed. The overall certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination Ethical approval is not a requirement since no primary data will be collected. The findings of this systematic review will be submitted for peer-reviewed publication and disseminated in national and international conferences.

Discussion Although cannabinoids are now being used to manage different pain conditions, the evidence for the clinical effects are unclear. The present review will systematically assess the current evidence for the benefits and harms of cannabinoids to inform practice and future research.

Strengths and limitations of this study

- Our methodology is based on the Cochrane Handbook for Systematic Reviews of Interventions, the PRISMA guideline, and a systematic eight step procedure for valid assessments of statistical and clinical significance
- We systemically plan to assess risks of random errors ('play of chance') and systematic errors ('bias')
- We have systematically predefined minimal important differences for all outcomes
- The certainty of the evidence will be assessed using the GRADE approach

Pain is the most commonly reported symptom in the general population and in a medical setting [1-3]. Persistent pain is a major international health problem [4], prompting the World Health Organization (WHO) to endorse a global campaign against pain [5]. Pain is the leading reason for use of alternative medicines (i.e. acupuncture, etc.) [6]. Pain has been associated with a low degree of health-related quality of life and may lead to psychosocial distress, insomnia, and depressive symptoms [7-15]. Pain is also among the most common reasons for temporary or permanent work disability [16]. Pain is always subjective and may be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [17].

Cannabinoids have emerged as a potential alternative to other painkillers for the treatment of intractable pain [18]. Before the healthcare systems globally can endorse the applicability of cannabinoids for pain, the potential short-time and long-term benefits and harms with use of cannabinoids must be investigated. This is of utmost importance because patients who consume cannabinoids to alleviate their chronic pain will most likely need to consume cannabinoids for the rest of their lifespan.

Description of pain

Pain may be caused by or be related to different clinical disorders and classified according to several different characteristics [19-22]. Below, we describe shortly some of these classifications.

Acute and chronic pain

Pain may be classified as 'acute pain' or 'chronic pain'.

- Acute pain usually has a well-defined onset and most often a readily identifiable cause (i.e. surgery, etc.). Acute pain is expected to run its course in a short time frame and management typically focuses on symptomatic relief until this happens [23]. Acute pain is a common symptom, affecting between 37% to 84% of hospitalised patients [24].

- Chronic pain is often characterised by an ill-defined onset and a prolonged, fluctuating course [23]. Chronic pain often persists past normal healing time and hence lacks the acute warning function of physiological nociception [25]. Pain is usually regarded as chronic when it lasts or recurs for more than three to six months [17, 26]. Chronic pain is a frequent condition, affecting an estimated 20% of people worldwide [27-30] and accounting for 15% to 20% of physician visits according to European observational studies [31, 32].

Cancer-related pain

Pain may also be classified based on whether it is cancer-related or non-cancer-related. Cancer-related pain is pain caused by the cancer itself (primary tumour and metastases) or its treatment (i.e. radiation therapy, etc.) [23, 33].

Postoperative pain

Postoperative pain includes pain from inflammation caused by tissue trauma (i.e. surgical incision, dissection, burns, etc.) or direct nerve injury (e.g. nerve transection, stretching, or compression) [34]. Inflammation results in activation and sensitisation of nociceptive pain pathways, resulting in primary and secondary hyperalgesia and central sensitisation, which is characterized by clinically increased pain, allodynia, and increased sensitivity from surrounding non-damaged anatomical areas [35].

Other types of pain

Pain in one or more anatomic regions where the aetiology is unknown is defined as idiopathic pain [36]. Examples of idiopathic pain are chronic widespread pain, fibromyalgia, irritable bowel syndrome, and back pain that is not diagnosed as musculoskeletal or as neuropathic pain [33].

Pain types defined according to specific mechanism causing the pain

Somatic nociceptive pain

Nociceptive pain is the most frequent type of pain. It results from activity in neural pathways caused by actual tissue damage or potentially tissue-damaging stimuli [31, 37] originating from somatic nociceptors from skin, bone, joints, or muscles [38].

Visceral nociceptive pain

The visceral nociceptive pain is pain resulting from viscera in the thoracic, pelvis, or abdominal organs [39-41]. Visceral pain is diffuse, less distinctive, and difficult to localise [41] and is often characterised by referred visceral pain [42].

Neuropathic pain

The 2011 International Association for the Study of Pain definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" [43]. Neuropathic pain may be classified as central neuropathic pain or peripheral neuropathic pain. Central neuropathic pain conditions are mainly attributed to multiple sclerosis and post-stroke pain [44], while peripheral neuropathic pain is largely due to post-herpetic neuralgia and diabetic neuropathy [45].

Description of the intervention

Cannabis (also called marijuana) is the most common illegally used psychoactive substance worldwide [46]. Cannabinoids refer to a heteromorphic group of molecules that demonstrate activity upon cannabinoid receptors [47]. Cannabinoids may be classified into three groups: 1) endocannabinoids, 2) phytocannabinoids, and 3) synthetic cannabinoids [47].

Endocannabinoids

Endocannabinoids are characterised by being the endogenously generated cannabinoids [48]. The primary types of endocannabinoids are the lipid endocannabinoid arachidonoyl ethanolamide (named anandamide) [49] and the endocannabinoid 2-arachidonoylglycerol (2-AG) [50, 51].

Phytocannabinoids

Phytocannabinoids are cannabinoids found in the cannabis plant [52]. The best characterised phytocannabinoids are the psychotropic tetrahydrocannabinol (THC) and the primarily anti-inflammatory cannabidiol (CBD) [53]. Nabiximols (marketed as Sativex®) is a sublingually administered oromucosal spray based on a mixture of tetrahydrocannabinol and cannabidiol [54].

Synthetic cannabinoids

Synthetic cannabinoids are analogues of the cannabinoids found in natural marijuana that are chemically synthesised. The most commonly prescribed cannabinoid-based medicines are the synthetic cannabinoids dronabinol (marketed as Marinol®) and nabilone (marketed as Cesamet®) [54].

Endocannabinoid system

All cannabinoids act on cannabinoid receptors. These cannabinoid receptors are located throughout the body but are mostly located in the brain [55]. The cannabinoid receptors and endocannabinoids (see paragraph above) are together named the endocannabinoid system [56].

Cannabinoid receptors

There are two types of cannabinoid receptors, type I and type II [57]. Cannabinoid receptor type I are most abundant in the central nervous system, especially in areas promoting nociception, short-term memory, and in the basal ganglia, but are also found in the peripheral nerves, uterus, testis, and bones [57]. Tetrahydrocannabinol activates cannabinoid type I receptors in the dopaminergic mesolimbic brain circuit, resulting in enhanced release of dopamine [58]. Such activation of the so-called 'brain reward system' is hypothesised to mediate the positive reinforcing and rewarding effects of almost all drugs of abuse [58].

In contrast, cannabinoid receptor type II, is mostly found in the periphery, often in conjunction with immune cells, but may appear in the central nervous system particularly under conditions of inflammation in association with microcytes [57]. The physiological responses that result from cannabinoid receptor activation are euphoria, psychosis, impaired memory and cognition, reduced locomotor function, increased appetite, as well as anti-emetic, pain-relieving, anti-spasticity, and sleep-promoting effects [59].

Administration of cannabinoids

Cannabis is most commonly consumed via smoked, inhaled vapor, or oral routes of administration [60]. Vaporising cannabis ('vaping') heats the material without burning which theoretically minimises potential carcinogens compared to smoking and may produce less respiratory irritation [61, 62]. Sublingual administration is used for some medical cannabis preparations (i.e. nabiximols, etc.).

