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Cannabinoids for fibromyalgia (Review)

Walitt B, Klose P, Fitzcharles MA, Phillips T, Häuser W

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[Intervention Review]

Cannabinoids for fibromyalgia

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ABSTRACT

Background

This review is one of a series on drugs used to treat fibromyalgia. Fibromyalgia is a clinically well-defined chronic condition of unknown aetiology characterised by chronic widespread pain that often co-exists with sleep problems and fatigue affecting approximately 2% of the general population. People often report high disability levels and poor health-related quality of life (HRQoL). Drug therapy focuses on reducing key symptoms and disability, and improving HRQoL. Cannabis has been used for millennia to reduce pain and other somatic and psychological symptoms.

Objectives

To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE to April 2016, together with reference lists of retrieved papers and reviews, three clinical trial registries, and contact with trial authors.

Selection criteria

We selected randomised controlled trials of at least four weeks' duration of any formulation of cannabis products used for the treatment of adults with fibromyalgia.

Data collection and analysis

Two review authors independently extracted the data of all included studies and assessed risk of bias. We resolved discrepancies by discussion. We performed analysis using three tiers of evidence. First tier evidence was derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for drop-outs; at least 200 participants in the comparison, eight to 12 weeks' duration, parallel design), second tier evidence from data that did not meet one or more of these criteria and were considered at some risk of bias but with adequate numbers (i.e. data from at least 200 participants) in the comparison, and third tier evidence from data involving small numbers of participants that were considered very likely to be biased or used outcomes of limited clinical utility, or both. We assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation).

Main results

We included two studies with 72 participants. Overall, the two studies were at moderate risk of bias. The evidence was derived from group mean data and completer analysis (very low quality evidence overall). We rated the quality of all outcomes according to GRADE as very low due to indirectness, imprecision and potential reporting bias.

The primary outcomes in our review were participant-reported pain relief of 50% or greater, Patient Global Impression of Change (PGIC) much or very much improved, withdrawal due to adverse events (tolerability) and serious adverse events (safety). Nabilone was compared to placebo and to amitriptyline in one study each. Study sizes were 32 and 40 participants. One study used a cross-over design and one used a parallel group design; study duration was four or six weeks. Both studies used nabilone, a synthetic cannabinoid, with a bedtime dosage of 1 mg/day. No study reported the proportion of participants experiencing at least 30% or 50% pain relief or who were very much improved. No study provided first or second tier (high to moderate quality) evidence for an outcome of efficacy, tolerability and safety. Third tier (very low quality) evidence indicated greater reduction of pain and limitations of HRQoL compared to placebo in one study. There were no significant differences to placebo noted for fatigue and depression (very low quality evidence). Third tier evidence indicated better effects of nabilone on sleep than amitriptyline (very low quality evidence). There were no significant differences between the two drugs noted for pain, mood and HRQoL (very low quality evidence). More participants dropped out due to adverse events in the nabilone groups (4/52 participants) than in the control groups (1/20 in placebo and 0/32 in amitriptyline group). The most frequent adverse events were dizziness, nausea, dry mouth and drowsiness (six participants with nabilone). Neither study reported serious adverse events during the period of both studies. We planned to create a GRADE 'Summary of findings' table, but due to the scarcity of data we were unable to do this. We found no relevant study with herbal cannabis, plant-based cannabinoids or synthetic cannabinoids other than nabilone in fibromyalgia.

Authors' conclusions

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.

PLAIN LANGUAGE SUMMARY

Cannabis products for people with fibromyalgia

Background

Fibromyalgia is characterised by chronic (longer than three months) widespread pain that often co-exists with sleep problems, problems with thinking and fatigue (exhaustion). People often report severe limitations of daily functioning and poor health-related quality of life. Therapies focus on reducing key symptoms and disability, and improving health-related quality of life. Cannabis has been used for 3000 years to reduce pain and other symptoms, such as loss of appetite and anxiety.

Key results and quality of the evidence

In April 2016 we searched for reports of clinical trials that used cannabis products to treat symptoms in adults with fibromyalgia. We found two small, moderate quality studies, of four and six weeks long, including 72 participants. Both studies tested nabilone, a synthetic (man-made) cannabis product, comparing it with placebo (a dummy pill) or amitriptyline (an antidepressant frequently used in the treatment of fibromyalgia).

Nabilone did not convincingly relieve fibromyalgia symptoms (pain, sleep, fatigue) better than placebo or amitriptyline (very low quality evidence). Compared with placebo and amitriptyline, more people experienced side effects and left the study due to side effects (very low quality evidence). There were no serious side effects reported. We found no relevant study with herbal cannabis, plant-based cannabinoids or other synthetic cannabinoids than nabilone in fibromyalgia.

There was not enough high quality evidence available to draw any robust conclusions. We found no studies on medical cannabis in fibromyalgia.

BACKGROUND

This review was based on a template for reviews of drugs used to relieve fibromyalgia-associated symptoms. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1).

Description of the condition

Fibromyalgia is defined as widespread pain that lasts for longer than three months, with tenderness on palpation at 11 or more of 18 specified tender points (Wolfe 1990). Chronic widespread pain is frequently associated with other symptoms such as poor sleep, fatigue and depression. People often report high disability levels and poor quality of life along with extensive use of medical care (Wolfe 2014). Fibromyalgia symptoms can be assessed by self report of the person using the fibromyalgia criteria and severity scales for clinical and epidemiological studies, which is a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia (Wolfe 2011). For a clinical diagnosis, the 1990 American College of Rheumatology (ACR) classification criteria (Wolfe 1990) and the ACR 2010 preliminary diagnostic criteria (Wolfe 2010) can be used. Lacking a specific laboratory test, a diagnosis is established by a history of the key symptoms and the exclusion of somatic diseases that sufficiently explain these symptoms (Wolfe 2010). How fibromyalgia is considered within the international classification of diseases is under debate. While some rheumatologists have thought of it as specific pain disorder (Clauw 2014), and central sensitivity syndrome (Yunus 2008), some neurologists conceptualise fibromyalgia as a small fibre neuropathy (Oaklander 2013). In psychiatry and psychosomatic medicine, fibromyalgia symptoms are characterised as a functional somatic syndrome, as a bodily distress syndrome, as a somatic symptom disorder or as a somatoform disorder (Häuser 2014a).

Fibromyalgia is a heterogeneous condition. The definite aetiology (causes) of this syndrome remains unknown. A model of interacting biological and psychosocial variables in the predisposition to, triggering of, and sustaining the chronicity of fibromyalgia symptoms has been suggested (Sommer 2012). Depression (Forseth 1999), some genes (Arnold 2013; Lee 2012), obesity combined with physical inactivity (Mork 2010), physical and sexual abuse in childhood (Häuser 2011), sleep problems (Mork 2012), and smoking (Choi 2011) are risk factors for the future development of fibromyalgia. Psychosocial stress (e.g. workplace and family conflicts) and physical stress (e.g. infections, surgery, accidents) might trigger the onset of chronic widespread pain and fatigue (Clauw 2014; Sommer 2012). Depression and post-traumatic stress disorder worsen fibromyalgia symptoms (Häuser 2013a; Lange 2010).

Several physiological factors are associated with fibromyalgia, but it is unclear if they cause fibromyalgia or are the result of fibromyalgia. Alterations in pain processing in the brain, reduced reactivity of the hypothalamus-pituitary-adrenal axis to stress, increased pro-inflammatory and reduced anti-inflammatory cytokine profiles (produced by cells involved in inflammation), disturbances in neurotransmitters such as dopamine and serotonin (Sommer 2012), and small fibre pathology (Oaklander 2013; Üçeyler 2013a) have all been demonstrated. Prolonged exposure to stress, as outlined above, may contribute to these functional changes in predisposed individuals (Bradley 2009).

Fibromyalgia is common. Numerous studies have investigated prevalence in different settings and countries. One review gave a global mean prevalence of 2.7% (range 0.4% to 9.3%), and a mean in the Americas of 3.1%, in Europe of 2.5% and in Asia of 1.7%. It is more common in women, with a female to male ratio of 3:1 (4.2%:1.4%) (Queiroz 2013). The change in diagnostic criteria does not appear to have significantly affected estimates of prevalence (Wolfe 2013). Estimates of prevalence in specific populations vary greatly, but have been reported to be as high as 9% in female textile workers in Turkey and 10% in metalworkers in Brazil (59% in people with repetitive strain injury) (Queiroz 2013).

