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Cannabis and cannabinoids for people with multiple sclerosis (Protocol)

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[Intervention Protocol]

Cannabis and cannabinoids for people with multiple sclerosis

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ABSTRACT

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

To assess benefit and safety of cannabis-based medicines, including synthetic, or herbal and plant-derived cannabinoids, for people with MS.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) that leads to a progressive functional decline. The worldwide prevalence of MS is reported to be 50 to 300 per 100,000 people. About 2.3 million people are estimated to live with MS globally, although this number may be underestimated because data are lacking from large populations, such as populations in India and China (Thompson 2018a). Although the aetiology of MS remains unknown, associations with genetic, environmental, and lifestyle factors have been reported (Thompson 2018a). MS is commonly classified into different forms: relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive-relapsing (PRMS). Symptoms vary widely from person to person, and include fatigue, muscle painful spasms and stiffness, weakness, chronic neuropathic and musculoskeletal pain, mobility restrictions, visual impairment, depression, anxiety, and bladder and bowel dysfunction (Newsome 2017; Rommer 2018).

People with MS have multiple symptoms; for example, people with spasticity may also have chronic pain resulting from their spasticity. Therefore it is necessary to consider the overlap of indications people have when use a symptomatic treatment. Spasticity (muscle stiffness) is a common and serious feature of MS that increases with disease progression and leads to disability worsening, weakness, and fatigability. Adaptive features may develop including contractures in muscle, tendons, and joints which can further worsen limb positioning, movement, and function. Spasticity causes also pain, bed sore, fatigue, instability, and difficulties in maintaining hygiene. Treatment with anti-spasticity medication is made for different reasons in people with MS. People with severe mobility disability are treated for symptomatic relief (pain and spasms) and are treated in order to make nursing care and seating easier. Those who are able to walk are treated with the additional aim of improving or preserving mobility (Amatya 2013; Shakespeare 2003). Chronic neuropathic pain occurs in more than half of people with MS and is directly related to MS pathology (Newsome 2017).

Description of the intervention

Cannabis is a plant (*Cannabis sativa*) that contains over 120 phytocannabinoids. The most well-known cannabinoids are: delta-9-tetrahydrocannabinol (THC), which produces a variety of effects including altered cognition and motor function, analgesia, psychotropic effects; and cannabidiol (CBD), a non-psychoactive molecule (Hazekamp 2018; Izzo 2009; Morales 2017). Several standardized medicinal cannabis-based products are currently manufactured. Nabiximols (Sativex) is made from extracts of *Cannabis sativa* plant and contains an equal mix of the cannabinoids THC and CBD. It is taken as an oral spray. Bedrocan and Bedrobinol are standardized preparations of cannabis flowers containing a CBD-level below 1% (in both preparation) and 22% and 13.5% THC, respectively. Bediol (6.3% THC and 8% CBD) and Bedrolite (less than 1% THC and 9% CBD) are standardized cannabis flowers both available in granular form. Bedica, featuring 14% THC and less than 1% CBD, is a standardized preparation, available in granular form, obtained from the variety indica of Cannabis flowers. Dronabinol (Marinol or Syndros) is a plant-derived cannabinoid containing synthetic delta-9-THC. It is administered as oral capsules or oral solution. Nabilone (Cesamet or Canemes) is a synthetic THC analogue and it is administered as oral capsules. Both Dronabinol and Dabilone and other synthetic compounds, which are identical in structure to naturally occurring cannabinoids such as THC, have been evaluated in many studies that have investigated medicinal cannabis.

A titration period is required to reach optimal dose of nabiximols. The number and timing of sprays vary between patients. The dose is gradually increased by one spray per day, up to a maximum of 12 sprays per day, until optimum symptom relief is achieved. The median dose in clinical trials for people with MS is eight sprays per day. After oral administration of nabiximols, plasma levels of THC and other cannabinoids are lower compared with the levels achieved following smoking or inhalation of cannabinoids at a similar dose. According to the literature, elimination of oral cannabinoids from plasma is biphasic with an initial half-life of approximately four hours, and the terminal elimination half-lives are of the order of 24 to 36 hours or longer due to its slow release from fatty tissue (MHRA 2014).

An international survey found that MS was one of the five medical conditions for which cannabinoids were most often used; with back pain, sleep disorders, depression, and post-injury pain being the other four conditions (Hazekamp 2013). The UK MS Society conducted a survey of 3994 people with MS from across the UK in September 2014, requesting their attitudes and experiences of cannabis and Sativex. The survey was conducted anonymously through various channels to capture the range of experiences and views that people with MS hold. More than 1 in 5 people (22%) reported they had used cannabis to try to manage their MS symptoms and 7% of those surveyed were still using cannabis. Most people (56%) currently using cannabis for medicinal purposes felt that the benefits outweighed the side effects. Of those currently using cannabis, 40% were doing so because they were unable to obtain a prescription for a licensed alternative. Medical cannabis use was associated with recreational cannabis use. The symptoms reported by medical cannabis users to be most effectively relieved were stress, sleep, mood, stiffness/spasm, and pain (MS Society 2014). A recent internet-based survey in the USA found that 66% of people with MS used cannabis for symptom treatment (Kindred 2017), and a study from Canada reported that about 50% of people with MS would consider the legal use of cannabis if evidence of benefit is available (Banwell 2016).

