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Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis (Review)

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[Intervention Review]

Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis

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ABSTRACT

Background

Spasticity and chronic neuropathic pain are common and serious symptoms in people with multiple sclerosis (MS). These symptoms increase with disease progression and lead to worsening disability, impaired activities of daily living and quality of life. Anti-spasticity medications and analgesics are of limited benefit or poorly tolerated. Cannabinoids may reduce spasticity and pain in people with MS. Demand for symptomatic treatment with cannabinoids is high. A thorough understanding of the current body of evidence regarding benefits and harms of these drugs is required.

Objectives

To assess benefit and harms of cannabinoids, including synthetic, or herbal and plant-derived cannabinoids, for reducing symptoms for adults with MS.

Search methods

We searched the following databases from inception to December 2021: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), CINAHL (EBSCO host), LILACS, the Physiotherapy Evidence Database (PEDro), the World Health Organisation International Clinical Trials Registry Platform, the US National Institutes of Health clinical trial register, the European Union Clinical Trials Register, the International Association for Cannabinoid Medicines databank. We hand searched citation lists of included studies and relevant reviews.

Selection criteria

We included randomised parallel or cross-over trials (RCTs) evaluating any cannabinoid (including herbal *Cannabis, Cannabis* flowers, plant-based cannabinoids, or synthetic cannabinoids) irrespective of dose, route, frequency, or duration of use for adults with MS.

Data collection and analysis

We followed standard Cochrane methodology. To assess bias in included studies, we used the Cochrane Risk of bias 2 tool for parallel RCTs and crossover trials. We rated the certainty of evidence using the GRADE approach for the following outcomes: reduction of 30% in the spasticity Numeric Rating Scale, pain relief of 50% or greater in the Numeric Rating Scale-Pain Intensity, much or very much improvement in the Patient Global Impression of Change (PGIC), Health-Related Quality of Life (HRQoL), withdrawals due to adverse events (AEs) (tolerability), serious adverse events (SAEs), nervous system disorders, psychiatric disorders, physical dependence.

Main results

We included 25 RCTs with 3763 participants of whom 2290 received cannabinoids. Age ranged from 18 to 60 years, and between 50% and 88% participants across the studies were female. The included studies were 3 to 48 weeks long and compared nabiximols, an oromucosal spray with a plant derived equal (1:1) combination of tetrahydrocannabinol (THC) and cannabidiol (CBD) (13 studies), synthetic cannabinoids mimicking THC (7 studies), an oral THC extract of C*annabis sativa* (2 studies), inhaled herbal C*annabis* (1 study) against placebo. One study compared dronabinol, THC extract of C*annabis sativa* and placebo, one compared inhaled herbal C*annabis*, dronabinol and placebo. We identified eight ongoing studies.

Critical outcomes

• Spasticity: nabiximols probably increases the number of people who report an important reduction of perceived severity of spasticity compared with placebo (odds ratio (OR) 2.51, 95% confidence interval (CI) 1.56 to 4.04; 5 RCTs, 1143 participants; I^2 = 67%; moderate-certainty evidence). The absolute effect was 216 more people (95% CI 99 more to 332 more) per 1000 reporting benefit with cannabinoids than with placebo.

• Chronic neuropathic pain: we found only one small trial that measured the number of participants reporting substantial pain relief with a synthetic cannabinoid compared with placebo (OR 4.23, 95% CI 1.11 to 16.17; 1 study, 48 participants; very low-certainty evidence). We are uncertain whether cannabinoids reduce chronic neuropathic pain intensity.

• Treatment discontinuation due to AEs: cannabinoids may increase slightly the number of participants who discontinue treatment compared with placebo (OR 2.41, 95% CI 1.51 to 3.84; 21 studies, 3110 participants; I^2 = 17%; low-certainty evidence); the absolute effect is 39 more people (95% CI 15 more to 76 more) per 1000 people.

Important outcomes

• PGIC: cannabinoids probably increase the number of people who report 'very much' or 'much' improvement in health status compared with placebo (OR 1.80, 95% CI 1.37 to 2.36; 8 studies, 1215 participants; I^2 = 0%; moderate-certainty evidence). The absolute effect is 113 more people (95% CI 57 more to 175 more) per 1000 people reporting improvement.

• HRQoL: cannabinoids may have little to no effect on HRQoL (SMD -0.08, 95% CI -0.17 to 0.02; 8 studies, 1942 participants; I^2 = 0%; low-certainty evidence);

• SAEs: cannabinoids may result in little to no difference in the number of participants who have SAEs compared with placebo (OR 1.38, 95% CI 0.96 to 1.99; 20 studies, 3124 participants; I^2 = 0%; low-certainty evidence);

• AEs of the nervous system: cannabinoids may increase nervous system disorders compared with placebo (OR 2.61, 95% CI 1.53 to 4.44; 7 studies, 1154 participants; I^2 = 63%; low-certainty evidence);

• Psychiatric disorders: cannabinoids may increase psychiatric disorders compared with placebo (OR 1.94, 95% CI 1.31 to 2.88; 6 studies, 1122 participants; I^2 = 0%; low-certainty evidence);

• Drug tolerance: the evidence is very uncertain about the effect of cannabinoids on drug tolerance (OR 3.07, 95% CI 0.12 to 75.95; 2 studies, 458 participants; very low-certainty evidence).

Authors' conclusions

Compared with placebo, nabiximols probably reduces the severity of spasticity in the short-term in people with MS. We are uncertain about the effect on chronic neurological pain and health-related quality of life. Cannabinoids may increase slightly treatment discontinuation due to AEs, nervous system and psychiatric disorders compared with placebo. We are uncertain about the effect on drug tolerance. The overall certainty of evidence is limited by short-term duration of the included studies.

PLAIN LANGUAGE SUMMARY

Cannabis and cannabinoids for people with multiple sclerosis

Key messages

• Treatment with nabiximols likely results in improvement of spasticity and may not increase serious harmful effects compared with placebo

• Compared with placebo, cannabinoids (nabiximols, C*annabis* extract, synthetic cannabinoids) likely improve well-being when measured with patient-reported outcomes

• Due to a lack of robust evidence, the benefit of these medicines for treating chronic neuropathic pain is unclear.

What is the issue?

Many people with multiple sclerosis (MS) experience spasticity that causes also pain and impacts on the ability to carry out daily activities. Spasticity is a form of increased muscle tone. *Cannabis*-based medicines refer to the use of *Cannabis*, or its ingredients called cannabinoids, as medical therapies to alleviate spasticity, chronic pain and other symptoms in MS. An international survey found that MS was one of the five medical conditions for which C*annabis* was most often used. Another survey conducted in the UK found that more than one in five people with MS reported they had used C*annabis* to try to manage their symptoms.

What did we want to find out?

We wanted to find out if cannabinoids were better than placebo in adults with MS to improve:

• spasticity;

• chronic neuropathic pain;

• well-being,

We also wanted to find out if cannabinoids were associated with:

• treatment discontinuation due to unwanted effects;

• serious harmful effects;

• nervous system disorders or psychiatric disorders;

• drug tolerance defined as a condition that occurs when the body gets used to a medicine so that more medicine is needed.

What did we do?
We searched for studies that compared cannabinoids against placebo in adult people with MS. We compared and summarised their results, and rated our confidence in the evidence, based on factors such as study methods and certainty of evidence.

What did we find?

We found 25 studies that involved 3763 people with MS, 2290 of whom received cannabinoids. Fifteen studies were very short term or short-term studies (two to 12 weeks), seven were intermediate term (12 to 26 weeks), and two were long term (50 and 156 weeks). One study reported results at three days only. The biggest study was conducted in 657 people and the smallest study involved 14 people. Most studies were done in European countries. Thirteen studies evaluated an oral spray (nabiximols) containing two compounds derived from the C*annabis* plant. The other studies compared different cannabinoids with placebo. Pharmaceutical companies funded 15 of the studies.

Main results

Compared with placebo, cannabinoids:

• probably increase the number of people who report an important reduction of perceived severity of spasticity for up to 14 weeks (evidence from five studies in 1143 people);

• may increase the number of people who report an important reduction of perceived severity of chronic neuropathic pain, but the evidence is very uncertain (evidence from one study in 48 people).

We are uncertain whether cannabinoids reduce chronic neuropathic pain intensity:

• probably increase the number of people who perceive their well-being as 'very much' or 'much' improved (evidence from eight studies in 1215 people);

• may increase slightly the number of people who discontinue treatment due to unwanted effects (evidence from 21 studies in 3110 people);

• may result in little to no difference in the number of people who have serious harmful effects (evidence from 20 studies in 3124 people);

• may increase nervous system disorders (evidence from seven studies in 1154 people) or psychiatric disorders (evidence from six studies in 1122 people);

• may have little to no effect on the number of people who have drug tolerance, but the evidence is very uncertain (two studies in 458 people).

What are the limitations of the evidence?

There is no high-quality evidence.

We are moderately confident that cannabinoids work better versus no cannabinoids to improve severity of spasticity and well-being in adults with MS. We have little confidence in our results for the effect on chronic neuropathic pain because the available evidence is limited.

There is limited evidence to determine the effects of cannabinoids on serious harmful effects, nervous system or psychiatric disorders, and drug tolerance.

How up to date is the evidence?
The evidence is up-to-date to December 2021.

Summary of findings 1. Summary of findings table - Cannabis compared to Placebo for health problem or population

Cannabis compared to Placebo for health problem or population

Patient or population: health problem or population
Setting: inpatient or outpatient
Intervention: Cannabis
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Cannabis				
Spasticity: number of participants reporting reduction of 30% in the spasticity NRS (follow up 6-14 weeks) follow-up: range 6 weeks to 14 weeks	287 per 1000	**502 per 1000** (385 to 619)	**OR 2.51** (1.56 to 4.04)	1143 (5 RCTs)	⊕⊕⊕⊖ Moderate[a]	Our confidence in this result is moderate, downgraded one level for serious risk of bias. Cannabis likely results in an increase in the number of participants with reduction of spasticity over 6-14 weeks' follow-up, when compared with placebo
Pain:number of participants reporting pain relief of 50% or greater in the NRS-PI (follow up 3 weeks)	167 per 1000	**458 per 1000** (182 to 764)	**OR 4.23** (1.11 to 16.17)	48 (1 RCT)	⊕⊖⊖⊖ Very low[b]	Our confidence in this result is very low, downgraded one level for serious risk of bias, two levels for very serious imprecision. The evidence is very uncertain about the effect of cannabis on the number of participants with reduction of pain over 3 weeks' follow-up, when compared with placebo.
PGIC:number of participants reporting much or very much improvement in the PGIC (follow up 4-48 weeks) follow-up: range 4 weeks to 48 weeks	209 per 1000	**323 per 1000** (266 to 385)	**OR 1.80** (1.37 to 2.36)	1215 (8 RCTs)	⊕⊕⊕⊖ Moderate[c]	Our confidence in this result is moderate, downgraded one level for serious risk of bias. Cannabis likely results in an increase in the number of participants who reported improvement in the PGIC over 4-48 weeks' follow-up, when compared with placebo
Health-related quality of life. Mean change from baseline	The mean health-related quality of life. Mean change	SMD **0.08 lower** (0.17 lower to 0.02 higher)	-	1942 (8 RCTs)	⊕⊕⊖⊖ Low[d]	Based on Cohen's effect sizes, and SMD of 0.08 represents a small effect. Our confidence in this result is low, downgraded two levels due to very serious risk of bias. We did not downgrade

assessed with: EQ-5D, SF-36 PCS, MSIS-29, Spitzer Quality of Life Index follow-up: range 3 weeks to 48 weeks	from baseline was **See comments**					for imprecision given the quite tight confidence intervals and very modest effects at either end of the confidence intervals.
Withdrawn due to adverse events (follow up 3-48 weeks) follow-up: range 3 weeks to 48 weeks	30 per 1000	**69 per 1000** (44 to 106)	**OR 2.41** (1.51 to 3.84)	3110 (21 RCTs)	⊕⊕⊖⊖ Low[e]	Our confidence in this result is low, downgraded one level for serious risk of bias, one level for imprecision. Cannabis may result in an increase in the number of participants who withdrew due to AEs over 3-48 weeks' follow-up, when compared with placebo
SAEs: number of participants with SAEs (follow up 3-48 weeks) follow-up: range 3 weeks to 48 weeks	33 per 1000	**44 per 1000** (31 to 63)	**OR 1.38** (0.96 to 1.99)	3124 (20 RCTs)	⊕⊕⊖⊖ Low[f]	Our confidence in this result is low, downgraded one level for serious risk of bias, one level for imprecision. Cannabis may result in a slight increase in the number of participants who had SAEs over 3-48 weeks' follow-up, when compared with placebo
Specific AEs:number of participants reporting nervous system disorders (follow up 4-48 weeks) follow-up: range 4 weeks to 48 weeks	250 per 1000	**465 per 1000** (338 to 597)	**OR 2.61** (1.53 to 4.44)	1154 (7 RCTs)	⊕⊕⊖⊖ Low[g]	Our confidence in this result is low, downgraded one level for serious risk of bias, one level for inconsistency. Cannabis may result in an increase in the number of participants who had nervous system disorders over 3-48 weeks' follow-up, when compared with placebo
Specific AEs: number of participants reporting psychiatric disorders (follow up 4-48 weeks) follow-up: range 4 weeks to 48 weeks	75 per 1000	**136 per 1000** (96 to 189)	**OR 1.94** (1.31 to 2.88)	1122 (6 RCTs)	⊕⊕⊖⊖ Low[h]	Our confidence in this result is low, downgraded one level for serious risk of bias, one level for imprecision. Cannabis may result in an increase in the number of participants who had psychiatric disorders over 3-48 weeks' follow-up, when compared with placebo
Specific AEs: number of participants reporting drug tolerance (follow up 14-48 weeks)	0 per 1000	**0 per 1000** (0 to 0)	**OR 3.07** (0.12 to 75.95)	458 (2 RCTs)	⊕⊖⊖⊖ Very low[i]	Our confidence in this result is very low, downgraded one level for serious risk of bias, two levels for imprecision. The evidence is very uncertain about the effect of cannabis on drug tolerance over 14-48 weeks' follow up.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_426325342660720441.

[a] Downgraded one level due to study limitations because all the included studies have an overall risk-of-bias judgement of some concerns.
[b] Downgraded one level due to study limitations (single study at high risk of attrition bias) and 2 levels for very serious imprecision because of the very small information size (wide confidence intervals).
[c] Downgraded one level due to studies' limitations (high risk of bias for 3 studies or of concerns for 5 studies).
[d] Downgraded 2 levels due to studies' limitations (2 studies due to missing outcome data, one due to deviations from intended interventions and missing outcome data, and one study due to missing outcome data and measurement of the outcome) and one level due to imprecision (wide confidence intervals crossing the line of no effect).
[e] Downgraded one level due to studies' limitations (one study at high risk of bias arising from the randomization process and the other studies with some concerns) and one level for imprecision (small number of events).
[f] Downgraded one level due to studies' limitations (one study at high risk of bias due to deviations from intended interventions, one study at high risk of bias due to randomization process and deviations from intended interventions, the other studies with some concerns) and one level due to imprecision (small number of events and confidence intervals crossed the line of no effect).
[g] Downgraded one level due to studies' limitations (2 studies at high risk of bias due to deviations from intended interventions, one study at high risk of bias due to deviations from intended interventions and in measurement of the outcome) and one level for inconsistency (heterogeneity P = 0.01; I^2 = 63%). Four studies suggest harm and three studies on either side of the line of no effect. One study reported no nervous system disorders over 4 weeks' follow up.
[h] Downgraded one level due to studies' limitations (one study at high risk of bias due to deviations from intended interventions and in measurement of the outcome, five studies with some concerns) and one level for imprecision (small number of events).
[i] Downgraded one level due to studies' limitations (2 studies with some concerns) and 2 levels due to imprecision (small number of events in one study; the other study reported no drug tolerance disorders).

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), and primary progressive (PPMS). Symptoms vary widely from person to person, and include fatigue, muscle spasticity, 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 tightening of their muscles. Therefore, it is necessary to consider the overlap of indications people have when use a symptomatic treatment. Spasticity is a form of increased muscle tone and it is a common and serious feature of MS that increases with disease progression and leads to deterioration in disability, weakness, and fatigue. Adaptive features may develop including contractures in muscle, tendons, and joints which can further worsen limb positioning, movement, and function. Spasticity also causes pain, bed sores, instability, and difficulty in maintaining hygiene. Treatment with anti-spasticity medication is made for different reasons in people with MS. People with severe mobility disability are treated to relieve pain, spasticity and make nursing care 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. Medical cannabis refers to the use of the plant C*annabis* or cannabinoids as a medical therapy to relieve symptoms. The most well-known phytocannabinoids are: delta-9-tetrahydrocannabinol (THC), which produces a variety of effects including altered cognitive and motor functions, psychotropic effects; and cannabidiol (CBD), a non-euphoric molecule (Hazekamp 2018; Izzo 2009; Morales 2017). Several standardised cannabinoids-based medicines are currently manufactured. Nabiximols (Sativex®) is made from extracts of the *Cannabis sativa* plant and contains an equal mix of the cannabinoids THC and CBD. It is taken as an oromucosal spray. Bedrocan® and Bedrobinol® are standardised preparations of C*annabis* flowers with a CBD content of less than 1% (in both preparation), 22% and 13.5% THC, respectively. Bediol® (6.3% THC and 8% CBD) and Bedrolite® (less than 1% THC and 9% CBD) are standardised *Cannabis* flowers both available in granular form. Bedica®, with 14% THC and less than 1% CBD, is a standardised preparation, available in granular form, obtained from the variety *indica* of *Cannabis* flowers.

There are several routes of administration for *Cannabis*, including inhalation, oral, oromucosal, sublingual, transdermal, eye drops, topical and rectal (Russell 2018). In clinical practice, inhalation, oromucosal and oral administration are most commonly used. Depending on the mode of administration, the onset and duration of *Cannabis* effects may vary. Due to the lipophilicity of cannabinoids, inhalation, i.e. smoking and vaporising, leads to a rapid onset of action (within minutes) and a short duration of action (maximum two hours). Smoking is not used for medicinal purposes due to the inhalation of toxic by-products (such as carbon monoxide and polycyclic aromatic hydrocarbons) produced by the combustion of cigarettes. Oral and oromucosal administration results in a slow onset of action but a longer duration of action. Following *Cannabis* use, the bioavailability of cannabinoids after inhalation and oral or oromucosal administration is high and low (due to liver metabolism), respectively. Among the *Cannabis* products, nabiximols is the most commonly used in clinical trials. A titration phase is required to achieve the optimal dose of nabiximols. The number and timing of sprays vary from patient to patient. The dose is gradually increased by one spray per day, up to a maximum of 12 sprays per day, until optimal symptom relief is achieved. The median dose in clinical trials for people with MS are eight sprays per day. After oromucosal spray administration of nabiximols, plasma levels of THC and other cannabinoids are lower than after smoking or inhaling cannabis at a similar dose.

Several cannabinoids identical in structure to naturally occurring cannabinoids have been synthesised. Dronabinol (Marinol® or Syndros®) and nabilone (Cesamet® or Canemes®) are synthetic delta-9-THC analogues. They are administered as oral capsules (both drugs) or oral solutions (dronabinol). According to the literature, elimination of oral cannabinoids from plasma is biphasic with an initial half-life of about four hours, and the final elimination half-life is 24 to 36 hours or longer due to slow release from adipose 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 on *Cannabis* and Sativex® use. The survey was conducted anonymously through various channels to capture the range of experiences and views that people with MS hold. More than one in five 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 medical 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. Use of medical *Cannabis* was associated with recreational C*annabis* use. The symptoms reported by medical *Cannabis* users to be most effectively relieved were stress, sleep, mood, spasticity, 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). A large (2009 participants; response rate of 62%) and comprehensive questionnaire survey on the use of *Cannabis* in Danish MS patients found that illegal *Cannabis* use was common among Danes with MS as only 21% of the current *Cannabis* users received prescribed *Cannabis*-based medicine. Current *Cannabis* users reported high efficacy in relieving pain, spasticity and sleep

disturbances. In addition, only mild to moderate severity of adverse effects were reported (Gustavsen 2019). A study from Canada reported that about 50% of people with MS would consider the legal use of *Cannabis* if evidence of benefit was 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 [endocannabinoid, chiefly anandamide (AEA) and 2-arachidonoylglycerol (2-AG)], and the enzymes responsible for the synthesis and degradation of the endocannabinoid (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 the cannabinoid receptors CB1 and CB2, acting as a partial agonist. CB1 receptors are mainly located in the CNS or highly expressed 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.

The endocannabinoid system has been shown to be modulated in MS patients. AEA levels, but not 2-AG levels, were found to be elevated in the cerebrospinal fluid (CSF) of RRMS patients experiencing current relapse (Centonze 2007). Similarly, Jean-Gilles and colleagues reported both the presence of higher plasma AEA levels in patients with RRMS or SPMS compared to controls, and a decrease in mRNA expression of fatty acid amide hydrolase (FAAH, an enzyme responsible for endocannabinoids degradation) in SPMS but not in RRMS or PPMS blood (Jean-Gilles 2009). In contrast, in another study, low levels of endogenous cannabinoids were found in the CSF of patients with MS compared to controls (Di Filippo 2008). However, the authors also reported an increase in AEA levels in the CSF during relapses or in RRMS patients with gadolinium-enhancing lesions, which were, however, lower than those of control subjects, suggesting a relationship between AEA levels and the number of inflammatory lesions (Di Filippo 2008). Up-regulation of CB1 and CB2 expression was also found in glial cells within demyelinated plaques from MS patients (Benito 2007) and in blood samples from PPMS patients (Jean-Gilles 2009). These findings have raised the interesting possibility that drugs targeting the endocannabinoid system (i.e. the use of cannabinoids or inhibitors of FAAH) may represent a potential pharmacological strategy to reduce the symptoms and slow disease progression in MS.

The use of cannabinoids-containing products has been demonstrated to have the potential to affect both pathogenic mechanisms and symptoms of MS, as they are able to suppress neuro inflammation (via CB2 activation) (Mestre 2018), and 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 given the autoimmune hypothesis of MS aetiology (Fitzpatrick 2017; Mestre 2018; Oláh 2017), the increased CB1 and CB2 receptors in blood samples from PPMS patients (Jean-Gilles 2009) and a variety of animal studies demonstrating the immunomodulatory effects of cannabinoids during the inflammatory processes that occur in MS (Gonçalves 2019; Furgiuele 2021). In addition, a recent prospective case-control study has shown that cannabis use reduces and increases the serum pro-inflammatory and anti-inflammatory cytokines levels in MS patients, respectively (Mustafa 2021).

Why it is important to do this review

Results of available surveys show that the demand of people with MS for symptomatic treatment with cannabinoid-based medicines is high (Banwell 2016; Hazekamp 2013; Kindred 2017; MS Society 2014). Therapies that relieve the disabling symptoms of MS include botulinum toxin injections, baclofen or tizanidine for spasticity, anticonvulsants, antidepressant or analgesics for neuropathic pain, and anticholinergic drugs for bladder dysfunction. However, these symptomatic therapies are of limited efficacy or are poorly tolerated (Newsome 2017). Many patients with MS have a combination of pain and spasticity, and could benefit from cannabinoid-based medicines that have an overlap of indications.

International guidelines have reached different recommendations on the use of cannabinoids 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 cannabinoid-based medicines are in development (NICE 2019). The Association of British Neurologists have advised clinicians to use nabiximols in people with MS who had an unsatisfactory response to conventional anti-spasticity medications (ABN 2018; RCP 2018). The American Academy of Neurology does not support the legalisation 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 cannabinoid-based medicines for MS, but was recently asked to place this therapy for progressive MS on the fast track (Reston 2019). The European Medicines Agency (EMA) authorised 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 showed 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 cannabinoid-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 authorisation and use of cannabinoid-based medicines for MS. Nabiximols is approved and available for MS related spasticity in 29 US states including the District of Columbia, in Canada, Israel, and 21 European countries (Abuhasira 2018), and 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) (Krcevski-Skvarc 2018). Approval of cannabinoid-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 cannabinoids can be prescribed to people with MS under strict controlled conditions, but there are differences between countries on who can and cannot prescribe cannabinoid-based medicines, e.g. in the UK nabiximols can be prescribed only by specialist doctors with expertise in treating MS.

There is a growing interest into the therapeutic benefit of cannabinoid-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 cannabinoid-based products were moved from Schedule 1 to Schedule 2 in the UK. This decision would allow these medicines to be prescribed under controlled conditions by registered practitioners. In addition, moving the whole class of cannabinoids out of Schedule 1, will allow the evidence base on benefits and harms associated with this class of drugs to be improved through research (Davies 2018).

Due to the conflicting conclusions of systematic reviews on benefits and harms of cannabinoids 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 harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in MS.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled (parallel or cross-over) trials (RCTs). We included cross-over trials irrespective of the length of the washout period.

Types of participants

We included studies in 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 progressive-relapsing MS (PRMS). We included participants regardless of disease duration and degree of disability.

Types of interventions

Any cannabinoids 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 included as a comparison intervention placebo or any active comparator. We included concomitant interventions if they were used in all the comparison groups.

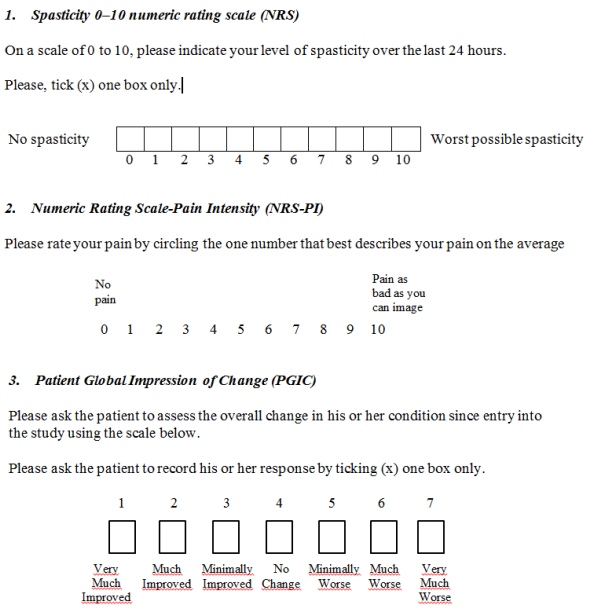
Types of outcome measures

We included 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 included short- and long-term outcomes reported in the included trials.

1. Critical outcomes

- Spasticity: number of participants reporting a reduction of 30% or greater in the spasticity Numeric Rating Scale (NRS), over baseline. This reduction has been identified as a change that represents a clinically important difference (CID) from baseline 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 (the worst possible spasticity) (Figure 1).
- Chronic neuropathic pain: number of participants reporting pain relief of 50% or greater in the Numeric Rating Scale-Pain Intensity (NRS-PI), over baseline. NRS-PI is a 0 to 10 rating scale with scores ranging from 0 ‘no pain' to 10 ‘worst possible pain' (Farrar 2010; Figure 1).

Figure 1. Spasticity and pain scales (NRS); Patient Global Impression of Change (PGIC)



1. Spasticity 0–10 numeric rating scale (NRS)

On a scale of 0 to 10, please indicate your level of spasticity over the last 24 hours.

Please, tick (x) one box only.

No spasticity ☐☐☐☐☐☐☐☐☐☐☐ Worst possible spasticity
0 1 2 3 4 5 6 7 8 9 10

2. Numeric Rating Scale-Pain Intensity (NRS-PI)

Please rate your pain by circling the one number that best describes your pain on the average

No pain — Pain as bad as you can image

0 1 2 3 4 5 6 7 8 9 10

3. Patient Global Impression of Change (PGIC)

Please ask the patient to assess the overall change in his or her condition since entry into the study using the scale below.

Please ask the patient to record his or her response by ticking (x) one box only.

1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐
Very Much Improved	Much Improved	Minimally Improved	No Change	Minimally Worse	Much Worse	Very Much Worse

Where studies measure these outcomes as continuous data only, we included them as separate analyses as important outcomes. The raw change CID cutoff points are –1.27 for the spasticity, 0–10 NRS (Farrar 2008) and -2.5 for the NRS-PI (Farrar 2010).

- Number of participants withdrawn due to adverse events (AEs) (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) (Dworkin 2008; Farrar 2008; Guy 1976) (Figure 1). Where studies measured the outcome as continuous data only, we included them as separate analyses as outcomes of limited importance.
- Health-related quality of life (HRQoL), measured with condition-specific HRQoL as the 54-item MSQoL (MSQoL-54) (Vickrey 1995), or generic HRQoL validated measures reported in the included studies, as the 36 item Short Form (SF-36) (Ware 1992), or Euroqol-5 dimensions (EQ-5D) (EuroQol Group 1990).
- The total number of serious adverse events (SAEs). If an insufficient number of studies reported the total number of SAEs and person-years, we used the number of participants with at least one SAE as defined in the study.
- Number of participants reporting specific AEs, 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 the Modified Ashworth scale (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, measured with the Fatigue Severity scale (FSS) or the Modified-Fatigue Impact Scale (M-FIS). FSS is a self-administered questionnaire with nine questions graded on a seven-point Likert-like scale where 1 indicates strong disagreement and 7 strong agreement, and the final score represents the mean value of the nine items questionnaire. 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) (Multiple Sclerosis Council 1998). 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, tremor, and daily functioning, specifically the activities of daily living (ADL), e.g.

the Barthel index (BI) which is a 10-item scale that measures daily function and gives a score out of 20 with higher scores suggesting greater independence (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. CGIC is assessed on a seven-point Likert-like scale that used three categories of improvement (slightly improved, much improved, or very much improved), three categories of worsening (slightly worse, much worse, or very much worse), and an option of "no change" (Collin 2010).
- Reduced use of other symptomatic treatments (e.g. for spasticity or pain).