Fibromyalgia pain is known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any single intervention. A multidisciplinary approach is recommended by evidence-based guidelines, with pharmacological interventions being combined with physical or cognitive interventions, or both (Eich 2012; Fitzcharles 2013). Conventional analgesics are usually not effective. Prescribed treatments typically include so-called pain modulators such as antidepressants like serotonin and noradrenaline reuptake inhibitors (Häuser 2013b; Lunn 2014), tricyclic agents such as amitriptyline (Moore 2012a), and antiepileptics such as gabapentin or pregabalin (Moore 2011a; Üçeyler 2013b; Wiffen 2013). The proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction (Moore 2013a)) is small, generally 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNTB) usually between 4 and 10 (Kalso 2013; Wiffen 2013). Fibromyalgia is not particularly different from other chronic pain disorders in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

Description of the intervention

Current pharmacological treatment options for fibromyalgia afford only modest benefit for most people, often with adverse effects that outweigh the benefits (Häuser 2014b). Therefore, there is a need to explore other treatment options, with different mechanisms of action and from different drug categories, for treatment of the constellation of symptoms that characterise fibromyalgia. The cannabinoid system is ubiquitous in the animal kingdom, with multiple functions that aid an organism in maintaining equilibrium. These stabilising effects for the organism, including modulation of pain and stress, suggest that manipulation of this system may have therapeutic potential for the management of fibromyalgia (Pacher 2006). A large body of evidence currently supports the presence of cannabinoid receptors and ligands in the peripheral and central nervous system, but also in other tissues such as bone and in the immune system (Pacher 2006).

The endocannabinoid system has three broad and overlapping functions in mammals. The first is a stress recovery role, operating in a feedback loop in which endocannabinoid signalling is activated by stress and functions to return endocrine, nervous and behavioural systems to homeostatic balance. The second function is to control energy balance through regulation of the intake, storage and utilisation of food. The third involves immune regulation; endocannabinoid signalling is activated by tissue injury and modulates immune and inflammatory responses (Hillard 2012). Thus, the endocannabinoid neuromodulatory system appears to be involved in multiple physiological functions, such as antinociception, cognition and memory, endocrine function,

nausea and vomiting, inflammation and immune recognition (de Vries 2014; Hillard 2012). The plant *Cannabis sativa*, commonly known as marijuana, has been used for pain relief for millennia, and has additional effects on appetite, sleep and mood (Kalant 2001). Data from clinical trials with synthetic and plant-based cannabinoids suggest a promising approach for the management of chronic neuropathic pain of different origins (de Vries 2014).

How the intervention might work

Cannabis sativa contains over 450 compounds, with at least 70 classified as phytocannabinoids. Two are of particular medical interest. Delta 9-tetrahydrocannabinol (delta 9-THC) is the main active constituent, with psychoactive and pain-relieving properties. The second molecule of interest is cannabidiol, which has lesser affinity for the cannabinoid (CB) receptors and the potential to counteract the negative effects of THC on memory, mood and cognition, but also has an effect on pain modulation. The specific roles of currently identified endocannabinoids that act as ligands at cannabinoid receptors within the nervous system (primarily but not exclusively CB 1 receptors) and in the periphery (primarily but not exclusively CB 2 receptors) are only partially elucidated, but there is abundant preclinical data to support their influence on nociception (Owens 2015; Pacher 2006).

A clinical endocannabinoid deficiency has been hypothesised to underlie the pathophysiology of fibromyalgia but there is no clear evidence to support this assumption (Russo 2008). It is also hypothesised that cannabinoids reduce sensitisation of nociceptive sensory pathways and alterations in cognitive and autonomic processing in chronic pain states (Guindon 2009). The frontal-limbic distribution of cannabinoid receptors in the brain suggests that cannabinoids may preferentially target the affective qualities of pain, believed to have an important contribution to the suffering of people with fibromyalgia (Lee 2013). In addition, cannabinoids may attenuate low-grade inflammation, another postulate for pathogenesis in people with fibromyalgia (Üçeyler 2011). Finally, some researchers believe that fibromyalgia is a stress-related disorder (van Houdenhove 2004). In this context, cannabinoids might function to buffer stress and modulate emotional and cognitive functions (Hillard 2012). Therefore, taking into consideration the complexity of symptom expression and the absence of an ideal treatment, the potential for manipulation of the cannabinoid system as a therapeutic modality is attractive.

Why it is important to do this review

Cannabinoids may be administered therapeutically as a pharmaceutic product that is either synthetic or derived from the plant base, or by use of the herbal product that is not pharmaceutically manufactured. The therapeutic use of synthetic and plant-based cannabinoids has been widely reviewed (de Vries 2014; Guindon 2009; Pacher 2006), but clinical use so far has been conflicting. Several practical problems, as well as ethical issues, arise in view of the illegality of the plant *Cannabis sativa* in many jurisdictions, the prevalent worldwide use of *Cannabis sativa* as a recreational drug and the potential for the abuse of cannabinoid preparations (de Vries 2014). However, various cannabinoid preparations are legally available for some medical treatment in some parts of the world (e.g. US, Canada, Europe, Africa) and herbal cannabis has been recently legalised for therapeutic use in over 20 states in the US and also in Canada and Israel. The use of synthetic cannabis has been tested in uncontrolled trials in fibromyalgia (Schley 2006; Weber 2009), and has been advocated by some pain specialists (Weber 2009). Therefore, physicians will be caring for people who may be self medicating with herbal cannabis or may request medical advice about cannabis (Fitzcharles 2014). Due to this, we see an immediate need to evaluate the efficacy, tolerability and safety of cannabinoids in fibromyalgia in order to assist people with fibromyalgia and doctors in shared decision-making on additional pharmacological treatment options.

The standards used to assess evidence in chronic pain trials have changed substantially, with particular attention being paid to trial duration, withdrawals and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using mean pain scores, or mean change in pain scores, to the number of participants who have a large decrease in pain (by at least 50%) and who continue in treatment, ideally in trials of eight to 12 weeks or longer. Pain intensity reduction of 50% or more correlates with improvements in co-morbid symptoms, function and quality of life. These standards are set out in the reference guide for pain studies (AUREF 2012).

This Cochrane review will assess evidence in ways that make both statistical and clinical sense, and will use developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Trials included and analysed will need to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc.), and size (ideally at least 500 participants in a comparison in which the NNTB is four or above (Moore 1998)). This sets high standards and marks a departure from how reviews were done previously.

OBJECTIVES

To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised, double-blind controlled trials (RCTs) of at least four weeks' duration. We included studies with a parallel, cross-over and enriched enrolment randomised withdrawal (EERW) design. Trials had at least 10 participants per treatment arm. We required full journal publication, with the exception of online clinical trial result summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis. We did not include short abstracts. We excluded studies that were non-randomised, studies of experimental pain, case reports and clinical observations.

Types of participants

We included studies with adults aged 18 years and above, diagnosed with fibromyalgia using the 1990 or 2010 criteria (Wolfe 1990; Wolfe 2010).

Types of interventions

Cannabinoids (either phytocannabinoids such as herbal cannabis (hashish, marihuana), plant-based cannabinoids (nabiximole)

or pharmacological (synthetic) cannabinoids (e.g. cannabidiol, dronabinol, levonantradol, nabilone)), at any dose, by any route, administered for the relief of fibromyalgia symptoms and compared to placebo or any active comparator. We did not include studies with drugs under development that manipulated the endocannabinoid system by inhibiting enzymes that hydrolysed endocannabinoids and thereby boosted the levels of the endogenous molecules (e.g. blockade of the catabolic enzyme fatty acid amide hydrolase (FAAH)) (Long 2009).

Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with the majority of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS) for pain intensity or pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These were defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very much improved on Patient Global Impression of Change (PGIC) (moderate) and very much improved on PGIC (substantial). These outcomes are different from those used in most earlier reviews, concentrating as they do on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50%, and with pain not worse than mild (Moore 2013a; O'Brien 2010).