How the intervention might work

Plant-derived and synthetic cannabinoids exert their biological effects primarily via interaction with the endocannabinoid system which includes cannabinoid receptors (CB1 and CB2), endogenous cannabinoids (endocannabinoids, chiefly anandamide (AEA) and 2-arachidonoylglycerol (2-AG)), and the enzymes responsible for the synthesis and degradation of the endocannabinoids (Di Marzo 2018; Kaur 2016; Papaseit 2018). Transient receptor potential (TRP) channels, peroxisome proliferator activated receptors (PPARs), glycine receptors, and the orphan G protein-coupled receptors (GPR55 and GPR18) are also engaged by cannabinoids (Morales 2017). The psychoactive effects of cannabis are mainly due to the presence of THC. THC binds to cannabinoid receptors CB1 and CB2, acting as a partial agonist. CB1 receptors are located in the CNS (cerebral cortex, hippocampus, basal ganglia, and cerebellum) and are involved in memory processing, motor function, appetite, and sensory perception. CB2 receptors are essentially expressed in immune cells and they have been attributed a role modulating the immune response. Cannabinoids have been considered to have the potential to affect both pathogenic mechanisms and symptoms of

MS due to their ability to suppress neuroinflammation (via CB2 activation) (Mestre 2018), and to exert neuroprotective effects in the CNS (via CB1 activation) (Constantinescu 2018; Gowran 2011; Kaur 2016; Mecha 2019). The effect of cannabinoids on the immune system may also play a role, in the light of the autoimmune hypothesis of MS etiology (Fitzpatrick 2017; Mestre 2018; Oláh 2017).

Why it is important to do this review

Results of available surveys show that the demand of people with MS for symptomatic treatment with cannabis-based medicines is high, even though these medicines are unavailable in the usual way (Banwell 2016; Hazekamp 2013; Kindred 2017; MS Society 2014). Many people with MS have a combination of pain and spasticity and would benefit from a symptomatic treatment. Available therapies that relieve the disabling symptoms of MS include botulinum toxin injections, baclofen or tizanidine for spasticity, anticonvulsants, antidepressant or analgesic medications for neuropathic pain, and anticholinergic drugs for bladder dysfunction. However, these symptomatic therapies are of limited efficacy or are often poorly tolerated (Mücke 2018; Newsome 2017). Moreover, many patients with MS have a combination of symptoms, e.g. pain and spasticity, and would benefit from a cannabis-based medicine that could have an overlap of indications.

Recent systematic reviews on the use of cannabis-based medicines in people with MS reported different conclusions on safety and benefit of these medicines in spasticity, chronic neuropathic pain, bladder dysfunction, and other symptoms (Amato 2017; Davies 2018; HPRA 2017; Koppel 2014; Lynch 2015; Meza 2017; Mücke 2018; NASEM 2017; Nielsen 2018; Whiting 2015; WHO 2018). Conclusive or substantial evidence that oral cannabinoids are effective for improving patient-reported MS spasticity or pain symptoms was reported by several studies (Amato 2017; HPRA 2017; NASEM 2017; moderate-quality evidence was reported by Whiting 2015; low- to moderate-quality evidence by the Australian Government 2017, whose results were based on an overview of 11 systematic reviews by Nielsen 2018). The overview by Nielsen 2018 reported modest effects in MS for pain or spasticity. Meza 2017 concluded that cannabinoids did not reduce spasticity or pain in MS and the certainty of the evidence was high. Mücke 2018 concluded that the potential benefits of cannabis-based medicine in chronic neuropathic pain might be outweighed by their potential harms. Discrepancies between the results and conclusions of these reviews are expected since they used different eligibility criteria of study design, participants, and outcomes measures and different analytic methods. Moreover, the search strategy of these reviews was updated to the end of 2016 and new studies are available for inclusion in our review (Table 1).

International guidelines have reached different recommendations on the use of cannabis-based medicines in people with MS. The NICE guidelines did not recommend nabiximols for MS on cost-effectiveness grounds for the NHS in England, Scotland, and Northern Ireland (NICE 2014). However, nabiximols is considered cost-effective in Wales. A new review and a guideline scoping document on cannabis-based medicines is in development (NICE 2019). The Association of British Neurologists on the use of cannabis-based products in neurology advised clinicians to use nabiximols only in people with MS who have had an unsatisfactory response to conventional spasticity drugs (ABN 2018; RCP 2018). The American Academy of Neurology does not support the legalization or prescribing of medical marijuana for use in MS, but supports scientific research to investigate the safety and potential benefits (AAN 2018). The Food and Drug Administration (FDA) has not approved any marketing application for cannabis-based medicine for MS, but was recently asked to place cannabis-based therapy for progressive MS on the fast track (Reston 2019). The European Medicines Agency (EMA) authorized in 2014 the use of nabiximols for the management of moderate to severe spasticity in adults with MS who have not responded to conventional treatment, and who show clear clinical improvement in the initial period with this therapy (EMA 2014). The guidance released in 2018 by the Australian Government Department of Health recommended to use cannabis-based medicines in people with MS who have not responded adequately to other anti-spasticity medication (Australian Government 2017).