Why it is important to do this review

We identified ten previous reviews with meta-analyses assessing the effects of cannabinoids on different types of pain [63-72]. Bearing in mind that some of the previous reviews investigated more than one type of pain, eight reviews assessed the effects of different cannabinoids on neuropathic pain [63-69, 72]; four reviews assessed the effects of different cannabinoids on nociceptive pain (i.e. rheumatoid arthritis, etc.) [63, 64, 67, 68]; three reviews assessed the effects of different cannabinoids on cancer-related pain [63, 67, 68]; four reviews assessed the effects of different cannabinoids on fibromyalgia-related pain [63, 64, 67, 71]; and three reviews assessed the effects of different cannabinoids on postoperative pain [63, 68, 70]. All the previous reviews included randomised clinical trials, but only two of the ten reviews systematically assessed the risk of bias in the trials [65, 72], and none of the previous reviews took into account the risks of random errors [63-72]. Only two out of the ten reviews used predefined Cochrane methodology [71, 72] and only four reviews used the GRADE approach [65, 70-72].

Most of the reviews concluded that the assessed cannabinoids were effective against pain [63-67, 69, 72]. In **Table 1** (**Additional file 1**)**,** we have summarised the results and conclusions of the previous reviews. Five of the reviews reported serious adverse events (i.e. agitation, impaired memory, abuse, dissociation, acute psychosis, death, etc.) [63, 65-67, 72]. The reviews also showed that the most commonly reported adverse events were sedation, dizziness, dry mouth, increased appetite, somnolence, confusion, nausea, and disturbances in concentration [63-66, 68, 69, 71, 72].

A correlation between psychiatric disorders (schizophrenia, psychosis, etc.) and increased cannabinoid consumption has previously been hypothesised [73-79]. Di Forti et al. recently conducted a study indicating that daily cannabis use was associated with increased odds of psychotic disorders compared with never users (adjusted odds ratio [OR] 3.2, 95% confidence interval (CI) 2.2 to 4.1), increasing to nearly five-times increased odds for daily use of high-potency (THC ≥ 10%) types of cannabis (adjusted OR 4.8, 95% CI 2.5 to 6.3) [80].

Compared to previous systematic reviews on cannabinoids, we want to assess the effects of all types of cannabinoid versus placebo or no intervention for all different forms of pain. Depending on the data results provided by the included trials this could increase the power and precision of the overall analysis and make it possible to conduct subgroup analyses and sensitivity analyses that may identify pain areas where cannabinoid could be especially beneficial and cause the least harms. In addition, we will implement a minimal clinically important threshold regarding analgesic efficacy based on previously conducted methodological studies which ensures that analgesic efficacy is of a firm significance before acceptance. Finally, by instigating all types of cannabinoids treated for any type of pain this systematic review will aid trialist in optimising the design of future randomised clinical trials by illuminating any research pitfalls of all previously conducted randomised clinical trials on this topic.

Objective

The objective of our systematic review is to assess the analgesic efficacy and adverse events encumbered with the use of cannabinoids compared with placebo or no intervention in participants with any type of pain (acute and chronic pain, cancer-related pain, headache, neuropathic pain, or any other types of pain). A secondary objective of this systematic review is to assess the impact of cannabinoid use on the quality of sleep and quality of life which is especially decreased in participants with chronic pain.

Methods

This systematic review protocol has been developed based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews evaluating healthcare interventions [81, 82]. A PRISMA-P checklist file is attached (**Additional file 2**).

Criteria for considering studies for this review

Type of studies

Randomised clinical trials irrespective of trial design, setting, publication status, publication year, and language. If we identify quasi-randomised studies and observational studies during our searches for randomised clinical trials, we will only include their reporting on harms in a narrative way. By not systematically searching for all

observational studies on harm, we run the risk of putting more focus on benefit than harm. We are aware that this is a limitation of our review.

Types of participants

Participants with any type of pain, i.e. acute and chronic pain, cancer-related pain, headache, neuropathic pain, or any other types of pain (as defined by the trialists). Participants will be included irrespective of age, sex, and comorbidities.

Types of interventions

Experimental intervention

Any type of cannabinoids such as: herbal cannabis (hashish, marihuana), plant-based extracts (i.e. nabiximols, etc.), or synthetic cannabinoids (i.e. cannabidiol, dronabinol, levonantradol, nabilone, etc.). We will accept cannabinoids at any dose, by any route, administered for the relief of pain.

Control intervention

Placebo or no intervention.

Co-interventions

We will accept any co-intervention but only if this co-intervention is planned to be delivered similarly in both intervention groups. If this plan is not followed, then these trials will be assessed as a subgroup due to potential confounding.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Pain assessment on visual analogue scale (VAS) or numerical rating scale (NRS)
- Proportion of participants with a serious adverse event defined as any untoward medical occurrence that resulted in death; was life threatening; was persistent; or led to significant disability, nephrotoxicity, superinfection, need for respiratory support, need for circulatory support, or prolonged hospitalisation [83]. As we expect the trialists' reporting of serious adverse events to be heterogeneous and not strictly

according to the ICH-GCP recommendations, we will include the event as a serious adverse if the trialists either: 1) use the term 'serious adverse event' but not refer to ICH-GCP, or 2) report the proportion of participants with an event we consider fulfils the ICH-GCP definition. If several of such events are reported then we will choose the highest proportion reported in each trial.

- Quality of life measured on any valid continuous scale

Secondary outcomes

- Dependence (as defined by trialists)
- Psychosis (as defined by trialists)
- Proportion of participants with one or more adverse event not considered to be serious
- Quality of sleep measured on any valid continuous scale

Exploratory outcomes

- Each serious adverse event separately
- Each adverse event not considered serious separately
- Twenty-four-hour morphine consumption (as defined by trialists)
- Physical function (as defined by trialists)
- Depressive symptoms (e.g. Hamilton Depression Rating Scale)

We will for all outcomes use the trial results reported at maximal follow-up except for acute pain. For acute pain, we will use the trials' results reported at the time point closest to 24 hours after the intervention is given.

Patient and public Involvement

We have had email correspondence with several relevant patient associations in Denmark to select the most patient-relevant outcomes. The patient associations we have been in contact with included: The Danish Diabetes Association, Steno Diabetes Centre Copenhagen, The Danish Rheumatism Association, The Danish Multiple Sclerosis Society, and Danish Cancer Society. Initially we presented our potential outcomes for the patient associations and requested for their opinion. We had not included quality of sleep as an outcome, however, this was mentioned by almost all patient associations and it was included as a crucial secondary outcome. All-cause mortality was questioned by one of the patient associations, however, we want to keep this

outcome because of potential increased risk of both acute coronary syndrome and chronic cardiovascular disease associated with cannabis use [84].

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), Science Citation Index Expanded on Web of Science, and BIOSIS in order to identify relevant trials. The preliminary search strategy for CENTRAL, MEDLINE (Ovid), Embase (Ovid), LILACS, Web of Science and BIOSIS is given in **Additional file 3**.

We will search all databases from their inception to the 1st of October 2019.