Search methods for identification of studies

We did not apply any language restrictions to the search.

Electronic searches

We designed search strategies for electronic databases according to methods suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2019). The Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System group's Information Specialist peer-reviewed them. We searched all potential relevant trials registries in detail to detect ongoing as well as completed studies, but not yet published studies.
We searched the following databases and sources, updated on 31 December 2021.

Databases of medical literature

- Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR; 2021, Issue 12) in the Cochrane Library (searched 27 December 2021; Appendix 1);
- MEDLINE (PubMed) (1966 to 31 December 2021; Appendix 1);
- Embase (EMBASE.com) (1974 to 31 December 2021; Appendix 1);
- CINAHL (EBSCO host) (Cumulative Index to Nursing and Allied Health Literature; 1981 to 27 December 2021; Appendix 1);
- LILACS (Bireme) (Latin American and Caribbean Health Sciences Literature; 1982 to 27 December 2021; Appendix 1);
- Physiotherapy Evidence Database (PEDro) (1990 to 27 December 2021; Appendix 1).

Trials registries and registry platforms to identify ongoing studies and results of completed studies

- World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP; trialsearch.who.int; searched 20 December 2021; Appendix 1);
- US National Library of Medicine ClinicalTrials.Gov study registry (www.ClinicalTrials.gov; searched 29 December 2021; Appendix 1);
- European Union Clinical Trials Register (www.clinicaltrialsregister.eu; searched 29 December 2021; Appendix 1);
- International Association for Cannabinoid Medicines (IACM) databank (www.cannabis-med.org/studies/study.php; searched 29 December 2021; Appendix 1).

Searching other resources

We reviewed the references of any RCTs identified and relevant reviews. Because of the comprehensive nature of the electronic search and handsearching, we did not contact authors of included studies on information provision for the review. We considered AEs described in included studies only.

Data collection and analysis

Selection of studies

We used 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) independently screened the titles and abstracts and discarded studies that were not applicable; however, they initially retained studies and reviews that might include relevant data or information on trials. The two review authors compared multiple reports of the same study and used the most comprehensive report. They linked together multiple publications as companion reports, but excluded true duplicates. FB and GF resolved discrepancies in judgement by discussion and reported excluded studies and their reasons for exclusion in the 'Characteristics of excluded studies' table. We include a PRISMA flow chart (Figure 2) reporting the selection process (Moher 2009).

Figure 2. Search updated to December 27, 2021

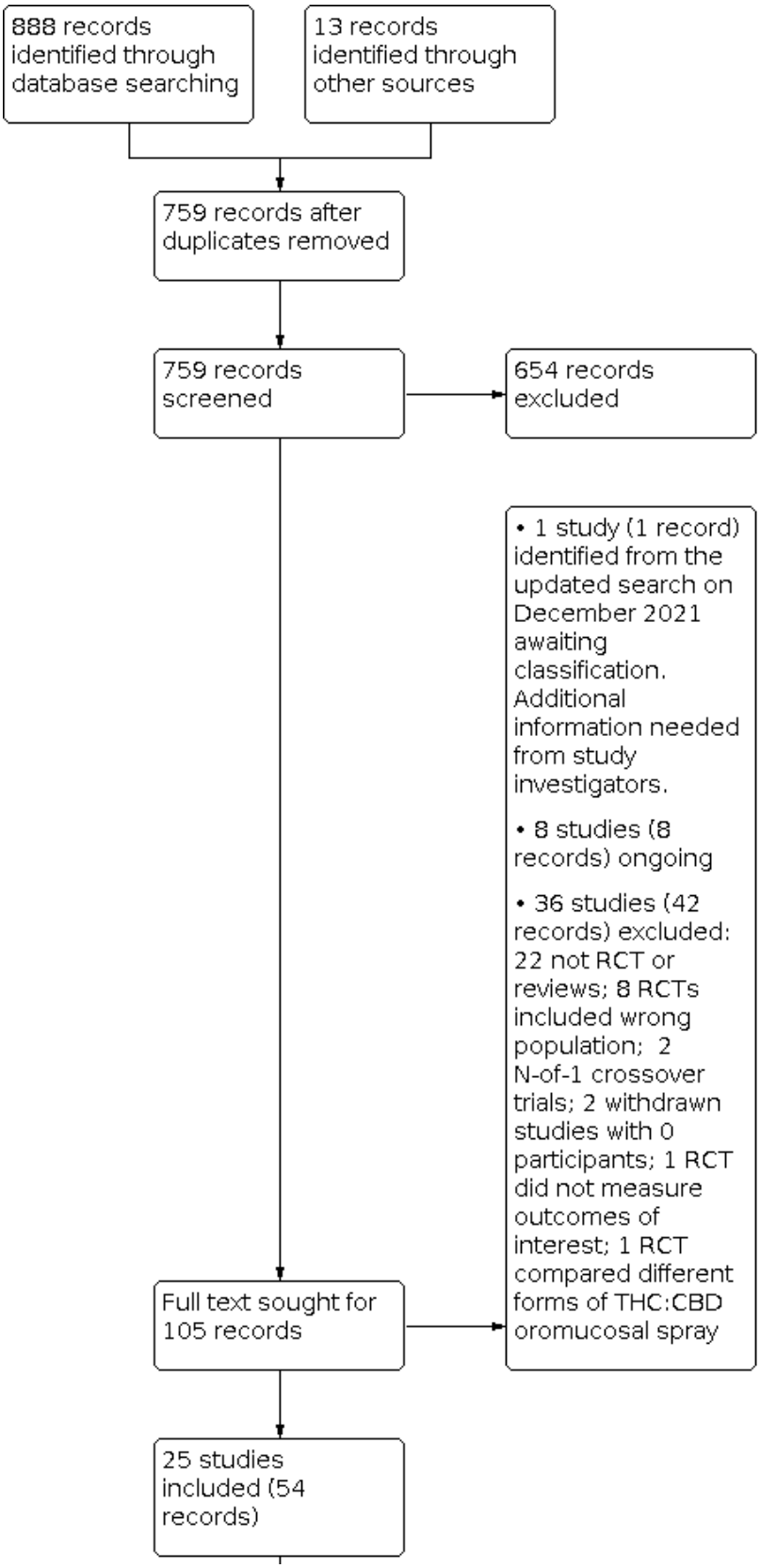
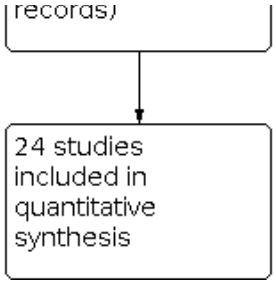


Figure 2. (Continued)



Data extraction and management

Two teams of two review authors each (FB and GF; SM and MC) independently extracted study characteristics and outcome data from the included parallel trials and cross-over trials using a predefined data extraction form in an Excel spreadsheet. They resolved any disagreements by discussion all together.

Study characteristics

From each included study we extracted data on the following:

- 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);
- design (parallel or cross-over); inclusion and exclusion criteria; number of randomised participants; early termination of trial;
- length of the washout period in cross-over trials.
- conflict of interests of study authors;
- funding of the study.

Outcome data

We extracted the number of participants who had critical and important outcomes and outcomes of limited importance. For the spasticity and pain relief outcomes, we extracted 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 AE outcomes, we extracted from cross-over trials the number of withdrawals due to any AE, and the number of SAEs on each treatment in each treatment period (when possible).

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

We extracted authors' definition and instruments used to measure spasticity, neuropathic pain, and important outcomes. We extracted arm-level data when possible, or effect sizes when arm-level data were not available. We extracted data at the authors' defined timing points.

We noted in the Characteristics of included studies table if outcome data were not reported, or were reported but not in a usable way.

Data on potential effect modifiers

We considered the following potential effect modifiers in each included study:

- population: forms of MS; baseline severity and duration of spasticity and pain; prior and actual treatment with anti-spasticity medications or analgesics; prior use of cannabinoids;
- study design: placebo or active control; enriched design; 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.

Assessment of risk of bias in included studies

For the scope of the review, we assessed 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 AEs we assessed the effect of adhering to the intervention ('per protocol effect').

Four review authors (FB, GF, KD, SM) independently assessed the risk of bias of each included study using version 2 of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2) (Higgins 2019) (version 22 August 2019). Review authors did a calibration exercise (i.e. a pilot run of the RoB 2 tool for RCTs, comparison of all the evaluations and agreement on the answers to the signalling questions (SQs) and the final judgments for each domain). On the basis of the results of this exercise, both in terms of the inter-rater reliability and of the difficulties found in the interpretation and application of the SQs to the specific condition and intervention assessed by the review, all the review authors prepared a detailed implementation document where, for each SQ, explanation was provided on how to interpret the question from a practical point of view (i.e. providing examples) and how to respond considering the issues specific for the condition and the interventions assessed in the review (see Appendix 2 for the implementation document). After the completion of this document, raters reassessed all the included studies (Minozzi 2021).

We assessed critical and important outcomes reported in the Summary of findings 1' using RoB 2, which is structured into the following bias:

- arising from the randomisation process;
- due to deviations from intended interventions;
- due to missing outcome data;

- in measurement of the outcome;
- in selection of the reported result.

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

- period effect;
- carry-over 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 RoB 2 assessment, we used the Excel tool available at sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2.

We judged each domain as being at low risk of bias, some concerns, or high risk of bias. We reached 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.

Measures of treatment effect

We calculated dichotomous outcomes as odds ratios (ORs) and 95% confidence intervals (CIs) for parallel and cross-over trials. For continuous outcomes, we calculated mean difference (MD) or standardised mean difference (SMD) for the same continuous outcome measured with different metric. The SMD is the difference in mean effects in the experimental and control groups divided by the pooled standard deviation of participants' outcomes.

Unit of analysis issues

Studies with multiple treatment groups

For multi-arm trials, relevant intervention groups were those that could be included in a pairwise comparison which, if investigated alone, would meet the review inclusion criteria. For example, if we identified a study comparing 'Nabiximols versus tizanidine versus nabiximols plus tizanidine', only one comparison ('Nabiximols versus tizanidine') was used since it addressed the review objective. Thus, we would not have used data from the 'Nabiximols plus tizanidine' treatment as it was not relevant to the review. However, if the study compared 'Nabiximols versus tizanidine versus baclofen', all three pairwise comparisons of interventions were relevant to the review. In this case we treated the multi-arm studies as multiple independent two-arm studies. We converted 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 combined means and SDs using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over studies

When possible, we planned to enter mean difference (MD) and standard errors (SEs) from paired data for cross-over studies with the generic inverse variance (GIV) function in RevMan Web (Review Manager Web). Unfortunately this was mostly not possible due to the way eligible cross-over trials reported data. These have been included in the meta-analysis as though data were from parallel trials and footnotes have been included in the forest plot.

Dealing with missing data

We used data that reflected the intention-to-treat (ITT) analysis for each included outcome except for safety outcomes, as noted above in Assessment of risk of bias in included studies. In the protocol we had planned to evaluate methods for monitoring and detecting AEs in included studies. This has been removed since we assessed this aspect for SAEs and specific AEs using RoB 2. Different scenarios for assessing the impact of missing data on outcomes were not feasible, and on adverse outcomes is not likely to be plausible (i.e. assuming that participants whose data were missing experienced AEs). For continuous outcomes, where SDs were missing, we calculated 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 clinical heterogeneity, we had planned to assess differences in characteristics of included participants, e.g. MS course, disease duration, baseline severity of spasticity or chronic neuropathic pain across trials using information reported in Characteristics of included studies. However, this was not possible because most studies included grouped data as relapsing and progressive forms of MS, data on disease duration were not available, and studies measured baseline severity of spasticity and pain with different instruments.

Assessment of statistical heterogeneity

We assessed the presence of statistical heterogeneity using the I^2 statistic. When the I^2 statistic value was greater than 50% (substantial heterogeneity), we considered possible reasons for this.

Assessment of reporting biases

We evaluated the possibility of non-reporting bias by means of contour-enhanced funnel plots, if a meta-analysis included at least 10 studies (Peters 2008).

Data synthesis

We had planned to combine dichotomous outcomes from parallel-group and cross-over trials according to the method of Becker 1993. This was not possible because data were not available. We used the Mantel-Haenszel method in random-effects meta-analysis to calculate odds ratios. For continuous outcomes, we calculated MD or SMD, if the outcome was measured on different scales (e.g. pain or quality of life), with 95% CIs. We used a random-effects model because we assumed that the studies were not all estimating the same intervention effect, and were estimating intervention effects that follow a distribution across studies (DerSimonian 1986). We conducted analyses using RevMan Web (Review Manager Web).

Subgroup analysis and investigation of heterogeneity

We did prespecify subgroup analyses of number of participants reporting spasticity or pain reduction over baseline for study

design and duration of follow-up, baseline severity score, different cannabinoids and co-therapies, to assess whether treatment effects varied across subgroups. However, we did not conduct subgroup analyses for the following reasons. First, the variation in treatment effect on spasticity and pain tended to be explained by outlying single studies rather than variation across all the studies. Second, less than 10 studies for subgroup analyses as planned were available leading to imbalance in studies when defined by subgroups. Third, there was a predominance of parallel-group studies and short duration of follow-up.

Sensitivity analysis

In the protocol we had planned a sensitivity analysis on the exclusion of trials that we judged to be at high risk of bias or to raise some concerns in at least one domain of RoB 2. However, since we judged all included trials at high risk of bias or with some concerns we did not seek to conduct a sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review as summary of findings tables, according to Cochrane guidance (Schünemann 2011). We provided estimates based on the methodology developed from the GRADE Working Group (Atkins 2004).

In the summary of findings tables we included comparison of cannabinoids with placebo and an overall assessment of the evidence for critical and important outcomes and number of participants.

- Reporting reduction of 30% in the spasticity Numeric Rating Scale (NRS).
- Reporting pain relief of 50% or greater in the NRS-PI.
- Reporting much or very much improvement in the Patient Global Impression of Change (PGIC).
- Reporting improvement in quality of life.
- Withdrawn due to AEs (tolerability).
- Who had at least one SAE.
- Reporting specific AEs including nervous system disorders, psychiatric disorders, or physical dependence.

In the summary of findings table, we prioritised long-term outcomes if they were available, otherwise we included short-term outcomes.

We assessed 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 assigned one of four levels of certainty of evidence: high, moderate, low, or very low.

RESULTS

Description of studies

For a full description of studies please see the Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The results of our searches are detailed in a PRISMA diagram (Figure 2) (Moher 2009). Our electronic searches retrieved 888 records. Our handsearching of other resources produced 13 additional references. After removing 142 duplicate references, we evaluated a total of 759 records, of which we excluded 654 on the basis of title and abstract. From the remaining 105 records, we categorised 1 record (one study identified from the updated search on December 2021) as awaiting classification, because we could not identify the randomisation process and the control intervention, therefore additional information is needed from study investigators. Available details for the study are provided in the Studies awaiting classification table. Eight studies (eight reports) may be eligible as ongoing; further information is in the Ongoing studies table. We excluded 36 studies (42 full-text reports) (see Figure 2 for details).

Included studies

This review included 25 completed RCTs with 3763 participants of whom 2290 received cannabinoids, (Aragona 2009; Collin 2007; Collin 2010; Corey-Bloom 2012; Fox 2004; Kavia 2010; Killestein 2002; Langford 2013; Leocani 2015; Markova 2018; NCT00682929; NCT01606176; Notcutt 2012; Novotna 2011; Rog 2005; Schimrigk 2017; Svendsen 2004; Turcotte 2015; Vachova 2014; Van Amerongen 2017; Vaney 2004; Wade 2004; Zajicek 2003_CAMS; ZAJICEK 2012 MUSEC; Zajicek 2013_CUPID). The included studies were published between 2002 and 2018. The table "Characteristics of included studies" provides details of individual studies.

Study design

We included 18 parallel RCTs (Collin 2007; Collin 2010; Kavia 2010; Langford 2013; Markova 2018; NCT00682929; NCT01606176; Notcutt 2012; Novotna 2011; Rog 2005; Schimrigk 2017; Turcotte 2015; Vachova 2014; Van Amerongen 2017; Wade 2004; Zajicek 2003_CAMS; ZAJICEK 2012 MUSEC; Zajicek 2013_CUPID) and seven cross-over RCTs (Aragona 2009; Corey-Bloom 2012; Fox 2004; Killestein 2002; Leocani 2015; Svendsen 2004; Vaney 2004). Two studies (Markova 2018; Novotna 2011) used an enriched enrolment two-phases design, and two studies (Langford 2013; Notcutt 2012) used an enriched enrolment randomised withdrawal design.

Outcome timing

Five studies were very short-term studies (two to four weeks) (Aragona 2009; Fox 2004; NCT01606176; Svendsen 2004; Vaney 2004), 10 were short-term studies (four to 12 weeks) (Collin 2007; Kavia 2010; Killestein 2002; Leocani 2015; NCT00682929; Notcutt 2012; Rog 2005; Turcotte 2015; Van Amerongen 2017; Wade 2004), seven were intermediate-term studies (12 to 26 weeks) (Collin 2010; Langford 2013; Markova 2018; Novotna 2011; Schimrigk 2017; Zajicek 2003_CAMS; ZAJICEK 2012 MUSEC) and two were long-term studies (50 weeks in Vachova 2014 and 156 weeks in Zajicek 2013_CUPID). Corey-Bloom 2012 reported outcome at three days.

Study setting

Fifteen studies were multicentre and originated from UK (Fox 2004; NCT01606176; Notcutt 2012; Wade 2004; Zajicek 2003_CAMS; ZAJICEK 2012 MUSEC; Zajicek 2013_CUPID); Germany (Schimrigk 2017); Czech Republic (Vachova 2014); UK and Romania (Collin 2007); UK and Czech Republic (Collin 2010); UK, Belgium and

Romania (Kavia 2010); UK, Canada, Spain, France and Czech Republic (Langford 2013); Czech Republic and Austria (Markova 2018); UK, Spain, Poland, Czech Republic and Italy (Novotna 2011). Ten studies were single-centre and originated from Italy (Aragona 2009; Leocani 2015); the USA (Corey-Bloom 2012; NCT00682929); the Netherlands (Killestein 2002; Van Amerongen 2017); UK (Rog 2005); Denmark (Svendsen 2004); Canada (Turcotte 2015); and Switzerland (Vaney 2004).

Sample sizes

The sample sizes ranged from 14 (Fox 2004) to 657 (Zajicek 2003_CAMS) participants.

Study funding

Fifteen studies were funded by the manufacturer of the drug (Collin 2007; Collin 2010; Kavia 2010; Langford 2013; Leocani 2015; Markova 2018; NCT01606176; Notcutt 2012; Novotna 2011; Rog 2005; Schimrigk 2017; Turcotte 2015; Vachova 2014; Van Amerongen 2017; Wade 2004), eight studies were founded by public funds (Aragona 2009; Corey-Bloom 2012; Fox 2004; Killestein 2002; NCT00682929; Vaney 2004; Zajicek 2003_CAMS; Zajicek 2013_CUPID,) and two studies were funded by mixed funds (Svendsen 2004; ZAJICEK 2012 MUSEC)

Participants

- Type of MS. Most studies included all types of MS, except the Turcotte 2015 study that included participants with RRMS only and three studies (Leocani 2015; Van Amerongen 2017; Zajicek 2013_CUPID) that included participants with SPMS and PPMS.
- Type of symptom. Thirteen studies (Aragona 2009; Collin 2007; Collin 2010; Corey-Bloom 2012; Killestein 2002; Leocani 2015; Markova 2018; NCT00682929; Notcutt 2012; Novotna 2011; Vachova 2014; Vaney 2004; Zajicek 2003_CAMS) included participants with spasticity, six studies with central neuropathic pain (Langford 2013; NCT01606176; Rog 2005; Schimrigk 2017; Svendsen 2004; Turcotte 2015), two studies (Van Amerongen 2017; ZAJICEK 2012 MUSEC) with spasticity and central neuropathic pain, one study (Fox 2004) with tremor, one study (Kavia 2010) with overactive bladder due to MS, one study (Wade 2004) with multiple symptoms associated with MS, and one study (Zajicek 2013_CUPID) included participants with disease progression in the year preceding randomisation.
- Age and gender. Age of the participants ranged from 18 to 60 years. The percentage of females ranged from 50% to 88%.
- Inclusion criteria at baseline for spasticity. Four studies (Collin 2010; Markova 2018; Novotna 2011; ZAJICEK 2012 MUSEC) required a score of 4 or above on the spasticity: numeric rating scale (NRS) (moderate to severe spasticity) scale, six studies (Aragona 2009; Collin 2007; Killestein 2002; Van Amerongen 2017; Vaney 2004; Zajicek 2003_CAMS) an Ashworth score of 2 or above (moderate to severe spasticity), one study (Corey-Bloom 2012) a modified Ashworth score of 3 or above, and one study (Leocani 2015) a modified Ashworth score greater than 1. The remaining studies (NCT00682929; Notcutt 2012; Vachova 2014) did not report on an inclusion criterion of a defined spasticity intensity. Most studies required for inclusion that spasticity was not wholly relieved with current antispastic therapy.
- Inclusion criteria at baseline for pain. Four studies (Langford 2013; NCT01606176; Rog 2005; Schimrigk 2017) required a pain score of 4 or above on the NRS-PI, one study (Svendsen 2004) a score of 3 or above on the NRS-PI, and one study (Turcotte 2015) a visual analogue score (VAS) pain score of 50 or above. All the included studies stipulated that pain had to be refractory to previous analgesics.
- Exclusion criteria. All studies excluded participants with major medical diseases (history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders) and with a history of alcohol or substance abuse. Most studies excluded women who were pregnant, breastfeeding, or planning pregnancy during the course of the study.
- Previous experience of participants with cannabinoids. Two trials (Markova 2018; Novotna 2011) were with an enriched-design and one trial (Notcutt 2012) was an enriched enrolment withdrawal study. Ten studies (Collin 2007; Collin 2010; Corey-Bloom 2012; Fox 2004; Killestein 2002; Langford 2013; Rog 2005; Vachova 2014; Vaney 2004; Wade 2004) reported previous cannabis experience of participants for medical or recreational use. The percentage of participants with previous cannabis experience ranged from 6% to 80%. One study (Aragona 2009) excluded participants with previous experience with cannabinoids.

Interventions

Thirteen RCTs used an oromucosal spray with a plant-derived combination of tetrahydrocannabinol (THC) and cannabidiol (CBD) (Sativex®) (Aragona 2009; Collin 2007; Collin 2010; Kavia 2010; Langford 2013; Leocani 2015; Markova 2018; NCT01606176; Notcutt 2012; Novotna 2011; Rog 2005; Vachova 2014; Wade 2004). Five studies used oral synthetic cannabinoids mimicking THC (dronabinol: Schimrigk 2017; Svendsen 2004; Zajicek 2013_CUPID; nabilone: Turcotte 2015; namisol: Van Amerongen 2017). Three studies used oral THC extract of *Cannabis sativa* (Fox 2004; Vaney 2004; ZAJICEK 2012 MUSEC). One study used inhaled herbal *Cannabis* (Corey-Bloom 2012). All these studies compared cannabinoids with placebo. Two studies compared dronabinol, THC extract of *Cannabis sativa* and placebo (Killestein 2002; Zajicek 2003_CAMS), and one compared dronabinol, inhaled herbal *Cannabis*, and placebo (NCT00682929).

Co-interventions

Two studies (Langford 2013; Svendsen 2004) allowed paracetamol as rescue medication and one study (Schimrigk 2017) allowed tramadol. Studies including spasticity outcome allowed stable doses of anti-spasticity medications (e.g. baclofen, tizanidine, benzodiazepines, dantrolene) (Collin 2010; Langford 2013; Markova 2018; Notcutt 2012; Novotna 2011; Van Amerongen 2017; Vaney 2004; ZAJICEK 2012 MUSEC). Studies including pain outcome allowed stable doses of analgesics co-interventions (e.g. gabapentin) and amitriptyline (Collin 2010; Langford 2013; Markova 2018; Rog 2005; Schimrigk 2017; Van Amerongen 2017).

Critical outcomes

Spasticity. Eight parallel trials (Collin 2007; Collin 2010; Langford 2013; Markova 2018; Notcutt 2012; Novotna 2011; Van Amerongen 2017; ZAJICEK 2012 MUSEC) provided data for the spasticity outcome measured with the NRS 0-10. We could not include data from one cross-over study (Leocani 2015) because authors

defined benefit as ≥ 20 % improvement in the NRS 0-10 score that we considered an inappropriate threshold in our protocol. A reduction of 30% or greater in the NRS over baseline is the minimum clinically important difference (MCID) in participants with MS-related spasticity. We included 11 studies (Collin 2007; Collin 2010; Markova 2018; NCT00682929; Notcutt 2012; Novotna 2011; Vachova 2014; Van Amerongen 2017; Vaney 2004; Wade 2004; Zajicek 2003_CAMS) in the meta-analysis of spasticity measured with the Ashworth scale or MAS. We could not include data from two cross-over studies. One (Corey-Bloom 2012) because authors did not report suitable data accounting for design. Authors of the other study (Killestein 2002) reported the Ashworth scores only in one figure and the numerical data were not available.

Chronic neuropathic pain. We evaluated pain measured with NRS-PI from nine studies (Collin 2010; Langford 2013; Markova 2018; NCT01606176; Rog 2005; Schimrigk 2017; Svendsen 2004; Van Amerongen 2017; ZAJICEK 2012 MUSEC). We could not include data from two parallel RCTs and one cross-over trial. One parallel RCT provided data only in one figure demonstrating daily VAS pain trajectories by comparison groups and numerical data were not available (Turcotte 2015). The other parallel RCT (Zajicek 2003_CAMS) provided the number of participants with a clinically relevant response defined as categories 0-3 of the NRS 0-10 that we considered an inappropriate threshold in our protocol. The cross-over study (Leocani 2015)reported data but did not account for design.

Withdrawals due to AEs (tolerability). Data were available from 19 studies that contributed to the analysis of the outcome (Aragona 2009; Collin 2007; Collin 2010; Langford 2013; Leocani 2015; Markova 2018; NCT00682929; NCT01606176; Notcutt 2012; Novotna 2011; Rog 2005; Schimrigk 2017; Turcotte 2015; Vachova 2014; Van Amerongen 2017; Vaney 2004; Wade 2004; Zajicek 2003_CAMS; ZAJICEK 2012 MUSEC).

Important outcomes

PGIC. Eight parallel trials (Collin 2007; Langford 2013; Markova 2018; Novotna 2011; Rog 2005; Turcotte 2015; Vachova 2014; Wade 2004) provided data for the outcome. We could not include data from two trials, one (Notcutt 2012) because the reported outcome did not meet our predefined criteria of much or very much improvement in the PGIC, and one study (Van Amerongen 2017) because it measured the outcome as continuous data only.

HRQoL. There were several HRQoL outcome measures used, including the SF-36 (Langford 2013; Markova 2018; NCT00682929; Novotna 2011; Schimrigk 2017), EQ-5D (Collin 2010; Langford 2013; Novotna 2011), and the Spitzer QoL-index (NCT01606176). Some trials incorporated condition-specific HRQoL measures such as the 54-item MSQoL (Collin 2010) and the 29-item Multiple Sclerosis Impact Scale (MSIS-29) (ZAJICEK 2012 MUSEC; Zajicek 2013_CUPID). Four studies provided data for each of the eight SF-36 scales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) (Langford 2013; Markova 2018; NCT00682929; Novotna 2011).

SAEs. Data on SAEs were reported for 20 studies and all of them were included in analysis (Aragona 2009; Collin 2007; Collin 2010; Killestein 2002; Langford 2013; Leocani 2015; Markova 2018; NCT00682929; Notcutt 2012; Novotna 2011; Rog 2005; Schimrigk 2017; Svendsen 2004; Turcotte 2015; Vachova 2014; Van Amerongen 2017; Vaney 2004; Wade 2004; Zajicek 2003_CAMS; ZAJICEK 2012 MUSEC).

Nervous system disorders. Seven trials provided outcome data that were included in analysis (Collin 2010; Killestein 2002; Langford 2013; Notcutt 2012; Novotna 2011; Svendsen 2004; Vachova 2014).

Psychiatric disorders. Six studies contributed to the analysis of the outcome (Collin 2010; Langford 2013; Notcutt 2012; Novotna 2011; Svendsen 2004; Vachova 2014).

Drug tolerance. Information on this outcome was available from two trials only (Collin 2010; Vachova 2014).

Other outcomes of limited importance

One small cross-over study reported changes on a tremor index, measured using a validated tremor rating scale (Fox 2004). A parallel RCT reported the reduction in daily number of urinary incontinence episodes from baseline to end of treatment (eight weeks) (Kavia 2010).

Ongoing studies

Of the eight ongoing RCTs, three evaluate nabiximols versus placebo (Hansen 2021; NCT04984278; NCT05092191), of which two studies evaluate THC alone, CBD alone, THC and CBD versus placebo: one is expected to be completed in December 2021 with 448 participants (Hansen 2021), and one is expected in March 2025 with 250 participants (NCT05092191). One ongoing RCT is expected to be completed in November 2021 and plan to evaluate 52 participants (NCT04657666), one is expected in November 2022 with 446 participants (NCT04203498), and one is expected in September 2022 with 190 participants (NCT04984278). Recruitment in one study is reported as completed in May 2021 and results are not published yet. This study evaluated dronabinol versus placebo in 397 participants (NCT03756974). Recruitment in one study, which evaluated nabiximols versus placebo in 70 participants, is reported as unknown in the study registry, results are not published yet, and we are waiting for reply from study investigators (NCT03005119). We found one completed study, but with unpublished results, of which we are awaiting information from the authors. This study compared Sativex plus Lokomat training with other anti-spasticity medications plus Lokomat training in 40 participants (Russo 2017). Please refer to Characteristics of ongoing studies for more detailed information.