We planned to include a 'Summary of findings' table as set out in the author guide (AUREF 2012). The 'Summary of findings' table was planned to include outcomes of at least 50% pain reduction, PGIC, adverse event withdrawals, serious adverse events and death.

Primary outcomes

1. Participant-reported pain relief of 50% or greater.
2. PGIC much or very much improved.
3. Withdrawal due to adverse events (tolerability).
4. 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 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.

Secondary outcomes

1. Participant-reported pain relief of 30% or greater.
2. Sleep problems.
3. Fatigue.
4. Depression.
5. Anxiety.
6. Health-related quality of life (HRQoL).
7. Disability.
8. Withdrawals due to lack of efficacy.
9. Participants experiencing any adverse event.
10. Other specific adverse events, particularly somnolence, dizziness and drug prescription abuse (addiction).

Search methods for identification of studies

Electronic searches

We searched the following databases, without language restrictions:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 3 of 12, 2016);
2. MEDLINE (via Ovid) (to 26 April 2016);
3. EMBASE (via Ovid) (to 26 April 2016).

See Appendix 2 for the CENTRAL search strategy, Appendix 3 for the MEDLINE search strategy and Appendix 4 for the EMBASE search strategy.

Searching other resources

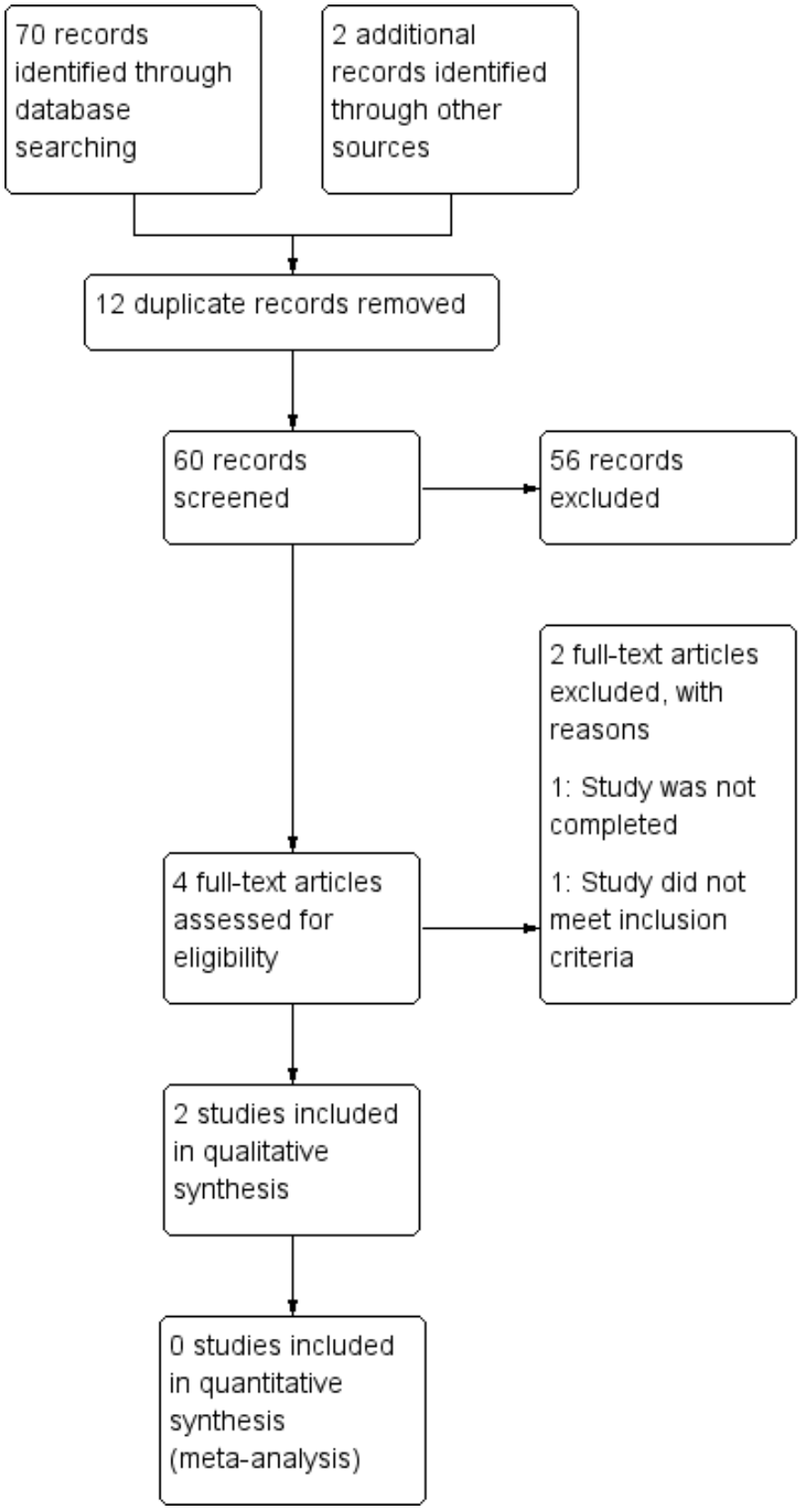
We reviewed the bibliographies of any randomised trials identified and review articles, contacted the authors and known experts in the field, and searched clinical trial databases (ClinicalTrials.gov (ClinicalTrials.gov), International Association for Cannabinoid Medicines (IACM) databank (www.cannabis-med.org/studies/study.php), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) to identify additional published or unpublished data and ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (WH, BW) determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors (MAF, WH) independently read these studies and reached agreement by discussion. We did not anonymise the studies before assessment. We created a PRISMA flow chart of the screening process (see Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (MAF, WH) independently extracted data using a standard form and checked for agreement. One review author (WH) entered suitable data Review Manager 5 (RevMan 2014). We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (placebo or active control), inclusion and exclusion criteria, study setting, study duration and follow-up, outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event or serious adverse event).

Assessment of risk of bias in included studies

We used the Oxford Quality Score as the basis for inclusion (Jadad 1996), limiting inclusion to studies that were randomised and double-blind as a minimum.

Two review authors (WH, MAF) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies at high risk of bias that used a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation and were therefore at a high risk of bias (e.g. open list).
3. Blinding of participants and personnel/treatment providers (systematic performance bias). We assessed the methods used to blind participants and personnel/treatment providers from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved); high risk of bias (blinding of participants was not ensured, e.g. tablets different in form or taste).
4. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, e.g. identical tablets, matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies at a high risk of bias that were not double-blind.
5. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (i.e. less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used last observation carried forward (LOCF) analysis); or high risk of bias (used completer analysis).
6. Reporting bias due to selective outcome reporting (reporting bias). We checked if an a priori study protocol was available and if all outcomes of the study protocol were reported in the publications of the study. There was low risk of reporting bias if the study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that were of interest in the review were reported in the pre-specified way, or if the study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). There was a high risk of reporting bias if not all of the study's pre-specified primary outcomes were reported; one or more primary outcomes was reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the study report did not include results for a key outcome that would be expected to have been reported for such a study.
7. Group similarity at baseline (selection bias). We assessed similarity of the study groups at baseline for the most important prognostic clinical and demographic indicators. There was low risk of bias if groups were similar at baseline for demographic factors, value of main outcome measure(s) and important prognostic factors. There was unclear risk of bias if important prognostic clinical and demographic indicators were not reported. There was high risk of bias if groups were not similar at baseline for demographic factors, value of main outcome measure(s), and important prognostic factor.
8. Size of study (checking for possible biases confounded by small size). We assessed studies at low risk of bias (i.e. 200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (fewer than 50 participants per treatment arm).

Two review authors (WH, MFA) made quality ratings separately for each of the seven methodology quality indicators as defined by the 'Risk of bias' tool. We defined a study to be of high quality when it fulfilled six to eight of the indicators (no risk of bias), to be of moderate quality when it fulfilled three to five of the indicators and to be of low quality if it fulfilled zero to two of the quality indicators (Schaefert 2015).