There are differences between countries in the legal authorization and use of medical cannabis for MS. Nabiximols is approved and available for MS related spasticity in Canada, the USA, Israel, and 21 European countries and it is reimbursed by health insurance companies or state social security systems in 11 European countries (Austria, Belgium, Germany, Israel, Italy, Portugal, San Marino, Spain, Turkey, UK, and Norway) (Abuhasira 2018; Krcevski-Skvarc 2018). Approval of cannabis-based medicines (i.e. the cannabis flowers Bedrocan, Bediol, Bedica, Bedrobinol, Bedrolite) for treatment of chronic neuropathic pain that is refractory to conventional treatment is available in Canada, Croatia, Czech Republic, Denmark, Germany, Israel, Italy, the Netherlands, Norway, Serbia, Slovenia, and Switzerland, but with striking differences in legal and reimbursement rules (Krcevski-Skvarc 2018). Medical cannabis can be prescribed to people with MS under strict controlled conditions, but there are differences between countries on who can and cannot prescribe cannabis-based medicines, e.g. in the UK nabiximols can be prescribed only by specialist doctors with expertise in treating MS.

The legalization of cannabis has allowed new studies to be carried out and therefore new clinical data are available. The evidence that will come from these studies (if they are positive) might encourage the legalization of medicinal cannabis in countries where cannabis is not yet legal.

There is a growing interest into the therapeutic benefit of cannabis-based medicines in the treatment of illness including MS. Following the review of the Chief Medical Advisor to the UK Government, on 1 November 2018, unlicensed cannabis based products were moved from Schedule 1 to Schedule 2 in the UK. This decision would allow cannabis medicines to be prescribed under controlled conditions by registered practitioners for medical benefit. In addition, moving the whole class of cannabis based medicinal products out of Schedule 1, will allow the evidence base on the therapeutic benefits associated with using this class of drugs to be improved through research, maximising benefits to patients. enabling them to be prescribed for the first time (Davies 2018). Moreover, the FDA recently asked to place cannabis-based therapy for progressive MS on fast track (Reston 2019).

Due to the conflicting conclusions of recent systematic reviews on the benefit and safety of cannabis-based medicines for symptomatic treatment of MS, as well as different recommendations in international guidelines, we see the need for a Cochrane Review undertaken according to rigorous standards.

OBJECTIVES

To assess benefit and safety of cannabis-based medicines, including synthetic, or herbal and plant-derived cannabinoids, for people with MS.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized parallel or cross-over trials (RCTs). We will include cross-over trials irrespective of the length of the washout period.

Types of participants

We will include adults, males and females (18 years or older), diagnosed with MS, according to the Poser (Poser 1983) or McDonald criteria and its revisions (McDonald 2001; Polman 2005; Polman 2011; Thompson 2018b), and all types of MS such as RRMS, SPMS, PPMS, and PRMS. We will include participants regardless of disease duration and disability degree.

Types of interventions

Any cannabinoid-based medicine including herbal cannabis (e.g. marijuana), cannabis flowers (Bedrocan, Bedrobinol, Bediol, Bedrolite, Bedica), plant-based cannabinoids (Nabiximols, Cannabidiol), or synthetic cannabinoids (Dronabinol, Nabilone), irrespective of dose, route, frequency, or duration of use. We will include as a comparison intervention placebo or any active comparator. We will include concomitant interventions if they were used in all the comparison groups.

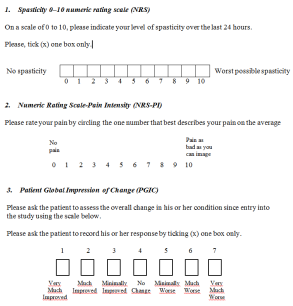
Types of outcome measures

We will include patient-reported outcomes as critical or important outcomes, because the primary scope and aim of this Cochrane Review is to assess the effects of the intervention on symptoms such as chronic pain and functional limitations due to spasticity. These symptoms are better known to the patients themselves than to clinicians, and the patients' perspective on treatment benefit is a priority. We will include short- and long-term outcomes reported in the included trials.

1. Critical outcomes

- Spasticity: number of participants reporting reduction of 30% in the spasticity Numeric Rating Scale (NRS), over baseline. This reduction has been identified as a change that represented a minimum clinically important difference (MCID) in participants with MS–related spasticity (Farrar 2008). NRS is a patient-rated measure of the perceived severity of spasticity. Scores range from 0 (no spasticity) to 10 (worst possible spasticity) (Figure 1).

Figure 1. Spasticity and Pain scales; Patient Global Impression of Change



- Chronic neuropathic pain: number of participants reporting pain relief of 50% or greater, over baseline. According to Cochrane Pain, Palliative and Supportive Care (Moore 2010), we will prefer composite neuropathic pain scores (e.g. pain intensity and physical function) over single-scale generic pain scores if both measures were used by studies, or the Numeric Rating Scale-Pain Intensity (NRS-PI), a 0 to 10 rating scale with scores ranging from 0 ‘no pain' to 10 ‘worst possible pain' (Farrar 2010; Figure 1).

Where studies measure these outcomes as continuous data only, we will include them as separate analyses as important outcomes.

- Number of participants withdrawn due to adverse events (tolerability).

2. Important outcomes

- Patient Global Impression of Change (PGIC): number of participants reporting much or very much improvement in the PGIC. PGIC provides a patient reported assessment of overall change in health status on a seven point categorical scale with scores ranging from 1 (very much improved) to 7 (very much worse) (Guy 1976; Farrar 2008; Dworkin 2008) (Figure 1).
- Quality of life, e.g. Multiple Sclerosis Quality of Life-54 (MSQOL-54) (Vickrey 1995) or other QOL validated measures reported in the included studies. MSQOL-54 is a multidimensional health-related quality of life measure.The questionnaire includes the generic Short-Form 36-item QoL instrument, supplemented with 18 MS-specific items that were based on expert opinion and literature review. There is no single overall score for MSQOL-54. Two summary scores — physical health and mental health — can be derived from a weighted combination of scale scores (scale scores range from 0 to 100 and a higher scale score indicates improved quality of life). No MCIDs were identified for the summary scores.