Excluded studies

We excluded 36 full-text articles (42 records) that did not match our inclusion criteria: 22 studies were non randomised trials or reviews; eight included wrong population; one because the aim of the trial was not consistent with this review, and the authors measured no outcomes of interest relevant to this review; two were N-of-1 cross-summary of findings table over trials; two because the studies had been withdrawn, and no participants had been included; and a dose-comparison trial of nabiximols without a placebo group. Please refer to the Characteristics of excluded studies for more detailed information.

Risk of bias in included studies

For details of the risk of bias judgements for each study, see Characteristics of included studies. A graphical representation of risk of bias for critical and important outcome can be seen in Analysis 1.1; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12.

For the spasticity outcome (number of participants reporting reduction of 30% in the spasticity NRS), we assumed an overall risk of bias with some concerns, as all the trials (Collin 2007; Collin 2010; Markova 2018; Novotna 2011; ZAJICEK 2012 MUSEC) reporting the outcome were with some concerns (Analysis 1.1)

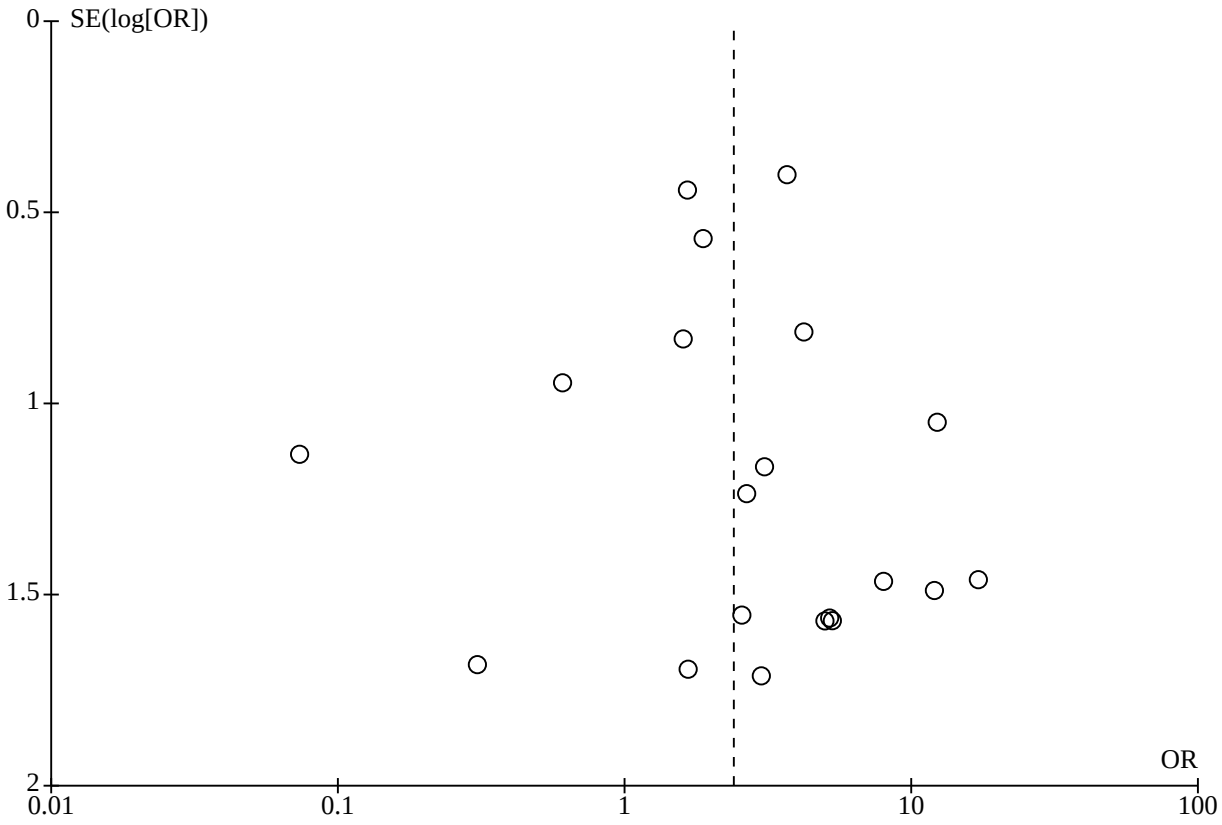
We also analysed continuous data for spasticity as an important outcome, but we did not include the results in the summary of findings table. We judged all trials as 'some concerns' (Collin 2007; Collin 2010; Langford 2013; Markova 2018; Novotna 2011; Van Amerongen 2017), excluding Notcutt 2012 which we classified as 'high risk' for missing outcome data (Analysis 1.2).

Only Svendsen 2004 reported the pain outcome (number of participants reporting pain relief of 50% or greater in the NRS-PI) and we judged the study at an overall high risk of bias because outcome data were not available for all randomised participants, and it is likely that missingness in the outcome depended on its true value (Analysis 1.3).

We also analysed continuous data for chronic pain as an important outcome, but we did not include the results in the summary of findings table. We judged all trials as 'some concerns' (Collin 2010; Langford 2013; NCT01606176; Rog 2005; Schimrigk 2017; Van Amerongen 2017; ZAJICEK 2012 MUSEC), excluding Markova 2018 which we classified as 'high risk' for selection of the reported result (Analysis 1.4).

For withdrawals due to AEs, we assumed an overall risk of bias with some concerns for 18 trials reporting outcome data (Aragona 2009; Collin 2007; Collin 2010; Langford 2013; Leocani 2015; Markova 2018; NCT00682929; NCT01606176; Notcutt 2012; Novotna 2011; Rog 2005; Schimrigk 2017; Turcotte 2015; Vachova 2014; Van Amerongen 2017; Wade 2004; Zajicek 2003_CAMS; ZAJICEK 2012 MUSEC). We judged one cross-over trial (Vaney 2004) at high risk of bias because the method used to conceal the allocation of treatment was not reported and there was no sufficient time for carry-over effects to have disappeared before outcome assessment in the second period. Moreover, there were different periods by sequence (Analysis 1.5). We explored potential non-reporting bias by generating a funnel plot (Figure 3) which indicates, although not conclusively, a lack of bias for the outcome.

Figure 3. Funnel plot for withdrawn due to AEs



Important outcomes

We judged PGIC (number of participants reporting much or very much improvement in the PGIC) to be at an overall high risk of bias

as three of the studies (Markova 2018; Novotna 2011; Turcotte 2015) contributing 39% to the outcome estimate were at high risk of bias as they did not report any information on missing outcome data, and it is likely that missingness in the outcome depended on its true value. The other five studies (Collin 2007; Langford 2013; Rog 2005; Vachova 2014; Wade 2004) contributing to the effect estimate of the PGIC outcome were with some concerns (Analysis 1.6).

We analysed HRQoL as continuous data. Overall, we rated the risk of bias for the outcome to be high for Markova 2018, NCT01606176, Novotna 2011, and Zajicek 2013_CUPID because in these studies outcome data were not available for all participants. The data were not analysed in accordance with a pre-specified plan in Markova 2018, and the ascertainment of the outcome could have differed between intervention groups in NCT01606176. We judged risk of bias to be of some concern for Collin 2010, Langford 2013, NCT00682929, Schimrigk 2017, and ZAJICEK 2012 MUSEC; (Analysis 1.7; Analysis 1.8).

Twenty studies reported SAEs (Aragona 2009; Collin 2007; Collin 2010; Killestein 2002; Langford 2013; Leocani 2015; Markova 2018; NCT00682929; NCT01606176; Notcutt 2012; Novotna 2011; Rog 2005; Schimrigk 2017; Svendsen 2004; Turcotte 2015; Vachova 2014; Van Amerongen 2017; Wade 2004; Zajicek 2003_CAMS; ZAJICEK 2012 MUSEC). We assumed an overall risk of bias with some concerns in 18 trials and an overall high risk of bias in two cross-over trials (Aragona 2009; Vaney 2004). Aragona 2009 did not report information on whether deviations from intended intervention were balanced between sequences and whether an appropriate analysis was used to estimate the effect of adhering to intervention. In Vaney 2004 the method used to conceal the allocation of treatment was unclear, and no information was available on whether failures in implementation and non-adherence to the assigned intervention could have affected participants' outcomes (Analysis 1.9).

Seven trials reported the number of participants who had nervous system AEs (Collin 2010; Killestein 2002; Langford 2013; Notcutt 2012; Novotna 2011; Svendsen 2004; Vachova 2014). We judged Killestein 2002 and Svendsen 2004 at an overall high risk of bias as in these studies co-interventions were not reported and the method of measuring the outcome was inappropriate because participants, who were aware of the intervention received, used their own words to record AEs in their diaries during each treatment period. We rated the other five studies as some concerns (Analysis 1.10).

Six studies reported the number of participants who had psychiatric disorders (Collin 2010; Langford 2013; Notcutt 2012; Novotna 2011; Svendsen 2004; Vachova 2014). For this outcome, we assumed an overall risk of bias with some concern as five studies were rated as some concerns and one at overall high risk of bias (Svendsen 2004) (Analysis 1.11). Only two studies (Collin 2010; Vachova 2014) reported the number of participants who had drug tolerance and both studies were rated as some concerns (Analysis 1.12).

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Cannabis compared to Placebo for health problem or population

Critical outcomes

In Summary of findings 1 we provided a summary of the effect estimates of cannabinoids for spasticity, pain and withdrawals due to AEs, the certainty of evidence for comparisons with placebo and reasons for downgrading it.

Spasticity: number of participants reporting reduction of 30% over baseline in the spasticity NRS over baseline

I. Data were available from four studies comparing oromucosal spray of nabiximols (Sativex®) with placebo (Collin 2007; Collin 2010; Markova 2018; Novotna 2011) and one study comparing oral THC extract of *Cannabis sativa* (Cannador®) with placebo (ZAJICEK 2012 MUSEC). Most participants had progressive MS (range from 55% to 100%).

Nabiximols and Cannador® likely increased the number of participants who reported a clinically important reduction of perceived severity of spasticity over the baseline (OR 2.51, 95% CI 1.56 to 4.04; 5 studies, 1143 participants; I^2 = 67%; P = 0.02; moderate-certainty evidence; Analysis 1.1). The absolute effect was 216 more people (95% CI 99 more to 332 more) per 1000 reporting benefit when treated with cannabinoids compared with placebo over a follow-up range from 6 to 14 weeks.

Despite the high level of heterogeneity of the pooled estimate, we did not downgrade for inconsistency because the direction of effect across the studies consistently favoured cannabinoids compared with placebo. The heterogeneity was almost completely attributable to one small trial (I^2 = 36%; Markova 2018) that used an enriched enrolment two-phases design and reported the largest effect (OR 7.24, 95% CI 3.05 to 17.17; 106 participants). Excluding Markova 2018, heterogeneity decreased substantively and slightly attenuated the average effect (OR 2.04, 95% CI 1.45 to 2.86; 4 studies, 1037participants; I^2 = 31%).

II. Seven studies provided data on mean change from baseline in spasticity NRS (Collin 2007; Collin 2010; Markova 2018; Notcutt 2012; Novotna 2011; Van Amerongen 2017; Vaney 2004). Nabiximols likely resulted in a reduction in perceived severity of spasticity compared with placebo (MD -0.55, 95% CI -0.94 to -0.17; 7 studies, 1262 participants; I^2 = 68%; moderate-certainty evidence; Analysis 1.2). Despite the high level of heterogeneity of the pooled estimate, we did not downgrade for inconsistency because of the consistent benefit seen across the studies in favour of cannabinoids compared with placebo. As above, the heterogeneity is almost completely attributable to one small enriched-design trial (I^2 = 53%; Markova 2018). Excluding Markova 2018, heterogeneity decreased substantively (MD -0.39, 95% CI -0.63 to -0.14; 6 studies, 1156 participants; I^2 = 24%). Follow-up ranged from 2 to 14 weeks.

Chronic Pain: number of participants reporting pain relief of 50% or greater, over baseline in the NRS-PI

I. There was insufficient evidence from one small three-week trial (Svendsen 2004), that used synthetic THC (dronabinol) to determine the effects of treatment on the number of participants with pain relief of 50% or greater when compared with placebo, over three weeks' follow-up (OR 4.23, 95% CI 1.11 to 16.17; 48 participants; Analysis 1.3). The certainty evidence was very low (downgraded one level for risk of bias, two levels for very serious

imprecision). Participants with progressive MS were 62.5% and those with relapsing MS 37.5%.

II. Eight studies provided data on mean difference change from baseline in pain NRS-PI over a range from 3 to 16 weeks (Collin 2010; Langford 2013; Markova 2018; NCT01606176; Rog 2005; Schimrigk 2017; Van Amerongen 2017; ZAJICEK 2012 MUSEC). Except for Collin 2010, the direction of effect on pain reduction across the studies favoured nabiximols, C*annabis* extract or synthetic THC compared with placebo. There was a high level of statistical heterogeneity (MD -0.54, 95% CI -0.91 to -0.18; 8 studies, 1451 participants; I^2 = 62%, P = 0.01; Analysis 1.4). The certainty of this evidence was low (downgraded one level for risk of bias, one level for inconsistency). Excluding the enriched-design study of Markova 2018 led to a moderate heterogeneity (MD -0.43, 95% CI -0.78 to -0.09; 7 studies, 1345 participants; P = 0.05, I^2 = 53%).

Number of participants withdrawn due to AEs (tolerability)

Data were available from 19 studies, 12 of which evaluated nabiximols (Sativex®) against placebo. Treatment may have resulted in a slight increase in the number of participsants who withdrew due to AEs over 3 to 48 weeks' follow-up, when compared with placebo (OR 2.41, 95% CI 1.51 to 3.84; 3110 participants; I^2 = 17%, P = 0.25; Analysis 1.5). The absolute effect is 39 more people (95% CI 15 more to 76 more) per 1000 who withdrew due to AEs. The certainty evidence was low (downgraded one level for risk of bias, one level for imprecision). There was no evidence for small-study effects Figure 3.

Important outcomes

In Summary of findings 1 we provided a summary of the effect estimates of cannabinoids for the following important outcomes.

Number of participants reporting much or very much improvement in PGIC

Cannabinoids (nabiximols, C*annabis* extract, synthetic THC) likely resulted in an increase in the number of participants who reported improvement in the PGIC over 4 to 48 weeks' follow-up, compared with placebo (OR 1.80, 95% CI 1.37 to 2.36; 8 studies, 1215 participants; I^2 = 0%, P = 0.53; Analysis 1.6); the absolute effect was 113 more people (95% CI 57 more to 175 more) per 1000 having much or very much improvement in PGIC when treated with cannabinoids compared with placebo. The certainty evidence was moderate (downgraded one level for risk of bias).

HRQoL

HRQoL scores were available from eight trials. Three trials reported HRQoL scores from the EQ-5D (Collin 2010; Langford 2013; Novotna 2011), two reported scores from the SF-36 physical health component (PCS) (NCT00682929; Schimrigk 2017), one used the Spitzer Quality of Life Index (NCT01606176), and two trials used the MSIS-29 (ZAJICEK 2012 MUSEC; Zajicek 2013_CUPID). Several trials used more than one of these measures; we only included one trial in each measure. The effect of cannabinoids against placebo on mean change in HRQoL as a SMD was -0.08 (95% CI -0.17 to 0.02; I^2 = 0%, P = 0.65; 8 studies, 1942 participants; Analysis 1.7). The certainty of evidence was low, downgraded two levels for very serious risk of bias. Cannabinoids may have little to no effect on HRQoL compared with placebo over 3 to 48 weeks' follow-up.

Four trials (Langford 2013; Markova 2018; NCT00682929; Novotna 2011) reported change scores from baseline for each of the SF-36 domains at 12 to 14 weeks' follow-up. All confidence intervals were wide and none showed a difference between cannabinoids and placebo, except the bodily pain domain which improved in the group treated with nabiximols compared with placebo (MD 4.24, 95% CI 0.07 to 8.40; I^2 = 45%, P = 0.16; 3 studies, 683 participants; Analysis 1.8).

SAEs: number of participants with SAEs

Cannabinoids may have resulted in little to no difference in SAEs compared with placebo (OR 1.38, 95% CI 0.96 to 1.99; 20 studies, 3124 participants; I^2 = 0%, P = 0.60; Analysis 1.9); the absolute effect is 12 more people per 1000 (95% CI 1 fewer to 30 more) per 1000 having SAEs with cannabinoids compared with placebo. The certainty of evidence was low downgraded one level for risk of bias and one level for imprecision.

Number of participants reporting nervous system AEs

Cannabinoids may have resulted in an increase in the number of participants who had nervous system AEs over 4 to 48 weeks' follow-up, when compared with placebo (OR 2.61, 95% CI 1.53 to 4.44; 7 studies, 1154 participants; I^2 = 64%, P = 0.01; Analysis 1.10); the absolute effect is 210 more people (95% CI 85 more to 341 more) per 1000 having nervous system disorders with cannabinoids compared with placebo. The certainty of evidence was low, downgraded one level for risk of bias, one level for inconsistency. We were unable to find reasons for heterogeneity. Limiting the analysis to studies which evaluated only Sativex did not reduce heterogeneity.

Number of participants reporting psychiatric disorders

Cannabinoids may have resulted in a slight increase in the number of participants who had psychiatric disorders over 4to 48 weeks' follow-up, when compared with placebo (OR 1.94, 95% CI 1.31 to 2.88; 6 studies, 1122 participants; I^2 = 0%, P = 0.42; Analysis 1.11); the absolute effect is 61 more people (95% CI 21 more to 114 more) per 1000 having psychiatric disorders when treated with cannabinoids compared with placebo. The certainty of evidence was low, downgraded one level for risk of bias, one level for imprecision.

Number of participants reporting drug tolerance

The evidence was very uncertain about the effect of cannabinoids on drug tolerance over 14 to 48 weeks' follow-up (OR 3.07, 95% CI 0.12 to 75.95; 2 studies, 458 participants; very low-certainty evidence; Analysis 1.12). The certainty of evidence was very low, downgraded one level for risk of bias, two levels for very serious imprecision.

Outcomes of limited importance

Spasticity measured by the Ashworth scale or the MAS

Eleven studies provided usable data on severity of spasticity measured by the Ashworth scale or the MAS. Spasticity was slightly lower at the end of the study period with cannabinoids than with placebo (MD -0.23, 95% CI -0.44 to -0.03; 1777 participants; low-certainty evidence; Analysis 1.13). Compared with placebo, cannabinoids may have resulted in little to no difference

in reduction of spasticity measured with the Ashworth scale or the MAS over 2 to 50 weeks' follow-up, when compared to placebo. Our confidence in this result was low, downgraded one level for serious risk of bias, one level for imprecision. We judged all included studies with some concerns, excluding Notcutt 2012 judged at high risk of bias due to missing outcome data.

Pain relief of 30% or greater

One parallel RCT (Langford 2013) including 339 participants reported the outcome. At 10 weeks' follow-up, authors reported a treatment difference in favour of nabiximols compared with placebo (OR 1.61, 95 % CI: 1.01 to 2.57, P = 0.046).

Improvement of bladder symptoms

Kavia 2010 evaluated nabiximols as an add-on therapy in alleviating bladder symptoms in 335 patients with MS and overactive bladder. Authors reported no difference in daily number of urinary incontinence episodes (primary outcome) between nabiximols and placebo at eight weeks. There were significant differences favouring nabiximols against placebo in number of episodes of nocturia, number of voids day and PGIC (secondary outcomes).

Frequency and severity of muscle spasms

Two parallel trials reported the outcome. Wade 2004 reported no difference between nabiximols and placebo in 160 participants. ZAJICEK 2012 MUSEC found that self-reported spasms' relief was consistently higher with an oral C*annabis* extract (Cannador®) than with placebo. The effect increased over time due to an increase in the rate of relief with the C*annabis* extract and because of an extremely low responder rate in the placebo group at week 12. Response rates were 30.8% (143 participants) in the C*annabis* group and 13.4% (134 participants) in the placebo group (P value < 0.002).

Fatigue

Four parallel-group trials (Collin 2010; Langford 2013; Van Amerongen 2017; Wade 2004) and one cross-over trial (Corey-Bloom 2012) provided data for the analysis of fatigue. Collin 2010 and Langford 2013 used the 0-10 NRS; Van Amerongen 2017 and Wade 2004 used the Fatigue Severity scale; Corey-Bloom 2012 used the Modified-Fatigue Impact Scale. All included studies found no differences between cannabinoids (nabiximols, synthetic THC, smoked C*annabis*) and placebo (SMD 0.04, 95% CI -0.26 to 0.34; 5 studies, 928 participants; Analysis 1.14).

Sleep quality

Seven parallel RCTs provided data of this outcome (Collin 2010; Langford 2013; Markova 2018; Notcutt 2012; Novotna 2011; Rog 2005; Wade 2004). The most commonly reported measure was sleep quality assessed using a 0-10 NRS. One study (Wade 2004) used a 0-100 VAS scale. We transformed the 0-100 VAS results to a 0-10 scale by dividing by 10 so that these were comparable to the other studies evaluating this outcome. The pooled estimate suggested improvement in sleep quality associated with cannabinoids compared with placebo (MD -0.66, 95% CI -1.10 to -0.22; 7 studies, 1205 participants). There was substantial evidence of heterogeneity (P = 0.001, I^2= 73%) (Analysis 1.15). Two studies evaluated sleep quality using a 0-10 NRS and provided information on the number of participants reporting much or very much improvement in sleep. Both studies reported a significant improvement in sleep quality associated with cannabinoids compared with placebo (OR 1.79, 95% CI 1.30 to 2.46; 2 studies, 756 participants; I^2 = 0%; Analysis 1.16).

Depression

Three parallel RCTs (Novotna 2011; Vachova 2014; Wade 2004) used the BDI scale and suggested no difference between nabiximols and placebo on depression (MD 0.17, 95% CI -0.90 to 1.24; 3 studies, 495 participants; I^2= 0%; Analysis 1.17). One parallel trial (Rog 2005) used the HADS) and reported no difference between nabiximols and placebo (MD 0.09, CI -1.06 to 1.23; 66 participants). In BDI and HADS, higher score indicated more severe depression and thus a negative MD favoured cannabinoids while a positive MD favoured control.

Anxiety

One parallel-group trial (Rog 2005) evaluated anxiety with the HADS and found no difference between nabiximols and placebo (MD -0.64, CI -1.75 to 0.46; 66 participants).

ADL

Four parallel-group trials (Collin 2010; Markova 2018; Wade 2004; Zajicek 2003_CAMS) evaluated ADL using the Barthel Index. The overall effect estimate suggested no difference between cannabinoids (nabiximols, C*annabis* extract, synthetic THC) and placebo (MD -0.08, 95% CI -0.32 to 0.16; 4 studies, 1134 participants; Analysis 1.18). There was no evidence of heterogeneity across studies (I^2= 0%, P = 0.49). One small cross-over study (Corey-Bloom 2012) evaluated walk time and showed no difference between smoked C*annabis* and placebo.

Tremor

A small (14 participants) cross-over study (Fox 2004) assessed the outcome, however available data did not allow quantitative assessment. The study was judged at high risk of bias arising from the randomisation process, deviations from the intended interventions and measurement of the outcome. Authors concluded that an oral C*annabis* extract (Cannador®) did not result in a functionally significant improvement in MS-associated tremor, however the evidence is very uncertain.

CGIC

Four parallel trials (Collin 2010; Notcutt 2012; Novotna 2011; Vachova 2014) measured the CGIC outcome. The main carer was asked to assess the change in the participant's general functional abilities at the end of the study. CGIC was assessed on a 7-point Likert-like scale that used three categories of improvement (slightly improved, much improved, or very much improved), three categories of worsening (slightly worse, much worse, or very much worse), and an option of "no change". The participant's overall condition improved by at least one category on the CGIC in the nabiximols group as compared with the placebo group (OR 1.66, 95% CI 1.15 to 2.41; 4 studies, 582 participants; I^2 = 0%; Analysis 1.19).

Use of anti-spasticity medicines

None of the included studies reported the outcome.

Use of analgesics

One parallel-group trial (Langford 2013) and one cross-over study (Svendsen 2004) reported that paracetamol was provided for rescue analgesic use during the study and no difference was found between cannabinoids (nabiximols, synthetic THC) and placebo.

DISCUSSION

Summary of main results

This review summarises evidence from 25 studies in people with MS treated with cannabinoid-based medicines compared with placebo. Cannabinoids include synthetic, herbal, or plant-derived cannabinoids. Most studies included all types of MS, except one study that included participants with relapsing MS only, and three studies that included participants with SPMS and PPMS. The mean age of the participants ranged from 18 to 60 years. Thirteen trials evaluated nabiximols (Sativex®), five an oral synthetic cannabinoid (dronabinol, nabilone, namisol), three an oral extract of *Cannabis sativa,* and one trial evaluated inhaled herbal *Cannabis.* These trials compared cannabinoids against placebo. Two trials compared dronabinol, an oral THC extract of *Cannabis sativa* and placebo, and one trial compared dronabinol, inhaled herbal *Cannabis* and placebo. Five studies were of very short duration (two to four weeks), 10 were of short duration (four to 12 weeks), seven studies were of intermediate duration (12 to 26 weeks), and two were long-term studies (50 weeks and 156 weeks). One trial reported outcome at three days.

We found that nabiximols (Sativex®) probably reduce spasticity severity as perceived by patients at time points up to 14 weeks (moderate-quality evidence). Nabiximols were likely to increase the number of participants reporting a clinically important reduction of perceived severity of spasticity, and lead to improve average spasticity scores compared with placebo. There was low-certainty evidence that nabiximols, *Cannabis* extract or synthetic THC cannabinoids were more effective than placebo in mean change in chronic neuropathic pain relief at time points up to 16 weeks.

For the important outcome of PGIC we found moderate-certainty evidence of the benefit of nabiximols, *Cannabis* extract, or synthetic THC cannabinoids over placebo. There was evidence that cannabinoids were likely to increase the number of participants reporting much, or very much improvement in the PGIC at time points up to 48 weeks. We are uncertain about the effect of cannabinoids on HRQoL at time points up to 16 weeks (very low-certainty evidence).

Cannabinoid-based medicines may have increased slightly the number of participants who withdrew due to adverse events ((low-certainty evidence). We did not find any significant differences between cannabinoids and placebo in terms of serious adverse effects, but this was likely due to the small amount of data available for this outcome (low-certainty evidence). Cannabinoids may increase nervous system adverse events and psychiatric disorders slightly (low-certainty evidence). The evidence was very uncertain about the effect on drug tolerance (very low-certainty evidence).

Overall completeness and applicability of evidence

Eight (32%) of the 25 included studies provided data on the use of cannabinoids for spasticity outcomes. Most participants had a progressive form of MS (range from 55% to 100%) and cannabinoids were added when spasticity was not relieved by current anti-spasticity medications. Nine (36%) eligible studies provided data on chronic neuropathic pain relief, though most did not report the number of patients with different forms of MS. Cannabinoids were used as an add-on treatment in participants who had failed to gain adequate pain relief from current analgesics. Our literature search identified a number of ongoing trials which could provide valuable data in addition to that presented in this review; we will include these in future updates.

Several factors limit the applicability of the evidence in our review. First, the baseline level of spasticity or chronic neuropathic pain and their duration varied across participants, and when assessing severity of these symptoms at baseline authors used a number of different instruments. The included studies recruited a mixture of patients with different clinical manifestations of spasticity and chronic neuropathic pain. This led to significant clinical and statistical heterogeneity in the effect estimates that limited the applicability of the evidence to the wider population of people with MS. Second, the proportion of participants with previous or current *Cannabis* experience varied across the included studies (from 6% to 80%), with only one study excluding participants with previous experience. Benefits andAEs of cannabinoids may differ between *Cannabis* users and naive users. We do not know if the evidence presently reviewed may be generalisable to *Cannabis*-naive participants. Third, the administration of co-therapies during follow-up was variable among the included studies, and is another limitation of the evidence. Fourth, the short duration of the studies does not enable us to determine the long -term balance between benefits and harms of cannabinoid-based medicines for people with MS.

The included studies used a large variety of measures to evaluate effects of cannabinoid-based medicines on spasticity and pain. We prioritised patient-reported outcomes. This review is therefore not limited by outcomes which are not of primary importance to patients.

Quality of the evidence

The quality of the included studies was difficult to assess, because the majority of the risk of bias judgements were deemed 'some concerns'. In particular, we judged 'deviations from intended interventions' and 'measurement of outcome' with some concerns for most included studies. An important bias that may have occurred was in blinding procedures. Given that most participants in the included studies had previous or current *Cannabis* experience and our outcomes of interest were patient-reported outcomes, make it likely that participants and personnel could become unblinded during trials.

Half of the cross-over trials was at high risk of carry-over effect, as they did not have an adequate washout period or their second period was not long enough for the carry-over effect to disappear. Furthermore, none of the cross-over studies considered period effect in the analysis.