Measures of treatment effect

We planned to calculate numbers needed to treat as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the number needed to treat for an additional beneficial outcome (NNTB) became the number needed to treat

for an additional harm outcome (NNTH) and was calculated in the same manner. We planned to use dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model unless we found significant statistical or clinical heterogeneity (see below). We planned to calculate standardised mean differences (SMD) with 95% CI for continuous variables using a fixed-effect model unless we found significant statistical or clinical heterogeneity. We planned to calculate NNTBs for continuous variables (fatigue, sleep problems, HRQoL) using the Wells calculator software available at the Cochrane Musculoskeletal Group editorial office, which estimates, from the SMDs, the proportion of participants who will benefit from treatment (Norman 2001). We planned to use a minimal clinically important difference of 15% for the calculation of the NNTB from SMDs for all continuous outcomes. This approach has been used by previous Cochrane reviews in drug therapies for fibromyalgia (Häuser 2013b; Üçeyler 2013b).

Where means or standard deviations (SDs) were missing, we attempted to obtain these data through contacting trial authors. Where SDs were not available from trial authors, we calculated them from t values, P values, CIs or standard errors, where reported in articles (Higgins 2011). Where 30% and 50% pain reduction rates were not reported or provided on request, we planned to calculate them from means and SDs using a validated imputation method (Furukawa 2005).

Unit of analysis issues

We intended to split the control treatment arm between active treatment arms in a single study if the active treatment arms were not combined for analysis. We included studies with a cross-over design where separate data from the two periods were reported, where data were presented that excluded a statistically significant carry-over effect, or where statistical adjustments were carried out in case of a significant carry-over effect.

Dealing with missing data

We planned to use an intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication and provided at least one post-baseline assessment. We would have assigned missing participants zero improvement wherever possible.

Assessment of heterogeneity

We assessed clinical heterogeneity by analysing the inclusion and exclusion criteria of the studies included. We assessed statistical heterogeneity visually (L'Abbé 1987), and with the use of the I^2 statistic. When the I^2 value was greater than 50%, we would have considered possible reasons for this.

Assessment of reporting biases

We aimed to use dichotomous outcomes of known utility and of value to participants as primary outcomes (Moore 2010b; Moore 2013a). We extracted and used continuous data, which probably reflect efficacy and utility poorly, for illustrative purposes only.

Data synthesis

We planned to analyse data in three tiers, according to outcome and freedom from known sources of bias (Moore 2010a).

1. The first tier used data meeting current best standards, where studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of LOCF or other imputation method for drop-outs, reported an ITT analysis, lasted eight or more weeks, had a parallel-group design and had at least 200 participants (preferably at least 400) in the comparison (Moore 1998; Moore 2010a; Moore 2012a; Moore 2012b). We planned to report these first-tier results first.
2. The second tier used data from at least 200 participants but where one or more of the first-tier conditions were not met (e.g. reporting at least 30% pain intensity reduction, using LOCF or a completer analysis, or lasting four to eight weeks).
3. The third tier of evidence related to data from fewer than 200 participants, or where there were significant problems because, for example, of very short duration studies of fewer than four weeks, where there was major heterogeneity between studies, or where there were shortcomings in allocation concealment, attrition or incomplete outcome data. For this third tier of evidence, no data synthesis was reasonable and may be misleading, but an indication of beneficial effects might be possible.

There was only third-tier evidence available. For this third-tier evidence, no data synthesis was reasonable and may have been misleading. Therefore, we did not conduct the planned meta-analysis.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the overall quality of evidence (Balshem 2011; GRADEpro GDT 2015), defined as the extent of confidence in the estimates of treatment benefits and harms. We downgraded the quality of evidence by one level for each of the following factors that we encountered.

1. Limitations of study design: greater than 50% of the participants in low quality studies.
2. Inconsistency of effect size: I^2 greater than 50%.
3. Indirectness: we assessed whether the question being addressed in this systematic review was different from the available evidence regarding the population in routine clinical care, if people with inflammatory rheumatic diseases or depressive disorders (or both) were excluded in greater than 50% of participants.
4. Imprecision: there was only one trial or when there was more than one trial, the total number was fewer than 400 participants or when 95% CI of the effect size included zero.
5. High probability of reporting bias: all studies were sponsored by the manufacturer of the drug.

We categorised the quality of evidence as follows.

1. High: we were very confident that the true effect lay close to that of the estimate of the effect.
2. Moderate: we were moderately confident in the effect estimate; the true effect was likely to be close to the estimate of the effect, but there was a possibility that it was substantially different.
3. Low: our confidence in the effect estimate was limited; the true effect may be substantially different from the estimate of the effect.

4. Very low: we had very little confidence in the effect estimate; the true effect was likely to be substantially different from the estimate of effect; any estimate of effect was very uncertain.

We planned to present the main findings of the review in 'Summary of findings' tables in a transparent and simple tabular format. Due to the scarcity of data, we were unable to create a GRADE 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses (studies with and without stratification for co-morbid mental disorders; different cannabinoids; different routes of administration) if there were at least two studies available.

The planned subgroup analyses were not possible due to the lack of a sufficient number of studies.

Sensitivity analysis

We did not perform sensitivity analysis because we did not identify individual peculiarities of the studies under investigation during the review process that were suitable for sensitivity analyses.

RESULTS

Description of studies

Results of the search

Searches identified three potentially relevant studies in CENTRAL, 20 in MEDLINE and 47 in EMBASE. In addition, we identified two study protocols in clinicaltrials.gov. After reading the full reports, we included two studies into the review (Skrabek 2008; Ware 2010). We excluded two studies (NCT00176163; NCT01149018) (see Figure 1).

Included studies

We included two studies with 72 participants using nabilone in people with fibromyalgia (Skrabek 2008; Ware 2010). Study recruitment was from a chronic pain specialist clinic (Ware 2010), and from a Musculoskeletal Rehabilitation clinic (Skrabek 2008) (single centre studies). Both studies were conducted in Canada. Studies enrolled adults with aged between 26 and 76 years, with no upper age limits in one study (Ware 2010), and upper limit of 75 years in the other study (Skrabek 2008). In both studies, there was a preponderance of women (ca 90%). Inclusion criterion was continued pain despite the use of other oral medications (Skrabek 2008), or self reported chronic insomnia (Ware 2010) (see Appendix 5). Diagnosis of fibromyalgia was established by the ACR 1990 classification criteria in both studies (Wolfe 1990). Exclusion criteria in both studies included a history of substance abuse, current psychotic disorders and unstable cardiac disease. The extent of other exclusion criteria varied between studies. One study with the majority of participants in the review excluded people with "History of untreated non-psychotic emotional disorders" (Skrabek 2008) (see Appendix 5). Nabilone was compared with placebo (Skrabek 2008) and with amitriptyline (Ware 2010). One study used a parallel group design (Skrabek 2008); the other was a cross-over study (Ware 2010). Study duration was four weeks (Skrabek 2008) and six weeks (two weeks each for each period, separated by a two weeks' wash-out phase) (Ware 2010). Ware 2010 reported data from the first phase separately only for the main outcome sleep problems. To assess potential carryover effects, examination of treatment by period interactions was conducted. Other stable medication (including pain medication) was continued unchanged in both studies. There was a two-week washout between phases in the cross-over study (Ware 2010). The dosage of nabilone was progressively increased from 0.5 mg/day to 1 mg/day at bedtime in both studies.

See Characteristics of included studies table.