Where studies measure these outcomes as continuous data only, we will include them as separate analyses as outcomes of limited importance.

- The total number of serious adverse events (SAEs). If an insufficient number of studies reported the total number of SAEs and

person-years, we plan to use the number of participants with at least one SAE as defined in the study.

- Number of participants reporting specific adverse events, including nervous system (e.g. cognitive dysfunction, dizziness, somnolence, headache), psychiatric disorders (e.g. confusion state; paranoia, psychosis), and physical dependence effects (e.g. withdrawal and tolerance) according to the Medical Dictionary for Regulatory Activities (MedDRA) (ICH 2019), or as reported in the included studies.

3. Outcomes of limited importance

- Reduction in spasticity measured by clinical reported measure, e.g. the Ashworth scale (Ashworth 1964) or Modified Ashworth (MAS) (Ansari 2009), or the Tardieu or Modified Tardieu scale (Ansari 2008).
- Participant-reported pain relief of 30% or greater in a composite neuropathic pain scale or in a single generic pain scale, e.g. the NRS-PI (0-10 NRS-PI).
- Improvement of bladder symptoms measured by patient reported outcome, e.g. the Overactive Bladder questionnaire (OAB-q) (Coyne 2005).
- Participant-reported frequency and severity of spasms, e.g. Penn Spasm Frequency Scale (Penn 1989).
- Fatigue, e.g. questionnaire Modified-Fatigue Impact Scale (M-FIS) (Multiple Sclerosis Council 1998). M-FIS is a 21-item multidimensional questionnaire that measures the physical, cognitive, and psychosocial impact of fatigue using a five-point ordinal scale (range 0 to 84). Higher scores indicate greater impact or severity of fatigue symptoms. A difference of four points on the M-FIS as been identified as a clinically significant difference in fatigue (Rooney 2019).
- Sleep problems, e.g. the NRS (0-10 NRS).
- Improvement of mobility, balance, and daily functioning, specifically the activities of daily living (ADL), e.g. Barthel index (BI) (Mahoney 1965) or timed 10-metre walk test (Kempen 2011).
- Depression and anxiety measured by validated scales, e.g. the Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983).
- Caregiver's global impression of change (CGIC), rating ease of transfer, dressing, and perineal hygiene (Collin 2010).
- Reduced use of other symptomatic treatments (e.g. for spasticity or pain).

Search methods for identification of studies

Electronic searches

We will search the following databases:

- The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (latest issue).
- MEDLINE (PubMed) (1966 to date).
- Embase (1974 to date).
- CINAHL (EBSCO host) (1981 to date).
- LILACS (Bireme) (1982 to date).
- Physiotherapy Evidence Database (PEDro) (1990 to date).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch).
- US National Institutes of Health clinical trial register (www.ClinicalTrials.gov).
- European Union Clinical Trials Register (www.clinicaltrialsregister.eu).
- International Association for Cannabinoid Medicines (IACM) databank (www.cannabis-med.org/studies/study.php).

Information on the Group's Trials Register and details of search strategies used to identify trials can be found in the Specialized Register section on the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group's website (https://msrd-cns.cochrane.org/). We have listed the keywords that we will use for the electronic search in Appendix 1.

Searching other resources

We will review the references of any RCTs identified, review articles, and textbooks. We will contact study investigators to request missing data.

Data collection and analysis

Selection of studies

We will use the search strategy described in the 'Search methods for identification of studies' section to obtain titles and abstracts of studies. Two review authors (FB and GF) will independently screen the titles and abstracts and discard studies that are not applicable; however, they will initially retain studies and reviews that might include relevant data or information on trials. Two review authors (FB and AAI) will independently assess the retrieved abstracts and, when necessary, the full-text articles to determine which studies satisfy the inclusion criteria. The two review authors will compare multiple reports of the same study and use the most comprehensive report. They will link together multiple publications as companion reports, but exclude true duplicates. FB and AAI will resolve discrepancies in judgement by discussion with a third review author (GF), and will report excluded studies and their reasons for exclusion in the 'Characteristics of excluded studies' table. We will create a PRISMA flow chart reporting the selection process (Moher 2009).

Data extraction and management

Two review authors (FB and AAI) will independently extract data using a predefined data extraction form in an Excel spreadsheet. They will resolve any disagreements by discussion with a third review author (GF). When necessary data are unavailable from the study report, we will try to obtain them through correspondence with the study authors.

Outcome data

We will extract from each included study the number of participants who:

- had reduction of 30% in the spasticity NRS, or the PGIC much or very much improved;
- had pain relief of 50% or greater in a composite neuropathic pain score, or in the NRS-PI, or PGIC much or very much improved;
- withdrew due to any adverse event;
- had at least one SAE;
- measures and results of the secondary outcomes (Secondary outcomes) that were reported in the included studies.

For the spasticity and pain relief outcomes, we will extract from cross-over trials the number of participants who:

- improved with both treatments;
- improved with experimental treatment, deteriorated with control treatment;
- improved with control treatment, deteriorated with experimental treatment;
- deteriorated with both treatments.