Searching other resources

The reference lists of relevant publications will be checked for any unidentified randomised trials. We will contact authors of included studies, and major pharmaceutical companies, by email asking for unpublished randomised trials. Further, we will search for ongoing trials on:

- ClinicalTrials.gov (www.clinicaltrials.gov)
- Google Scholar (https://scholar.google.dk/)
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/)
- European Medicines Agency (EMA) (http:// www.ema.europa.eu/ema/)
- United States Food and Drug Administration (FDA) (www.fda.gov)
- China Food and Drug Administration (CFDA) (http://eng.sfda.gov.cn/WS03/CL0755/)
- Medicines and Healthcare products Regulatory Agency (https://www.gov.uk/government/organisations/ medicines-and-healthcare-products-regulatory-agency)
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/ trialsearch/)

We will also consider relevant for the review unpublished and grey literature trials, if we identify such trials.

Data collection and analysis

We will perform the review following the recommendations of Cochrane [85]. The analyses will be performed using Review Manager 5 [86] and Trial Sequential Analysis [87]. In case of Review Manager statistical software is not being sufficient, we will use STATA 15 [88].

Selection of studies

Two authors (JB, SKK) will independently screen titles and abstracts. We will retrieve all relevant full-text study reports/publications, and four review authors (JB, SKK, JRF, MM) will independently screen the full texts and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a fifth author (JCJ). Trial selection will be displayed in an adapted flow diagram as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [89].

Data extraction and management

Four authors (JB, SKK, JRF, MM) will in pairs extract data independently from included trials. Disagreements will be resolved by discussion with a fifth author (JCJ). We will assess duplicate publications and companion papers of a trial together to evaluate all available data simultaneously (maximise data extraction, correct bias assessment). We will contact the trial authors by email to specify any additional data, which may not have been reported sufficiently or at all in the publication.

Trial characteristics

Bias risk components (as defined below); trial design (parallel, factorial, or crossover); number of intervention arms; length of follow-up; estimation of sample size; inclusion and exclusion criteria.

Participant characteristics and diagnosis

Number of randomised participants; number of analysed participants; number of participants lost to follow-up/ withdrawals/crossover; compliance with medication; age range (mean or median) and sex ratio; type of pain (acute and chronic pain, cancer-related pain, headache, neuropathic pain or any other types of pain); baseline pain score; drug and dosing regimen; study design (placebo or active control); study duration and follow-up;

analgesic outcome measures and results; adverse events (participants experiencing any adverse event, or serious adverse event).

Co-intervention characteristics

Type of co-intervention; dose of co-intervention; duration of co-intervention; and mode of administration.

Outcomes

All outcomes listed above will be extracted from each randomised clinical trial, and we will identify if outcomes are incomplete or selectively reported according to the criteria described later in 'incomplete outcome data' bias domain and 'selective outcome reporting' bias domain.

Notes

Funding of the trial and notable conflicts of interest of trial authors will be extracted, if available.

We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Four review authors (JB, SKK, JRF, MM) will independently transfer data into the Review Manager file [86]. Disagreements will be resolved through discussion or, if required, we will consult with a fifth author (JCJ).

Assessment of risk of bias in included studies

We will use the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions [85] in our evaluation of the methodology and hence the risk of bias of the included trials. We will evaluate the methodology in respect of:

- Random sequence generation
- Allocation concealment
- Blinding of participants and treatment providers
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- For-profit bias
- Overall risk of bias

These components enable classification of randomised trials as being at low risk of bias and at high risk of bias. The latter trials tend to overestimate positive intervention effects and underestimate negative effects [90-96].

We will classify the trials according to the following criteria.

Random sequence generation

- Low risk: If sequence generation was achieved using computer random number generator or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.
- Unclear risk: If the method of randomisation was not specified, but the trial was still presented as being randomised.
- High risk: If the method of sequence generation was inadequate e.g. alternate medical record numbers or other non-random sequence generation.

Allocation concealment

- Low risk: If the allocation of patients was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, drug bottles, or containers prepared by an independent pharmacist or investigator.
- Uncertain risk: If the trial was classified as randomised but the allocation concealment process was not described.
- High risk: If the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

- Low risk: If the participants and the treatment providers were blinded to intervention allocation and this was described.
- Uncertain risk: If the procedure of blinding was insufficiently described.
- High risk: If blinding of participants and the treatment providers was not performed.

Blinding of outcome assessment

- Low risk of bias: If it was mentioned that outcome assessors were blinded and this was described.
- Uncertain risk of bias: If it was not mentioned if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described.
- High risk of bias: If no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

- Low risk of bias: If missing data were unlikely to make treatment effects depart from plausible values. This could be either (1) there were no drop-outs or withdrawals for all outcomes or (2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups. Generally, the trial is judged as at a low risk of bias due to incomplete outcome data if drop-outs are less than 5%. However, the 5% cut-off is not definitive.
- Uncertain risk of bias: If there was insufficient information to assess whether missing data were likely to induce bias on the results.
- High risk of bias: If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (i.e. last observation carried forward, etc.).

Selective outcome reporting

- Low risk of bias: If a protocol was published before or at the time the trial was begun, and the outcomes specified in the protocol were reported on. If there is no protocol or the protocol was published after the trial has begun, reporting pain assessment on VAS or NRS and serious adverse events will grant the trial a grade of low risk of bias.
- Uncertain risk of bias: If no protocol was published and the outcome pain assessment on VAS or NRS and serious adverse events were not reported on.
- High risk of bias: If the outcomes in the protocol were not reported on.

For-profit bias

- Low risk of bias: If the trial appeared to be free of other components of for-profit bias.
- Unclear risk of bias: If it was unclear whether the trial was free of for-profit bias.
- High risk of bias: If there was a high risk of for-profit bias.

Overall risk of bias

- Low risk of bias: The trial will be classified at overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified at 'low risk of bias'.

- High risk of bias: The trial will be classified at 'high risk of bias' if any of the bias risk domains described in the above are classified at 'unclear' or 'high risk of bias'.

We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective outcome reporting' for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of our primary outcome results at overall low risk of bias. Both our primary and secondary analyses will be presented in the summary of findings tables.

Differences between the protocol and the review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between the protocol and the review' section of the systematic review.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well as the Trial Sequential Analysis- adjusted CIs (see below).

Continuous outcomes

We will calculate the mean differences (MDs) and the standardised mean difference (SMD) with 95% CI for continuous outcomes, as well as the Trial Sequential Analysis-adjusted CIs (see below).

Dealing with missing data

We will, as first option, contact all trial authors to obtain any relevant missing data (i.e. for data extraction and for assessment of risk of bias, as specified above).

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

Continuous outcomes

We will primarily analyse scores assessed at single time points. If only changes from baseline scores are reported, we will analyse the results together with follow-up scores [85]. If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible. We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis (see paragraph below) for continuous outcomes, we will impute data.

Assessment of heterogeneity

We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by chi^2 test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the I^2 statistic [97, 98]. We will investigate for heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided [85].

Assessment of reporting biases

We will use a funnel plot to assess reporting bias if ten or more trials are included. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (i.e. a funnel plot assesses bias due to small sample size, etc.). From this information, we assess possible reporting bias. For dichotomous outcomes, we will test asymmetry with the Harbord test [99] if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test [100] and the adjusted rank correlation [101].

Unit of analysis issues

We will only include randomised clinical trials. For trials using crossover design, only data from the first period will be included [85, 102]. There will therefore not be any unit of analysis issues.

Minimal important difference

In clinical intervention research it is of utmost importance always to define minimal important differences (MID) and to define thresholds for clinical significance [103]. If a large number of trial participants are randomised, small and clinically irrelevant intervention effects may lead to statistically significant results and rejection of the null hypothesis [104]. Jaeschke et al. defined the minimal important difference as “the smallest difference in score in the domain of interest which patients perceive as beneficial” [105].