We are moderately confident in the effect estimate of an important reduction in spasticity in the cannabinoid group compared with the placebo group. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. With respect to chronic neuropathic pain relief, our confidence in the effect estimate is limited because of the small sample size available from only one small trial that reported the number of participants with pain relief of 50% or greater over baseline. Additional data provided by seven studies showed a reduction of mean chronic neuropathic pain intensity from baseline in cannabinoid-treated participants compared with placebo, but there was a wide variation in reporting across the included studies. The majority of the evidence was low or very low-certainty for SAEs, nervous system or psychiatric disorders and drug tolerance, due to most trials having at least one risk of bias domain and some estimates being imprecise.

Potential biases in the review process

To avoid a possible risk of non-reporting bias, we searched a range of databases and trials registries to identify and include results of unpublished completed studies, and did not apply any language or period restrictions to the search. However, the possible presence of non-reporting bias could not be totally excluded.

There is a high proportion of risk of bias assessments given as 'some concerns' across the studies in our review. The overall risk of bias judgements were deemed 'some concerns' for seven (88%) of the eight included studies available for the spasticity outcome and for seven (78%) of the nine studies for the chronic neuropathic pain outcome. This may well reflect an inadequate reporting of information by the studies. Consequently, we may have overestimated the impact of bias on our findings by downgrading the certainty of evidence of the critical and important outcomes due to risk of bias. We did not account for the crossover design due to inadequate information presented in the studies. This leads to the potential for unit of analysis errors in several analyses of outcomes in our Summary of findings 1 where crossover studies provide data (see Analysis 1.3; Analysis 1.5; Analysis 1.9; Analysis 1.10). However, the number of participants recruited to these studies is small, the number of crossover studies included in the analysis is low, and they contribute only small weights to these outcomes. We decided not to attempt adjustment of these effect estimates, and we think it is unlikely that the summary effect estimates will be distorted by their lack of adjustment for crossover design.

The influence of allowed co-interventions on benefits and harms of cannabinoids was unclear because type and dosage of co-interventions were not clearly reported or controlled for in the included studies.

Agreements and disagreements with other studies or reviews

Other systematic reviews (Amato 2017; Meza 2017; Torres-Moreno 2018; Whiting 2015) and one overview (Nielsen 2018) have explored the effects of cannabinoids in the treatment of spasticity and pain among people with MS. See Table 1 for details of these reviews. Comparing these reviews together and with ours highlights challenges inherent in grading the certainty of evidence since the reviews used different criteria for study selection and inclusion, characteristics of participants, assessment of study quality, outcomes measures and different analytic methods. The search strategy of other reviews was not updated (most recent to 7 November 2017 in Mücke 2018), and new studies are available for inclusion in our review. Finally, we assessed risk of bias using the new Revised Cochrane risk-of-bias tool for randomised trials (RoB 2).

Our results agree with and update the findings reported by Amato 2017, Nielsen 2018, and Whiting 2015 who showed that cannabinoid-based medicines reduced severity of spasticity as perceived by people with MS. However, the certainty of evidence for the treatment effects varied among the reviews. It was judged high by Amato and Nielsen, and moderate by Whiting. We also judged the evidence for cannabis versus placebo as moderate certainty. Our results are not consistent with those reported by Meza 2017. This author included four parallel RCTs in spasticity and concluded that cannabinoids did not reduce spasticity in people with MS. However, the authors interpreted the small treatment effect measured with the Ashworth scale as conferring no effect, which is usually found using the scale. Meza 2017 used GRADE and judged the effect estimate at high-certainty evidence, but they did not downgrade for risk of bias and imprecision in the results of included trials. Torres-Moreno 2018 included 17 RCTs and concluded for a limited efficacy of cannabinoids for spasticity in MS, but authors did not assess the certainty of evidence.

We found low-certainty evidence that nabiximols, C*annabis* extract, or synthetic THC were more effective than placebo in terms of chronic neuropathic pain relief measured as the continuous outcome. Our conclusion is consistent with the findings reported in a Cochrane Review by Mücke 2018, and in other published reviews (Nielsen 2018; Torres-Moreno 2018).

One Cochrane Review (Mücke 2018) found a moderate-certainty evidence that more people withdrew due to AEs in the cannabinoid group than in the placebo group. Our findings were similar, but our confidence in the effect estimate was limited. In accordance with other systematic reviews (Mücke 2018; Nielsen 2018; Whiting 2015), we found that cannabinoid-based medicines were associated with a slight increased risk of short-term AEs, especially nervous system and psychiatric disorders. Different results were found by Amato 2017 who reported that for AEs no differences were observed between cannabinoids and placebo, and by Torres-Moreno 2018 who concluded that treatment with these drugs can be considered as safe.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, this review provides moderate-certainty evidence for an antispastic effect of nabiximols (as an add-on therapy to anti-spasticity medications) compared with placebo in people with MS in spasticity outcomes at 6 to 14 weeks. An important clinical indication for nabiximols in MS would be where spasticity is moderate to severe and other pharmacological and rehabilitation treatments are not effective. Our focus on patient-reported outcomes gives reasonable grounds to assume that people with MS would value the benefit identified in our review. However, this would need to be traded against their psychotropic effect and the risk of drug intolerance of cannabinoid medicines. In our review, there was limited evidence found on serious adverse events and long-term adverse events, which does not rule out the possibility

of abuse and liability in prescribing these medicines to people with MS in clinical practice. Possible major adverse events from long-term use of these medicines include cognitive impairment and psychiatric disorders. It is therefore important that both short- and long-term adverse effects are thoroughly evaluated in considering the clinical application of cannabinoids medicines.

Implications for research

We assessed the certainty of evidence in the present review as low to very low for most critical and important outcomes, excluding spasticity and PGIC (moderate certainty), according to GRADE. In order for robust conclusions to be drawn regarding the antispastic and analgesic effects of cannabinoids-based medicines for people with MS, we need studies of a high methodological quality, with large sample sizes and longer follow-up periods. There is also a need for randomised studies which compare these medicines with other active anti-spasticity medications and analgesics, in order to draw reliable conclusions about comparative efficacy between treatments.

Long-term adverse effects and drug tolerance of repeated exposure to cannabinoids remain a major concern. The present review did not find definitive evidence on SAEs and other AEs, and therefore we do not know the balance between desirable and undesirable effects of the cannabinoids, particularly the possible increased risk of cognitive impairment in people with MS. Therefore, further research is needed in order to assess the short-and long-term adverse effects of these drugs.

In the currently reviewed studies, there is inconsistency regarding the use of co-therapies. This is something that should be addressed in future studies, owing to the frequent use of disease-modifying therapies and symptomatic treatments by people with MS in clinical practice. Researchers should ensure that any observed effects cannot be attributed to co-therapies by monitoring that no deviations from intended intervention arise because of the trial context.

It would be beneficial for future research to assess whether (and how) cannabinoids' effects would differ between relapsing and progressive forms of MS, which was not considered in the trials included in the review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aragona 2009

Study characteristics	
Methods	**Design**: Randomised cross-over study **Setting**: Italy; single-centre **Recruitment**: NR **Number screened:** NR **Number randomised**: 17 **Outcome timing**: 3 weeks
Participants	**Psycho pathological and cognitive effects of therapeutic cannabinoids in MS**

Aragona 2009 *(Continued)*

	Inclusion criteria: age between 18 and 60 years; right-handed with normal right-hand function; a baseline EDSS score from 3.5 to 6.5; a stable disease for at least 30 days before study entry and no systemic corticosteroid therapy within 4 weeks of randomisation; significant spasticity in at least 2 muscle groups; anti spastic and immunomodulatory agents stable, before the study entry, for at least 1 and 6 months, respectively **Exclusion criteria**: history of epilepsy, alcohol or substance abuse, major medical illnesses; history of psychiatric disorders or cognitive impairment; concomitant therapy with psychoactive drugs; female patient who was pregnant, lactating, or planning pregnancy during the course of the study; previous use of cannabis **Randomised:** N = 17; % female: 64.7; mean age: 49.8 (SD 6.64) years; % SPMS 100; mean EDSS: 6.1 (SD 0.3); mean duration of MS: 20.76 (SD 8.42) years
Interventions	**Sativex versus placebo**. Each actuation delivered 100 µL of spray, containing delta-9-THC 2.7 mg and CBD 2.5 mg. Placebo had the appearance, smell, and taste of the active formulation but contained no active components. Study duration: 2 x3 weeks treatment periods. Washout period: 2 weeks
Outcomes	**Spasticity**: not assessed **Pain**: not assessed **Withdrawal due to AE**: N/phase **PGIC much or very much improved:** not assessed **HRQoL. Measure:** VAS. **Data**: mean (SD) difference of the absolute post-intervention (post placebo vs post Sativex) **Serious AEs**: N/phase **AEs**: N/phase **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: N/phase **Somnolence**: N/phase **Headache**: N/phase **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity**: not assessed **Fatigue. Measure**: Fatigue Severity Scale (FSS). **Data**: mean (SD) difference of the absolute post-intervention (post placebo vs post Sativex) **Sleep quality**: not assessed **Mobility/ADLs**: not assessed **Anxiety. Measure**: Self-rating Anxiety Scale (SAS). **Data**: mean (SD) difference of the absolute post-intervention (post placebo vs post Sativex) **Depression. Measure**: Symptom Checklist-90 Revised (SCL-90-R).**Data**: mean (SD) difference of the absolute post-intervention (post placebo vs post Sativex) **CGIC much or very much improved**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed.
Notes	Funding: public. The study was supported by a grant in the project of University Research year 2004 by the University "Sapienza" of Rome

Collin 2007

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: multicentre, 8 centres in the UK and 4 centres in Romania

Collin 2007 *(Continued)*

	Recruitment: April 2002 - March 2004 **Number randomised**: 189 **Outcome timing**: 6 weeks
Participants	**Spasticity in MS** **Inclusion criteria.** Age >18 years; diagnosis of MS; stable disease for >3 months; significant spasticity in at least two muscle groups with an Ashworth score ≥2; failed to gain adequate relief using current therapy; stable treatment for at least 30 days before randomization and during the study **Exclusion criteria.** Psychosis or severe psychiatric disorder other than depression; known alcohol or substance abuse; severe cardiovascular disorder including poorly controlled hypertension; history of seizures; pregnancy or lactation; sensitivity to cannabinoids **Treatment group** (**Nabiximols/Sativex**). N: 124; % female: 64.5; mean age: 49.7 (SD 10.2) years; disease severity: NR; mean duration of MS: 13.6 (SD 8.6) years; % previous cannabis use: 41.9 **Placebo group**. N: 65; % female: 52.3; mean age: 47.8 (SD 9.5) years; disease severity: NR; mean duration of MS: 12.2 (SD 7.7) years; % previous cannabis use: 41.5
Interventions	**Sativex**. Oromucosal spray containing 2.7 mg of delta-9-THC and 2.5 mg of CBD per 100 µL spray, max 48 sprays in 24 h **Placebo.** Oromucosal spray containing peppermint oil, 0.05% (v/v), quinoline yellow, 0.005% (w/v), sunset yellow, 0.0025% (w/v), in ethanol:propylene glycol (50:50) excipients **Concomitant medication during the study.** NR
Outcomes	**Spasticity. Measure:** NRS 0-10. **Data:** number of participant reporting improvement ≥ 30% (change from baseline in the severity of spasticity based on a daily diary assessment) reported. Mean difference, p value and 95% CI **Spasticity. Measure:** Ashworth Scale composite score. **Data**: Mean difference, SE, P value and 95% CI **Pain**: not assessed **Withdrawal due to AE**: N / group **PGIC. Measure:** seven point scale (very much improved to very much worse). **Data**: number of participants reporting much or very much improved **HRQoL**: not assessed **Serious AE**: N / group **Specific AE**: N / group **Nervous system disorders-related AE**: incompletely reported **Psychiatric disorders-related AE**: incompletely reported **Dizziness**: N / group **Somnolence**: N / group **Headache**: N / group **Confusion- disorientation**: N / group **Paranoia**: not assessed **Psychosis**: not assessed **Hallucinations**: not assessed **Drug tolerance**: not assessed **Urinary incontinence**: not assessed **Muscle spasms. Measure**: five point spasm frequency score. **Data**: mean difference, SE, P value and 95% CI **Fatigue. Measure**: NR. **Data**: N / group **Sleep**: not assessed **Mobility/ADLs**: not assessed **Anxiety**: not assessed **Depression**. **Measure**: NR. **Data**: N / group **CGIC**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: industry - drug manufacturer

Collin 2010

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: multicentre, 15 centres in the UK and 8 centres in Czech Republic **Recruitment**: NR **Number screened:** 388 **Number randomised**: 337 **Outcome timing**: 14 weeks
Participants	**Spasticity in MS** **Inclusion criteria:** any MS subtype; ≥6 months duration; ≥ 3 month history of spasticity due to MS not wholly relieved with current therapy; mean daily score of ≥4 on spasticity NRS (moderate spasticity) during the last 6 days of the baseline period; stable anti-spasticity regimen ≥ 30 days preceding study entry **Exclusion criteria:** spasticity not due to MS; concurrent history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders **Treatment group** (**Nabiximols/Sativex**): N = 167; % female: 63.0; mean age: 48.0 (SD 10.06) years; mean EDSS: 6.0 (SD 1.56); mean duration of MS: 14.4 (SD 8.29) years; % previous cannabis use: 20; mean duration of spasticity: 7.5 (SD 5.14) years **Placebo group:** N = 170; % female: 59.0; mean age: 47.1 (SD 9.15) years; mean EDSS: 6.0 (SD 1.50); mean duration of MS: 16.0 (SD 8.48) years; % previous cannabis use: 28; mean duration of spasticity: 8.0 (SD 5.51) years
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** oromucosal spray containing peppermint oil flavouring, 0.05%(v/v); quinoline yellow, 0.005% (w/v) and sunset yellow, 0.0025% (w/v) colourants, in ethanol:propylene glycol (50:50) excipients **Dose frequency:** maximum 24 sprays in any 24 hour period. Daily number of sprays taken during the study: Sativex: mean 8.5 (range: 1–22); Placebo: mean 15.4 (range: 2– 23) **Concomitant medication during the study:** % Baclofen: Sativex 79; Placebo 81. % Tizanidine: Sativex 41; Placebo 45. % Benzodiazepines: Sativex 26; Placebo 30. % Gabapentin: Sativex 16; Placebo 15. % Dantrolene: Sativex 8; Placebo 6. % Other: Sativex 62; Placebo 59. % No previous or concomitant anti-spasticity medications: Sativex 4; Placebo 2
Outcomes	**Spasticity** 1. **Measure:** NRS 0-10. **Data:** number of participant reporting ≥ 30% improvement (OR, 95% CI and P value). Mean baseline score without SD. Mean change (SD) from baseline defined as the mean NRS spasticity score from the last 14 days of the treatment period (7 days if the participant withdrew before day 50) minus the mean NRS score at baseline. Mean treatment difference (95% CI and P value) 2. **Measure:** MAS. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) **Pain**. **Measure:** NRS 0-10. **Data**: number of participant reporting ≥ 50% improvement not reported. Mean change from baseline without SD reported. Mean treatment difference (P value) reported **Withdrawal due to AE**: N/group **PGIC much or very much improved:** not assessed **HRQoL** 1. **Measure:** MSQoL-54 physical and mental health composites. **Data:** mean difference change from baseline with SE 2. **Measure:** EQ-5D health state index; EQ-5D health status VAS score. **Data:** mean difference change from baseline with P value **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: N/group **Psychiatric disorders-related AE**: N/group **Dizziness**: N/group

Collin 2010 *(Continued)*

	Somnolence: N/group **Headache**: N/group **Confusion- disorientation**: N/group **Paranoia**: N/group **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: N/group **Urinary incontinence**: not assessed **Muscle spasms severity. Measure**: NRS 0-10. **Data**: mean change from baseline without SD. Mean treatment difference (P value) **Fatigue. Measure**: NRS 0-10. **Data**: mean change from baseline without SD. Mean treatment difference (P value) **Sleep quality. Measure**: NRS 0-10 sleep quality. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Mobility/ADLs. Measure:** Barthel ADL index score. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Anxiety**: not assessed **Depression:** not assessed **CGIC much or very much improved. Measure:** 7-point Likert-type scale with the markers "very much improved, much improved, lightly improved, no change, slightly worse, much worse or very much worse. **Data**: number of participants reporting "very much improved" or "much improved" reported (OR, 95% CI and p value) **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: industry - drug manufacturer

Corey-Bloom 2012

Study characteristics	
Methods	**Design**: Randomised cross-over study. **Setting**: US, single-centre **Recruitment**: NR **Number screened:** 196 **Number randomised**: 37 **Outcome timing**: 3 days
Participants	**Spasticity in MS** **Inclusion criteria:** spasticity and at least moderate increase in tone (score ≥ 3 points on the modified Ashworth scale at the elbow, hip or knee) **Exclusion criteria**: history of major psychiatric disorder (other than depression) or substance abuse, neurologic disease other than MS (e.g. epilepsy, head trauma) and severe or unstable medical illnesses, known pulmonary disorders (tuberculosis, asthma), patients who used benzodiazepines to control spasticity or high doses of narcotic medications for pain, and women who were pregnant or breast-feeding **Randomised:** N = 37 participants; % female: 63.0; mean age: 51 (SD 8) years; RRMS 33.0 %; SPMS 67.0 %; mean EDSS: 5.3 (SD 1.5); mean duration of MS: 8.5 (SD 7.4) years; % previous cannabis use: 80; % anti spastics use: 60; % undergoing disease-modifying therapy: 70
Interventions	**Smoked cannabis versus placebo**. Cannabis cigarettes contained about 4% delta-9-THC by weight. Placebo cigarettes had the same base material but with the delta-9-THC removed. Inhalation for 5 seconds, followed by a 10-second breath-hold and exhalation, with a 45-second wait between puffs. Participants completed an average of four puffs per cigarette. Study duration: 2 x 3 days treatment periods. Washout period: 11 days

Corey-Bloom 2012 *(Continued)*

	Concomitant medication during the study: DMDs stable for at least 6 months; antispastics
Outcomes	**Spasticity. Measure:** MAS. **Data**: mean change (95% CI) in the difference (after to before smoking) in the cannabis and placebo phases **Pain**. **Measure:** VAS 0-100. **Data**: mean change (95% CI) in the difference (after to before smoking) in the cannabis and placebo phases **Withdrawal due to AE**: not assessed **PGIC much or very much improved:** not assessed **HRQoL. Measure:** The Multiple Sclerosis Quality of Life-Inventory. This outcome was reported in the study protocol but results are missing in the article **Serious AEs**: N/phase **AEs**: N/phase **Nervous system disorders-related AE**: N/phase **Psychiatric disorders-related AE**: N/phase **Dizziness**: N/phase **Somnolence**: NR **Headache**: N/phase **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity**: not assessed **Fatigue. Measure**: the modified Fatigue Impact Scale (mFIS). **Data**: overall differences before and after treatment with placebo and cannabis **Sleep quality**: not assessed **Mobility/ADLs**: not assessed **Anxiety**: not assessed **Depression:** not assessed **CGIC much or very much improved**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed.
Notes	**Funding**: public. The study was funded by grant number C00-SD-103 from the University of California, Centre for Medicinal Cannabis Research (CMCR).

Fox 2004

Study characteristics	
Methods	**Design**: Randomised cross-over study **Setting**: UK; two centres **Recruitment**: 3 May to 31 May 2002 **Number screened:** 27 **Number randomised**: 14 **Outcome timing**: 2 weeks
Participants	**Tremor in MS** **Inclusion criteria:** diagnosis of definite MS (Poser 1983), age between 18 and 64 years, and a visible upper limb tremor **Exclusion criteria**: cognitive impairment; history of ischaemic heart disease or psychotic illness, or unwilling to stop driving for the period of the study **Randomised:** N = 14; % female: 57.1; mean age: 45 (range: 35 to 56) years; mean EDSS: 6.25 (range: 3.5 to 7.5); previous cannabis use: 1 participant

Fox 2004 *(Continued)*

Interventions	**Cannador versus placebo**. Cannador is an ethanolic extract of cannabis sativa standardised to 2.5 mg of THC per capsule. Identical placebo capsule. In a titration phase the dose was escalated at 3-day intervals until either the patient reached a maximum dose of 0.125 mg/kg of THC twice a day or they began to experience intolerable side effects, in which case the dose was dropped to the last tolerated dose. Study duration: 2 x2 weeks treatment periods. No washout **Concomitant medication during the study:** NR
Outcomes	**Tremor**: change on a tremor index, measured using a validated tremor rating scale **Spasticity**: not assessed **Pain**: not assessed **PGIC**: not assed **HRQoL**: not assessed **Serious AEs**: NR **AEs**: N/phase **Dizziness**: N/phase **Somnolence**: N/phase
Notes	Funding: public. One author was funded by a grant from the Medical Research Council

Kavia 2010

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: multicentre, nine centres in the UK, three in Belgium and three in Romania **Recruitment**: January 2003 - December 2004 **Number screened:** 168 **Number randomised**: 135 **Outcome timing**: 10 weeks
Participants	**Overactive bladder due to MS** **Inclusion criteria:** adults with a diagnosis of MS with symptoms of overactive bladder**(**OAB) who had failed to respond adequately to first-line therapies, principally anticholinergics. Stable dose of anti-cholinergic medication for at least 14 days prior to study entry which remained unchanged throughout the study; at least three incontinence episodes over five consecutive days during the baseline period, as assessed by a self-report voiding diary, completed daily **Exclusion criteria:** presence of symptomatic urinary tract infection or any other known cause for de-trusor overactivity; performing intermittent self-catheterisation; use of cannabis or cannabis-derived medicines within 7 days of study entry; hypersensitivity to cannabinoids or any of the excipients of the medication; history of major psychiatric disorder or severe personality disorder; history of alcohol or substance abuse; severe cardiovascular disorder, epilepsy or significant renal or hepatic impairmen-t; concomitant use of fentanyl, levodopa, or sildenafil citrate **Treatment group** (**Nabiximols/Sativex**): N = 67; % female: 77.6; mean age: 48.6 (SD 9.3) years; EDSS: NR; duration of MS: NR; previous cannabis use: NR **Placebo group:** N = 68; % female: 67.6; mean age: 46.8 (SD 11.2) years; EDSS: NR; duration of MS: NR; previous cannabis use: NR
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** oromucosal spray containing excipients plus colorants and flavouring **Dose frequency:** eight sprays in any 3-hour period, and 48 sprays in any 24-hours. Daily number of sprays taken during the study: Sativex: mean 8.91 (median 7.19); Placebo: mean 17.5 (median 14.22) **Concomitant medication during the study:** anticholinergic medication

Kavia 2010 *(Continued)*

Outcomes	**Urinary incontinence. Measure:** participants completed a daily diary for the duration of the study recording the time and frequency of incontinence episodes. **Data**: mean change from baseline (without SD) and P value **Spasticity**: not assessed **Pain**: not assessed **Withdrawal due to AE**: N/group **PGIC much or very much improved. Measure:** seven-point scale (very much improved to very much-worse). **Data**: number of participants reporting improvement **HRQoL. Measure:** I-QOL. **Data:** mean change from baseline (without SD) and P value **Serious AEs**: N/group **AEs**: NR **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: N/group **Somnolence**: NR **Headache**: N/group **Confusion- disorientation**: N/group **Paranoia**: NR **Psychosis**: N/group **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence. Measure:** participants completed a daily diary for the duration of the study recording the time and frequency of incontinence episodes. **Data**: mean change from baseline (without SD) and P value
Notes	**Funding**: industry - drug manufacturer

Killestein 2002

Study characteristics	
Methods	**Design**: Randomised twofold cross-over study **Setting**: the Netherlands; single-centre **Recruitment**: NR **Number screened:** NR **Number randomised**: 16 **Outcome timing**: 4 weeks
Participants	**Spasticity in MS** **Inclusion criteria:** disease duration >1 year, severe spasticity (mean Ashworth spasticity score ≥ 2 in at least one limb and EDSS score between 4 and 7.5 **Exclusion criteria**: other disease of clinical importance, use of other investigational drug, disease exacerbation, steroid treatment or use of cannabinoids in the 2 months preceding study entry, and history of alcohol or drug abuse, depression, psychosis, or schizophrenia **Randomised:** N = 16; % female: NR; mean age: 46 (SD 7.9) years; SPMS 62.5 %; PPMS 37.5 %; mean EDSS: 6.2 (SD 1.2); mean duration of MS: 15.0 (SD 10.7) years; % previous cannabis use: 37.5
Interventions	**THC capsules (Marinol, Dronabinol) versus Cannabis sativa plant extract (20 to 30% CBD and < 5% other cannabinoids) versus placebo.** Medication was administered in two daily doses of 2.5 mg THC or plant extract, containing the same level of THC. If well-tolerated, the dose was elevated to 5 mg twice a day for the next 2 weeks. Study duration: 3 x 4 weeks treatment periods. Washout period: 4 weeks **Concomitant medication during the study:** NR

Killestein 2002 *(Continued)*

Outcomes	**Spasticity. Measure:** the Ashworth scale. **Data**: mean (95% CI) scores at baseline and at the study end in the THC, plant extract and placebo phases (data not available because they were presented only in one figure) **Pain**. **Measure:** VAS 0-100 reported in the Method section of the article. **Data**: NR **Withdrawal due to AE**: NR **PGIC much or very much improved:** VAS "subject's global impression". **Data**: F and P values **HRQoL. Measure:** the Medical Outcomes Study Short Form 36. **Data**: F and P values **Serious AEs**: N/phase **AEs**: N/phase **Nervous system disorders-related AE**: N/phase **Psychiatric disorders-related AE**: N/phase **Dizziness**: N/phase **Somnolence**: N/phase **Headache**: N/phase **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity**: not assessed **Fatigue. Measure**: the MS specific Fatigue Severity Scale. **Data**: NR **Sleep quality**: not assessed **Mobility/ADLs**: not assessed **Anxiety**: not assessed **Depression:** not assessed **CGIC much or very much improved**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: public. The study was supported by the Dutch Ministry of Health, Welfare and Sport

Langford 2013

Study characteristics	
Methods	**Design**: two phases study. Phase A was a parallel group RCT, placebo controlled, of 1-week baseline and 14-week treatment. Phase B was an 18-week randomised withdrawal study (14-week, open-label treatment period plus a double-blind, 4-week, randomised-withdrawal phase) to investigate time to treatment failure and show maintenance of efficacy. **Setting**: multicentre, UK (12), Canada (5), Spain (5), France (4), Czech Republic (7) **Recruitment**: NR **Number screened:** 393 **Number randomised**: 339 **Outcome timing**: 14 weeks (phase A)
Participants	**Central neuropathic pain in MS (phase A)** **Inclusion criteria:** chronic neuropathic pain due to MS, ≥ 3 months' duration, ≥ 24 sum score on pain NRS 0-10 on the last 6 days during the baseline period. Analgesic regimen stable for ≥ 2 weeks preceding the study entry day **Exclusion criteria:** severe pain from other concomitant conditions including pain of a nociceptive, musculoskeletal (including spasms), peripheral neuropathic or psychogenic origin, or due to trigeminal neuralgia. Significant psychiatric, renal, hepatic, cardiovascular, or convulsive disorders, or sensitivity to cannabis or cannabinoids **Treatment group** (**Nabiximols/Sativex**): N = 167; % female: 68; mean age: 48.42 (SD 10.43) years; RRMS 48%, SPMS 39%, PPMS 11%, PRMS 2%; EDSS: NR; mean duration of MS: 11.42 (SD 8.00) years; %

Langford 2013 *(Continued)*

	previous cannabis use: 7.0; mean duration of CNP at randomisation: 5.59 (SD 6.12) years; duration of spasticity at randomisation not reported **Placebo group:** N = 172; % female: 68; mean age: 49.51 (SD 10.50) years; RRMS 45%, SPMS 41%, PPMS 13%, PR 1%; EDSS: NR; mean duration of MS: 12.53 (SD 8.50) years; % previous cannabis use: 6.0; mean duration of CNP at randomisation: 5.33 (SD 4.80) years; duration of spasticity at randomisation not reported
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** excipients plus colourants **Dose frequency:** 12 sprays in any 24-hour period. Daily number of sprays taken during the study: Sativex: mean 8.8 (SD 3.87). Placebo: mean 11.1 (SD 4.6) **Rescue medication**: paracetamol **Allowed co-therapies**: pain medication: stable for at least 2 weeks **Concomitant analgesic medication during the study:** Sativex 92%; Placebo 97%. Disease-modifying drugs: Sativex 60%; Placebo 58%
Outcomes	**Phase A (parallel)** **Spasticity. Measure:** NRS 0-10. **Data:** number of participant reporting ≥ 30% improvement not reported. Mean change (without SD) from baseline reported. Mean treatment difference and P value reported **Pain** 1. **Measure**: NRS 0-10. **Data**: number of participant reporting ≥ 50% improvement not reported. Number of participant reporting ≥30% improvement reported, calculated by imputation method (OR, 95% CI and p value). Mean (SD) daily score average over 7 days at baseline and final 7 days reported. Mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported 2. **Measure**: NPS. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported 3. **Measure**: BPI. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Withdrawal due to AE**: N/group **PGIC much or very much improved:** reported (OR, 95% CI and P value) **HRQoL** 1. **Measure:** SF36 (eight dimensions). **Data:** Mean difference change from baseline with P value 2. **Measure**: EQ-5D index and EQ-5D VAS scores. **Data:** Mean difference change from baseline with P value **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: N/group **Psychiatric disorders-related AE**: N/group **Dizziness**: N/group **Somnolence**: N/group **Headache**: N/group **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence:** not assessed **Muscle spasms. Measure:** NRS 0-10 spasm severity. **Data:** mean change (without SD) from baseline reported. Mean treatment difference and P value reported **Fatigue. Measure:** NRS 0-10. **Data:** mean change (without SD) from baseline reported. Mean treatment difference and P value reported **Sleep disruption due to neuropathic pain. Measure:** NRS 0-10. **Data:** mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Mobility/ADLs:** not assessed **Anxiety**: not assessed **Depression**: not assessed **CGIC**: not assessed