For the adverse event outcomes, we will extract from cross-over trials the number of withdrawals due to any AE, and the number of SAEs on each treatment in each treatment period (if possible).

For continuous outcomes we will extract mean and standard deviation of the comparison groups, where possible, and between-period correlation in cross-over studies. To analyse carry-over, where possible, we will extract also mean and standard deviation by sequence in period I and period II.

We will extract the authors' definition of spasticity, neuropathic pain, and secondary outcomes included in the review. We will extract the measure used in the trial to assess each reported outcome. We will extract arm-level data when possible. When arm-level data are not available we will extract effect sizes. We will extract data at the authors' defined timing points.

Data on potential effect modifiers

We will extract data on the following potential effect modifiers from each included study:

- population: types of MS (RRMS, SPMS, PPMS, and PRMS), disability, spasticity, and pain score baseline; prior or actual or both treatment with anti-spasticity or analgesic or both; prior cannabis use; duration of spasticity or pain or both;
- study design: placebo or active control; co-therapies allowed; rescue medication; study duration (less than four weeks; 4 to 12 weeks; 13 to 26 weeks; more than 26 weeks);
- intervention: drug, dose, frequency, or duration of treatment.

Other data

From each included study we will extract data on the following:

- study: first author or acronym; number of centres; year of publication; years that the study was conducted (recruitment and follow-up); publication (full-text publication, abstract publication, unpublished data);
- study design (parallel or cross-over); inclusion and exclusion criteria; number of randomized participants; early termination of trial;
- conflict of interests of study authors;
- funding of the study.

We will extract length of the washout period in cross-over trials.

Assessment of risk of bias in included studies

For the scope of this review, we will assess the effect of the assignment to the intervention ("Intention to treat effect") for critical and important outcomes. For the total number of SAEs and specific adverse events we will assess the effect of adhering to the intervention ('per protocol effect').

Three review authors (SM, GF, and TL) will independently assess the risk of bias of each included study using version 2 of the Cochrane 'Risk of bias' tool (RoB2) for both parallel and cross-over trials (Higgins 2019). We will assess RoB2 for the critical and important outcomes reported in the 'Summary of findings' table. RoB2 assesses:

- bias arising from the randomization process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome;
- bias in selection of the reported result.

Additional considerations for cross-over trials include (Higgins 2016):

- period effect;
- carryover effect;
- selection of the reported results, i.e. selective reporting of first period data on the basis of a test for carry-over (Freeman 1989).

To implement RoB2 assessment, we will use the Excel tool available at: drive.google.com/file/d/18ilz6dx9voaTGH1mb_UN8WFTaic9-p9z/view?usp=drive_open.

We will judge each domain as being at low risk of bias, some concerns, or high risk of bias. We will reach an overall risk of bias of each included study according to the following criteria:

- low risk of bias: low risk of bias for all domains;
- some concerns: some concerns in at least one domain, but not at high risk of bias for any domain;
- high risk of bias: high risk of bias in at least one domain or some concerns for multiple domains in a way that substantially lowers confidence in the result.

We will assess characteristics associated with the monitoring and reporting of adverse events considering specific factors that may have a large influence on adverse event data. We will evaluate methods of monitoring and detecting adverse events in each primary study:

- did the researchers actively monitor for adverse events, or did they simply provide spontaneous reporting of adverse events that arose?
- did the authors define adverse events according to an accepted international classification and report the number of SAEs?

We will report this information in an additional table called 'Assessment of adverse events monitoring'.

We will resolve any disagreement by discussion to reach consensus and, if needed, by discussion with a fourth review author (RD).

Measures of treatment effect

We will calculate dichotomous outcomes as odds ratios (OR) and 95% confidence intervals (CIs) for parallel and cross-over trials. We will attempt to analyse paired data from cross-over trials given that spasticity and chronic neuropathic pain do not resolve over time in people with MS. For continuous outcomes, we will calculate mean difference (MD) or standardized mean difference (SMD) for the same continuous outcome measured with different metric. We will back calculate any results that we generate with a SMD based on scales that most closely reflect the outcome measure of interest to the review as listed under secondary outcomes.

Unit of analysis issues

Studies with multiple treatment groups

For multi-arm trials, the intervention groups of relevance will be all those that could be included in a pairwise comparison of intervention groups which, if investigated alone, would meet the review inclusion criteria. For example, if we identify a study comparing 'Nabiximols versus tizanidine versus nabiximols plus tizanidine', only one comparison ('Nabiximols versus tizanidine') would be used since it addresses the review objective. Thus, data from the 'Nabiximols plus tizanidine' treatment group is not relevant to the review. However, if the study compares 'Nabiximols versus tizanidine versus baclofen', all three pairwise comparisons of interventions are relevant to the review. In this case we will treat the multi-arm studies as multiple independent two-arm studies. We will convert multi-arm trials involving the same agent at different doses compared to a control treatment into a single arm by merging of doses and summing the number of participants who had the event and the sample size. For continuous outcomes, we will combine means and standard deviations using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over studies

We will enter MD and standard errors from paired data for cross-over studies with the generic inverse variance (GIV) function in Review Manager 5 (RevMan 5) (Review Manager 2014). We will assume that participants unavailable for primary outcome assessment had not improved, as that is probably a conservative estimate effect. We will conduct sensitivity analyses to explore this assumption.