Estimations of minimal important differences should be used as arbitrary strict precise thresholds. However, to avoid erroneous conclusions minimal important differences need to be estimated and predefined when assessing the effects of interventions for pain. Olsen et al. have conducted two systematic reviews on this matter in order to gather the evidence and present an estimate of the minimal important difference [106, 107]. Olsen et al. conducted a systematic review on the minimal important difference in patients with acute pain and concluded that the median of the studies' results was 17 mm on VAS (IQR 14 mm to 23 mm) [106]. Another systematic review conducted by Olsen et al. was on the minimal important difference in patients with chronic pain and the results showed a median of 23 mm on VAS (IQR 12 mm to 39 mm) when using the within-patient anchor-based method, while the median in studies using the sensitivity- and specificity-based method was 20 mm on VAS (IQR 15 mm – 30 mm) [107]. We have described detailed considerations about minimal important differences in **Appendix 1**.

Based on the previously conducted systematic reviews we will choose at minimal important difference equivalent to 10 mm or 1 point on the visual analogue scale and the numerical rating scale, respectively, regarding an analgesic effect.

Data synthesis

Meta-analysis

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions [85], Keus et al. [108], and the eight-step assessment suggested by Jakobsen et al. [103]. We will use the statistical software Review Manager 5.3 [86] provided by Cochrane to analyse data. We will assess our intervention effects with both random-effects meta-analyses [109] and fixed-effect meta-analyses [110]. We will use the more conservative point estimate of the two [103]. The more conservative point estimate is the estimate closest to zero effect. If the two estimates are similar, we will use the estimate with the highest P value [103]. We use four primary and four secondary outcomes, and therefore, we will consider a P value of 0.02 as the threshold for statistical significance [103, 111]. We will investigate for heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided [85]. We will use the eight-step procedure to assess if the thresholds for statistical and clinical significance are crossed [103]. Our primary conclusion will be based on results with low risk of bias [103].

Where multiple trial intervention groups are reported in a single trial, we will include only the relevant groups. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting [85]. Trials with a factorial design will be included.

If quantitative synthesis is not appropriate, we will report the results in a narrative way.

Trial Sequential Analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We wish to control the risks of type I errors and type II errors. We will therefore perform Trial Sequential Analysis on the outcomes, in order to calculate the required information size (that is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries [87, 112-120]. A more detailed description of Trial Sequential Analysis can be found in the Trial Sequential Analysis manual [113] and at http://www.ctu.dk/tsa/. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction of 20%, an alpha of 2.0% for our primary and secondary outcomes, a beta of 10%, and diversity as suggested by the trials in the meta-analysis. For the outcome "pain assessment on visual analogue scale (VAS) or numerical rating scale (NRS)", we will use a minimal important difference estimate based on previously conducted systematic reviews [106, 107]. We will accept an analgesic effect equivalent to 10 mm or 1 point on the visual analogue scale and the numerical rating scale, respectively, or a consumption of at least 5 mg morphine.

For all remaining continuous outcome, we will in the Trial Sequential Analysis use the observed SD, a mean difference of the observed SD/2, an alpha of 2.0% for our primary and secondary outcomes, and a beta of 10%.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis

We will perform the following subgroup analysis when analysing the primary outcomes (All-cause mortality, pain assessment on VAS or NRS, serious adverse event, and quality of life).

- Trials at high risk of bias compared to trials at low risk of bias

- Trials at risk of vested interests compared to trial with no risk of vested interests
- Trials compared according to type of pain (acute pain, chronic pain, and cancer pain)
- Trials compared according to type of chronic pain
- Trials compared according to type of cannabinoids used

We will use the formal test for subgroup interactions in Review Manager [86].

Sensitivity analysis

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on both the primary and secondary outcomes.

- 'Best-worst-case' scenario: We will assume that all participants lost to follow-up in the cannabinoid intervention group have survived and had no serious adverse event, and that all those participants lost to follow-up in the placebo group have not survived, and had a serious adverse event.
- 'Worst-best-case' scenario: We will assume that all participants lost to follow-up in the cannabinoid intervention group have not survived, and had a serious adverse event, and that all those participants lost to follow-up in the placebo group have survived, and had no serious adverse event.

We will present results of both scenarios in our review.

For all continuous outcome when analysing a 'beneficial outcome' will be the group mean plus two standard deviations (SDs) (we will secondly use one SD in another sensitivity analysis) of the group mean and a 'harmful outcome' will be the group mean minus two SDs (we will secondly use one SD in another sensitivity analysis) of the group mean [103].

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis.

- Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials.

We will present results of this scenario in our review. Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results [103].

Summary of Findings

We will create a Summary of Findings table using each of the primary outcomes (all-cause mortality, pain assessment on VAS or NRS, serious adverse event, and quality of life). We will use the five GRADE considerations (bias risk of the trials, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes [103, 121-123]. We will use methods and recommendations described in Chapter 8 (Section 8.5) and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions [85] using GRADEpro software. We will justify all decisions to downgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. Firstly, we will present our results in the Summary of Findings table based on the results from the trials with low risk of bias, and secondly, we will present the results based on all trials.

Ethics and dissemination

Ethical approval is not a requirement since no primary data will be collected. The findings of this systematic review will be submitted for peer-reviewed publication and disseminated in national and international conferences and is expected to inform healthcare workers and providers about the occurrence of serious and non-serious adverse events following cannabinoid consumption. It is expected that the findings of this systematic review will identify some research gaps for future trials.

Discussion

This protocol aims at investigating the beneficial and harmful effects of cannabinoids in patients with any type of pain condition. The outcomes will be all-cause mortality, pain assessment on VAS or NRS, serious adverse events, quality of life, dependence, psychosis, non-serious adverse events, and sleep quality.

This protocol has several strengths. The predefined methodology is based on the Cochrane Handbook for Systematic Reviews of Interventions [85], the eight-step assessment suggested by Jakobsen et al. [103], Trial Sequential Analysis [84], and GRADE assessment [121-123]. Hence, this protocol takes both the risk of random

error and the risk of systematic error into account. We predefined evidence-based estimations of minimal important differences which will limit the risk of focusing on statistically significant results with questionable clinical importance. This threshold of minimal important difference is based on the estimations of several previously conducted studies and reviews [106, 107]. Moreover, we are including all types of cannabinoids and all types of pain which will increase the statistical power and make it possible to perform essential subgroup analyses. We have been in contact with several relevant patient associations which has assisted us in choosing the most clinically relevant outcomes.

Our protocol also has several limitations. One of the potential limitations is that we include participants with all types of pain; cannabinoids might have different effects on different types of pain. It might, e.g. be problematic to combine trials assessing the effects of cannabinoids on acute pain and chronic pain because of different underlying pathophysiological mechanisms [124]. On the other hand, the effects of cannabinoids on acute pain and chronic pain might be comparable and hence it might be valid to combine trials assessing the effects of cannabinoids on acute pain and chronic pain in meta-analysis, which would increase the statistical power. The results of the subgroup analysis comparing trials including participants with acute pain to participants with chronic pain will therefore be highlighted when reporting our review results. Moreover, we only intend to assess cannabinoids versus placebo or versus no intervention. Further systematic reviews with meta-analyses and Trial Sequential Analyses need to assess the benefits and harms of cannabinoids versus other pain killers, provided that cannabinoids show more benefit than harm in the present systematic review.