Langford 2013 *(Continued)*

	Reduced use of anti spastics: not assessed **Reduced use of analgesics:** number of paracetamol tablets taken. Mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported
Notes	**Funding**: industry - drug manufacturer

Leocani 2015

Study characteristics	
Methods	**Design**: Randomised cross-over study **Setting**: Italy; single-centre **Recruitment**: April 2012 to June 2013 **Number screened:** NR **Number randomised**: 44 **Outcome timing**: 4 weeks
Participants	**Spasticity in MS** **Inclusion criteria:** males and females aged ≥ 18 years; SPMS or PPMS of at least 12 months' duration; relapse-free for at least 3 months prior to screening; EDSS score between 3.0 and 6.5; moderate to severe spasticity at inclusion as defined by a MAS score of at least '1+' in one limb; stable doses of anti spasticity medication for at least 2 months prior to screening **Exclusion criteria**: any concomitant disease with the potential to cause or interfere with spasticity; botulinum toxin injection for spasticity in the 4 months prior to screening; any known or suspected history of psychotic illness, alcohol or substance abuse; epilepsy or hypersensitivity to cannabinoids; significant cardiac, renal or hepatic disease; females who were pregnant or lactating, or subjects of childbearing potential unless willing to use contraception; known contraindications to Sativex. **Randomised:** N = 44 participants; % female: 46.5; mean age: 48 (SD 8) years; mean EDSS: 5.5 (SD 1.0); mean duration of MS: 17.1 (SD 8.4) years; % previous cannabis use: NR; % anti spastics use: 68; % undergoing disease-modifying therapy: 64
Interventions	**Sativex (THC 2.7 mg and CBD 2.5 mg) oromucosal spray versus placebo**. The maximum permitted-dose was 12 sprays over 24 hours. Study duration: 2 x 4 weeks treatment periods. Washout period: 2 weeks **Concomitant medication during the study:** antispastic medicines stable for at least 2 months prior to screening. No modifications to DMDs in the 6 months prior to inclusion or during the study period
Outcomes	**Spasticity.** • **Measure:** MAS. **Data**: number of participant reporting ≥ 20 % improvement in the score. • **Measure:** NRS 0-10. **Data**: number of participant reporting ≥ 20 % improvement in the score **Pain**. **Measure:** NRS 0-10. **Data**: pre-post treatment change difference between Sativex and placebo **Withdrawal due to AE**: N/phase **PGIC much or very much improved:** not assessed **HRQoL**: not assessed **Serious AEs**: NR **AEs**: N/phase **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: N/phase **Somnolence**: N/phase **Headache**: NR **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR

Leocani 2015 *(Continued)*

	Hallucinations: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity. Measure:** number of spasms within the last 24 hours. **Data**: NR **Fatigue**: **Measure:** Fatigue Severity Scale. **Data**: pre-post treatment change difference between Sativex and placebo **Sleep quality**: **Measure:** NRS 0-10. **Data**: pre-post treatment change difference between Sativex and placebo **Mobility/ADLs**: not assessed **Anxiety**: not assessed **Depression:** not assessed **CGIC much or very much improved**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed.
Notes	**Funding**: private. The study was sponsored by Laboratorios Almirall S.A., Barcelona, Spain

Markova 2018

Study characteristics	
Methods	**Design**: a two-phase enriched-design trial. In phase A, eligible patients received add-on Sativex spray for 4 weeks to identify initial responders (≥ 20% improvement from baseline in spasticity NRS 0-10 score). Following washout (up to 28 days), eligible initial responders were randomised to receive Sativex or placebo for 12 weeks (Phase B) **Setting**: multicentre, 14 centres in Czech Republic and 1 centre in Austria **Recruitment**: NR **Number screened**: NA **Number randomised**: 106 **Outcome timing**: 12 weeks
Participants	**Spasticity in MS** **Inclusion criteria:** age >18 years; any MS subtype; ≥ 12 months history of spasticity due to MS not wholly relieved with current therapy; score of ≥4 on spasticity NRS (moderate-to-severe spasticity); currently receiving optimised treatment with one or more oral anti spasticity drugs (baclofen or tizanidine or both, or dantrolene as monotherapy or in combination therapy) for at least 3 months prior to screening **Exclusion criteria:** prior administration of THC:CBD spray; current consumption of cannabis herb or other cannabinoid-based drugs within 30 days prior to study entry; treatment with botulinum toxin injection within the previous 6 months; medical history or family history of major psychiatric disorders other than depression; known or suspected history of a dependence disorder or heavy alcohol consumption; possibility of pregnancy or lactation; history of myocardial infarction or clinically significant cardiac dysfunction, impaired renal or hepatic function. **Treatment group** (**Nabiximols/Sativex**): N = 53; % female: NR; age: NR; EDSS: NR; duration of MS: NR; % previous cannabis use: 100 (all participants received Sativex in phase A); duration of spasticity at randomisation: at least 1 year (study protocol) **Placebo group:** N = 53; % female: NR; age: NR; EDSS: NR; duration of MS: NR; % previous cannabis use: 100 (all participants received Sativex in phase A); duration of spasticity at randomisation: at least 1 year (study protocol)

Markova 2018 *(Continued)*

	Most patients had secondary progressive MS (n = 92; 48.2%) or relapsing remitting MS (n = 78; 40.8%).
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** NR **Dose frequency:** maximum 12 sprays in any 24-hour period. Daily number of sprays taken during the study: Sativex: mean 7.3 (SD 2.7); Placebo: mean 8.5 (SD 3.0) **Allowed co-therapies:** optimisation of underlying anti spasticity medications was permitted in both groups across all study periods **Concomitant medication during the study:** baclofen 84.9%; tizanidine 31.1%; combined therapy 16%
Outcomes	**Phase B (parallel)** **Spasticity** 1. **Measure:** NRS 0-10. **Data:** number of participants reporting ≥ 30% improvement reported (OR, 95% CI and P value). Mean change (95% CI) from baseline defined as the mean NRS spasticity score from the last 7 days of the treatment period minus the mean NRS score at baseline (measured at the day of randomisation and the 2 previous days). Mean treatment difference (95% CI and P value) reported 2. **Measure:** MAS. **Data**: Mean change (95% CI) from baseline reported. Mean treatment difference (95% CI and P value) reported **Pain**. **Measure:** NRS 0-10. **Data**: number of participant reporting ≥ 50% improvement not reported. Mean change (95% CI) from baseline reported. Mean treatment difference (95% CI and P value) reported **Withdrawal due to AE**: N/group **PGIC much or very much improved:** reported (OR, 95% CI and P value) **HRQoL**: **Measure:** SF36 (eight dimensions). **Data:** Mean change (95% CI) from baseline reported for the eight dimensions. Mean difference change from baseline (95% CI and p value) between groups for the eight dimensions **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: N/group **Dizziness**: N/group **Somnolence**: N/group **Headache**: N/group **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed

Markova 2018 *(Continued)*

	Muscle spasms severity. Measure: 3 levels categorical scale, i.e. mild, moderate, severe. **Data**: change from baseline reported (least square means and 95% CI). Mean treatment difference (95% CI and P value) reported **Fatigue:** not assessed **Sleep disruption. Measure**: NRS 0-10. **Data**: mean change (95% CI) from baseline reported. Mean treatment difference (95% CI and P value) reported **Mobility/ADLs. Measure:** Barthel ADL index score. **Data**: number of participants reporting an MCID (8.5 points) improvement from baseline reported (OR, 95% CI and P value). Mean change (95% CI) from baseline reported. Mean treatment difference (95% CI and P value) reported **Anxiety**: not assessed **Depression**: not assessed **CGIC**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: industry - drug manufacturer

NCT00682929

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: US, single-centre **Recruitment** period began in April 2004 and continued through 2016 **Number screened:** NR **Number randomised**: 41 **Outcome timing**: 7 weeks
Participants	**Spasticity in MS** **Inclusion criteria:** diagnosis of clinically definite MS as defined by Poser criteria (Poser 1983); moderate or severe spasticity; age 21 or older; must live close to the Sacramento, CA area **Exclusion criteria:** pre-existing pulmonary or cardiac conditions; poorly controlled psychiatric illness or dementia; inability to abstain from tobacco or marijuana smoking, or use of alcohol or sedative or hypnotic medications during the study; history of or currently meets DSM-IV criteria for dependence on cannabis; use of cannabis, marijuana, or THC in the last four weeks; current use of cyclophosphamide, mitoxantrone, or cladribine; arthritis, bony and soft tissue disorders interfering with spasticity measures; for females of child bearing potential, inability to comply with adequate contraception **Treatment group** (**Marijuana**): N = 13; % female: 38.5; age: 18-65 years; type of MS: NR; EDSS: NR; duration of MS: NR; % previous cannabis use: NR; duration of spasticity at randomisation: NR **Treatment group** (**Dronabinol/Marinol**): N = 14; % female: 50.0; age: 18-64 years (N 13), ≥65 years (N 1); type of MS: NR; EDSS: NR; duration of MS: NR; % previous cannabis use: NR; duration of spasticity at randomisation: NR **Placebo group:** N = 14; % female: 57.1; age: 18-64 years (N 12), ≥65 years (N 2); type of MS: NR; EDSS: NR; duration of MS: NR; % previous cannabis use: NR; duration of spasticity at randomisation: NR
Interventions	**Marijuana:** cannabis cigarette, inhaled (smoked). Participants take their oral medication (two pills of placebo) two and a half hours prior to smoke one cannabis cigarette, daily. **Synthetic Delta 9- THC (Dronabinol/Marinol):** 5 mg tablet. Participants take their oral medication (two 5mg Dronabinol tablets) two and a half hours prior to the inhaled medication (placebo). They take two pills and smoke one cigarette, daily.

NCT00682929 *(Continued)*

	Placebo: participants take their oral medication (placebo) two and a half hours prior to the inhaled medication (placebo). They take two pills and smoke one cigarette, daily. **Concomitant medication during the study:** NR
Outcomes	**Spasticity. Measure:** MAS. **Data**: mean change (SD) from baseline reported. **Pain:** not assessed **Withdrawal due to AE**: n/N **PGIC much or very much improved:** not assessed **HRQOL. Measure:** SF3 physical and mental summary domains. **Data**: mean difference change from baseline (SD) between groups at 7 weeks **Serious AEs**: n/N **AEs**: n/N **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: n/N **Somnolence**: n/N **Headache**: n/N **Confusion- disorientation**: n/N **Paranoia**: n/N **Psychosis**: NR **Hallucinations**: n/N **Drug tolerance**: NR **Urinary incontinence:** not assessed **Muscle spasms:** not assessed **Fatigue:** not assessed **Sleep disturbance:** not assessed **Mobility/ADLs:** not assessed **Anxiety**: not assessed **Depression**: not assessed **CGIC**: not assessed **Reduced use of anti spastics:** not assessed **Reduced use of analgesics:** not assessed.
Notes	Unable to complete subject recruitment. The study terminated early due to difficulty with enrolment and logistical issues. Departure of the principal investigator. No data analysis. **Funding**: public

NCT01606176

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: multicentre in the UK. Number of centres not reported **Recruitment**: NR **Number screened:** NR **Number randomised**: 70 **Outcome timing**: 3 weeks
Participants	**Chronic pain in MS or other defect of neurological function** **Inclusion criteria:** chronic refractory pain due to MS or other defects of neurological function. Neuropathic pain with a mean severity NRS score at ≥ 4 during last 7 days of the baseline period. Relatively stable neurological condition during the preceding 6 months. Stable medication regimen during the preceding 4 weeks. Had not used cannabis-based medicines for at least the preceding 7 days and willing to abstain from any use of cannabis-based medicines during the study **Exclusion criteria:** history of schizophrenia, other psychotic illness, severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition. History of alcohol or substance abuse. Severe cardiovascular disorder, such as ischaemic heart disease,

NCT01606176 *(Continued)*

	arrhythmias (other than well-controlled atrial fibrillation), poorly-controlled hypertension or severe heart failure. History of autonomic dysreflexia. History of epilepsy. Renal and liver problems **Treatment group** (**Nabiximols/Sativex**): N = 36; % female: 61.8; mean age: 51.72 (SD 12.11) years, 24 in MS-subset; type of MS: NR; EDSS: NR; duration of MS: NR; % previous cannabis use: NR; duration of-pain at randomisation: NR **Placebo group:** N = 34; % female: 66.7; mean age: 57.61 (SD 10.28) years, 19 in MS-subset; type of MS: NR; EDSS: NR; duration of MS: NR; % previous cannabis use: NR; duration of pain at randomisation: NR
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** no active drug, delivered in 100 microlitre oromucosal spray **Dose frequency:** maximum permitted dose of Sativex 8 sprays in any 3-hour period (20 mg THC/20 mg CBD) and 48 sprays in any 24 hours period (120 mg THC/120 mg CBD). Placebo same number of sprays possible. Daily number of sprays taken during the study: NR **Concomitant medication during the study:** NR
Outcomes	**Spasticity:** not assessed **Pain.** 1. **Measure:** NRS 0-10. **Data**: number of participant reporting ≥ 50% improvement not reported. NRS 0-10, 3 measures/day, average of the last 7 days. The last day was taken as the last day with complete diary card pain data that occurred on or before the last day the patient took study medication. Mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported 2. **Measure:** BPI (short form). **Data:** Mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Withdrawal due to AE**: NR **PGIC much or very much improved:** the number of participants reporting "Very Much Improved" or "Much Improved" reported. Comparison between groups (95% CI and Pp value) reported **HRQOL. Measure**: Spitzer Quality of life index 15-0. Mean change (SD) from baseline reported. Mean difference change from baseline (95% CI and P value) **Serious AEs**: NR **AEs**: NR **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: NR **Somnolence**: NR **Headache**: NR **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence:** not assessed **Muscle spasms:** not assessed **Fatigue:** not assessed **Sleep disturbance. Measure:** NRS 0-10. **Data:** Mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Mobility/ADLs:** not assessed **Anxiety**: not assessed **Depression**: not assessed **CGIC**: not assessed **Reduced use of anti spastics:** not assessed **Reduced use of analgesics. Measure:** the percentage of days on treatment on which analgesic escape medication was used. Mean (SD) reported. Mean treatment difference (95% CI and P value) reported
Notes	**Funding**: industry - drug manufacturer

Notcutt 2012

Study characteristics	
Methods	**Design**: an enriched enrolment placebo-controlled parallel randomised withdrawal design. During a 7-day baseline period, participants continued stable dose with nabiximols at their current effective dose level. At the end of the baseline period, participants were randomised to either nabiximols or placebo. **Setting**: multicentre, 5 centres in UK **Recruitment**: NR **Number screened:** 37 **Number randomised**: 36 **Outcome timing**: 4 weeks
Participants	**Spasticity in MS** **Inclusion criteria:** people with MS and receiving Sativex for the relief of spasticity for at least 12 weeks prior to screening, and who were judged to have been receiving benefit from and showing tolerability to Sativex; stable anti spastic medication unchanged ≥3 months **Exclusion criteria:** concomitant disease or disorder that had spasticity-like symptoms or that may have influenced the subject's level of spasticity; use of botulinum toxin or rimonabant, a cannabinoid receptor antagonist, in the 3 months prior to study entry; current or past history of substance or alcohol abuse; significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders **Treatment group** (**Nabiximols/Sativex**): N = 18; % female: 50.0; mean age: 59.7 (SD 9.0) years; RRMS 16.7%; SPMS 55.5%; PPMS 27.8%; mean EDSS: 6.75 (median 7.0, range 4.0-8.5); mean duration of MS: 17.8 (SD 8.5) years; % previous cannabis use: 100 at current effective dose level; mean duration of Sativex use: 4.2 (median 2.0) years; mean spasticity severity (NRS) 3.6 (SD 1.7); mean duration of spasticity 14.38 (SD 9.90) years **Placebo group:** N = 18; % female: 66.7; mean age: 54.4 (SD 10.4) years; RRMS 22.2%; SPMS 50.0%; PPMS 27.8%; EDSS: mean EDSS: 6.92 (median 7.0, range 5.5-8.5); mean duration of MS: 15.1 (SD 10.1) years; % previous cannabis use: 100 at current effective dose level; mean duration of Sativex use: 3.0 (median 1.9) years; mean spasticity severity (NRS) 4.1 (SD 2.2); mean duration of spasticity 11.01 (SD 8.25) years
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** no active drug, delivered in 100 microlitre oromucosal spray **Dose frequency:** maximum 48 sprays in any 24-hour period. Daily number of sprays taken during the study Sativex: mean 7.7 (median 6.4); Placebo: mean 9.0 (median 6.0) **Concomitant medication during the study.** Sativex: DMDs 3 participants, Benzodiazepines 1 participants and Tizanidine or Baclofen 6 participants; Placebo: DMDs 3 participants, Benzodiazepines 4 participants and Tizanidine or Baclofen 9 participants
Outcomes	**Spasticity.** 1. **Measure**: NRS 0-10. **Data**: number of participant reporting ≥ 30% improvement not reported. Mean baseline score (SD) reported. Mean change (SD) from baseline defined as baseline (week 1) to week 5. Mean treatment difference (95% CI and P value) reported 2. **Measure:** MAS. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Pain**: not assessed **Withdrawal due to AE**: N/group **PGIC much or very much improved:** reported (OR, 95% CI and P value) **HRQoL:** not assessed **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: N/group **Psychiatric disorders-related AE**: N/group **Dizziness**: N/group **Somnolence**: N/group **Headache**: NR **Confusion- disorientation**: NR **Paranoia**: NR

Notcutt 2012 *(Continued)*

	Psychosis: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity**: not assessed **Fatigue**: not assessed **Sleep quality. Measure**: NRS 0-10 sleep quality. **Data**: mean baseline score (without SD) reported. Mean (SD) at the outcome timing reported. Mean change (without SD) from baseline reported. Mean treatment difference (90% CI and P value) reported **Mobility/ADLs**: not assessed **Anxiety**: not assessed **Depression:** not assessed **CGIC for functional ability much or very much improved. Measure:** 7-point Likert-type scale with the markers "very much improved, much improved, lightly improved, no change, slightly worse, much worse or very much worse. **Data**: number of participants reporting "very much improved" or "much improved" (OR, 90% CI and P value) reported **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: industry - drug manufacturer

Novotna 2011

Study characteristics	
Methods	**Design**: an enriched enrolment two-phases design. In phase A, eligible patients received add-on Sativex (Nabiximol) spray for 4 weeks to identify initial responders (≥20% improvement from baseline in spasticity NRS 0-10 score). Eligible initial responders were randomised to receive Sativex or placebo for 12 weeks (phase B). A washout period between phase A and phase B was not done. **Setting**: multicentre, UK (18); Spain (11); Poland (10); Czech Republic (8); Italy (5) **Recruitment**: NR **Number screened:** NA **Number randomised**: 241 **Outcome timing**: 12 weeks
Participants	**Spasticity in MS** **Inclusion criteria:** age ≥18 years; any MS subtype for ≥6 months; ≥ 3 months history of spasticity due to MS not wholly relieved with current therapy; score of ≥4 on spasticity NRS (moderately severe spasticity); ≥20% reduction in their NRS spasticity score at the end of the first study phase (phase A); no new anti spasticity or disease-modifying medication and no alterations to dosage of anti spasticity or disease-modifying medication throughout Phase A; blindness to treatment allocation throughout-Phase A. **Exclusion criteria:** any other medical condition which was expected to influence the participants spasticity; cannabis or cannabinoid-based medications in the 30-day period prior to study entry; medical history of psychiatric, renal, hepatic, cardiovascular or convulsive disorders; known or suspected history of a dependence disorder, alcohol or substance abuse; current non-prescribed use of any prescription drug. **Treatment group** (**Sativex/Nabiximols**): N = 124; % female: 58.1; mean age: 49.1 (SD 9.09) years; mean EDSS: 6.5 (SD 1.46); mean duration of MS: 13.3 (SD 8.29) years; % previous cannabis use: 100 (all participants received Sativex in phase A); mean duration of spasticity: 8.6 (6.89) years

Novotna 2011 *(Continued)*

	Placebo group: N = 117; % female: 62.4; mean age: 48.1 (SD 9.59) years; mean EDSS: 6.0 (SD 1.44); mean duration of MS: 11.8 (SD 7.38) years; % previous cannabis use: 100 (all participants received Sativex in phase A); mean duration of spasticity: 6.7 (5.40) years
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** ethanol:propylene glycol (50:50) excipients, peppermint oil (0.05%) flavouring and colouring **Dose frequency:** maximum 12 sprays in any 24 hour period. Daily number of sprays taken during the study: Sativex: mean 8.3 (SD 2.43); Placebo: mean 8.9 (SD 2.31) **Allowed co-therapies:** the treatment regimen of all medications that might have affected the subjects spasticity was required to remained stable in phase A **Concomitant anti spasticity medication during the study:** centrally acting agents (Baclofen, Tizanidine, Tolperisone): Sativex 70%, Placebo 77%; Anti-epileptics: Sativex 29%, Placebo 18%; Benzodiazepine-related derivatives: Sativex 18%, Placebo 25%; Adamantane derivatives: Sativex 14%, Placebo13%; Others: Sativex 2%, Placebo 0
Outcomes	**Phase B (parallel)** **Spasticity** 1. **Measure:** NRS 0-10. **Data:** number of participants reporting ≥ 30% improvement reported (OR, 95% CI and P value) reported. Mean baseline score (SD), defined as the mean of the last 7-day scores of phase A, reported. Mean (SD) from the last 7 days of the treatment period reported. Mean change from baseline without SD reported. Mean treatment difference (95% CI and P value) reported 2. **Measure:** MAS. **Data**: Mean change from baseline without SD reported. Mean treatment difference (95% CI and P value) reported **Pain:** not assessed **Withdrawal due to AE**: N/group **PGIC much or very much improved:** reported (OR, 95% CI and P value) **HRQoL** 1. **Measure:** SF36 (eight scales). **Data:** mean score without SD at 12 weeks reported. Mean difference change from baseline (P value) 2. **Measure:** EQ-5D health state index; EQ-5D health status VAS score. **Data:** mean score (without SD) at 12 weeks reported. Mean change (SD) from baseline reported. Mean difference change from baseline (95% CI and P value) **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: N/group **Dizziness**: N/group **Somnolence**: N/group **Headache**: N/group **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR

Novotna 2011 *(Continued)*

	Drug tolerance: NR **Urinary incontinence:** not assessed **Muscle spasms frequency. Measure**: NRS. **Data**: mean score (SD) at the end of treatment reported. Mean treatment difference (95% CI and P value) reported **Fatigue:** not assessed **Sleep disruption. Measure**: NRS 0-10. **Data**: mean score (SD) at the outcome timing reported. Mean change from baseline without SD reported. Mean treatment difference (95% CI and P value) reported **Mobility/ADLs. Measure:** Barthel ADL index score. **Data**: Number of participants reporting improvement from baseline reported (OR, 95% CI and P value) **Anxiety**: not assessed **Depression**. **Measure:** Beck Depression Inventory - II. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **CGIC**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: industry - drug manufacturer

Rog 2005

Study characteristics	
Methods	**Design**: parallel group RCT, placebo controlled **Setting**: UK, single-centre **Recruitment**: March 2002 - July 2002 **Number screened:** 85 **Number randomised**: 66 **Outcome timing**: 4 weeks
Participants	**Central neuropathic pain in MS.** **Inclusion criteria:** at least 6 months after MS diagnosis; at least 3 months central pain with unlikely other cause, both with dysaesthetic characteristics or painful spasm; 2 weeks of stable analgesic regimen; no cannabinoid use the last 7 days **Exclusion criteria:** spasticity-related pain, visceral pain, headache, acute MS-related pain; major psychiatric disorder; other than pain-related depression; severe concomitant illness, seizures; history or suspicion of substance abuse; diabetes mellitus; levodopa use; hypersensitivity to cannabis-based medicines **Treatment group** (**Nabiximols/Sativex**): N = 34; % female: 82; mean age: 50.3 (SD 6.7) years; mean EDSS: 6.0 (SD 1.1); mean duration of MS: 10.4 (SD 7.3) years; % previous cannabis use: 44.0; duration of CNP not reported **Placebo group:** N = 32; % female: 75; mean age: 48.1 (SD 9.7) years; mean EDSS: 5.8 (SD 1.5); mean duration of MS: 12.8 (SD 8.1) years; % previous cannabis use: 65.6; duration of CNP not reported **Combined groups**: RRMS 35%, SPMS 50%, PPMS 14%, Benign MS 1%
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** ethanol:propylene glycol (50:50) excipients **Dose frequency:** maximum 48 sprays in any 24 hour period. Daily number of sprays taken during the study: Sativex: mean 9.6 (SD 6.1), range: 2–25; Placebo: mean 19.1 (SD 12.9), range: 1–47 **Allowed co-therapies**: amitriptyline maximally 75 mg/day

Rog 2005 *(Continued)*

	Concomitant analgesics medication during the study: Sativex mean 1.8 (SD 1.2) range 0–5; Placebo mean 1.8 (SD 1.3) range 0–4
Outcomes	**Spasticity:** not assessed **Pain** 1. **Measure:** NRS 0-10. **Data:** number of participant reporting ≥ 50% or ≥ 30% improvement not reported. Mean score (SD and 95% CI) of the 7 days before the first treatment dose reported (baseline score). Mean score (SD and 95% CI) of the last 7 days of treatment (outcome timing) reported. Mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported 2. **Measure:** NPS. **Data:** Mean score (range) of the 3 days in the run-in week (baseline score). Mean score (95% CI) of the last 3 days of treatment (outcome timing) reported. Mean change (SD) from baseline reported. Mean treatment difference (95% CI and p value) reported **Withdrawal due to AE**: N/group **PGIC much or very much improved:** reported (OR, 95% CI and P value) **HRQoL**: not assessed **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: N/group **Somnolence**: N/group **Headache**: N/group **Confusion- disorientation**: N/group **Paranoia**: N/group **Psychosis**: NR **Hallucinations**: N/group **Drug tolerance**: NR **Urinary incontinence:** not assessed **Muscle spasms:** not assessed **Fatigue:** not assessed **Sleep disruption due to neuropathic pain: Measure:** NRS 0-10. **Data:** mean baseline score (95% CI) reported. Mean score (95% CI) at the outcome timing reported. Mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Mobility/ADLs:** not assessed **Anxiety**: **Measure:** HADS. **Data:** mean change (SD) from baseline reported. Mean treatment difference (95% CI and p value) reported **Depression**: HADS. **Data:** mean change (SD) from baseline reported. Mean treatment difference (95% CI and p value) reported **CGIC**: not assessed **Reduced use of anti spastics:** not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: industry - drug manufacturer

Schimrigk 2017

Study characteristics	
Methods	**Design**: parallel group RCT, placebo-controlled **Setting**: multicentre, Germany (30 centres) **Recruitment**: NR **Number screened:** 260 **Number randomised**: 240

Schimrigk 2017 *(Continued)*

	Outcome timing: 16 weeks
Participants	**Central neuropathic pain in MS** **Inclusion criteria:** age 18-70 years; MS according to McDonald criteria (McDonald 2001); stable MS symptoms; ≥ 3 months history of CNP due to MS; score of ≥4 on pain NRS (moderate to severe pain) **Exclusion criteria:** any peripheral pain syndromes, pre-existing psychotic disorders, severe cardiac diseases, or known substance abuse **Treatment group** (**Dronabinol**): N = 124; % female: 71; mean age: 48.4 (SD 9.6) years; mean EDSS: 5.0 (SD 1.5); mean duration of MS: 10.9 (SD 7.98) years; % previous cannabis use: NR; mean duration of CNP at randomisation: 54.0 (SD 53.8; range 2.0–357.0) months **Placebo group:** N = 116; % female: 75; mean age: 47.0 (SD 9.7) years; mean EDSS: 4.9 (SD 1.6); mean duration of MS: 11.5 (SD 8.17) years; % previous cannabis use: NR; mean duration of CNP at randomisation: 59,5 (SD 58.1; range 4.0 to 419.0) months
Interventions	**Synthetic Delta 9- THC (Dronabinol):** oral solution. **Placebo:** oral solution. Description NR **Treatment duration**: 4 weeks' titration, followed by a 12-week maintenance phase. 32 weeks open-label **Dose:** between 7.5 and 15.0 mg daily. Mean daily dose of Dronabinol taken during the study: 12.7 (SD 2.9) mg **Rescue medication**: oral intake of tramadol **Allowed co-therapies**: amitriptyline and gabapentin, if started at least 3 months earlier with a stable dose **Concomitant analgesics medication during the study:** Dronabinol 39.5% of participants. Placebo 44.0% of participants
Outcomes	**Spasticity:** not assessed **Pain**. **Measure:** NRS 0-10. **Data:** number of participant reporting ≥ 50% improvement not reported. Mean score (SD) of patients' retrospective rating of weekly pain intensity reported (baseline score). Mean change (SD) from baseline to mean weekly pain scores within a maximum of 16 weeks reported. P value of the mean treatment difference reported **Withdrawal due to AE**: N/group **PGIC much or very much improved:** not assessed **HRQoL. Measure:** SF3 physical and mental summary domains. Mean change (without SD) at 16 weeks **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: N/group **Somnolence**: NR **Headache**: N/group **Confusion- disorientation**: NR

Schimrigk 2017 *(Continued)*

	Paranoia: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence:** not assessed **Muscle spasms:** not assessed **Fatigue:** not assessed **Sleep disruption:** not assessed **Mobility/ADLs:** not assessed **Anxiety**: not assessed **Depression**: not assessed **CGIC**: not assessed **Reduced use of anti spastics:** not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: industry - drug manufacturer

Svendsen 2004

Study characteristics	
Methods	**Design**: Randomised cross-over study **Setting**: Denmark; single-centre **Recruitment**: 27 February to 21 May 2002 **Number screened:** 25 **Number randomised**: 24 **Outcome timing**: 3 weeks
Participants	**Central neuropathic pain in MS** **Inclusion criteria:** diagnosis of MS (Poser 1983); age 18 to 55 years; CNP intensity score ≥ 3 on a 0-10 NRS **Exclusion criteria**: hypersensitivity to cannabinoids or sesame oil; heart disease; mania, depression, or schizophrenia; previous or present alcohol or drug misuse; treatment with tricyclic antidepressants, anticholinergic agents, antihistamine, or central nervous system depressant drugs (with the exception of spasmolytic drugs); use of analgesic drugs except paracetamol; pregnancy or lactation; sexually active women without reliable contraception; patients unable to cooperate or complete the study; participation in other clinical trials within the previous month; use of marihuana within the three months before the study; and unwillingness to abstain from the use of marihuana during the entire period **Randomised:** N = 24; % female: 58.3; median age: 50 (range 23-55) years; % RRMS 37.5; % SPMS 37.5 ; % PPMS 25; median EDSS: 6.0 (range 2.5-6.5); median duration of MS: 7.0 (range 0.3-25.0) years; median duration of pain: 4.5 (range 0.3-12.0) years; % previous cannabis use: NR
Interventions	**THC capsules (Dronabinol) versus placebo**. Dose: 2.5 mg daily increased by 2.5 mg every other day to a maximum dose of 10 mg daily. Placebo capsules were administered as identical looking capsules. The active capsules contained dronabinol solution in sesame oil, and the placebo capsules contained pure sesame oil. Study duration: 2 x 3 weeks treatment periods. Washout period: 3 weeks

Svendsen 2004 *(Continued)*

	Allowed co-therapies: spasmolytic drugs, paracetamol
Outcomes	**Spasticity**: not assessed **Pain**. **Measure:** NRS 0-10. **Data:** number of participant reporting ≥ 50% improvement (end of treatment period) **Withdrawal due to AE**: number of participants **PGIC much or very much improved:** not assessed **HRQoL. Measure:** SF-36 health survey. **Data**: medians (25th to 75th centiles and P values active versus placebo) **Serious AEs**: NR **AEs**: N/phase **Nervous system disorders-related AE**: N/phase **Psychiatric disorders-related AE**: N/phase **Dizziness**: N/phase **Somnolence**: N/phase **Headache**: N/phase **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity**: not assessed **Fatigue**: not assessed **Sleep quality**: not assessed **Mobility/ADLs**: not assessed **Anxiety**: not assessed **Depression:** not assessed **CGIC much or very much improved**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed.
Notes	**Funding**: mixed. The study was supported by grants from the Danish MS Society (grant no 2002/71045), and the Warwara Larsen Foundation (grant no 664.28), Denmark. Solvay Pharmaceuticals provided study medication and placebo, labelling, and packaging. In addition, the company provided financial support for study monitoring and data analysis. IPC-Nordic, Denmark, packaged and labelled the study medication and monitored the study. These companies were not involved in the design or execution of the study or writing the manuscript.