Excluded studies

We excluded two studies after reading the full reports (NCT00176163; NCT01149018). Reasons for exclusion of individual studies are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

Each study had at least two high risks of bias (Assessment of risk of bias in included studies). See Figure 2; Figure 3. The reported methodology quality of the trials was moderate according to the pre-defined criteria.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

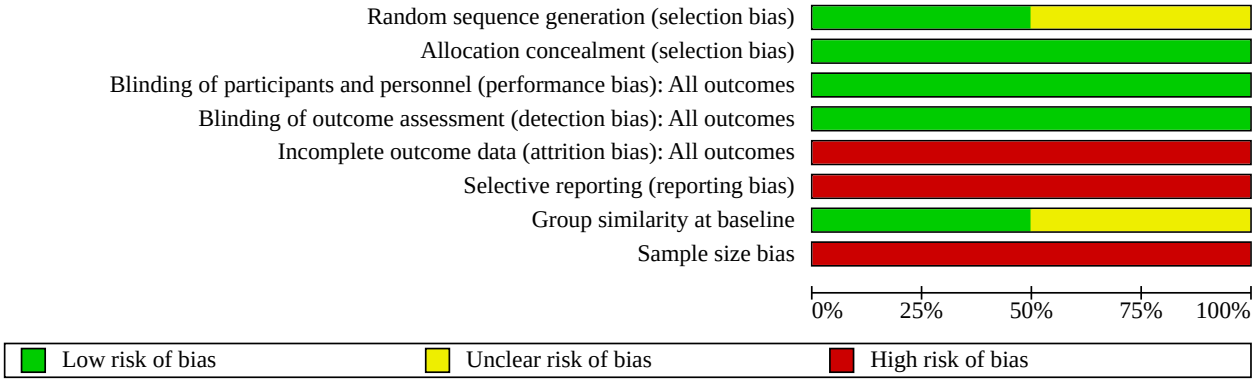
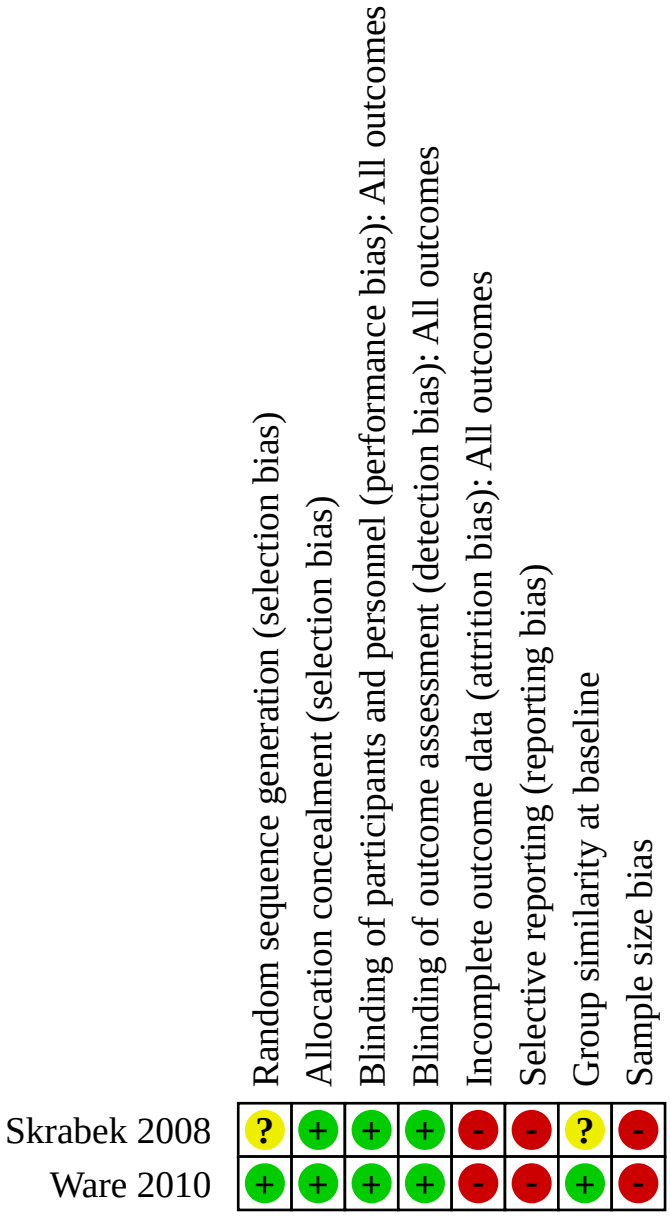


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Both studies were randomised. Random sequence generation and allocation concealment were of low risk in Ware 2010. In Skrabek 2008, the details of randomisation were unclear.

Blinding

Both studies were double blind. Both studies adequately described the method used to achieve double blinding.

Incomplete outcome data

Both studies did not perform ITT, but completer analysis.

Selective reporting

A study protocol was not available for either study.

Other potential sources of bias

The demographic characteristics of the study groups were not different in both studies. The sample size of both studies were small. Both studies were partially funded by the manufacturer of nabilone.

Effects of interventions

Both included studies reported at least one pain-related outcome. Due to the scarcity of data, we did not create a 'Summary of findings' table. See Appendix 6 and Appendix 7 for details of data from individual studies. There was no first- or second-tier (high to moderate quality) evidence of efficacy, tolerability and safety. The studies did not report outcomes for proportion of participants experiencing at least 30% or 50% pain relief or who were very much improved. The quality of evidence for all outcomes was downgraded by three levels because of indirectness, imprecision and potential reporting bias to very low.

Third-tier evidence

Efficacy

The quality of evidence for all outcomes of efficacy was very low.

Using a responder analysis, Skrabek 2008 reported that statistically significant improvements were detected in pain, anxiety and HRQoL. However, calculating SMDs by the means and SDs extracted from figures, we did not find a significant difference between nabilone and placebo. There were no significant differences between nabilone and placebo noted for fatigue and depression. The outcome disability was not reported. No participant dropped out due to lack of efficacy in the nabilone or placebo group.

Nabilone had better effects on sleep than amitriptyline (adjusted difference -3.25, 95% CI -5.26 to -1.24; P value < 0.05) on a 0 to 28 scale (Insomnia severity index). There were no significant differences between the two drugs for pain and HRQoL. There were no data for the Fibromyalgia Impact Questionnaire (FIQ) subscales anxiety, disability, fatigue and depression. There were no significant differences between the two drugs in the Profile of Mood States. One participant dropped out due to the lack of efficacy. The authors did not report if the drop-out due to the lack of efficacy was in the nabilone or amitriptyline group. All results were based on a responder analysis (Ware 2010).

Neither study assessed the outcomes participant-reported pain relief of 30% or 50% or greater, or PGIC much or very much improved. The data provided by both studies did not allow the use of the planned imputation method to calculate 30% and 50% pain responder rates (Furukawa 2005).

Tolerability

The quality of evidence for all outcomes of tolerability was very low.

Both studies did not report the numbers of participants who experienced any adverse event. Skrabek 2008 did not report the total number of adverse events. Ware 2010 reported 187 adverse events. Fifty-three adverse events were possibly or probably related to amitriptyline therapy and 91 AEs to nabilone therapy.

Three out of 20 participants in the nabilone group and 1/20 participant in the placebo group dropped out due to adverse events in the Skrabek 2008 study. Ware 2010 reported that 1/32 participant dropped out in the nabilone group and no participants in the amitriptyline group dropped out due to adverse events. The most frequent adverse events were drowsiness (seven participants with nabilone, one participant with placebo), dry mouth (five participants with nabilone, one participant with placebo) and vertigo (four participants with nabilone, no participants with placebo) in Skrabek 2008. The most frequent adverse events were dizziness (10 participants with nabilone, four participants with amitriptyline), nausea (nine participants with nabilone, one participant with amitriptyline), dry mouth (seven participants with nabilone, three participants with amitriptyline) and drowsiness (six participants with nabilone, one participant with amitriptyline) in Ware 2010. Neither study reported on abuse of prescribed nabilone.

Safety

The quality of evidence for all outcomes of safety was very low. Both studies reported no serious adverse events during the study period.

DISCUSSION

Summary of main results

The review found two studies testing the synthetic cannabinoid nabilone in 72 participants with FM. No first- or second-tier evidence was available.

There was no unbiased evidence of a superiority of nabilone over placebo to reduce fibromyalgia symptoms. Third-tier evidence indicated a superiority of nabilone over placebo in pain relief and HRQoL, but not in fatigue, but this was derived from group mean data and completer analysis in a small, short duration study, where major bias was possible. Third-tier evidence indicated a superiority of nabilone over amitriptyline in improving sleep quality, but not for pain and HRQoL, but this was derived from group mean data and completer analysis in a small, short duration study, where major bias is possible. Participants taking nabilone experienced more adverse events (but not serious adverse events) than did participants taking placebo or amitriptyline. More participants dropped out due to adverse events in the nabilone than in the control groups. The most frequent adverse events with nabilone were dizziness/drowsiness, dry mouth and vertigo. We found no RCTs with other cannabinoids than nabilone.