Furthermore, more than one active cannabinoid agent is often combined in the different intervention options provided to the patients with a pain condition, thereby making difficult to explore the analgesic effect and adverse event associated with a single cannabinoid agent. Hence, if we show a difference between the intervention options, it will be difficult to conclude what exactly caused the difference in effect. To minimise these limitations, we have planned a careful assessment of statistical and clinical heterogeneity as well as several subgroup analyses and sensitivity analyses. Another limitation is the large number of comparisons which increase the risk of type 1 error. We have adjusted our thresholds for significance according to the number of primary outcomes, but, as mentioned, we have also included multiple subgroup analyses. This large risk of type 1 error will be taken into account when interpreting the review results.

Acknowledgements

We hugely appreciate the contribution of The Danish Diabetes Association, Steno Diabetes Centre Copenhagen, The Danish Rheumatism Association, The Danish Multiple Sclerosis Society, and Danish Cancer Society in guiding us to select the most patient relevant outcomes.

The expert help from Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Copenhagen, Denmark) in making the search strategy is hugely appreciated.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

JB drafted the protocol. JCJ, SKK, OM, CG, JRF, and MM amended the protocol. All authors read and approved the final manuscript.

Competing interests

None declared

Ethics approval and consent to participate

Not applicable.

Word Count

10191 words, including the full references.

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First author	Title	Year of publication	Design	Type of cannabinoid	Types of participants	Information sources	No. of trials	No. of participants	Published protocol	Outcomes	Assessment of adverse events	Assessment of risk of bias	Accounts for random error	Use of the GRADE	Conclusion
Lynch & Campbell	Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials	2011	Systematic Review	**Phytocannabinoids;** Smoked cannabis, oromucosal extracts of cannabis-based medicine, and **synthetic cannabinoids;** nabilone, dronabinol and a novel THC analogue.	Neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.	PubMed, EMBASE, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library, ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search Premier (EBSCO), Clinical Trials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline, OAIster (OCLC) and Google Scholar.	18	1750	Yes	The primary outcome was pain in subjects with chronic non-cancer pain. The secondary outcomes were sleep, function, and quality of life.	Yes	Yes, except for reporting bias, publication bias and for-profit bias	No	No	Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis. Did not pool data for meta-analysis but data was described qualitatively.
Meng et. al	Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis	2017	Systematic Review and Meta-analysis	Dronabinol, nabilone and nabiximols	Neuropathic pain	Medline, Embase, Cochrane Library, PROSPERO, clinicaltrials.gov, and Google Scholar. Pain societies (American Society of Anesthesiologists, European Society of Anaesthesiology, International Association for the Study of Pain, American Society of Regional Anesthesia and Pain Medicine, European Society of Regional Anesthesia and Pain Therapy, and World Institute of Pain) in the last 2 years were also searched.	11 (10 trials comparing the intervention with placebo)	1219	No	The primary outcome was Intensity of pain recorded after a minimum of 2 weeks following initiation of selective cannabinoid and placebo/comparator administration, expressed on an NRS (0—no pain to 10—worst possible pain). Secondary outcomes were presence or absence of analgesia defined as reduction in pain scores (NRS/VAS) by ≥30% at 2 weeks or more after initiation of intervention, quality of life (QoL), physical function, psychological function, sleep, overall patient satisfaction, and the incidence of adverse effects of selective cannabinoids.	Yes	Yes	Bonferroni adjustment for multiple testing was not performed as per recommendations in the Cochrane Handbook.	Yes	Selective cannabinoids provide a small analgesic benefit in patients with chronic neuropathic pain.
Martín-Sánchez et. al	Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain	2009	Meta-analysis	**Phytocannabinoids** and synthetic derivates of THC, such as dronabinol, nabilone, or benzopyranoperidine (a synthetic nitrogen analog of THC)	Chronic pain of a pathologic al or traumatic origin	Medline/Pubmed, Embase, and The Cochrane Controlled Trials Register (CENTRAL)	18	?	No	The primary outcome was Intensity of pain as scored by numerical rang scales. The Secondary outcomes were CNS related events	Yes	Yes, except for reporting bias, detection bias and for-profit bias	No	No	Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms.
Boychuk et. al	The Effectiveness of Cannabinoids In the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Review	2015	Systematic Review	**Phytocannabinoids;** smoked cannabis, cannabis-based medicinal extracts (CBME) in the form of oromucosal sprays (nabiximols), vaporized cannabis, and **synthetic cannabinoids;** dronabinol, nabilone, and CT-3	Neuropathic pain	PubMed, Embase, Web of Science, and all evidence-based medicine reviews and databases (Cochrane Database of Systematic Reviews, ASP Journal Club, Database of Abstracts of Reviews of Effects [DARE], and Cochrane Controlled Trials Register [CCTR])	13	771	No	Outcomes considered were reduction in pain intensity and adverse events.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabis-based medicinal extracts used in different populations of chronic non-malignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments.
Mücke et. al	Cannabis products for adults with chronic neuropathic pain	2018	Cochrane Review	**Phytocannabinoids:** oromucosal spray containing THC or THC/CBD mix, smoked cannabis containing THC, THC and CBD as extract of cannabis sativa L., and **synthetic cannabinoids;** nabilone, dronabinol	Neuropathic pain	Cochrane Library, MEDLINE and EMBASE. Following clinical trials databases were searched for additional data including unpublished data: US National Institutes of Health clinical trial register (www.ClinicalTrials.gov), European Union Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and International Association for Cannabinoid Medicines (IACM) databank (www.cannabis-	16 (15 of the trials comparing the intervention with placebo)	1750	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. We preferred composite neuropathic pain scores over single-scale generic pain scores if both measures were used by studies; PGIC (Patient Global Impression of Change) much or very much improved; Withdrawals due to adverse events (tolerability); Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in	Yes	Yes	No	Yes	The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms.
Aviram et. al	Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials	2017	Meta-Analysis	**Phytocannabinoids:** Sativex/nabiximol, cannabidiol, cannabinoid cigarettes/vaporizer, and **synthetic cannabinoids:** dronabinol and nabilone, CT-3, ajulemic acid, synthetic nitrogen analog of tetrahydrocannabinol (NIB), fatty	Chronic (cancer and non-cancer) pain and acute postoperative pain	MEDLINE/Pubmed and in Google Scholar using Medical Subject Heading (MeSH) terms	43 trials comparing the intervention with both 'active drugs' and placebo	2437	No	The outcome measure that was chosen was the variable "pain intensity", as scored by the numerical rating scale (NRS-11), numerical 11-point box (BS-11), visual analog scale (VAS), and the VAS section of the questionnaire short form McGill Pain Questionnaire	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	The current systematic review suggests that cannabinoid-based medicines might be effective for chronic pain treatment, based on limited evidence, primarily for neuropathic pain patients.
Campbell et. al	Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review	2001	Systematic Review	Oral THC, an oral synthetic nitrogen analogue of THC (NIB), oral benzopyranoperidine (BPP), and Intramuscular levonantradol	Acute, chronic non-malignant pain, and cancer pain	MEDLINE, EMBASE, Oxford Pain Database, and Cochrane Library	9	222	No	Outcome measures for pain intensity; pain relief; the use of supplementary analgesia; patients' preferences; and adverse effects.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used.
Deshpande et. al	Efficacy and adverse effects of medical marijuana for chronic noncancer pain	2015	Systematic Review	Cigarettes or vaporizer containing delta-9-THC	Neuropathic pain	MEDLINE, EMBASE, and the International Pharmaceutical Abstracts	6 trials comparing interventions with placebo. Placebo being cigarettes or vaporizer containing 0% delta-9-THC or with cannabinoid removal	226	No	For outcomes, pain scores were extracted using the visual analogue scale (VAS) or an alternative numerical pain rating tool. If pain scores were not reported, surrogate measures of effectiveness were included (sleep, function, and quality of life). Frequency of serious and most commonly reported adverse effects was collected.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and strength of delta-9-tetrahydrocannabinol, and lack of functional outcomes. Although well tolerated in the short term, the long-term effects of psychoactive and neurocognitive effects of medical marijuana remain unknown.
Stevens et. al	A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain	2017	Systematic Review	Levonantradol, nabilone, AZD1940, GW842166, dronabinol, ∆-9-THC	Acute postoperative pain	MEDLINE, EMBASE, Cochrane Library, and the World Health Organization International Clinical Trials Registry Platform	7 trials comparing interventions with placebo, Ketoprofen, Pethidine, Naproxen, and Ibuprofen	611	Yes	The primary outcome was the qualitative analysis of the analgesic efficacy of cannabinoids in the management of acute pain compared to placebo or active comparator. The secondary outcome was the qualitative analysis of the reported adverse effects	Yes	Yes, except for, publication bias and for-profit bias	No	Yes	Based on the available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain.
Wallitt et. al	Cannabinoids for fibromyalgia	2016	Cochrane Review	Nabilone	Fibromyalgia	Cochrane Library, MEDLINE and EMBASE	2 trials comparing the intervention with either (1) placebo or (1) amitriptyline	72 (40)	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. PGIC (Patient Global Impression of Change) much or very much improved. Withdrawal due to adverse events (tolerability). Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or	Yes	Yes, except for publication bias.	No	Yes	We found no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone was low in people with fibromyalgia.