Dealing with missing data

We will use data that reflect the intention-to-treat (ITT) analysis for each included outcome with the exception of safety outcomes where assessment of risk of bias will be in relation to the effect of assignment. We will attempt to retrieve missing data from study authors. In order to assess the effect of missing outcome data where not reported or provided, we will assume that treated and control group participants who are missing both had an unfavourable outcome. For continuous outcomes, where standard deviations are missing, we will calculate them according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

Assessment of clinical heterogeneity within treatment comparisons

To evaluate the presence of heterogeneity deriving from different characteristics of study participants, where possible we will assess differences in types of MS; disability; spasticity and pain score at baseline; duration of spasticity, or pain, or both; prior, or actual, or both treatment with anti-spasticity, or analgesic, or both; prior cannabis use; type of interventions across the trials, using information reported in the 'Characteristics of included studies' table. We will assess differences in design and duration of included studies.

Assessment of statistical heterogeneity

We will assess the presence of statistical heterogeneity using the I^2 statistic. When the I^2 statistic value is greater than 50% (substantial heterogeneity), we will consider possible reasons for this by performing subgroup and sensitivity analyses.

Assessment of reporting biases

We will evaluate the possibility of reporting bias by means of contour-enhanced funnel plots (Peters 2008). Contour-enhanced funnel plots show areas of statistical significance, and can help in distinguishing reporting bias from other possible reasons for asymmetry. Note that any asymmetry in the plot indicates the presence of small study effects and not necessarily reporting bias.

Data synthesis

We will combine data from parallel-group and cross-over trials. For dichotomous outcomes, we will combine ORs with 95% CIs from parallel and cross-over trials according to the method of Becker 1993 that combines lnORs from parallel trials with marginal cross-over lnORs, which are estimators independent from the correlation, where these data are available (Becker 1993; Curtin 2002). We will report adverse event outcomes narratively if a quantitative analysis is not possible.

For continuous outcomes, we will calculate MD or SMD, if the outcome is measured on different assessment scales (such as pain), with 95% CIs. We will use a random-effects model because we assume that the studies are not all estimating the same intervention effect, and are estimating intervention effects that follow a distribution across studies (DerSimonian 1986). We will conduct analyses using RevMan 5 and Stata (Review Manager 2014; Stata).

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses for efficacy outcomes by using the following effect modifiers as possible sources of heterogeneity:

- population: types of MS, disability, spasticity, and pain score baseline; prior or actual or both treatment with anti-spasticity or analgesic or both; prior cannabis use;
- study design: parallel or cross-over; co-therapies allowed; rescue medication;
- study duration: very short-term (less than four weeks), short-term (4 to 12 weeks), intermediate-term (13 to 26 weeks), and long-term (more than 26 weeks);
- intervention: different cannabis-based medicine; CBD only product versus THC only product, versus THC-CBD combination; herbal product versus pharmaceutical products;
- intervention: different dose, frequency, or duration of treatment.

We will restrict subgroup analyses to outcomes that have a sufficient number of studies available. We will consider the relevance of subgroups where at least 10 studies for a subgroup analysis are available. We will interpret the results with caution.

Sensitivity analysis

We will assess the impact of studies that have results for critical and important outcomes that we judge to be at high risk of bias or to raise some concerns in at least one domain of RoB2, by removing them from the analysis. We will use the sensitivity analyses to inform the downgrading decisions relating to risk of bias.

We will consider different assumptions relating to missing outcome as the basis for sensitivity analyses.

Assessing the certainty of evidence and 'Summary of findings' tables

We will present the main results of the review as 'Summary of findings' tables, according to Cochrane guidance (Schünemann 2011). We will provide estimates based on the methodology developed from the GRADE Working Group (Atkins 2004).

In the 'Summary of findings' tables we will include comparison of cannabinoids with placebo and an overall assessment of the evidence for critical and important outcomes :

- number of participants reporting reduction of 30% in the spasticity NRS;
- number of participants reporting pain relief of 50% or greater in the NRS-PI;
- number of participants reporting much or very much improvement in the Patient Global Impression of Change (PGIC);
- number of participant reporting improvement in quality of life;
- number of participants withdrawn due to adverse events (tolerability);
- total number of SAEs;
- number of participants reporting specific adverse events including nervous system disorders, psychiatric disorders, or physical dependence.

In the SoF, we will prioritise long-term outcomes if they will be available, otherwise we will include short term outcomes.

We will assess the certainty of evidence for each outcome considering risk of bias, indirectness, inconsistency, imprecision of effect estimates, and risk of publication bias. Using GRADEpro GDT software, GRADEpro GDT, we will assign one of four levels of certainty of evidence: high, moderate, low, or very low.

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ADDITIONAL TABLES

Table 1. Published systematic reviews on the use of cannabis-based medicines in people with MS