Overall completeness and applicability of evidence

Overall completeness and applicability of evidence were poor. The usefulness of the available evidence was limited because reporting quality was poor by current standards (Moore 2010a). RCTs of up to six weeks' duration do not necessarily provide information about longer term use, which is important in treatment of a chronic condition (Moore 2010a). In particular, concern has been raised about the lack of evidence on potential problems with long term recreational use of cannabis (such as safety issues, addiction and misuse) (Hoch 2015; Volkow 2014). A very limited population was studied, who may not be representative for people with fibromyalgia in routine clinical care.

Quality of the evidence

While both the included studies were randomised and double-blind, neither provided data that met pre-defined criteria for first- or second-tier analysis (high to moderate quality evidence). Both studies were small (the largest treatment group consisted

of 40 participants). The studies were of short duration (maximum treatment period of four weeks) and one was of cross-over design without separate reporting of first period data. Both studies used completer analysis. The quality of evidence according to GRADE for all outcomes of efficacy, tolerability and safety was very low, downgraded for the reasons given in Risk of bias in included studies.

Potential biases in the review process

The absence of publication bias (unpublished trials showing no benefit of cannabinoids over placebo) can never be proved. We carried out a broad search of studies and felt it was unlikely that significant amounts of relevant data remain unknown to us. The degree of exaggeration of treatment effects in cross-over trials compared to parallel group designs is a potential source of major bias (Elbourne 2002).

Agreements and disagreements with other studies or reviews

The evidence for efficacy of cannabinoids for fibromyalgia symptoms in uncontrolled trials and surveys is as inconsistent as the RCTs reviewed. In one experimental study designed to examine the effect of orally administered delta 9-THC on electrically induced pain, nine people with fibromyalgia from Germany received a daily dose of 2.5 to 15 mg of delta 9-THC, with a weekly increase of 2.5 mg, as long as no adverse events were reported. Five participants withdrew due to adverse events. Daily recorded pain of the people with fibromyalgia was significantly reduced over a three-month period (Schley 2006). One case series of 172 participants reported from Germany included 32 people with fibromyalgia. On average, participants received delta 9-THC 7.5 mg over seven months. Participants were assessed retrospectively in a telephone survey. On average, maximum pain intensity as determined using an NRS was recorded as 9.3 ± 1.1 prior to delta 9-THC and 6.1 ± 2.1 thereafter, but without identification of the time period for assessment for change in pain. Data on HRQoL, disability, depression and drop-out rates due to adverse events were not reported separately for people with fibromyalgia. About 25% of the total sample did not tolerate the treatment (Weber 2009). In another study, 28 Spanish people with fibromyalgia who were herbal cannabis users and 28 non-users, without differences in demographics and clinical variables, were compared. After two hours of cannabis use, there was a statistically significant reduction of pain and stiffness, enhancement of relaxation and an increase in somnolence and feeling of well-being (all P values < 0.001). The mental health component summary score of the 36-item Short Form (SF-36) was significantly higher in cannabis users than in non-users. There were no significant differences in the other SF-36 domains, or in the FIQ (Fiz 2011). In one Canadian case series of a tertiary care pain centre, cannabinoids were being used by 13% of people with fibromyalgia, of whom 80% used herbal cannabis (marijuana). Current unstable mental illness, opioid drug-seeking behaviour and male sex were all associated with herbal cannabis use. There was a trend for cannabinoid users to be unemployed and receiving disability payments (Ste-Marie 2012). In one survey of the US National Pain Foundation, over 1300 people with fibromyalgia rated marijuana more effective than Food and Drug Administration (FDA)-approved duloxetine, milnacipran and pregabalin. The survey showed that only 8% of duloxetine, 10% of pregabalin and 10% of milnacipran users found the medication to be "very effective," while 60% of duloxetine, 61% of pregabalin and 68% of milnacipran users replied that the medications, "does not help at all." In contrast, 62% of marijuana users rated it very effective. Only 5% said it did not help at all (National Pain Foundation 2014).

The findings of this review regarding the most frequent adverse events associated with cannabinoids (drowsiness, dizziness, dry mouth) were in line with the findings of one systematic review of cannabinoids in chronic non-cancer pain that included 18 RCTs with 766 participants (Lynch 2011). One Canadian case series point to low tolerability and poorer mental health and functionality for cannabinoid users with fibromyalgia (Ste-Marie 2012).

AUTHORS' CONCLUSIONS

Implications for practice

For people with fibromyalgia

Clinical trial evidence on the use of cannabis products in fibromyalgia was limited to two small studies with short-term duration. No convincing, unbiased evidence suggests that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone was low in people with fibromyalgia. Adverse events (particularly somnolence, dizziness, vertigo) may limit its clinical usefulness. We found no relevant study with herbal cannabis, plant-based cannabinoids or other synthetic cannabinoids than nabilone in fibromyalgia.

For physicians

Herbal, plant-based and synthetic cannabis products are not licensed for fibromyalgia in any country. Other than one weak recommendation from a trial of a pharmacological cannabinoid preparation in people with fibromyalgia in the setting of important sleep disturbance in the Canadian fibromyalgia guidelines (Fitzcharles 2013), there is no other current guideline recommendation for use of any cannabis preparation in the management of fibromyalgia.

For policy makers

The use of herbal cannabis at present cannot be considered evidence-based and this should be explained to people requesting this treatment (in jurisdictions where it is allowed, e.g. Canada and Israel).

For funders

Randomised controlled trials with cannabis products may be worth funding, as there are few confirmed effective drug treatments, in order to establish the efficacy and safety of cannabinoids compared to established treatments in this population.

Implications for research

Design

To establish whether cannabis products can have a place in the treatment of fibromyalgia would require large (at least 200 participants), randomised, double-blind, parallel group or enriched enrolment randomised withdrawal (EERW) studies, of adequate duration (greater than 12 weeks), with outcome measures that are relevant to clinical practice (responder analysis), and analysis that does use baseline observation carried forward imputation for withdrawals.

It might be expected that, at best, only a few people with fibromyalgia will benefit from long term use of cannabis products, and cohort studies in fibromyalgia link cannabis use to negative health-related measures (Ste-Marie 2012). A further area of research would be to identify clinical and demographic characteristics that predict which people are likely to benefit or to be harmed from cannabis products, in order to target treatment more effectively.

Population

Studies in any continent and the inclusion of people with major medical diseases and mental disorders are necessary to provide external validity of the study findings.

Measurement (endpoints)

Responder criteria for pain, global impression of change and health-related quality of life have been established (Bennett 2009; Dworkin 2008). Responder criteria for sleep problems and fatigue have not yet been developed.

Comparison between active treatments

Any comparisons should be made with placebo and other drugs with known efficacy, such as pregabalin. In addition, studies comparing single therapies (e.g. cannabis products) versus combination therapies (e.g. cannabis products and aerobic exercise) are necessary.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Skrabek 2008

Study characteristics	
Methods	**Study setting:** single centre study, Outpatient Musculoskeletal Rehabilitation clinic, Canada **Study design:** parallel **Duration therapy:** 4 weeks **Follow-up:** 4 weeks
Participants	40 (93% women, race not reported, mean age 49 years)
Interventions	**Active drug:** nabilone 0.5 mg to 1 mg/day twice a day at bedtime: 20 participants **Placebo:** 20 participants **Rescue or allowed medication:** no details reported. Participants were asked to continue any current medication including breakthrough medications, but not to begin any new therapy
Outcomes	**Pain:** daily diary mean pain VAS 0-10 **Fatigue:** FIQ subscale VAS 0-100 **Sleep:** Not assessed **Depression:** FIQ subscale VAS 0-100 **Anxiety:** FIQ subscale VAS 0-100 **Disability:** FIQ subscale VAS 0-100 * **Health-related quality of life:** FIQ total score (0-100) **Participant-perceived improvement:** not assessed **AEs:** recorded at each visit. No details of assessment reported *Outcome not reported
Notes	**Oxford Quality Score:** R1, DB2, W1, Total 4/5 **Funding sources and any declaration of interest of primary investigators:** supported by Valeant Canada and an HSC Medical Stuff Council Fellowship Fund. No declaration of interest of primary investigators included
Risk of bias	