Appendix

Minimal important difference

For the determination of minimal important differences in clinical trials two types of methods are available; anchor-based methods and distributional-based methods [1].

Anchor-based methods

Anchor-based methods relate the change in on a person reported outcome score, (e.g. a score on the visual analog scale (VAS)) to a subjective global assessment rating (e.g. scores from the Clinical Global Impressions-Improvement (CGI-I)) which is used as an 'anchor' [1]. Ideally, there needs to be an established association between the person reported outcome score and the 'anchor' to make any meaningful inference about a minimal important difference [2].

There are two subtypes of anchor-based methods, i.e., the '*within-patient score'* and the *'between-patients score'* [1].

- Within-patient score defines minimal important difference as the average minimal change in a given person's reported outcome score that leads to a clinically observable change in the subjective global assessment rating (the latter is used as an anchor) [1]. For example, to ascertain the minimal important difference regarding depression management, Moncrieff et. al describes the linking of within-patient scores (change from baseline) scores on the Hamilton Depression Rating Scale (the most commonly used depression rating scale) to scores on the Clinical Global Impressions-Improvement (CGI-I) scale, a scale which rates improvement on a scale of 1 (very much improved from baseline) through 4 (no change from baseline) to 7 (very much worse from baseline) [3]. Moncrieff et. al conclude that seven points on the Hamilton Depression Rating Scale correspond to a minimal important difference when using within-patient scores [3].
- The between-patients score method, also known as 'the group difference' method, compare the reported outcome scores between a group of people with no clinically observable change (based on a subjective global assessment rating (used as an anchor)) to a group of people with clinically observable change (based on a subjective global assessment rating (used as an anchor)). The minimal important difference is then estimated as the mean difference between these two groups [4]. For example, Musoro et. al defines the minimal important difference (MID) as the group difference in terms of quality of life assessed by HRQOL scores [5]. Participants were assigned to distinct subgroups reflecting various levels of change (e.g. no change, small positive changes, large positive changes, small negative changes or large negative changes). The group difference was identified by the

comparison of the average of the HRQOL scores of the group of participants with at 'small change' to the HRQOL scores of the group of participants with 'no change' [5].

There are also other anchor-based methods (e.g. the sensitivity- and specificity-based method and the social comparison method) [1]. The sensitivity- and specificity-based method aims to identify the minimal important difference that allows for the best discrimination between groups of patients (i.e., the score that produces the greatest sensitivity and specificity) [1]. For example, an outcome measure (e.g. NRS score) is considered a 'diagnostic test' and the anchor (e.g. Global Perceived Effect) is used as gold standard and hence standard methods may be used to estimate sensitivity and specificity. Sensitivity is the proportion of patients who report an improvement on the external criterion (anchor) and whose person reported outcome scores are above the threshold minimal important difference value [1]. Specificity is the proportion of patients who do not report an improvement on the external criterion (anchor) and whose person reported outcome scores are below the threshold minimal important difference value [1]. Receiver operating characteristic (ROC) curves are then used to identify the person reported outcome score with the greatest sensitivity and specificity [6-8].

The distributional-based methods

Distribution-based methods are based on the statistical characteristics of the obtained sample [9]. Crosby et. al [9] have identified two general types of distribution-based methods for estimations of minimal important differences:

- The first type of distribution-based method evaluate change in relation to sample variation [9]. Different types of variation can be used: effect size, standardised response mean, and responsiveness statistic [9]. The effect size represents individual change in relation to the number of pre-test standard deviations (SDs) [9]. Cohen et. al has suggested benchmarks to better interpret the effect sizes: .20 for ''small'' effects, .50 for ''moderate'' effects, and .80 for ''large'' effects [10]. Whereas the effect size is the ratio of individual change to the baseline standard deviation of the sample, standardised response mean is the ratio of individual change to the standard deviation of that change [11]. A large standardised response mean indicates that the change is large in comparison to the background variability in the measurements [9]. Guyatt et. al has proposed a responsiveness statistic as a variation of standardised response mean; calculated by dividing the difference between pre-test and post-test by the standard deviation of change observed for a group of stable participants [12].

- The second type distribution-based method is based on the measurement precision of the instrument [9]. This method include the standard error of the mean (SEM) and evaluate the change in relation to variation of the instrument as opposed to variation in the sample [9]. Standard error of the mean (SEM) is a measure of the precision of a test instrument and considered an attribute of the measure and not a characteristic of the sample per se [13]. The standard error of the mean (SEM) for a given measure is likely to vary across samples depending upon the method used to estimate reliability and the presence of extreme scores [9]. Different thresholds for a minimal important difference have been suggested, i.e., values of 1 SEM [14], 1.96 SEM [15], and 2.77 SEM [13, 15].

In conclusion, different methods for estimating minimal important differences exist, but no single method has been shown to be the optimal method. The question of whether to use anchor-based or distribution-based methods for determining clinically meaningful change has received considerable attention and debate [9]. Dworkin et. al defined the clinical importance of patient improvement as the clinically important changes in individuals that can be identified using either within-patient anchor-based method or distributional-based method [16, 17], while the clinical importance of group differences could be the clinical difference between a treatment group and a placebo group or between two different treatment groups [18]. Dworkin et. al claim that the clinical important difference identified in individuals cannot be directly extrapolated to the evaluation of group differences [17, 19-22]. The U.S. Food and Drug Administration also states in their web site “When defining meaningful change on an individual patient basis, that definition is generally larger than the minimum important difference for application to group mean comparisons” [22].

While it is claimed that the within-patient differences are larger than the between-group difference [22], based on the studies included in our review we are not able to find a significant difference between the minimal important difference estimated by the two different methods.