Turcotte 2015

Study characteristics	
Methods	**Design**: parallel group RCT, placebo-controlled **Setting**: Canada, single-centre **Recruitment**: May 2008- July 2012 **Number screened:** 22 **Number randomised**: 15 **Outcome timing**: 9 weeks
Participants	**Neuropathic pain in MS.** **Inclusion criteria:** RRMS according to the revised McDonald criteria (Polman 2005). Neuropathic pain defined as a direct consequence of a lesion or disease affecting the somatosensory system, diagnosed by a neurologist and scored 4 as per the Douleur Neuropathique 4 questions (DN4) criteria (Bouhassira 2005); age 18–65 years old; EDSS score <6.5; VAS pain score ≥50; at least 3 months neuropathic pain with unlikely other cause; current pain treatment with Gabapentin not effective at a stabilised dose of 1,800 mg daily

Turcotte 2015 *(Continued)*

	Exclusion criteria: past or current non psychotic or psychotic emotional disorders; severe concomitant illness; pregnancy or breastfeeding; history or alcohol of substance abuse; hypersensitivity to nabilone or its derivatives and current reported use of cannabinoids or related products **Treatment group** (**Synthetic Delta 9- THC/Nabilone)** : N = 8; % female: 88; mean age: 42.12 (SD 11.20) years; RRMS 100%; mean EDSS: 2.56 (SD 0.77); median duration of MS: 5.5 (IQR 4.5-7.25) years; % previous cannabis use: NR; median duration of NP: 41.5 (IQR 24–64.5)months **Placebo group:** N = 7; % female: 86; mean age: 50.0 (SD 8.48) years; RRMS 100%; mean EDSS: 3.17 (SD 1.07); median duration of MS: 8.0 (IQR 6.25–9.0) years; % previous cannabis use: NR; median duration of NP: 62 (IQR 1–86) months
Interventions	**Nabilone: s**ynthetic THC 0.5 or 1 mg capsules **Placebo:** placebo capsules identical in colour, shape, and size to the nabilone capsules **Dose frequency:** 2 mg/day. Daily number of capsules taken during the study: NR **Allowed co-therapies**: Gabapentin 1800 mg daily **Concomitant analgesics medication during the study:** no additional medications
Outcomes	**Spasticity:** not assessed **Pain. Measure**: VAS 0-100 pain intensity over the previous 24 hours. **Data:** Mean (SD) baseline scores. RR and p value calculated by imputation method for mean daily neuropathic pain collapsed across all times **Withdrawal due to AE**: N/group **PGIC much or very much improved:** number of participants and P value of RR reported **HRQoL**: not assessed **Serious AEs**: N/group **AEs**: NR **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: reported for nabilone group **Somnolence**: NR **Headache**: reported for nabilone group **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence:** not assessed **Muscle spasms:** not assessed **Fatigue:** not assessed **Sleep disruption due to neuropathic pain:** not assessed **Mobility/ADLs:** not assessed **Anxiety**: **Measure:** not assessed **Depression**: not assessed **CGIC**: not assessed **Reduced use of anti spastics:** not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: industry - drug manufacturer

Vachova 2014

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: multicentre, 6 centres in Czech Republic **Recruitment**: NR **Number screened:** 121 **Number randomised**: 121

Vachova 2014 *(Continued)*

	Outcome timing: 50 weeks
Participants	**Long-term adverse effects on cognitive function or mood in MS** **Inclusion criteria:** any MS subtype; moderate levels of spasticity due to MS not wholly relieved with current therapy; stable in the last three months or four weeks for disease-modifying or anti spasticity or cognition medications, respectively; be willing to abstain from alternative cannabinoid use for 30 days prior to screening and throughout the study **Exclusion criteria:** current or past history of drug, alcohol abuse or significant psychiatric illness, hypersensitive to cannabinoids; female and of child bearing potential or male whose partner was of child bearing potential; female and pregnant, lactating or planning pregnancy; received experimental medicinal product within 12 weeks of screening; had any concomitant disorders or abnormalities that could either put the patient at risk, affect the patient's ability to participate or influence the result of the study **Treatment group** (**Nabiximols/Sativex**): N = 62; % female: 48.0; mean age: 49.0 (SD 8.95) years; RRMS 42%, SPMS 39%, PPMS 18%, PR 2%; EDSS: NR; mean duration of MS: 13.9 (SD 8.09) years; % previous cannabis use: 40; mean duration of spasticity: 8.0 (SD 6.08) years **Placebo group:** N = 59; % female: 48.0; mean age: 48.2 (SD 10.4) years; RRMS 56%, SPMS 32%, PPMS 8%, PR 3%; EDSS: NR; mean duration of MS: 13.9 (SD 9.08) years; % previous cannabis use: 25; mean duration of spasticity: 7.7 (SD 6.57) years
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** oromucosal spray containing excipients plus colorants **Dose frequency:** maximum 12 sprays in any 24-hour period. Daily number of sprays taken during the study: Sativex: first month mean 7.6 (SD 3.1); end of treatment mean 6.4 (SD 3.1). Placebo: first month mean 9.5 (SD 2.4); end of treatment mean 9.5 (SD 2.6) **Concomitant medication during the study:** Sativex: ≥ 1 anti spastics: 82%; analgesics and antipyretics: 16%. Placebo: ≥ 1 anti spastics: 85%; analgesics and antipyretics: 20%
Outcomes	**Spasticity. Measure:** MAS. **Data**: baseline scores (SD) reported. Mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Pain:** not assessed **Withdrawal due to AE**: N/group **PGIC much or very much improved:** reported (OR, 95% CI and P value) **HRQoL:** not assessed **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: N/group **Psychiatric disorders-related AE**: N/group **Dizziness**: N/group **Somnolence**: N/group **Headache**: N/group **Confusion- disorientation**: N/group **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: N/group **Urinary incontinence**: not assessed **Muscle spasms severity:** not assessed **Fatigue:** not assessed **Sleep quality:** not assessed **Mobility/ADLs:** not assessed **Anxiety**: not assessed **Depression. Measure:** Beck Depression Inventory - II total score. **Data**: mean change (SD) from baseline reported. Mean treatment difference (97.5% CI one tail and SE) reported **CGIC much or very much improved. Measure:** 7-point Likert-type scale with the markers "very much improved, much improved, lightly improved, no change, slightly worse, much worse or very much worse. **Data**: number of participants reporting "very much improved" or "much improved" reported (OR, 95% CI and p value) **Reduced use of anti spastics**: not assessed

Vachova 2014 *(Continued)*

	Reduced use of analgesics: not assessed
Notes	**Funding**: industry - drug manufacturer

Van Amerongen 2017

Study characteristics	
Methods	**Design**: A two phases study. The phase A was designed as a randomised, double-blind, placebo-controlled, 2-way cross-over design to determine the optimal effective dose of namisol. Following a washout period of 7 to 14 days, patients were randomised to receive namisol or placebo for 4-weeks (parallel phase B) **Setting**: one centre in the the Netherlands **Recruitment**: August 2011 - January 2013 **Number screened:** 66 **Number randomised**: 24 **Outcome timing**: 4 weeks
Participants	**Spasticity and central neuropathic pain in MS.** **Inclusion criteria:** secondary progressive or primary progressive MS according to the revised McDonald criteria (Polman 2005); > 1 year duration, clinical stable for at least 30 days; baseline score ≥2 on the Ashworth scale and an EDSS score between 4.5 and 7.5 (moderate spasticity) **Exclusion criteria:** current use of Delta 9- THC confirmed per urine drug screen; presence or a significant history of any cardiac or vascular disorder, asthma or other pulmonary disease, major gastrointestinal abnormalities, peptic ulceration, hepatic, psychiatric, haematological (including bleeding disorders), endocrine, renal, or major genitourinary disease or neurological disease other than MS or uses any kind of concomitant medication that - in the opinion of the investigator - may interfere with the study **Treatment group** (**Namisol**): N = 12; % female: 66.7; mean age: 57.3 (SD 9.0; range 41-73) years; mean EDSS: 6.2 (SD 1.2; range 4.5 -7.5); mean duration of MS: 10.3 (SD 6.5; range 3.0 - 27.0) years; % previous cannabis use: 100 (all participants received D9-THC in phase A); duration of spasticity and pain not reported **Placebo group:** N = 12; % female: 66.7; mean age: 51.4 (SD 8.0; range 38-64) years; mean EDSS: 6.3 (SD 0.5; range 5.5 -7.5); mean duration of MS: 12.6 (SD 4.9; range 6.0 - 21.0) years; % previous cannabis use: 100 (all participants received D9-THC in phase A); duration of spasticity and pain not reported
Interventions	**Synthetic Delta 9- THC (Namisol):** oral tablets 1.5 mg and 5 mg **Placebo:** matching placebo tablets **Treatment duration**: 4 weeks **Dose:** 24 mg daily. After 2 weeks of treatment, the daily dose was increased with 4.5 mg in all patients, except 1. For 2 patients, the dose was subsequently decreased to the starting dose (15 mg/dsy and 24 mg/day, respectively) because of adverse events **Rescue medication**: not reported **Allowed co-therapies**: spasmolytic therapy, if started at least 30 days earlier with a stable dose **Concomitant medication during the study:** not reported

Van Amerongen 2017 *(Continued)*

Outcomes	**Phase B (parallel)** **Spasticity** 1. **Measure:** NRS 0-10. **Data:** number of participant reporting ≥ 30% improvement not reported. Mean score (without SD) at the outcome timing reported. Mean change (without SD) from baseline reported. Mean treatment difference (95% CI and P value) reported 2. **Measure:** Ashworth scale. **Data**: mean score (without SD) at the outcome timing reported. Mean change (without SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Pain. Measure**: NRS 0-10. **Data**: number of participant reporting ≥ 50% improvement not reported. Mean score (without SD) at the outcome timing reported. Mean change (without SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Withdrawal due to AE**: N/group **PGIC much or very much improved:** mean score (without SD) at the outcome timing reported. Mean change (without SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **HRQoL:** not assessed **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: N/group **Somnolence**: N/group **Headache**: N/group **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence:** not assessed **Muscle spasms:** not assessed **Fatigue. Measure:** NRS 0-10. **Data:** mean change (without SD) from baseline reported. Mean treatment difference and P value reported **Sleep. Measure:** PSQI. **Data:** mean score (without SD) at the outcome timing reported. Mean change (without SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Mobility/ADLs:** not assessed **Anxiety**: not assessed **Depression**: not assessed **CGIC**: not assessed **Reduced use of anti spastics:** not assessed

Van Amerongen 2017 *(Continued)*

	Reduced use of analgesics: not assessed
Notes	**Funding**: industry - drug manufacturer

Vaney 2004

Study characteristics	
Methods	**Design**: Randomised cross-over study **Setting**: Switzerland; single-centre **Recruitment**: April 2000 to April 2001 **Number screened:** NR **Number randomised**: 57 **Outcome timing**: 2 weeks for active treatment and 1 week for placebo
Participants	**Spasticity in MS** **Inclusion criteria:** clinically-confirmed MS and clinically stable spasticity with at least one joint scoring ≥ 2 on the Ashworth scale **Exclusion criteria**: significant neurological (other than MS), cardiovascular or infectious diseases; clinical disease exacerbation or treatment with steroids during the two months preceding study entry; history of alcohol or drug abuse; depression; history of psychosis; use of cannabinoids during the week prior to inclusion; or significant cognitive impairment **Randomised:** N = 28 in phase one, N= 29 in phase two; % female: 50.9; mean age: 54.9 (SD 10.0) years; mean EDSS: 7.0 (SD 6.0); mean duration of MS: 17.0 (SD 8.4) years; % previous cannabis use: 58
Interventions	**Whole-plant cannabis extract containing 2.5 mg THC and 0.9 mg CBD versus placebo.** Overall maximum dose was 12 active capsules daily (equivalent to 30 mg THC/day). Study duration: 14 days cannabis treatment period and 7 days placebo period. Washout period: 3 days Phase one: 13 primary progressive, 14 secondary progressive, 1 relapsing-remitting. Phase two: 16/12/1 **Allowed co-therapies**: rehabilitation and all anti-spasticity medication
Outcomes	**Spasticity. Measure:** the Ashworth scale. **Data**: mean difference (SD) between treatments of the absolute change from baseline **Pain**: not assessed **Withdrawal due to AE**: N/phase **PGIC much or very much improved:** not assessed **HRQoL**: not assessed **Serious AEs**: N/phase **AEs**: N/phase **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: frequency/phase **Somnolence**: frequency/phase **Headache**: frequency/phase **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity. Measure**: spasm-frequency scales 0-3. **Data**: mean difference (SD) between treatments of the absolute change from baseline **Fatigue**: not assessed **Sleep quality**: not assessed

Vaney 2004 *(Continued)*

	Mobility/ADLs. Measure: the Rivermead Mobility Index. **Data**: mean difference (SD) between treatments of the absolute change from baseline **Anxiety**: not assessed **Depression:** not assessed **CGIC much or very much improved**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed.
Notes	**Funding**: public. This study was supported by the Swiss Ministry of Health

Wade 2004

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: multicentre, 3 centres in UK **Recruitment**: NR **Number screened:** 217 **Number randomised**: 160 **Outcome timing**: 6 weeks
Participants	**Multiple symptoms associated with MS** **Inclusion criteria:** MS clinically stable with no relapse ≤4 weeks; stable regular medication unchanged ≤4 weeks; abstaining from alternative cannabinoid use for 7 days prior to screening and throughout the study; have one of five target symptoms: spasticity, spasms, bladder problems, tremor or pain that was not obviously musculoskeletal. The most troublesome to be identified as the primary symptom **Exclusion criteria:** primary symptom was rated < 50% of maximal severity; current or past history of drug or alcohol abuse; significant psychiatric illness other than depression associated with MS; serious cardiovascular disorder; significant renal or hepatic impairment or history of epilepsy; specific contraindications to CBME excluded **Treatment group** (**Nabiximols/Sativex**): N = 80; % female: 59; mean age: 51.9 (SD 9.4; range 27 - 74) years; any subtypes of MS; EDSS: NR; duration of MS: NR; % previous cannabis use: 37.5; duration of CNP and spasticity at randomization not reported **Placebo group:** N = 80; % female: 65; mean age: 50.4 (SD 9.3; range 27 - 74) years; any subtypes of MS; EDSS: NR; duration of MS: NR; % previous cannabis use: 40; duration of CNP and spasticity at randomisation not reported
Interventions	**Sativex:** oromucosal spray: 100 µl containing 2.7 mg of delta-9-THC and 2.5 mg of CBD **Placebo:** oromucosal spray containing ethanol:propylene glycol (50:50) excipients and peppermint oil (0.05%) flavouring **Dose frequency:** maximum 48 sprays in any 24-hour period. Daily number of sprays taken during the study not reported **Concomitant medication during the study:** not reported
Outcomes	**Spasticity. Measure:** Ashworth scale. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI, SE and P value) reported **Pain:** not assessed **Withdrawal due to AE**: N/group **PGIC much or very much improved:** reported (OR, 95% CI and P value) **HRQoL:** not assessed **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: N/group **Somnolence**: N/group **Headache**: N/group

Wade 2004 *(Continued)*

	Confusion- disorientation: N/group **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity. Measure:** VAS (0=no problem; 100 = very bad). **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI and P value) reported **Fatigue. Measure:** Fatigue Severity Scale. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI, SE and P value) reported **Sleep quality:. Measure:** VAS. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI, SE and p value) reported **Mobility/ADLs. Measure:** Barthel ADL index. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI, SE and P value) reported **Anxiety**: not assessed **Depression. Measure:** Beck Depression Inventory - II total score. **Data**: mean change (SD) from baseline reported. Mean treatment difference (95% CI, SE and P value) reported **CGIC much or very much improved:** not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: industry - drug manufacturer

Zajicek 2003_CAMS

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: multicentre, 33 centres in the UK **Recruitment**: December 2000 - October 2002 **Number screened:** 821 **Number randomised**: 657 **Outcome timing**: 13 weeks
Participants	**Spasticity in MS** **Inclusion criteria:** age 18–64 years; confirmed MS; stable for ≥6 months; spasticity (Ashworth score of ≥2 in ≥ 2 limb muscle groups) **Exclusion criteria:** ischaemic heart disease; physiotherapy regimen or medication likely to affect spasticity ≤30 days; active infection; illness which could affect spasticity; immunisations associated with foreign travel; unable to avoid driving; fixed-tendon contractures; severe cognitive impairment; past history of psychotic illness; major illness in another body area; pregnancy; use of Δ9-THC at any time; use of cannabis ≤30 days **Treatment group. Cannador**: N = 219; % female: 64.0; mean age: 50.5 (SD 7.6) years; RRMS 3%, SPMS 72.0%, PPMS 25.0%; EDSS scores: 0-3.5 (0%), 4-5.5 (3%), 6-6.5 (49%), 7-9 (47%); duration of MS: NR; previous cannabis use: NR; duration of spasticity: NR **Treatment group. Marinol (Dronabinol)**: N = 216; % female: 69.4; mean age: 50.2 (SD 8.2) years; RRMS 7%, SPMS 72.0%, PPMS 21.0%; EDSS scores: 0-3.5 (0.5%), 4-5.5 (4%), 6-6.5 (46%), 7-9 (48%); duration of MS: NR; previous cannabis use: NR; duration of spasticity: NR **Placebo group:** N = 222; % female: 63.4; mean age: 50.9 (SD 7.6) years; RRMS 6%, SPMS 71.0%, PPMS 23.0%; EDSS scores: 0-3.5 (1%), 4-5.5 (4%), 6-6.5 (47%), 7-9 (47%); duration of MS: NR; previous cannabis use: NR; duration of spasticity: NR
Interventions	**Cannabis extract (Cannador)**: soft gelatine capsules (oral) containing Δ9-THC 2.5 mg, CBD 1.25 mg and less than 5% other cannabinoids per capsule **Synthetic Δ9-THC (Marinol)**: capsules (oral) **Placebo:** capsules (oral) contained the respective vegetable oil vehicle

Zajicek 2003_CAMS *(Continued)*

	Dose frequency: 25 mg /day. Dose of study medication was based on bodyweight, with a maximum possible dose of 25 mg daily **Concomitant medication during the study:** 34 patients commenced new medication for their spasticity (12 in the Cannador group, 11 in the Marinol group and 11 in the placebo group
Outcomes	**Spasticity. Measure**: Ashworth scale. **Data**: mean (SD) baseline score reported. Mean change (SD) from baseline, defined as the mean of two baseline pre-treatment visits to the end of the 13-week treatment period, calculated by imputation method **Pain**. **Measure:** CRS 0-10 perceived change in body pain. Categories 0-3 of the CRS defined a clinical relevant response. **Data**: N/group **Withdrawal due to AE**: N/group **PGIC much or very much improved:** not assessed **HRQoL:** not assessed **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: NR **Somnolence**: NR **Headache**: NR **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity. Measure**: CRS 0-10 perceived change in muscle spasms. Categories 0-3 of the CRS defined a clinical relevant response. **Data**: N/group **Fatigue**: not assessed **Sleep quality. Measure**: CRS 0-10 perceived change in sleep quality. Categories 0-3 of the CRS defined a clinical relevant response. **Data**: N/group. OR (95%CI) **Mobility/ADLs. Measure:** Barthel ADL index score. **Data**: mean change (SD) and p value from baseline reported **Anxiety**: not assessed **Depression. Measure**: CRS 0-10 perceived change in depression. Categories 0-3 of the CRS defined a clinical relevant response. **Data**: N/group **CGIC much or very much improved**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: public

ZAJICEK 2012 MUSEC

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: multicentre, 22 centres in the UK **Recruitment**: June 2006- September 2008 **Number screened:** 330 **Number randomised**: 279 **Outcome timing**: 12 weeks
Participants	**Spasticity and central neuropathic pain in MS.**

ZAJICEK 2012 MUSEC *(Continued)*

	Inclusion criteria: age between 18 and 64 years; diagnosis of MS according to the McDonald criteria (McDonald 2001); > 1 year duration; clinical stable for the previous 6 months; spasticity for ≥ 3 months and a baseline disability score ≥ 4 on CRS 0-10 **Exclusion criteria:** active sources of infection; use of immunomodulatory drugs; fixed tendon contractures; severe cognitive impairment; history of psychosis or major illness; pregnancy; cannabis use in the 30 days before study start **Treatment group** (**Cannador**): N = 143; % female: 61.5; age: mean 51.9 (SD 7.7) , median 53.0 (range 32-64) years; RRMS 9%, SPMS 67%, PPMS 24%; EDSS: NR; duration of MS: mean 14.5 (SD 9.5), median 13.0 (range 0-40) years; previous cannabis use: NR; duration of spasticity and pain: NR **Placebo group:** N = 134; % female: 64.9; age: mean 52.0 (SD 7.9), median 54.0 (range 28-64) years; RRMS 6%, SPMS 70%, PPMS 24%; EDSS: NR; duration of MS: mean 15.1 (SD 8.4), median 14.0 (range 2-34) years; previous cannabis use: NR; duration of spasticity and pain: NR
Interventions	**Cannabis extract (Cannador®):** oral soft gelatine capsules containing delta-9-THC 2.5mg, CBD 0.8 mg-1.8 mg **Placebo:** matched placebo oral capsules contained the same partial glyceride vehicle **Treatment duration**: 12 weeks **Dose:** 25 mg THC daily. At the end of the titration period, approximately 87% of participants in the placebo group were taking the maximum daily dose of 25 mg. 47% of participants in the Cannador group had up titrated to a maximum daily dose of 25 mg and most of the others were taking daily doses of 10.0 or 15.0 mg **Rescue medication**: not reported **Allowed co-therapies**: physiotherapy regimens or spasmolytic therapy were adjusted, where necessary, before study entry and remained stable in the 30 days before study start **Concomitant medication during the study:** 59.4% of the participants in the Cannador group used anti spastics and 58% of them used analgesics. 63.4% of the participants in the placebo group used anti spastics and 56.7% of them used analgesics
Outcomes	**Spasticity. Measure:** CRS 0-10. Categories 0-3 of the CRS defined a clinical relevant response. **Data**: OR (95% CI and p value) reported. Mean score (SD) at the outcome timing reported. Mean change (SD and P value) from baseline reported **Pain. Measure**: CRS 0-10. **Data**: rate of relief from body pain (P value). Mean score (SD) at the outcome timing reported. Mean change (SD and P value) from baseline reported **Withdrawal due to AE**: N/group **PGIC much or very much improved:** not assessed **HRQoL. Measure:** MSIS-29. **Data**: mean change from baseline (SD) of physical and psychological impact at 12 weeks **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: N/group **Somnolence**: NR **Headache**: N/group

ZAJICEK 2012 MUSEC *(Continued)*

	Confusion- disorientation: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence:** not assessed **Muscle spasms. Measure:** CRS 0-10. **Data**: rate of relief from muscle spasms (P value). Mean score (SD) at the outcome timing reported. Mean change (SD and P value) from baseline reported **Fatigue:** not assessed **Sleep. Measure:** CRS 0-10. **Data**: rate of improvement in sleep quality (P value). Mean score (SD) at the outcome timing reported. Mean change (SD and P value) from baseline reported **Mobility/ADLs:** not assessed **Anxiety**: not assessed **Depression**: not assessed **CGIC**: not assessed **Reduced use of anti spastics:** not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: public and industry - drug manufacturer

Zajicek 2013_CUPID

Study characteristics	
Methods	**Design**: parallel group RCT **Setting**: multicentre, 27 centres in the UK **Recruitment**: May 2006 - July 2008 **Number screened:** 558 **Number randomised**: 498 **Outcome timing**: 36 months
Participants	**Progression in MS** **Inclusion criteria:** age 18–65 years; confirmed MS according to the McDonald 2001 criteria and disease progression in the preceding year; EDSS score of 4.0–6.5 at baseline; abstain from other cannabis use- during the trial **Exclusion criteria:** RRMS; use of DMDs in the previous 12 months; systemic corticosteroid use in the previous 3 months; history of previous psychosis or other serious medical illness; pregnancy; serious cognitive impairment; cannabinoid use within the previous 4 weeks **Treatm6ent group. Dronabinol**: N =332; % female: 60.0; mean age: 52.29 (SD 7.6) years; SPMS 62.0%, PPMS 38.0%; mean EDSS 5.8 (SD 0.69); duration of MS: NR; previous cannabis use: NR **Placebo group:** N = 166; % female: 59.0; mean age: 51.97 (SD 8.2) years; SPMS 60.0%, PPMS 40.0%; mean EDSS 5.9 (SD 0.67); duration of MS: NR; previous cannabis use: NR
Interventions	**Synthetic Δ9-THC (Marinol)**: capsules (oral) 3.5 mg **Placebo:** identically matched (in terms of appearance and smell) placebo vegetable oil capsules (oral) **Dose frequency:** the maximum dose was 28 mg per day

Zajicek 2013_CUPID *(Continued)*	**Concomitant medication during the study:** NR
Outcomes	**Spasticity:** not assessed **Pain:** not assessed **Withdrawal due to AE**: NR **PGIC much or very much improved:** not assessed **HRQoL. Measure:** MSIS-29-Physical. **Data**: mean difference change from baseline (95% CI and P value) **Serious AEs**: N/group **AEs**: N/group **Nervous system disorders-related AE**: NR **Psychiatric disorders-related AE**: NR **Dizziness**: N/group **Somnolence**: NR **Headache**: NR **Confusion- disorientation**: NR **Paranoia**: NR **Psychosis**: NR **Hallucinations**: NR **Drug tolerance**: NR **Urinary incontinence**: not assessed **Muscle spasms severity**: not assessed **Fatigue**: not assessed **Sleep quality**: not assessed **Mobility/ADLs**: not assessed **Anxiety**: not assessed **Depression**: not assessed **CGIC much or very much improved**: not assessed **Reduced use of anti spastics**: not assessed **Reduced use of analgesics:** not assessed
Notes	**Funding**: public