Author year country	SR (search)	Included studies	Interventions	Primary outcomes	RoB/quality	Meta-analysis	Conclusion
Amato 2017 Italy	SR: yes (updated September 2016)	RCTs (n 15) Parallel and cross-over	• Cannabis in any dose, used either as monotherapy or adjunct to conventional drugs • Placebo	• Spasticity - Ashworth scale* - NRS scale • Pain • Quality of sleep	RoB GRADE	Yes	Concerning the efficacy of cannabis (compared with placebo) in patients with MS. Quality or confidence in the estimate was high in favour of cannabis for spasticity (NRS and VAS scales but not the Ashworth scale) and pain but not for sleep (confidence in estimate moderate).
HPRA 2017 Ireland	SR: no Source: Barnes 2016 commissioned by the UK All-Party Parliamentary Group (APPG) and other reports	–	–	–	Criteria of the American Academy of Neurology	No	The scientific evidence, and the availability of an authorized medicine, support the use of cannabis in the treatment of spasticity associated with MS, where other treatments have failed.
NASEM 2017 USA	SR: yes (January 1999 to August 2016) Source: Koppel 2014; Whiting 2015 Updated search to 2016	• RCTs parallel (Koppel 2014; Whiting 2015) and cross-over (Koppel 2014) • Non randomised studies	• All types of plant derived and synthetic cannabis • Placebo	• Spasticity - Ashworth scale - NRS scale • Pain	RoB Newcastle-Ontario scale. Five weight-of-evidence categories	No (reported results of Whiting	Conclusion 4-1. There is substantial evidence that cannabis is an effective treatment for chronic pain in adults. Conclusion 4-7. There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported MS spasticity symptoms (NRS), but limited evidence for an effect on clinician-measured spasticity (Ashworth scale).*
Whiting 2015	S: yes (up to April 2015)	RCTs parallel and cross-over	• Cannabinoids	• Spasticity	RoB GRADE	Yes	• Cannabinoids (nabilone and nabiximols) were associated with a greater average improvement

Table 1. Published systematic reviews on the use of cannabis-based medicines in people with MS *(Continued)*

UK		Pain: 1 RCT Spasticity: 11 RCTs (2138 participants)	• Usual care, placebo, or no treatment	- Ashworth scale - NRS scale • Pain			in spasticity assessed using numerical rating scales (MD −0.76 (95% CI −1.38 to −0.14; 3 trials). There was no evidence of a difference in association according to type of cannabinoid for either analysis. • Cannabinoids (nabiximols, dronabinol, and THC/CBD) were associated with a greater average improvement on the Ashworth scale* for spasticity compared with placebo, although this did not reach statistical significance (WMD, −0.12, 95% CI, −0.24 to 0.01; 5 trials). • The average number of patients who reported an improvement on a global impression of change score was also greater with nabiximols than placebo (OR 1.44, 95% CI 1.07 to 1.94; 3 trials). This was supported by a further crossover trial of dronabinol and oral THC/CBD that provided continuous data for this outcome (Killestein 2002). • Sensitivity analyses that included crossover trials showed results consistent with those based on parallel group trials alone. Conclusion: there was moderate quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity.
Australian Government 2017	Based on overview of Nielsen 2018 and qualitative reviews done by 5 working groups	–	–	–	–	–	• Overall, there is low to moderate quality evidence that suggests pharmaceutical-grade THC (dronabinol or THC extract) is effective for treating symptoms of pain. • THC:CBD (nabiximols, Sativex) may be effective for treating symptoms of pain and spasticity in MS, in certain patient populations. • Findings were mixed as to whether cannabinoids assisted in improving bladder function, sleep, patient quality of life, ataxia or tremor, and disability/disease progression.

Table 1. Published systematic reviews on the use of cannabis-based medicines in people with MS *(Continued)*

							• No studies included active alternatives (non-cannabinoid medicines) as comparators, which is an important limitation.
Nielsen 2018 Australia	Yes, overview (1980 up to 30 November 2016)	SR (n = 11) (AMSTAR criteria 3 and 6). Included studies RCTs and non randomised studies	• Plant-based and pharmaceutical cannabinoids	• Disability and disability progression • Pain • Spasticity • Bladder function • Ataxia and tremor • Sleep • Quality of life • Adverse effects	SIGN (for the reviews) GRADE	No	Recent high-quality reviews find cannabinoids may have modest effects in MS for pain or spasticity.
Meza 2017 Chile	Epistemonikos database	SRs (n = 25) Spasticity: 4 RCTs (1247 participants) Pain: 3 RCTs (327 participants)	–	• Pain: evaluated according to VAS or NRS • Bladder dysfunction: evaluated according to NRS or irritative symptoms •Spasticity: evaluated according to Ashworth scale* or NRS • Adverse effects: such as sedation, dizziness, headache, euphoria, among others • Quality of life: according to subjective evaluation by participants • Coordination: according to subjective	GRADE	Yes	• Cannabinoids do not reduce spasticity in MS. The certainty of the evidence is high. • Cannabinoids do not reduce pain in MS. The certainty of the evidence is high. • Cannabinoids are associated to adverse effects, which are probably frequent in MS. The certainty of the evidence is moderate.

Table 1. Published systematic reviews on the use of cannabis-based medicines in people with MS *(Continued)*

				evaluation by participants • Mobility: according to subjective evaluation by participants • Others: sleep quality, tremor, posture and balance, dependence			
Mücke 2018 Germany	Cochrane Review	RCTs. Parallel, cross-over, and enriched enrolment randomized withdrawal design with at least 10 participants per treatment arm. Participants: different types of participants including central neuropathic pain (e.g. MS)	• Cannabis-based medicines, either herbal cannabis (hashish, marijuana), plant-based cannabinoids (dronabinol: nabiximols), or pharmacological (synthetic) cannabinoids (e.g. levonantradol, nabilone)	• Pain	RoB GRADE	Yes	The potential benefits of cannabis-based medicine in chronic neuropathic pain might be outweighed by their potential harms.

Abbreviations: SR systematic review; RCTs randomised controlled trials; RoB risk of bias; NRS Numeric Rating Scale; VAS Visual Analogue Scale; WMD weighted mean difference; CI confidence interval.
* The Ashworth scale (Ashworth 1964) has been criticized as unreliable, insensitive to therapeutic benefit, and reflective only of passive resistance to movement and not of other features of spasticity (Pandyan 1999; Wade 2010).