Previously conducted reviews on this subject

- Lynch & Campbell and Boychuk et. al both concluded that cannabinoids are a modestly effective and a safe treatment option for neuropathic pain [23, 24]. Lynch & Campbell and Boychuk et. al did not publish a protocol on beforehand [23, 24].
- Meng et. al concluded that there is moderate quality evidence to suggest that nabiximols (phytocannabinoid mixture) is effective in reducing neuropathic pain [25].

- Mücke et. al concluded that there is no high-quality evidence for the efficacy of any cannabis-based medicine in any condition with chronic neuropathic pain [26]. Mücke et. al further concluded that some adverse events may limit the clinical usefulness of cannabis-based medicines [26].
- Deshpande et. al concluded that current evidence suggests that very low-dose medical marijuana (< 34 mg/d) is associated with an improvement in refractory neuropathic pain of moderate severity in adults using concurrent analgesics. Deshpande et. al did not publish a protocol on beforehand [27].
- Martín-Sánchez et. al concluded that treatment of chronic pain based on cannabinoid compounds would entail more risk of adverse events than benefit [28]. Martín-Sánchez et. al included trials randomising participants with either neuropathic pain, cancer pain, fibromyalgia related pain and nociceptive pain [28]. Martín-Sánchez et. al did not publish a protocol on beforehand [28].
- Aviram et. al concluded that cannabinoid-based medicines were not effective for postoperative pain, however further investigation is advised [29]. Aviram et. al also concluded that evidence suggests a moderate to good treatment effect on neuropathic pain [29]. Furthermore, neuropathic pain patients should be advised that the inhalation of cannabinoids showed relatively better pain reduction effects than other routes of administration [29]. Aviram et. al stated that the total number of adverse events that were accumulated in the meta-analysis indicated that cannabinoid-based medicines should be used with caution [29]. Aviram et. al did not publish a protocol on beforehand [29].
- Campbell et. al concluded that levonantradol (synthetic cannabinoid analogue) was superior to placebo on postoperative pain but no more effective than codeine [30]. Campbell et. al also stated that there are suggestions of efficacy in spasticity and in neuropathic pain and that increasing the cannabinoid dose to increase the analgesia will increase adverse effects [30]. Campbell et. al did not publish a protocol on beforehand [30].
- Stevens et. al concluded that cannabinoids have no role in the management of acute pain, but cannabinoids were found to be well-tolerated, with most reported adverse effects only mild to moderate in severity [31].
- Walitt et. al concluded that no convincing, unbiased evidence suggests that nabilone (synthetic cannabinoid analog) is of value in treating people with fibromyalgia [32]. The tolerability of nabilone was low and adverse events (particularly somnolence, dizziness, vertigo) may limit its clinical usefulness [32].

TABEL 1

First author	Title	Year of publication	Design	Type of cannabinoid	Types of participants	Information sources	No. of trials	No. of participants	Published protocol	Outcomes	Assessment of adverse events	Assessment of risk of bias	Accounts for random error	Use of the GRADE	Conclusion
Lynch & Campbell [23]	Cannabinoids for treatment of chronic non-cancer pain; a systematic review of rando	2011	Systematic Review	**Phytocannabinoids;** Smoked cannabis, oromucosal extracts of cannabis-based medicine, and **synthetic cannabinoids**; nabilone, dronabin	Neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.	PubMed, EMBASE, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library, ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search	18 trials comparing the intervention with placebo	766	No	The primary outcome was pain in subjects with chronic non-cancer pain. The secondary outcomes were sleep, function, and quality of life.	Yes	Yes, except for reporting bias, publication bias and for-profit bias	No	No	Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy

	mized trials			ol and a novel THC analogue.		Premier (EBSCO), ClinicalTrials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline, OAIster (OCLC) and Google Scholar.									in fibromyalgia and rheumatoid arthritis. Did not pool data for meta-analysis but data was described qualitatively.
Meng et. al [25]	Selective Cannabinoids for Chro	2017	Systematic Review and Meta-	Dronabinol, nabilone and nabiximols	Neuropathic pain	Medline, Embase, Cochrane Library, PROSPERO, clinical	11 (10 trials comparing th	1219	No	The primary outcome was intensity of pain recorded	Yes	Yes	Bonferroni adjustment for multiple testi	Yes	Selective cannabinoids provide a small analgesic bene

	nic Neuropathic Pain: A Systematic Review and Meta-analysis		analysis			trials.gov, and Google Scholar. Pain societies (American Society of Anesthesiologists, European Society of Anaesthesiology, International Association for the Study of Pain, American Society of Regional Anesthesia and Pain Medicine, European	e intervention with placebo)			after a minimum of 2 weeks following initiation of selective cannabinoid and placebo/comparator administration, expressed on an NRS (0—no pain to 10—worst possible pain). Secondary outcomes were presence or absence of analgesia defined as			ng was not performed as per recommendations in the Cochrane Handbook.		fit in patients with chronic neuropathic pain.

						Society of Regional Anesthesia and Pain Therapy, and World Institute of Pain) in the last 2 years were also searched.				reduction in pain scores (NRS/VAS) by ≥30% at 2 weeks or more after initiation of intervention, quality of life (QoL), physical function, psychological function, sleep, overall patient satisfaction, and the incidence of adverse effects of selective cannabinoids.					

Martín-Sánchez et. al [28]	Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain	2009	Meta-analysis	**Phytocannabinoids** and **synthetic derivates of THC**, such as dronabinol, nabilone, or benzopyranopyridine (a synthetic nitrogen analog of THC)	Chronic pain of a pathological or traumatic origin	Medline/Pubmed, Embase, and The Cochrane Controlled Trials Register (CENTRAL)	18	?	No	The primary outcome was intensity of pain as scored by numerical rang scales. The Secondary outcomes were CNS related events	Yes	Yes, except for reporting bias, detection bias and for-profit bias	No	No	Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serio

															us harms.
Boychuk et. al [24]	The Effectiveness of Cannabinoids in the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Re	2015	Systematic Review	**Phytocannabinoids;** smoked cannabis, cannabis-based medicinal extracts (CBME) in the form of oromucosal sprays (nabiximols), vaporized cannabis, and **synthetic cannabinoids;** dron	Neuropathic pain	PubMed, Embase, Web of Science, and all evidence-based medicine reviews and databases (Cochrane Database of Systematic Reviews, ASP Journal Club, Database of Abstracts of Reviews of Effects [DARE], and Cochrane Controlled	13	771	No	Outcomes considered were reduction in pain intensity and adverse events.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabis-based medicinal extracts used in different populations of chronic non-malignant neuropathic pain patients may provide effective analgesia in conditions that are refractory

	view			abinol, nabilone, and CT-3		Trials Register [CCTR])									to other treatments.
Mücke et. al [26]	Cannabis products for adults with chronic neuropathic pain	2018	Cochrane Review	**Phytocannabinoids;** oromucosal spray containing THC or THC/CBD mix, smoked cannabis containing THC, THC and CBD as extract of cannabis sativa L., and **synt**	Neuropathic pain	Cochrane Library, MEDLINE and EMBASE. Following clinical trials databases were searched for additional data including unpublished data**:** US National Institutes of Health clinical trial register (www. Clinical	16 (15 of the trials comparing the intervention with placebo)	1750	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. We preferred composite neuropathic pain scores over single-scale generic pain scores if both measures were used by studies;	Yes	Yes	No	Yes	The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be

				hetic cann abin oids; nabil one, dron abin ol		Trials.gov), European Union Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and International Association for Cannabinoid Medicines (IACM) databank				PGIC (Patient Global Impression of Change) much or very much improved; Withdrawals due to adverse events (tolerability); Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence					outweighed by their potential harms.