Skrabek 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Low risk	Pharmacy controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study medication was identical in appearance to placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessed by the participants who were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT analysis
Selective reporting (reporting bias)	High risk	Outcome disability not reported and not provided on request
Group similarity at baseline	Unclear risk	No significant differences in demographic and clinical characteristics of the study groups
Sample size bias	High risk	< 50 participants per study arm

Ware 2010

Study characteristics	
Methods	**Study setting:** single centre study, pain clinic, Canada **Study design:** cross-over **Duration therapy:** 2 weeks each with 2 weeks' washout between the 2 periods **Follow-up:** none
Participants	32 (81% women, race not reported, mean age 50 years)
Interventions	**Active drug:** nabilone 0.5 or 1 mg/day orally flexible: 29 participants **Active comparator:** amitriptyline oral flexible 10 or 20 mg/day: 29 participants **Rescue or allowed medication:** no details reported
Outcomes	**Pain:** McGill Pain Questionnaire total score (1-78) **Fatigue:** FIQ subscale VAS 0-100 * **Sleep:** Insomnia Severity Index (0-25) and Leeds Sleep Evaluation Questionnaire **Depression:** FIQ subscale VAS 0-100 * **Anxiety:** FIQ subscale VAS 0-100 *

Ware 2010 *(Continued)*

	Disability: FIQ subscale VAS 0-100 *
	Health-related quality of life: FIQ total score (0-100)
	Participant-perceived improvement: not assessed
	AEs: recorded at each visit. No details of assessment reported
	*Outcome not reported and not provided on request
Notes	**Oxford Quality Score:** R2, DB1, W1, Total 4/5
	Funding sources and any declaration of interest of primary investigators: supported by a grant of Valeant (Canada) and McGill University Health Center. Declaration of interest of primary investigators included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned block sizes by a computer program
Allocation concealment (selection bias)	Low risk	Schedule retained by the study pharmacists only
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sealed opaque capsules containing study drugs identical in appearance for both arms (personal communication)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessed by the participants who were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT analysis
Selective reporting (reporting bias)	High risk	No data for the FIQ subscales anxiety, disability, fatigue and depression provided
Group similarity at baseline	Low risk	Cross-over design
Sample size bias	High risk	< 50 participants per study arm

AE: adverse event; DB: double blind; FIQ: Fibromyalgia Impact Questionnaire; ITT: intention-to-treat; R: randomisation; VAS: visual analogue scale; W: withdrawal.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
NCT00176163	After contacting trial author: study data were prepared for publication; study design with 4 groups (behavioural therapy + dronabinol, behavioural therapy + placebo, behavioural therapy alone, standard medical therapy) did not meet inclusion criteria

Study	Reason for exclusion
NCT01149018	After contacting trial author: study was not conducted due to organisational reasons

APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been several recent changes in how efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria for what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with "any improvement". Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be longer, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review.

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011b; Moore 2011c), back pain (Moore 2010c), arthritis (Moore 2010d), and fibromyalgia (Straube 2010); in all cases, mean results usually describe the experience of almost no-one in the trial. Data expressed as means are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the person either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate and substantial improvement (Dworkin 2008). In arthritis, trials shorter than 12 weeks, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010d); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of participants with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis, to 30% in fibromyalgia (Moore 2009; Moore 2010d; Moore 2013b; Moore 2014a; Sultan 2008). One Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Individual participant analyses indicate that people who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010b; Moore 2014b).
5. Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

Appendix 2. CENTRAL search strategy

1. MeSH descriptor: [Cannabis] this term only (263)

2. MeSH descriptor: [Cannabinoids] explode all trees (506)

3. (cannabis OR hemp OR marijuana OR ganja OR hashish OR marihuana OR bhang OR cannibinoid OR cannabinoids OR marinol OR dronabinol OR nabilone OR cesamet OR dexanabinol OR sativex OR tetrahydrocannabinol): ti,ab,kw (Word variations were searched) (1884)

4. OR/ 1-3 (1888)

5. (fibromyalgia):ti,ab,kw or (fibromyalgi$):ti,ab,kw or (fibrositis):ti,ab,kw or (fms):ti,ab,kw (1463)

6. MeSH descriptor: [Fibromyalgia] explode all trees (673)

7. OR/ 5-6 (1463)

8. (animal):ti,ab,kw (17838)

9. (human):ti,ab,kw (653277)

10. 9 not 8 (637801)

11. 4 and 7 and 10 in Trials (3)

Appendix 3. MEDLINE (via Ovid) search strategy

#1. ("cannabis"[MeSH Terms] OR "cannabis"[Tiab]) OR ("cannabis"[MeSH Terms] OR "cannabis"[Tiab] OR "hemp"[Tiab]) OR ("cannabis"[MeSH Terms] OR "cannabis"[Tiab] OR "marijuana"[Tiab]) OR ("Ganja"[Journal] OR "ganja"[Tiab]) OR ("cannabis"[MeSH Terms] OR "cannabis"[Tiab] OR "hashish"[Tiab]) OR ("cannabis"[MeSH Terms] OR "cannabis"[Tiab] OR "marihuana"[Tiab]) OR ("cannabis"[MeSH Terms] OR "cannabis"[Tiab] OR "bhang"[Tiab]) OR ("cannabinoids"[MeSH Terms] OR "cannabinoids"[Tiab]) OR ("cannabinoids"[MeSH Terms] OR "cannabinoids"[Tiab] OR "cannabinoid"[Tiab]) OR ("dronabinol"[MeSH Terms] OR "dronabinol"[Tiab] OR "marinol"[Tiab]) OR ("dronabinol"[MeSH Terms] OR "dronabinol"[Tiab]) OR ("nabilone"[Supplementary Concept] OR "nabilone"[Tiab]) OR ("nabilone"[Supplementary Concept] OR "nabilone"[Tiab] OR "cesamet"[Tiab]) OR ("HU 211"[Supplementary Concept] OR "HU 211"[Tiab] OR "dexanabinol"[Tiab]) OR ("tetrahydrocannabinol-cannabidiol combination"[Supplementary Concept] OR "tetrahydrocannabinol-cannabidiol combination"[Tiab] OR "sativex"[Tiab]) OR ("dronabinol"[MeSH Terms] OR "dronabinol"[Tiab] OR "tetrahydrocannabinol"[Tiab]) (34605)

#2. "fibromyalgia"[MeSH Terms] OR "fibromyalgia"[All Fields] OR "fibrositis"[All Fields] OR FMS[all] (13986)

#3. 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] (3589205)

#4. animals[mh] NOT humans[mh] (4011177)

#5.#3 NOT #4 (3091881)

#6. #1 AND #2 AND #5 (20)

Appendix 4. EMBASE (via Ovid) search strategy

1. (TITLE-ABS-KEY(cannabis) OR TITLE-ABS-KEY(hemp) OR TITLE-ABS-KEY(marijuana) OR TITLE-ABS-KEY(ganja) OR TITLE-ABS-KEY(hashish) OR TITLE-ABS-KEY(marihuana) OR TITLE-ABS-KEY(bhang) OR TITLE-ABS-KEY(cannibinoid) OR TITLE-ABS-KEY(cannabinoids) OR TITLE-ABS-KEY(marinol) OR TITLE-ABS-KEY(dronabinol) OR TITLE-ABS-KEY(nabilone) OR TITLE-ABS-KEY(cesamet) OR TITLE-ABS-KEY(dexanabinol) OR TITLE-ABS-KEY(sativex) OR TITLE-ABS-KEY(tetrahydrocannabinol)) AND DOCTYPE(ar OR re) (48947)

2. (TITLE-ABS-KEY(fibromyalgia) OR TITLE-ABS-KEY(fibrositis) OR TITLE-ABS-KEY(fms)) AND DOCTYPE (ar OR re) (19146)

3. (TITLE-ABS-KEY ("randomized controlled trial") OR TITLE-ABS-KEY ("controlled trial") OR TITLE-ABS-KEY (placebo) OR TITLE-ABS-KEY ("single blind") OR TITLE-ABS-KEY ("double blind")) AND DOCTYPE (ar OR re) (648952)