APPENDICES

Appendix 1. Draft search strategy

CENTRAL

#1 MESH DESCRIPTOR Cannabis

#2 ((cannabi* or hash* or hemp or marijuana or marihuana or ganka or bhang)):TI,AB,KY

#3 MESH DESCRIPTOR Dronabinol

#4 ((dronabinol or marinol or nabilone or cesamet or dexanabinol or tetrahydrocannabinol or sativex or “HU 211”)):TI,AB,KY

#5 #1 OR #2 OR #3 OR #4

#6 MESH DESCRIPTOR Multiple sclerosis EXPLODE ALL TREES

#7 #5 AND #6

MEDLINE (PubMed) search strategy

((("Cannabis"[Mesh]) OR ("cannabi*"[Text Word]) OR ("hash*"[Text Word]) OR (hemp[Text Word]) OR (marijuana[Text Word]) OR (marihuana[Text Word]) OR (ganka[Text Word]) OR (bhang[Text Word])) OR (("Dronabinol"[Mesh]) OR (dronabinol[Text Word]) OR (marinol[Text Word]) OR (nabilone[Text Word]) OR (cesamet[Text Word]) OR (cannabidiol[Text Word]) OR (nabiximols[Text Word]) OR (dexanabinol[Text Word]) OR (tetrahydrocannabinol[Text Word]) OR (sativex[Text Word])))) AND (((("Multiple Sclerosis"[mh]) OR ("Myelitis, Transverse"[mh:noexp]) OR ("Demyelinating Diseases"[mh:noexp]) OR ("Encephalomyelitis, Acute Disseminated"[mh:noexp]) OR ("Optic Neuritis"[mh])) OR ((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR (encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease*") OR ("acute disseminated encephalomyelitis"))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (human[mh])))))

Embase

#1 'encephalomyelitis'/exp OR 'demyelinating disease'/exp OR 'multiple sclerosis'/exp OR 'myelooptic neuropathy'/exp OR 'multiple sclerosis':ab,ti OR 'neuromyelitis optica':ab,ti OR encephalomyelitis:ab,ti OR devic:ab,ti

#2 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomized controlled trial'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover:ab,ti OR (cross:ab,ti AND over:ab,ti) OR placebo*:ab,ti OR 'double blind':ab,ti OR 'single blind':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti

#3 'cannabis'/exp OR hash* OR 'hemp'/exp OR cannabis:ab,ti OR hash*:ab,ti OR hemp:ab,ti OR marijuana:ab,ti OR 'marijuana'/exp OR marihuana:ab,ti OR 'marihuana'/exp OR ganka:ab,ti OR bhang:ab,ti OR 'dronabinol'/exp OR dronabinol:ab,ti OR marinol:ab,ti OR nabilone:ab,ti OR cesamet:ab,ti OR cannabidiol:ab,ti OR nabiximols:ab,ti OR dexanabinol:ab,ti OR tetrahydrocannabinol:ab,ti OR sativex:ab,ti

#4 #1 AND #2 AND #3

CINAHL (EBSCO host)

S1 (encephalomyelitis) OR (demyelinating disease) OR (multiple sclerosis) OR (AB multiple sclerosis) OR (AB neuromyelitis optica) OR (AB encephalomyelitis) OR (devic)

S2 (crossover procedure) OR (double blind procedure) OR (single blind procedure) OR (randomized controlled trial) OR (random*) OR (factorial*) (OR crossover) OR (cross AND over) OR (placebo) OR (double blind) OR (single blind) OR (assign*) OR (allocat*) OR (volunteer*) OR (AB crossover) OR (AB cross AND AB over) or (AB placebo*) OR (AB double blind) OR (AB single blind) OR (AB assign*) OR (AB allocat*) OR (AB volunteer*)

S3 (cannabis) OR (hash*) OR (hemp) OR (marijuana) OR (marihuana) OR (AB cannabis) OR (AB hash*) OR (AB hemp) OR (AB marijuana) OR (AB marihuana) OR (AB ganka) OR (AB bhang) OR (dronabinol) OR (AB dronabinol) OR (AB marinol) OR (AB nabilone) OR (AB cesamet) OR (AB cannabidiol) OR (AB nabiximols) OR (AB dexanabinol) OR (AB tetrahydrocannabinol) OR (AB sativex)

S4 S1 AND S2 AND S3

LILACS (Bireme)

multiple sclerosis or encephalomyelitis or demyelinating disease or devic [Words] AND cannabis OR hemp OR marijuana OR marihuana OR dronabinol OR marinol OR nabilone OR cesamet OR cannabidiol OR nabiximols OR dexanabinol OR tetrahydrocannabinol OR sativex [Words]

CONTRIBUTIONS OF AUTHORS

All protocol authors drafted the protocol, provided input into the protocol development, and agreed the final protocol version.
GF and SM are the guarantors of the review.

DECLARATIONS OF INTEREST

GF: none
SM: none
TJL: He is employed by Cochrane
RDA: none
KD: She is employed as statistical editor by Cochrane
AAI: He received research grants from GW pharmaceuticals (Cambridge, UK) to perform preclinical studies on phytocannabinoids and intestinal diseases, and patents on phytocannabinoids and colorectal cancer or inflammatory bowel diseases.
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