						(www.cannabis-med.org/studies/study.php)				or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medica					

										l event' that may jeopardise the person, or may require an intervention to prevent one of the above characteristics/consequences.				
Aviram et. al [29]	Efficacy of Cannabis-Based Medicines for Pain Manage	2017	Meta-Analysis	**Phytocannabinoids;** Sativex/nabiximol, cannabidiol, cannabinoid cigarettes/vaporizer,	Chronic (cancer and non-cancer) pain and acute posto	MEDLINE/Pubmed and in Google Scholar using Medical Subject Heading (MeSH) terms	43 trials comparing the intervention with both 'activ	2437	No	The outcome measure that was chosen was the variable "pain intensity", as scored by the numerical rating scale (NRS-11),	Yes	Yes, except for, reporting bias, publication bias an	No	No	The current systematic review suggests that cannabinoid-based medicines might be effec

	ment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials			and **synthetic cannabinoids**; dronabinol and nabilone, CT-3, ajulemic acid, synthetic nitrogen analog of tetrahydrocannabinol (NIB), fatty acid amide hydrolase-1 (FAAH1) inhibitor (PF-04457845) (bloc	perative pain		edrugs' and placebo			numerical 11-point box (BS-11), visual analog scale (VAS), and the VAS section of the questionnaire short form McGill Pain Questionnaire.		dfor-profit bias			tive for chronic pain treatment, based on limited evidence, primarily for neuropathic pain patients.

				king degradation of endocannabinoids), benzopyranoperidine (BPP), and levonantradol											
Campbell et. al [30]	Are cannabinoids an effective and safe treatment option in the mana	2001	Systematic Review	Oral THC, an oral synthetic nitrogen analogue of THC (NIB), oral benzopyranoperidine (BPP), and intramuscular	Acute, chronic non-malignant pain, and cancer pain	MEDLINE, EMBASE, Oxford Pain Database, and Cochrane Library	9	222	No	Outcome measures for pain intensity; pain relief; the use of supplementary analgesia; patients' preferences; and adverse effects.	Yes	Yes, except for, reporting bias, publication bias and for-pr	No	No	Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the centr

	gement of pain? A qualitative systematic review			levonantradol								ofit bias			al nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used.
Deshpa	Efficac	2015	Syste	Cigarettes	Neur	MEDLINE,	6 tri	226	No	For outco	Yes	Yes,	No	No	There is

nde et. al [27]	y and adverse effects of medical marijuana for chronic noncancer pain		matic Review	or vaporizer containing delta-9-THC	opathic pain	EMBASE, and the International Pharmaceutical Abstracts	als comparing intervention with placebo. Placebo being cigarettes or vaporizer containing 0% delta-9-THC or with ca			mes, pain scores were extracted using the visual analogue scale (VAS) or an alternative numerical pain rating tool. If pain scores were not reported, surrogate measures of effectiveness were included (sleep, function, and quality of life). Frequency of serious and		except for, reporting bias, publication bias and for-profit bias			evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and

							nn abi no id re m ov al			most comm only report ed advers e effects was collect ed.					stren gth of delta -9- tetra hydr ocan nabi nol, and lack of funct ional outc ome s. Altho ugh well toler ated in the short term , the long- term effec ts of psyc hoac tive and neur ocog nitiv e effec ts of medi cal marij

															uana remain unknown.
Stevens et. al [31]	A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain	2017	Systematic Review	Levonantradol, nabilone, AZD1940, GW842166, dronabinol, ▵-9-THC	Acute postoperative pain	MEDLINE, EMBASE, Cochrane Library, and the World Health Organization International Clinical Trials Registry Platform	7 trials comparing intervention with placebo, Ketoprofen, Pethidine, Naproxen, and Ibup	611	Yes	The primary outcome was the qualitative analysis of the analgesic efficacy of cannabinoids in the management of acute pain compared to placebo or active comparator. The secondary outcome was the qualitative	Yes	Yes, except for, publication bias and for-profit bias	No	Yes	Based on the available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain.

							rofen			analysis of the reported adverse effects.					
Walitt et. al [32]	Cannabinoids for fibromyalgia	2016	Cochrane Review	Nabilone	Fibromyalgia	Cochrane Library, MEDLINE and EMBASE	2 trials comparing the intervention with either (1) placebo or (1) amitriptyline	72 (40)	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. PGIC (Patient Global Impression of Change) much or very much improved. Withdrawal due to adverse events	Yes	Yes, except for publication bias.	No	Yes	We found no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone

										(tolerability). Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of					was low in people with fibromyalgia.

										existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the person, or may require an intervention to prevent one of the above					

										characteristics/consequences.					

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	25-26
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	25
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-9
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	10-12
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	12-13
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13-14
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	13
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	13-14
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	14
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	15-17
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	16
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	19-21
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	22-23
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	21
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	17
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	21

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Search strategies for
'Cannabinoids versus placebo for pain'
(J Barakji)
Preliminary searches performed 1 July 2019

Total number of records identified	**4106 records**
Number of duplicates removed	**1079 records**
Number of records in final list	**3027 records**

The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2019, Issue 6) (961 hits)

#1 MeSH descriptor: [Cannabis] explode all trees
#2 MeSH descriptor: [Cannabinoids] explode all trees
#3 (cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid*)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Pain] explode all trees
#6 (pain* or ache* or migraine*)
#7 #5 or #6
#8 #4 and #7

MEDLINE Ovid (1946 to July 2019) (465 hits)

1. exp Cannabis/
2. exp Cannabinoids/
3. (cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid* or 2-AG).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. 1 or 2 or 3
5. exp Pain/
6. (pain* or ache* or migraine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 5 or 6
8. 4 and 7
9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 8 and 9

Embase Ovid (1974 to July 2019) (1829 hits)

1. exp cannabis/
2. exp cannabinoid/
3. (cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid* or 2-AG).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4. 1 or 2 or 3
5. exp pain/
6. (pain* or ache* or migraine*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. 5 or 6
8. 4 and 7
9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. 8 and 9

LILACS (Bireme; 1982 to July 2019) (51 hits)

(cannabi$ or mari$uana or nabixmol$ or dronabinol$ or marinol$ or nabilon$ or cesamet$ or hash$ or hemp$ or levonantradol$ or anandamid$ or 2-AG) [Words] and (pain$ or ache$ or migraine$) [Words]

Science Citation Index Expanded (1900 to July 2019) and Conference Proceedings Citation Index – Science (1990 to July 2019) (Web of Science) (623 hits)
#5 #4 AND #3
#4 TS=(random* or blind* or placebo* or meta-analys*)
#3 #2 AND #1
#2 TS=(pain* or ache* or migraine*)
#1 TS=(cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid* or 2-AG)

BIOSIS (1969 to July 2019; Web of Science) (177 hits)
#5 #4 AND #3
#4 TS=(random* or blind* or placebo* or meta-analys*)
#3 #2 AND #1
#2 TS=(pain* or ache* or migraine*)
#1 TS=(cannabi* or mari*uana or nabixmol* or dronabinol* or marinol* or nabilon* or cesamet* or hash* or hemp* or levonantradol* or anandamid* or 2-AG)