4. #1 AND #2 AND #3 (47)

Appendix 5. Inclusion and exclusion criteria of the studies

Study	Inclusion criteria	Exclusion criteria
Skrabek 2008	• Participant met American College of Rheumatology (1990) criteria for the classification of fibromyalgia • Aged 18-70 years • Any gender • participant did not received benefit from a tricyclic antidepressant, muscle relaxant, paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs for management of their pain • No previous use of oral cannabinoids for pain management	• Participant's pain was better explained by a diagnosis other than fibromyalgia • Abnormalities on routine baseline blood work including electrolytes, urea and creatinine, a complete blood count and liver function tests (aspartate transaminase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase and lactate dehydrogenase). Normal tests taken within 3 months prior to the study were accepted if there was no history of acute illness since the time the blood was drawn • Heart disease (cannabinoids can reduce heart rate and blood pressure). People with heart disease were excluded based on a history of angina, myocardial infarction or congestive heart failure and clinical examination • Schizophrenia or other psychotic disorder • Severe liver dysfunction (participants excluded if there was an elevation of any of the baseline liver enzymes) • History of untreated non-psychotic emotional disorders • Cognitive impairment • Major illness in another body area

(Continued)

		• Pregnancy • Nursing mothers • Aged < 18 years old • History of drug dependency • Known sensitivity to marijuana or other cannabinoid agents
Ware 2010	• Aged ≥18 years • diagnosis according to the American College of Rheumatology classification criteria • Experiencing self reported disturbed sleep • Negative urine screen for cannabinoids • Women of childbearing potential agreed to use adequate contraception during study and for 3 months after study • Ability to attend research centre every second week for approximately 7-9 weeks and be able to be contacted by telephone during the study period • Stable drug regimen for 1 month prior to randomisation • Normal liver (aspartate transaminase < 3 x normal) and renal function (serum creatinine < 133 µmol/L) • Haematocrit > 38% • Negative serum beta subunit of human chorionic gonadotropin • Proficient in English or French • Willing and able to give written informed consent • Ability to follow study protocol (cognitive and situational)	• People currently using cannabis or cannabinoid or tricyclic antidepressants and who are unable to undergo a 2-week washout period before entering the study • Pain due to cancer • Unstable cardiac disease such as cardiac arrhythmias, cardiac failure, ischaemic heart disease or hypertension (or a combination) on clinical history and examination • History of psychotic disorder or schizophrenia • Known hypersensitivity to cannabinoids, amitriptyline or related tricyclic antidepressants • Currently taking or unable to stop taking monoamine oxidase inhibitors (a 2-week washout period is necessary for people taking monoamine oxidase inhibitors) • History of seizures/epilepsy • Diagnosis of glaucoma • Urinary retention • Pregnancy or breast-feeding, or both • Participation in other clinical trial in the 30 days prior to randomisation • Recent manic episode (within the past year) • Current suicidal ideation or history of suicide attempts

Appendix 6. Summary of efficacy in single studies

Study	Treatment	Efficacy outcomes at the end of treatment
Skrabek 2008	Nabilone 1 mg bid orally vs. placebo Titration from 0.5 mg to 1 mg bid from week 1 to 4	50% pain reduction: not reported and not provided on request PGIC: not assessed Pain: nabilone mean 4.8 (SD 2.2), placebo mean 5.7 (SD 1.8) * (P value = 0.02)*** Sleep: not assessed Fatigue: no significant difference ** Depression: no significant difference **

(Continued)

		Anxiety: nabilone mean 4.3 (SD 1.8); placebo mean 4.9 (SD 2.2) * (P value < 0.01)*** Health-related quality of life: mean 54 (SD 22.3); placebo mean 64 (SD 13.4) *; (P value < 0.01)***
Ware 2010	Nabilone 0.5 or 1 mg vs. amitriptyline 10 or 20 mg at bedtime each Titration in each of 2 periods of 2 weeks, with 2 weeks' washout between the 2 treatment periods	50% pain reduction: not reported and not provided on request PGIC: not assessed Mean pain intensity: no significant difference ** Sleep: nabilone: mean 9 (SD 10.8); amitriptyline mean 13 (SD 10.8) * Fatigue: not reported Depression: not reported Anxiety: not reported Health-related quality of life: no significant difference **

bid: twice daily; PGIC: Patient Global Impression of Change; SD: standard deviation; vs.: versus.

* Data extracted from figures. Data not provided on request.

** No means and SDs reported. Data not provided on request.

*** P values as reported by authors.

There were no significant differences between nabilone and placebo groups after the 4-week wash-out period (Skrabek 2008).

Appendix 7. Summary of tolerability and safety in single studies

Study	Adverse events (cannabinoid vs. control)	Withdrawal due to adverse events (nabilone vs. comparator)	Serious adverse events (nabilone vs. comparator)
Skrabek 2008	Nabilone vs. placebo: Drowsiness 47% vs. 6% Dry mouth 33% vs. 6% Vertigo 27% vs. 0% Ataxia 20% vs. 6% Confusion 13% vs. 6% Decreased concentration 13% vs. 6%	15% vs. 0%	0% vs. 0%
Ware 2010	Nabilone vs. amitriptyline: Dizziness 32% vs. 13% Headache 13% vs. 19% Nausea 29% vs. 3%	3% vs. 0%	0% vs. 0%

(Continued)

	Dry mouth 23% vs. 10%
	Drowsiness 23% vs. 3%
	Constipation 19% vs. 3%
	Insomnia 10% vs. 0%

vs: versus.

WHAT'S NEW

Date	Event	Description
7 August 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 5, 2015
Review first published: Issue 7, 2016

Date	Event	Description
20 July 2020	Amended	Minor error corrected in search strategy.
20 July 2020	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

MAF and WH drafted the protocol.

PK and WH developed and ran the search strategy.

The PaPaS information specialist provided support.

PK and WH selected which studies to include.

MAF and WH extracted data from studies.

WH entered data into Review Manager 5, carried out the analysis, drafted the final review and will be responsible for updates.

All review authors interpreted the analysis.

DECLARATIONS OF INTEREST

BW: none known; BW is a pain physician who treats people with fibromyalgia.

PK: none known.

MAF is a rheumatologist and pain physician who treats people with fibromyalgia. She is the head of the steering committee of the Canadian guideline on fibromyalgia. She has received:

1. Consulting fees from AMGEN (one each in 2013, 2015, two in 2014) and Bristol-Myers Squibb Canada (one in 2014);

2. Speaking/education fees from Janssen (one in 2014), Johnson & Johnson (one each in 2013, 2014), UCB Canada (one in 2015), Valeant (two in 2013), Pfizer (one in 2013) and Lilly (two in 2013, three in 2014);
3. In clinic training for ABBVIE staff (one each in 2014, 2015);
4. AD Board honoraria from Janssen (one in 2014), Pfizer (one in 2013), Purdue (one in 2013), Johnson & Johnson (one in 2014).

TP: none known; TP is a specialist pain physician and manages people with fibromyalgia.

WH is a specialist in general internal medicine, psychosomatic medicine and pain medicine, who treats people with fibromyalgia. He is a member of the medical board of the German Fibromyalgia Association. He is the head of the steering committee of the German guideline on fibromyalgia and a member of the steering committee of the European League Against Rheumatism (EULAR) update recommendations on the management of fibromyalgia. He received speaking fees for one educational lecture each from MSD Sharpe & Dohme (2014) and Grünenthal (2015) on pain management.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added selective outcome reporting (reporting bias) and group similarity at baseline (selection bias) in the risk of bias assessment. We defined criteria for assessing the reported methodology quality of the trials and for downgrading the quality of evidence.

NOTES

A new search within two years is not likely to identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be assessed for updating in four years. We will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Assessed for updating in 2020

A restricted search in July 2020 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in two years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Amitriptyline [therapeutic use]; Analgesics, Non-Narcotic [therapeutic use]; Cannabinoids [adverse effects] [*therapeutic use]; Dronabinol [adverse effects] [*analogs & derivatives] [therapeutic use]; Fibromyalgia [*drug therapy]; Health Status; *Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Aged; Humans; Middle Aged