ADLs: Activities of Daily Living; **AE**: adverse events; **BPI**: Brief Pain Inventory; **CBD**: cannabidiol; **CI**: confidence interval; **CGIC**: Caregiver's Global Impression of Change; **CNP**: central neuropathic pain; **CRS**: category rating scale; **DMDs**: disease modifying drugs; **EDSS**: Expanded Disability Status Scale; **EQ-5D**: EuroQol 5-Dimensions questionnaire; **HADS**: Hospital Anxiety and Depression Scale; **HRQoL**: Health Related Quality of Life;**I-QOL**: Incontinence Quality of Life; **IQR**: interquartile range; **LOCF**: last observation carried forward; **MAS**: Modified Ashworth scale; **MCID**: Minimum Clinically Important Difference; **µL**: microlitre; **MS**: Multiple Sclerosis; **MSQoL-54**: Multiple Sclerosis Quality of Life-54; **N**: number; **NA**: not applicable; **NP**: neuropathic pain; **NPS**: Neuropathic Pain Scale; **NR**: not reported; **NRS**: Numeric Rating Scale; **OR:** Odds Ratio; **PGIC**: Patient Global Impression of Change; **PPMS**: primary progressive MS; **PRMS**: progressive relapsing MS; **PSQI:** Pittsburgh Sleep Quality Index; **RCT**: Randomized Controlled Trial; RR;relative risk; **RRMS**: relapsing remitting MS; **SD**: Standard Deviation; **SE**: standard error; **SF-36**: 36 item Short Form health survey; **SPMS**: secondary progressive MS; **THC**: tetrahydrocannabinol; **VAS**: Visual Analog Scale; **v/v**: volume/volume; **w/v:** weight/volume

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

Study	Reason for exclusion
Alessandria 2020	A before-after (pre-post) study with no control group
Banister 2019	A review
Black 2019	A systematic review
Calabrò 2020	A controlled non randomised clinical trial
Centonze 2009	A before-after (pre-post) study with no control group

Study	Reason for exclusion
Cristino 2020	Review of a variety of neurological disorders
De Trane 2017	A before-after (pre-post) study with no control group
Ergul 2020	A review
Feinstein 2019	A case-control study
Flachenecker 2014	A before-after (pre-post) study with no control group
Frank 2008	Wrong population: mixed central or peripheral pain of various aetiologies
Friedman 2019	A review
Greenberg 1994	A randomised study comparing 10 patients with MS and 10 normal volunteers
Grimaldi 2019	A before-after (pre-post) study with no control group
Haleem 2020	A review
Johal 2020	A systematic review
Jones 2020	A review
Karst 2003	Wrong population: participants with MS not included
Katagigiotis 2012	Non randomised study of the expression of cannabinoid receptors in bladders with neurogenic detrusor overactivity and a possible local bladder effect of oral cannabinoid agonists
Lus 2018	A randomised study comparing sugar-free chewing gum or a refrigerated bottle or chewing gum and a refrigerated bottle of THC:CBD oromucosal spray to mitigate unpleasant taste and oral mucosal anomalies
Mantovani 2020	A cost-effectiveness study of Sativex based on the real-world data of a large registry of Italian patients
Martínez-Rodríguez 2008	A cross-sectional study with no control group
Martyn 1995	N-of-1 cross-over trial done in one patient
NCT01868048	Withdrawn. 0 participants enrolled. Last update posted: 11 August 2016
NCT03172741	Withdrawn. 0 participants enrolled. Last update posted: 18 July 2018
Notcutt 2004	N-of-1 cross-over trial done in 34 patients with chronic pain
Patti 2020	A before-after (pre-post) study with no control group
Petro 1981	A controlled non randomised clinical study
Pratt 2019	An overview
Rezapour-Firouzi 2013	Outcomes of interest were not measured
Trojano 2015	A before-after (pre-post) study with no control group

Study	Reason for exclusion
Ungerleider 1987	The investigators did 3 rerandomisation to increased doses of THC. Quoted: "Of the 13 patients randomised to the study, 12 completed at least two paired trials and five of these completed 3 pairs trials"
Wade 2003	The study included 24 patients with different diseases and separate data for MS patients are not provided
Ware 2010	Wrong participants. Quoted: "Included participants with neuropathic pain of at least three months in duration caused by trauma or surgery, with allodynia or hyperalgesia"
Wilsey 2008	Four (10%) of 38 included participants with MS. Separate data for MS patients are not provided
Wilsey 2013	Three (8%) of 39 included participants with MS. Separate data for MS patients are not provided

CBD: cannabidol; **MS:** Multiple sclerosis; **RCT**: Randomised controlled study; **THC:** tetrahydrocannabinol

Characteristics of studies awaiting classification *[ordered by study ID]*

De Blasiis 2021

Methods	RCT, parallel-group, single centre. Sample size: 32 participants. Country: Italy.
Participants	multiple sclerosis, relapsing or progressive forms.
Interventions	Nabiximols. Control intervention not reported.
Outcomes	Primary outcome not defined. Reported outcome measures: EDSS; Modified Tardieu Scale 24 for spasticity; 0-10 NRSs for patients' perception of spasticity, 2-Minutes Walk Test 25 for endurance, 10-Meter Walking Test 26 for gait speed, Berg Balance Scale 27 for the balance on the feet support surface and Timed Up Go Test (TUG)28 for coordination and speed during standing and walking. MS Spasticity Scale (MSSS-88)29, MS Walking Scale-12 (MSws-12) 30 and Modified Fatigue Impact Scale (MFIS) were also measured.
Notes	The randomisation process and control intervention need to be clarified.

EDSS: Expanded Disability Status Scale;**NRS:** Numrtic Rating Scale; **RCT:** randomised controlled trial.

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

Hansen 2021

Study name	The effect of cannabis-based medicine on neuropathic pain and spasticity in patients with multiple sclerosis and spinal cord injury: study protocol of a national multicenter double-blinded, placebo-controlled trial
Methods	• Trial design: RCT, multicentre, parallel-group, double-blind • Sample size: 448 participants • Country: Denmark • Number of centres: 5
Participants	• Definite or probable central neuropathic pain for more than 3 months with mean pain intensity in baseline NRS > 3 and NRS ≤ 9 and/or presence of spasticity of more than 3 months with an intensity of > 3 (NRS) • Stable disease (for patients with MS; no relapse within the past month and no change indisease-modifying treatment during the previous three months)

Hansen 2021 *(Continued)*

	• Age ≥ 18 years • Informed consent is available
Interventions	• Δ9-tetrahydrocannabinol (THC) • Cannabidiol (CBD) • THC and CBD • Placebo
Outcomes	Primary: patient-reported pain and spasticity on a NRS Secondary: quality of life and sleep, depression and anxiety, relief of pain and spasticity Adverse events
Starting date	February 2019
Contact information	Julie Schjødtz Hansen. Department of Neurology, Aarhus University Hospital, DK-8200 Aarhus N, Denmark. julihans@rm.dk
Notes	• Recruitment status: recruiting • Prospective completion date: December 2021 • Sponsor: This research is funded by The Danish Ministry of Health, The Danish Multiple Sclerosis • Society, Bdr. Hartmann Foundation, Karen A Tolstrup Foundation, ”Direktør Ejnar Jonasson kaldet Johnsen og Hustru’s Mindelegat”, Fonden for neurologisk forskning.

NCT03005119

Study name	Evaluation of the safety, tolerability, and efficacy of orally administered PTL201 in MS patients with spasticity-related symptoms
Methods	• Trial design: parallel-group, double-blind, RCT • Sample size: 70 participants • Country: Israel • Number of centres: 1
Participants	Definite diagnosis of MS, according to McDonald 2010 criteria at least 6 months prior to enrolment, with MS associated spasticity for at least 3 months prior to enrolment. Age 18-65 years
Interventions	Treatment group: PTL201. Each capsule contains 5 mg THC and 5 mg CBD filled with seamless gelatin matrix green beads Placebo group: each capsule seamless gelatin matrix green beads containing excipients only
Outcomes	Primary outcome study • Incidence of study treatment-related adverse events at 10 weeks • Change in NRS scores at 4 weeks
Starting date	Estimated: 1 March 2018
Contact information	Hagit Sacks - hsacks@mmjphytotech.com.au Anat Achiron — Anat.Achiron@sheba.health.gov.il
Notes	• Recruitment status: unknown • Prospective completion date: December 2018

NCT03005119 *(Continued)*

- Sponsor: PhytoTech Therapeutics, Ltd
- Principal Investigator: not reported
- Last update posted: September 28, 2017.
- No results posted in ClinicalTrials.gov

NCT03756974

Study name	A phase III, multi-centre, randomised, double-blind, placebo-controlled, parallel-group clinical trial to investigate the efficacy and safety of BX-1 for the symptomatic relief of spasticity in patients with multiple sclerosis (MS)
Methods	• Trial design: parallel-group, double-blind, RCT • Sample size: 397 participants • Country: Czech Republic; Germany; Hungary; Poland; Spain • Number of centres: 40
Participants	Patients with MS according to 2010 or 2017 revised McDonald criteria. Male or female patients aged 18 to 65 years. Ongoing spasticity for at least 3 months before enrolment
Interventions	BX-1 (dronabinol), oral solution. Placebo of BX-1, oral solution
Outcomes	Primary study outcome: proportion of participants showing improvement in spasticity of 18% or more in average Numerical Rating Scale for Spasticity (NRS-S) assessment at end of treatment (time frame: 16 weeks)
Starting date	18 February 2019
Contact information	Sabine Mitzenheim (drospas-1@bionorica.de). Luitgard Spitznagel-Schminke (drospas-1@bionorica.de)
Notes	• Recruitment status: completed • Prospective completion date: December 2018 • Sponsor: Bionorica SE • Principal Investigator: Luitgard Spitznagel-SchminkeBionorica SE • Last update posted: 5 May 2021. • No results posted in ClinicalTrials.gov

NCT04203498

Study name	Safety and effectiveness of Nabiximols oromucosal spray as add-on therapy in participants with spasticity due to multiple sclerosis
Methods	• Trial design: parallel-group, double-blind, RCT • Sample size: 446 participants • Country: Czech Republic; Poland • Number of centres: 7
Participants	MS according to the revised 2017 McDonald criteria; aged 18 years or above. Participant is currently receiving optimised treatment with at least 1 oral anti spasticity medication
Interventions	Nabiximols compared to placebo

NCT04203498 *(Continued)*

Outcomes	Primary study outcome: change from baseline in the average daily spasm count (time frame: baseline to day 84)
Starting date	October 1, 2020
Contact information	Medical Enquiries (medinfo@gbio.com)
Notes	• Recruitment status: recruiting • Prospective completion date: November 2, 2022 • Sponsor: GW Pharmaceuticals Ltd • Principal Investigator: not reported • Last update posted: 15 March 2021. • No results posted in ClinicalTrials.gov

NCT04657666

Study name	Trial to evaluate the effect of Nabiximols oromucosal spray on clinical measures of spasticity in patients with multiple sclerosis (RELEASE MSS1)
Methods	• Trial design: randomised, double-blind, cross-over • Sample size: 52 participants • Country: Czech Republic; Poland • Number of centres: 17
Participants	MS according to the revised 2017 McDonald criteria. Modified Ashworth Scale score of at least 2 in 2 or more of 6 muscle groups. Currently, receiving optimised treatment with at least one oral anti spasticity drug
Interventions	Nabiximols oromucosal spray compared to placebo
Outcomes	Primary study outcome: change from baseline in lower limb muscle tone to day 51
Starting date	21 December 2020
Contact information	Medical Enquiries (medinfo@greenwichbiosciences.com)
Notes	• Recruitment status: recruiting • Prospective completion date: November 2021 • Sponsor: GW Pharmaceuticals Ltd • Principal Investigator: not reported • Last update posted: July 1, 2021 • No results posted in ClinicalTrials.gov

NCT04984278

Study name	A randomised, double-blind, placebo-controlled, 2-way cross-over trial to evaluate the effect of nabiximols oromucosal spray on clinical measures of spasticity in patients with multiple sclerosis
Methods	• Trial design: RCT, cross-over, triple-blind (participant, investigator, outcomes assessor) • Sample size: 190 participants • Country: Australia; Belgium; Czech Republic; Poland; Spain; Sweden; UK

NCT04984278 *(Continued)*

	• Number of centres: not reported
Participants	Patients with MS (any subtype), according to the revised 2017 McDonald criteria. Male or female 18 years or older. Spasticity measured with the Modified Ashworth Scale (MAS) untransformed score of at least 2 in 2 or more of 6 muscle groups. A stable dosing regimen of anti-spasticity therapy for at least 30 days prior to visit 1 (screening).
Interventions	• Nabiximols oromucosal spray • Placebo oromucosal spray
Outcomes	Primary: change in lower limb muscle tone-6 (LLMT-6) from day 1 predose to day 21 (treatment period 1) and from day 31 predose to day 51 (treatment period 2) [time frame: predose on days 1 and 31; days 21 and 51]. LLMT-6 is defined as the average of the 6 individual MAS transformed scores of knee flexors, knee extensors, and plantar flexors on both sides of the body.
Starting date	July 2021
Contact information	Medical Enquiries 1-833-424-6724; medinfo@gbio.com; medinfo@gwpharm.com
Notes	• Recruitment status: Not yet recruiting • Prospective completion date: September 2022 • Sponsor: GW Pharmaceuticals Ltd • Principal Investigator: Not reported • Last update posted: August 2, 2021

NCT05092191

Study name	Cannabis as a complementary treatment in multiple sclerosis (CAN-SEP)
Methods	• Trial design: RCT, parallel-group, single-blind (participant) • Sample size: 250 participants • Country: Canada (Centre hospitalier de l'Université de Montréal) • Number of centres: not reported
Participants	Patients with MS (any subtype), according to the recent version of the McDonald criteria. Male or female 21 years or older. Spasticity due to MS of at least one-month duration and not relieved with current therapy, at a level of 4 or more on the numerical rating scale (NRS)
Interventions	• CBD alone • THC alone • THC and CBD combined • Placebo
Outcomes	Primary • Spasticity patient reported change assessment (time frame: change from baseline patient reported spasticity at 28 weeks and 16 weeks) • Patient-reported spasticity: a numerical rating scale - 0 (no pain) to 10 (worst pain)
Starting date	15 December 2021
Contact information	Not reported
Notes	• Recruitment status: Not yet recruiting

NCT05092191 *(Continued)*

- Prospective completion date: March 15, 2025
- Sponsor: Centre hospitalier de l'Université de Montréal (CHUM); Canadian Institutes of Health Research; Multiple Sclerosis Society of Canada
- Principal Investigator: not reported
- Last update posted: November 19, 2021

Russo 2017

Study name	The role of Sativex in robotic rehabilitation in individuals with multiple sclerosis: Rationale, study design, and methodology
Methods	• Trial design: parallel-group, single-blind, RCT • Sample size: 40 participants • Country: Italy • Number of centres: 1
Participants	MS patients affected by spasticity and undergoing a robotic rehabilitation training
Interventions	Sativex plus Lokomat training compared with other antispastics plus Lokomat training
Outcomes	Primary study outcomes: • Functional Independence Measure (time frame: eight months) • 10m walking test (time frame: eight months)
Starting date	28 December 2016
Contact information	Rocco Salvatore Calabrò, IRCCS Centro Neurolesi "Bonino-Pulejo," S.S. 113, Contrada Casazza, 98124 Messina, Italy (e-mail: salbro77@tiscali.it)
Notes	• Recruitment status: completed • Prospective completion date: June 2018 • Sponsor: IRCCS Centro Neurolesi "Bonino-Pulejo" • Principal Investigator: not reported • Last update posted: July 26, 2019 • No results posted in ClinicalTrials.gov (NCT03186664)

CBD: cannabidiol; **EDSS**: Expanded Disability Status Scala; **MS:** multip;e sclerosis;**NRS**: Numeric Rating Scale; **RCT**: Randomised controlled trial; **THC**: Δ9-tetrahydrocannabinol

RISK OF BIAS

Legend: Low risk of bias High risk of bias Some concerns

Risk of bias for analysis 1.1 Spasticity: number of participants reporting reduction of 30% in the spasticity NRS (follow up 6-14 weeks)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Collin 2007	~	~	✓	~	~	~
Collin 2010	~	~	✓	~	✓	~
Markova 2018	~	~	✓	~	✓	~
Novotna 2011	~	~	✓	~	✓	~
ZAJICEK 2012 MUSEC	✓	~	✓	~	✓	~

Risk of bias for analysis 1.2 Spasticity: NRS as continuous outcome (follow up 2-14 weeks)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Collin 2007	~	~	✓	~	~	~
Collin 2010	~	~	✓	~	✓	~
Langford 2013	~	✓	✓	~	~	~
Markova 2018	~	~	✓	~	✓	~
Notcutt 2012	~	~	✗	~	✓	✗
Novotna 2011	~	~	✓	~	✓	~
Van Amerongen 2017	~	~	✓	~	✓	~

Risk of bias for analysis 1.7 Health related quality of life: change score from baseline (follow up 3-48 weeks)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Collin 2010	~	~	✓	~	✓	~
Langford 2013	~	✓	✓	~	~	~
NCT00682929	~	~	✓	~	~	~
NCT00682929	~	~	✓	~	~	~
NCT01606176	~	~	✗	✗	✓	✗
Novotna 2011	~	~	✗	~	~	✗
Schimrigk 2017	✓	~	✓	~	~	~
ZAJICEK 2012 MUSEC	✓	~	✓	~	✓	~
Zajicek 2013_CUPID	✓	~	✗	~	~	✗

DATA AND ANALYSES

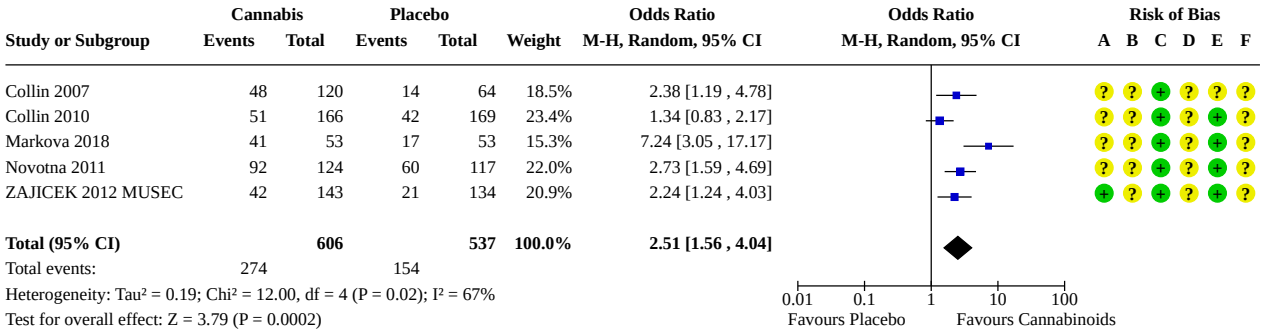
Comparison 1. Cannabis and cannabinoids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Spasticity: number of participants reporting reduction of 30% in the spasticity NRS (follow up 6-14 weeks)	5	1143	Odds Ratio (M-H, Random, 95% CI)	2.51 [1.56, 4.04]
1.2 Spasticity: NRS as continuous outcome (follow up 2-14 weeks)	7	1262	Mean Difference (IV, Random, 95% CI)	-0.55 [-0.94, -0.17]
1.3 Pain: number of participants reporting pain relief of 50% or greater in the NRS-PI (follow up 3 weeks)	1	48	Odds Ratio (M-H, Fixed, 95% CI)	4.23 [1.11, 16.17]
1.4 Pain: NRS-PI as continuous outcome (follow up 3-16 weeks)	8	1451	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.91, -0.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Withdrawn due to adverse events (follow up 3-48 weeks)	19	3110	Odds Ratio (M-H, Random, 95% CI)	2.41 [1.51, 3.84]
1.6 PGIC: number of participants reporting much or very much improvement in the PGIC (follow up 4-48 weeks)	8	1215	Odds Ratio (M-H, Random, 95% CI)	1.80 [1.37, 2.36]
1.7 Health related quality of life: change score from baseline (follow up 3-48 weeks)	8	1942	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.17, 0.02]
1.8 Health related quality of life: change score from baseline for each domain of SF-36 (follow up 12-14 weeks)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8.1 Physical functioning	4		Mean Difference (IV, Random, 95% CI)	-0.13 [-2.05, 1.80]
1.8.2 Role physical	3		Mean Difference (IV, Random, 95% CI)	-0.28 [-3.18, 2.63]
1.8.3 Bodily pain	3		Mean Difference (IV, Random, 95% CI)	4.24 [0.07, 8.40]
1.8.4 General health	3		Mean Difference (IV, Random, 95% CI)	-0.12 [-2.53, 2.29]
1.8.5 Vitality	3		Mean Difference (IV, Random, 95% CI)	1.38 [-2.85, 5.62]
1.8.6 Social functioning	3		Mean Difference (IV, Random, 95% CI)	-1.39 [-6.78, 4.01]
1.8.7 Role emotion	3		Mean Difference (IV, Random, 95% CI)	-2.09 [-5.50, 1.32]
1.8.8 Mental health	4		Mean Difference (IV, Random, 95% CI)	0.41 [-1.69, 2.50]
1.9 SAEs: number of participants with SAEs (follow up 3-48 weeks)	20	3124	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.96, 1.99]
1.10 Specific AEs: number of participants reporting nervous system disorders (follow up 4-48 weeks)	7	1154	Odds Ratio (M-H, Random, 95% CI)	2.61 [1.53, 4.44]
1.11 Specific AEs: number of participants reporting psychiatric disorders (follow up 4-48 weeks)	6	1122	Odds Ratio (M-H, Fixed, 95% CI)	1.94 [1.31, 2.88]
1.12 Specific AEs: number of participants reporting drug tolerance (follow up 14-48 weeks)	2	458	Odds Ratio (M-H, Fixed, 95% CI)	3.07 [0.12, 75.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.13 Spasticity: Ashworth or Modified Ashworth (follow up 2-50 weeks)	11	1777	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.44, -0.03]
1.14 Fatigue as continuous outcome (follow up 4-14 weeks)	5	928	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.26, 0.34]
1.15 Sleep quality: NRS as continuous outcome (follow up 4-14 weeks)	7	1205	Mean Difference (IV, Random, 95% CI)	-0.66 [-1.10, -0.22]
1.16 Sleep quality: number of participants reporting an improvement in the NRS sleep (follow up 6-14 weeks)	2	756	Odds Ratio (M-H, Random, 95% CI)	1.79 [1.30, 2.46]
1.17 Depression: Beck Depression Inventory as continuous outcome	3	495	Mean Difference (IV, Random, 95% CI)	0.17 [-0.90, 1.24]
1.18 Activities of daily living: Barthel index as continuous outcome	4	1134	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.32, 0.16]
1.19 Number of caregivers reporting improvement on the CGIC (follow up 4-48 weeks)	4	582	Odds Ratio (M-H, Random, 95% CI)	1.66 [1.15, 2.41]

Analysis 1.1. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 1: Spasticity: number of participants reporting reduction of 30% in the spasticity NRS (follow up 6-14 weeks)

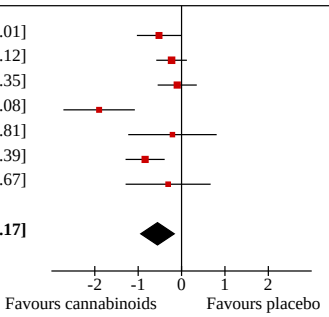


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 2: Spasticity: NRS as continuous outcome (follow up 2-14 weeks)

Study or Subgroup	MD	SE	Experimental Total	Control Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Collin 2007	-0.52	0.26	120	64	16.4%	-0.52 [-1.03 , -0.01]	? ? + ? ? ?
Collin 2010	-0.23	0.18	166	169	19.3%	-0.23 [-0.58 , 0.12]	? ? + ? + ?
Langford 2013	-0.1	0.23	167	172	17.5%	-0.10 [-0.55 , 0.35]	? + + ? ? ?
Markova 2018	-1.9	0.42	53	53	11.2%	-1.90 [-2.72 , -1.08]	? ? + ? + ?
Notcutt 2012	-0.21	0.52	18	18	8.8%	-0.21 [-1.23 , 0.81]	? ? - ? + -
Novotna 2011	-0.84	0.23	124	114	17.5%	-0.84 [-1.29 , -0.39]	? ? + ? + ?
Van Amerongen 2017	-0.31	0.5	12	12	9.3%	-0.31 [-1.29 , 0.67]	? ? + ? + ?
Total (95% CI)			**660**	**602**	**100.0%**	**-0.55 [-0.94 , -0.17]**	

Heterogeneity: Tau² = 0.17; Chi² = 18.94, df = 6 (P = 0.004); I² = 68%
Test for overall effect: Z = 2.82 (P = 0.005)
Test for subgroup differences: Not applicable

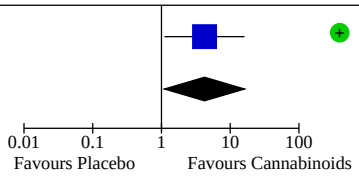


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 3: Pain: number of participants reporting pain relief of 50% or greater in the NRS-PI (follow up 3 weeks)

Study or Subgroup	Cannabis Events	Cannabis Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Svendsen 2004 (1)	11	24	4	24	100.0%	4.23 [1.11 , 16.17]	+ + - ? ? -
Total (95% CI)		**24**		**24**	**100.0%**	**4.23 [1.11 , 16.17]**	
Total events:	11		4				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.11 (P = 0.03)
Test for subgroup differences: Not applicable



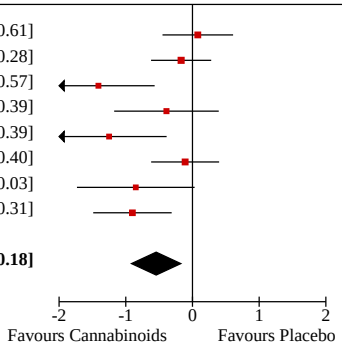
Footnotes
(1) Crossover trial treated as parallel

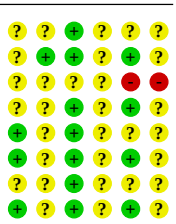
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 4: Pain: NRS-PI as continuous outcome (follow up 3-16 weeks)

Study or Subgroup	MD	SE	Cannabis Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Collin 2010	0.08	0.27	166	169	14.8%	0.08 [-0.45 , 0.61]
Langford 2013	-0.17	0.23	167	172	16.1%	-0.17 [-0.62 , 0.28]
Markova 2018	-1.41	0.43	53	53	10.1%	-1.41 [-2.25 , -0.57]
NCT01606176	-0.39	0.4	36	34	10.8%	-0.39 [-1.17 , 0.39]
Rog 2005	-1.25	0.44	33	32	9.8%	-1.25 [-2.11 , -0.39]
Schimrigk 2017	-0.11	0.26	124	116	15.1%	-0.11 [-0.62 , 0.40]
Van Amerongen 2017	-0.85	0.45	12	12	9.6%	-0.85 [-1.73 , 0.03]
ZAJICEK 2012 MUSEC	-0.9	0.3	143	129	13.8%	-0.90 [-1.49 , -0.31]
Total (95% CI)			**734**	**717**	**100.0%**	**-0.54 [-0.91 , -0.18]**

Heterogeneity: Tau² = 0.17; Chi² = 18.36, df = 7 (P = 0.01); I² = 62%
Test for overall effect: Z = 2.89 (P = 0.004)
Test for subgroup differences: Not applicable

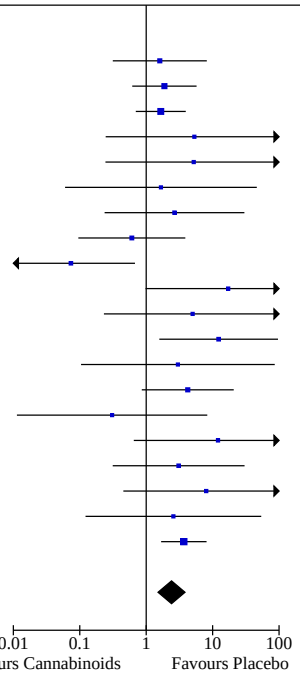




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 5: Withdrawn due to adverse events (follow up 3-48 weeks)

Study or Subgroup	Cannabis Events	Cannabis Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Aragona 2009 (1)	0	18	0	18		Not estimable	?	+	+	?	?	?
Collin 2007	6	124	2	65	6.6%	1.60 [0.31 , 8.17]	?	?	+	?	?	?
Collin 2010	9	167	5	170	11.5%	1.88 [0.62 , 5.73]	?	+	+	?	+	?
Langford 2013	14	167	9	172	15.6%	1.66 [0.70 , 3.94]	?	+	+	?	+	?
Leocani 2015 (1)	2	34	0	34	2.2%	5.31 [0.25 , 114.79]	?	?	+	?	+	?
Markova 2018	2	53	0	53	2.2%	5.19 [0.24 , 110.82]	?	?	+	?	+	?
NCT00682929	1	14	0	7	1.9%	1.67 [0.06 , 46.23]	?	?	+	?	+	?
NCT00682929	4	13	1	7	3.3%	2.67 [0.24 , 30.07]	?	?	+	?	+	?
NCT01606176	2	36	3	34	5.3%	0.61 [0.10 , 3.88]	?	?	+	?	+	?
Notcutt 2012	1	18	8	18	3.9%	0.07 [0.01 , 0.68]	?	+	+	?	+	?
Novotna 2011	8	124	0	117	2.5%	17.15 [0.98 , 300.49]	?	?	+	?	+	?
Rog 2005	2	34	0	32	2.2%	5.00 [0.23 , 108.25]	+	+	+	?	+	?
Schimrigk 2017	12	124	1	116	4.5%	12.32 [1.58 , 96.34]	+	?	+	?	+	?
Turcotte 2015	1	8	0	7	1.8%	3.00 [0.10 , 86.09]	+	+	+	?	+	?
Vachova 2014	8	62	2	59	6.8%	4.22 [0.86 , 20.78]	?	+	+	?	+	?
Van Amerongen 2017	0	12	1	12	1.9%	0.31 [0.01 , 8.31]	?	?	+	?	+	?
Vaney 2004 (1)	5	57	0	57	2.4%	12.05 [0.65 , 223.19]	-	+	+	?	+	-
Wade 2004	3	80	1	80	3.7%	3.08 [0.31 , 30.24]	+	?	+	?	?	?
Zajicek 2003_CAMS	7	206	0	106	2.4%	8.01 [0.45 , 141.56]	+	?	+	?	?	?
Zajicek 2003_CAMS	2	211	0	107	2.2%	2.57 [0.12 , 53.92]	+	?	+	?	?	?
ZAJICEK 2012 MUSEC	30	143	9	134	17.2%	3.69 [1.68 , 8.10]	+	?	+	?	+	?
Total (95% CI)		**1705**		**1405**	**100.0%**	**2.41 [1.51 , 3.84]**						
Total events:	119		42									



Heterogeneity: Tau² = 0.17; Chi² = 22.79, df = 19 (P = 0.25); I² = 17%
Test for overall effect: Z = 3.68 (P = 0.0002)
Test for subgroup differences: Not applicable

Footnotes

(1) Crossover RCT treated as parallel

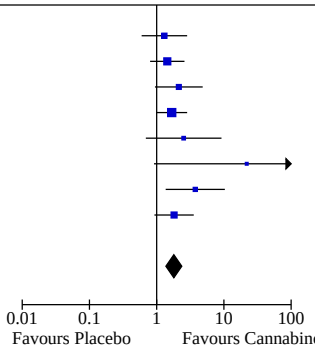
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

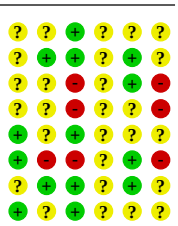
Analysis 1.6. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 6: PGIC: number of participants reporting much or very much improvement in the PGIC (follow up 4-48 weeks)

Study or Subgroup	Cannabis Events	Cannabis Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Collin 2007	26	124	11	65	12.2%	1.30 [0.60 , 2.84]
Langford 2013	31	165	23	166	21.4%	1.44 [0.80 , 2.59]
Markova 2018	23	53	14	53	11.1%	2.14 [0.94 , 4.84]
Novotna 2011	54	121	38	117	26.6%	1.68 [0.99 , 2.84]
Rog 2005	9	34	4	32	4.4%	2.52 [0.69 , 9.20]
Turcotte 2015	8	8	3	7	0.7%	21.86 [0.91 , 523.42]
Vachova 2014	18	58	6	56	7.2%	3.75 [1.36 , 10.33]
Wade 2004	32	79	21	77	16.3%	1.82 [0.93 , 3.56]
Total (95% CI)		**642**		**573**	**100.0%**	**1.80 [1.37 , 2.36]**
Total events:	201		120			

Odds Ratio M-H, Random, 95% CI



Risk of Bias (A B C D E F)



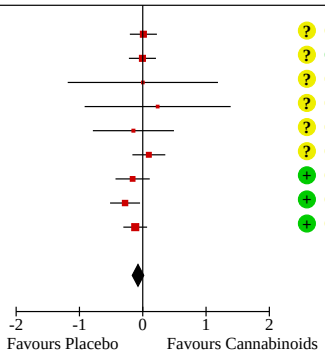
Heterogeneity: Tau² = 0.00; Chi² = 6.12, df = 7 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.23 (P < 0.0001)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.7. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 7: Health related quality of life: change score from baseline (follow up 3-48 weeks)

Study or Subgroup	SMD	SE	Cannabinoids Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Collin 2010 (1)	0.01	0.109	166	169	17.9%	0.01 [-0.20 , 0.22]
Langford 2013 (1)	-0.005	0.109	167	172	17.9%	-0.01 [-0.22 , 0.21]
NCT00682929 (2)	0.001501	0.60553	6	5	0.6%	0.00 [-1.19 , 1.19]
NCT00682929 (2)	0.235397	0.588468	7	5	0.6%	0.24 [-0.92 , 1.39]
NCT01606176 (3)	-0.147505	0.326745	21	17	2.0%	-0.15 [-0.79 , 0.49]
Novotna 2011 (1)	0.096324	0.132577	117	111	12.1%	0.10 [-0.16 , 0.36]
Schimrigk 2017 (2)	-0.15985	0.138	105	104	11.2%	-0.16 [-0.43 , 0.11]
ZAJICEK 2012 MUSEC (4)	-0.27941	0.120825	143	134	14.6%	-0.28 [-0.52 , -0.04]
Zajicek 2013_CUPID (5)	-0.1188	0.095663	329	164	23.2%	-0.12 [-0.31 , 0.07]
Total (95% CI)			**1061**	**881**	**100.0%**	**-0.08 [-0.17 , 0.02]**

Std. Mean Difference IV, Random, 95% CI



Risk of Bias (A B C D E F)

Heterogeneity: Tau² = 0.00; Chi² = 6.48, df = 8 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Not applicable

Footnotes
(1) EQ-5D (health state index)
(2) SF-36 physical health component (PCS)
(3) Spitzer Quality of Life Index
(4) Multiple Sclerosis Impact Scale (MSIS-29)
(5) Multiple Sclerosis Impact Scale (MSIS-29). It is a yearly change.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 8: Health related quality of life: change score from baseline for each domain of SF-36 (follow up 12-14 weeks)

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
1.8.1 Physical functioning						
Langford 2013	-0.45	1.65	35.4%	-0.45 [-3.68 , 2.78]		? + + ? ? ?
Markova 2018	0.43	2.6	14.3%	0.43 [-4.67 , 5.53]		? ? - ? - -
NCT00682929	0.011	3.333	8.7%	0.01 [-6.52 , 6.54]		? ? + ? ? ?
NCT00682929	1.976	3.816	6.6%	1.98 [-5.50 , 9.46]		? ? + ? ? ?
Novotna 2011	-0.46	1.66	35.0%	-0.46 [-3.71 , 2.79]		? ? - ? ? -
Subtotal (95% CI)			**100.0%**	**-0.13 [-2.05 , 1.80]**		
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
1.8.2 Role physical						
Langford 2013	-0.89	2.01	54.3%	-0.89 [-4.83 , 3.05]		? + + ? ? ?
Markova 2018	2.67	3.3	20.1%	2.67 [-3.80 , 9.14]		? ? - ? - -
Novotna 2011	-1.3	2.93	25.6%	-1.30 [-7.04 , 4.44]		? ? - ? ? -
Subtotal (95% CI)			**100.0%**	**-0.28 [-3.18 , 2.63]**		
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.8.3 Bodily pain						
Langford 2013	1.35	1.96	45.2%	1.35 [-2.49 , 5.19]		? + + ? ? ?
Markova 2018	9.3	3.98	20.5%	9.30 [1.50 , 17.10]		? ? - ? - -
Novotna 2011	5.01	2.65	34.3%	5.01 [-0.18 , 10.20]		? ? - ? ? -
Subtotal (95% CI)			**100.0%**	**4.24 [0.07 , 8.40]**		
Heterogeneity: Tau² = 6.15; Chi² = 3.65, df = 2 (P = 0.16); I² = 45%						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.8.4 General health						
Langford 2013	-1.7	2.21	30.9%	-1.70 [-6.03 , 2.63]		? + + ? ? ?
Markova 2018	-1.59	2.95	17.4%	-1.59 [-7.37 , 4.19]		? ? - ? - -
Novotna 2011	1.32	1.71	51.7%	1.32 [-2.03 , 4.67]		? ? - ? ? -
Subtotal (95% CI)			**100.0%**	**-0.12 [-2.53 , 2.29]**		
Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
1.8.5 Vitality						
Langford 2013	-2.75	2.68	33.1%	-2.75 [-8.00 , 2.50]		? + + ? ? ?
Markova 2018	5.34	3.3	26.2%	5.34 [-1.13 , 11.81]		? ? - ? - -
Novotna 2011	2.19	2.13	40.7%	2.19 [-1.98 , 6.36]		? ? - ? ? -
Subtotal (95% CI)			**100.0%**	**1.38 [-2.85 , 5.62]**		
Heterogeneity: Tau² = 6.93; Chi² = 3.96, df = 2 (P = 0.14); I² = 49%						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.8.6 Social functioning						
Langford 2013	-5.75	2.46	38.4%	-5.75 [-10.57 , -0.93]		? + + ? ? ?
Markova 2018	3.41	3.39	30.1%	3.41 [-3.23 , 10.05]		? ? - ? - -
Novotna 2011	-0.65	3.22	31.5%	-0.65 [-6.96 , 5.66]		? ? - ? ? -
Subtotal (95% CI)			**100.0%**	**-1.39 [-6.78 , 4.01]**		
Heterogeneity: Tau² = 13.72; Chi² = 5.05, df = 2 (P = 0.08); I² = 60%						
Test for overall effect: Z = 0.50 (P = 0.61)						
1.8.7 Role emotion						
Langford 2013	-3.33	2.69	41.8%	-3.33 [-8.60 , 1.94]		? + + ? ? ?
Markova 2018	1.22	3.63	23.0%	1.22 [-5.89 , 8.33]		? ? - ? - -

Analysis 1.8. (Continued)

Langford 2013	-3.33	2.69	41.8%	-3.33 [-8.60 , 1.94]
Markova 2018	1.22	3.63	23.0%	1.22 [-5.89 , 8.33]
Novotna 2011	-2.78	2.93	35.2%	-2.78 [-8.52 , 2.96]
Subtotal (95% CI)			**100.0%**	**-2.09 [-5.50 , 1.32]**

Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 2 (P = 0.58); I² = 0%

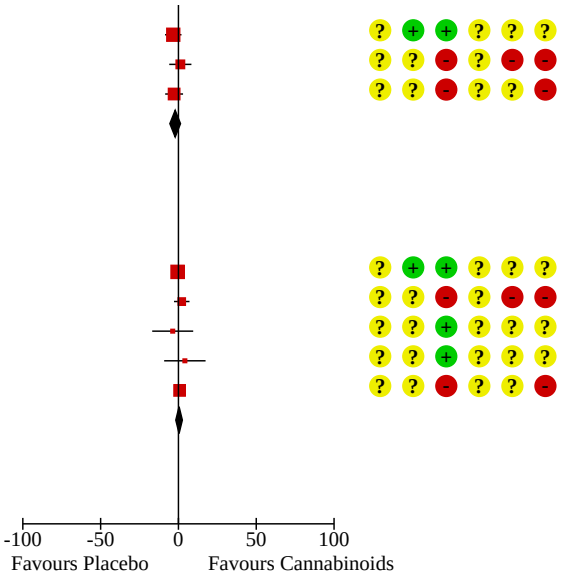
Test for overall effect: Z = 1.20 (P = 0.23)

1.8.8 Mental health

Langford 2013	-0.56	1.64	42.4%	-0.56 [-3.77 , 2.65]
Markova 2018	2.13	2.54	17.7%	2.13 [-2.85 , 7.11]
NCT00682929	-3.685	6.72	2.5%	-3.69 [-16.86 , 9.49]
NCT00682929	4.13	6.786	2.5%	4.13 [-9.17 , 17.43]
Novotna 2011	0.74	1.81	34.8%	0.74 [-2.81 , 4.29]
Subtotal (95% CI)			**100.0%**	**0.41 [-1.69 , 2.50]**

Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 4 (P = 0.82); I² = 0%

Test for overall effect: Z = 0.38 (P = 0.70)



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

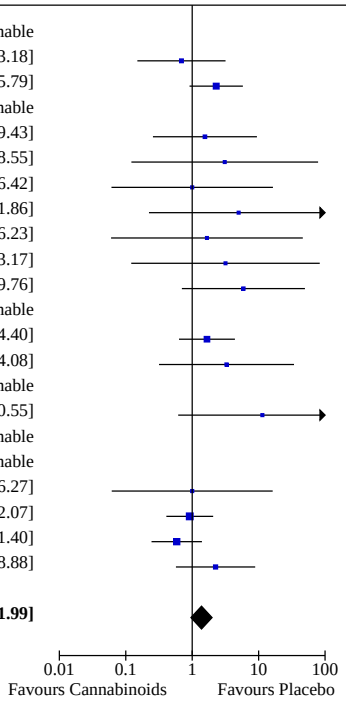
(E) Bias in selection of the reported result

(F) Overall bias

Analysis 1.9. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 9: SAEs: number of participants with SAEs (follow up 3-48 weeks)

Study or Subgroup	Cannabis Events	Cannabis Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Aragona 2009 (1)	0	17	0	17		Not estimable	?	-	+	+	+	-
Collin 2007	4	124	3	65	5.7%	0.69 [0.15 , 3.18]	?	?	+	+	?	?
Collin 2010	15	167	7	170	15.6%	2.30 [0.91 , 5.79]	?	?	+	+	+	?
Killestein 2002 (1)	0	16	0	16		Not estimable	?	?	+	+	+	?
Langford 2013	3	167	2	172	4.1%	1.55 [0.26 , 9.43]	?	?	+	+	+	?
Leocani 2015 (1)	1	34	0	34	1.3%	3.09 [0.12 , 78.55]	?	?	+	+	+	?
Markova 2018	1	53	1	53	1.7%	1.00 [0.06 , 16.42]	?	?	+	+	+	?
NCT00682929	3	13	0	7	1.4%	5.00 [0.22 , 111.86]	?	?	+	+	+	?
NCT00682929	1	14	0	7	1.2%	1.67 [0.06 , 46.23]	?	?	+	+	+	?
Notcutt 2012	1	18	0	18	1.3%	3.17 [0.12 , 83.17]	?	?	+	+	+	?
Novotna 2011	6	124	1	117	2.9%	5.90 [0.70 , 49.76]	?	?	+	+	+	?
Rog 2005	0	34	0	32		Not estimable	+	?	+	+	+	?
Schimrigk 2017	12	124	7	116	14.2%	1.67 [0.63 , 4.40]	+	?	+	+	+	?
Svendsen 2004 (1)	3	24	1	24	2.4%	3.29 [0.32 , 34.08]	+	?	+	+	+	?
Turcotte 2015	0	18	0	17		Not estimable	+	?	+	+	+	?
Vachova 2014	5	62	0	59	1.6%	11.38 [0.62 , 210.55]	?	?	+	+	+	?
Van Amerongen 2017	0	12	0	12		Not estimable	?	?	+	+	+	?
Vaney 2004 (1)	0	50	0	50		Not estimable	-	-	+	+	+	-
Wade 2004	1	80	1	80	1.7%	1.00 [0.06 , 16.27]	+	?	+	?	+	?
Zajicek 2003_CAMS	18	206	10	106	20.3%	0.92 [0.41 , 2.07]	+	?	+	+	+	?
Zajicek 2003_CAMS	12	211	10	107	17.5%	0.58 [0.24 , 1.40]	+	?	+	+	+	?
ZAJICEK 2012 MUSEC	7	143	3	134	7.1%	2.25 [0.57 , 8.88]	+	?	+	+	+	?
Total (95% CI)		**1711**		**1413**	**100.0%**	**1.38 [0.96 , 1.99]**						
Total events:	93		46									

Heterogeneity: Tau² = 0.00; Chi² = 13.05, df = 15 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Not applicable



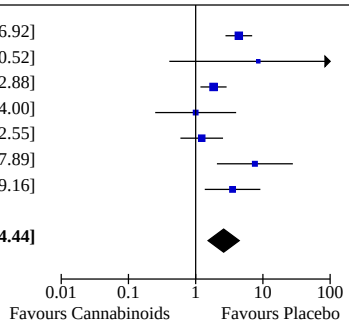
Footnotes
(1) Crossover RCT treated as parallel

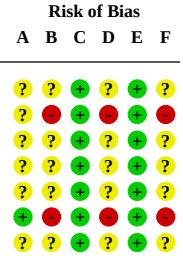
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.10. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 10: Specific AEs: number of participants reporting nervous system disorders (follow up 4-48 weeks)

Study or Subgroup	Cannabis Events	Cannabis Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Collin 2010	115	167	57	170	22.4%	4.38 [2.78 , 6.92]
Killestein 2002 (1)	3	16	0	16	2.7%	8.56 [0.41 , 180.52]
Langford 2013	73	167	51	172	22.6%	1.84 [1.18 , 2.88]
Notcutt 2012 (2)	6	18	6	18	9.5%	1.00 [0.25 , 4.00]
Novotna 2011	19	124	15	117	17.9%	1.23 [0.59 , 2.55]
Svendsen 2004 (1)	19	24	8	24	10.3%	7.60 [2.07 , 27.89]
Vachova 2014	20	62	7	59	14.5%	3.54 [1.37 , 9.16]
Total (95% CI)		**578**		**576**	**100.0%**	**2.61 [1.53 , 4.44]**
Total events:	255		144			

Heterogeneity: Tau² = 0.28; Chi² = 16.76, df = 6 (P = 0.01); I² = 64%
Test for overall effect: Z = 3.52 (P = 0.0004)
Test for subgroup differences: Not applicable





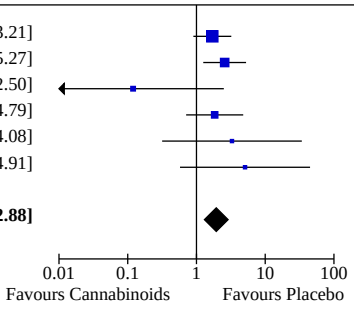
Footnotes
(1) Crossover RCT treated as parallel
(2) Note this study only reports incidence greater or equal to 10%

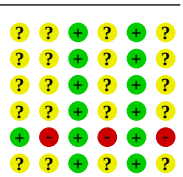
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.11. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 11: Specific AEs: number of participants reporting psychiatric disorders (follow up 4-48 weeks)

Study or Subgroup	Cannabis Events	Cannabis Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Collin 2010	28	167	18	170	40.8%	1.70 [0.90 , 3.21]
Langford 2013	27	167	12	172	27.2%	2.57 [1.26 , 5.27]
Notcutt 2012	0	18	3	18	9.4%	0.12 [0.01 , 2.50]
Novotna 2011	13	124	7	117	17.7%	1.84 [0.71 , 4.79]
Svendsen 2004 (1)	3	24	1	24	2.4%	3.29 [0.32 , 34.08]
Vachova 2014	5	62	1	59	2.6%	5.09 [0.58 , 44.91]
Total (95% CI)		**562**		**560**	**100.0%**	**1.94 [1.31 , 2.88]**
Total events:	76		42			

Heterogeneity: Chi² = 4.94, df = 5 (P = 0.42); I² = 0%
Test for overall effect: Z = 3.28 (P = 0.001)
Test for subgroup differences: Not applicable





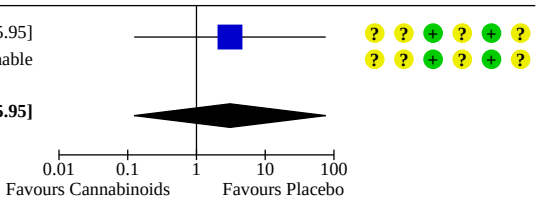
Footnotes
(1) Crossover RCT treated as parallel

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.12. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 12: Specific AEs: number of participants reporting drug tolerance (follow up 14-48 weeks)

Study or Subgroup	Cannabis Events	Cannabis Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Collin 2010	1	167	0	170	100.0%	3.07 [0.12 , 75.95]
Vachova 2014	0	62	0	59		Not estimable
Total (95% CI)		**229**		**229**	**100.0%**	**3.07 [0.12 , 75.95]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

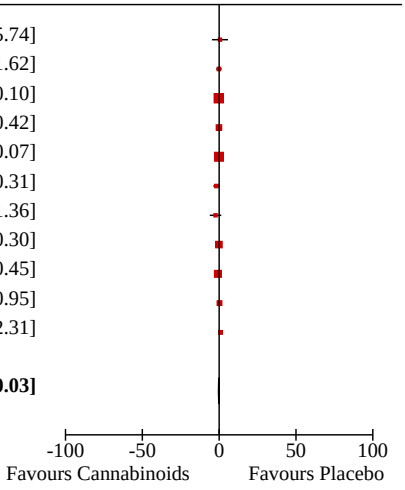


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.13. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 13: Spasticity: Ashworth or Modified Ashworth (follow up 2-50 weeks)

Study or Subgroup	MD	SE	Cannabis Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Collin 2007	0.53	2.66	114	63	0.2%	0.53 [-4.68 , 5.74]
Collin 2010	-0.16	0.91	156	160	1.3%	-0.16 [-1.94 , 1.62]
Markova 2018	-0.24	0.07	53	53	25.9%	-0.24 [-0.38 , -0.10]
NCT00682929	-0.13	0.28	15	12	9.6%	-0.13 [-0.68 , 0.42]
Notcutt 2012	-0.11	0.09	114	63	24.1%	-0.11 [-0.29 , 0.07]
Novotna 2011	-1.75	1.05	124	117	1.0%	-1.75 [-3.81 , 0.31]
Vachova 2014	-2.36	1.9	58	56	0.3%	-2.36 [-6.08 , 1.36]
Van Amerongen 2017	-0.11	0.21	12	12	13.5%	-0.11 [-0.52 , 0.30]
Vaney 2004 (1)	-0.8	0.18	14	14	15.8%	-0.80 [-1.15 , -0.45]
Wade 2004	0.22	0.37	73	70	6.4%	0.22 [-0.51 , 0.95]
Zajicek 2003_CAMS	0.94	0.7	211	213	2.1%	0.94 [-0.43 , 2.31]
Total (95% CI)			**944**	**833**	**100.0%**	**-0.23 [-0.44 , -0.03]**

Heterogeneity: Tau² = 0.04; Chi² = 19.97, df = 10 (P = 0.03); I² = 50%
Test for overall effect: Z = 2.22 (P = 0.03)
Test for subgroup differences: Not applicable

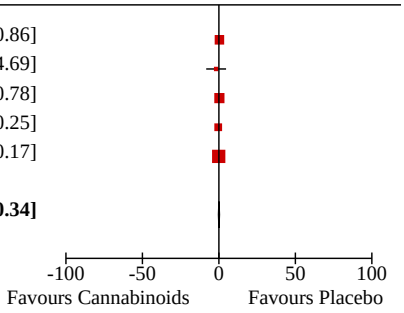


Footnotes
(1) Crossover RCT treated as parallel

Analysis 1.14. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 14: Fatigue as continuous outcome (follow up 4-14 weeks)

Study or Subgroup	SMD	SE	cannabis Total	placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Collin 2010	0.35	0.26	167	170	22.0%	0.35 [-0.16 , 0.86]
Corey-Bloom 2012 (1)	-1.8	3.31	37	37	0.2%	-1.80 [-8.29 , 4.69]
Langford 2013	0.32	0.235	167	172	24.9%	0.32 [-0.14 , 0.78]
Van Amerongen 2017	-0.44	0.35	12	12	14.5%	-0.44 [-1.13 , 0.25]
Wade 2004	-0.12	0.15	78	76	38.3%	-0.12 [-0.41 , 0.17]
Total (95% CI)			**461**	**467**	**100.0%**	**0.04 [-0.26 , 0.34]**

Heterogeneity: Tau² = 0.04; Chi² = 6.14, df = 4 (P = 0.19); I² = 35%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable

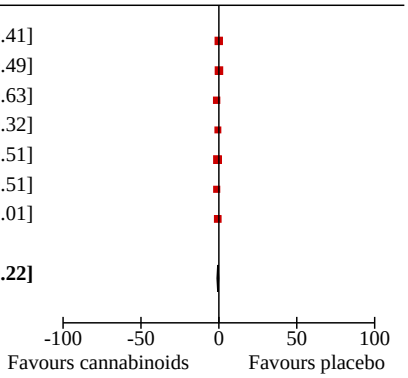


Footnotes
(1) Crossover RCT treated as parallel

Analysis 1.15. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 15: Sleep quality: NRS as continuous outcome (follow up 4-14 weeks)

Study or Subgroup	MD	SE	Cannabis Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Collin 2010	-0.07	0.2449	124	139	16.7%	-0.07 [-0.55 , 0.41]
Langford 2013	0.05	0.2245	167	172	17.3%	0.05 [-0.39 , 0.49]
Markova 2018	-1.43	0.4082	53	53	12.3%	-1.43 [-2.23 , -0.63]
Notcutt 2012	-0.64	0.4898	18	18	10.4%	-0.64 [-1.60 , 0.32]
Novotna 2011	-0.88	0.1888	124	117	18.2%	-0.88 [-1.25 , -0.51]
Rog 2005	-1.39	0.449	32	32	11.3%	-1.39 [-2.27 , -0.51]
Wade 2004	-0.71	0.355	79	77	13.7%	-0.71 [-1.41 , -0.01]
Total (95% CI)			**597**	**608**	**100.0%**	**-0.66 [-1.10 , -0.22]**

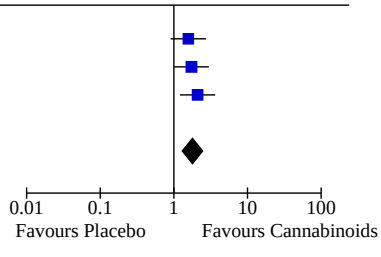
Heterogeneity: Tau² = 0.24; Chi² = 22.42, df = 6 (P = 0.001); I² = 73%
Test for overall effect: Z = 2.97 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 16: Sleep quality: number of participants reporting an improvement in the NRS sleep (follow up 6-14 weeks)

Study or Subgroup	Cannabis Events	Cannabis Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Zajicek 2003_CAMS	71	152	29	81	32.7%	1.57 [0.90 , 2.74]
Zajicek 2003_CAMS	82	164	30	82	34.1%	1.73 [1.01 , 2.99]
ZAJICEK 2012 MUSEC	48	143	26	134	33.2%	2.10 [1.21 , 3.64]
Total (95% CI)		**459**		**297**	**100.0%**	**1.79 [1.30 , 2.46]**
Total events:	201		85			

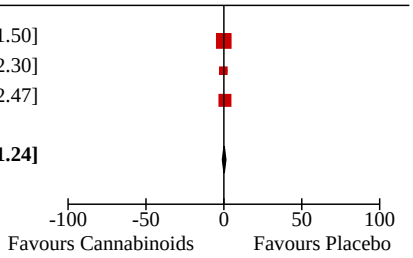
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 3.59 (P = 0.0003)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 17: Depression: Beck Depression Inventory as continuous outcome

Study or Subgroup	MD	SE	Cannabis Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Novotna 2011	-0.06	0.7959	114	113	47.0%	-0.06 [-1.62 , 1.50]
Vachova 2014	-0.29	1.323	57	56	17.0%	-0.29 [-2.88 , 2.30]
Wade 2004	0.69	0.91	78	77	36.0%	0.69 [-1.09 , 2.47]
Total (95% CI)			**249**	**246**	**100.0%**	**0.17 [-0.90 , 1.24]**

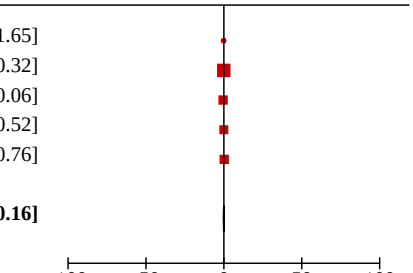
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 18: Activities of daily living: Barthel index as continuous outcome

Study or Subgroup	MD	SE	Cannabis Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Collin 2010	-0.15	0.9184	162	165	1.8%	-0.15 [-1.95 , 1.65]
Markova 2018	-0.07	0.199	53	53	37.9%	-0.07 [-0.46 , 0.32]
Wade 2004	-0.47	0.27	78	77	20.6%	-0.47 [-1.00 , 0.06]
Zajicek 2003_CAMS	-0.03	0.2798	185	92	19.2%	-0.03 [-0.58 , 0.52]
Zajicek 2003_CAMS	0.23	0.2703	176	93	20.5%	0.23 [-0.30 , 0.76]
Total (95% CI)			**654**	**480**	**100.0%**	**-0.08 [-0.32 , 0.16]**

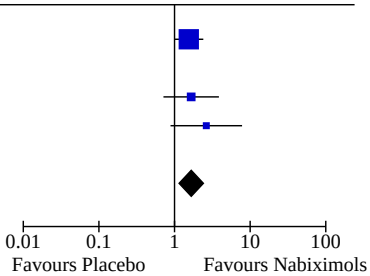
Heterogeneity: Tau² = 0.00; Chi² = 3.44, df = 4 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Cannabis and cannabinoids versus placebo, Outcome 19: Number of caregivers reporting improvement on the CGIC (follow up 4-48 weeks)

Study or Subgroup	Cannabis Events	Cannabis Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Collin 2010	72	167	56	170	69.4%	1.54 [0.99 , 2.40]
Notcutt 2012	0	10	0	14		Not estimable
Novotna 2011	17	71	11	69	19.1%	1.66 [0.71 , 3.86]
Vachova 2014	13	41	6	40	11.5%	2.63 [0.89 , 7.82]
Total (95% CI)		**289**		**293**	**100.0%**	**1.66 [1.15 , 2.41]**
Total events:	102		73			

Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Systematic reviews on cannabis-based medicines for 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* and NRS)	• Cochrane RoB • GRADE	Yes	High confidence in the effect estimate in favour of cannabis for spasticity (NRS and VAS, but not the Ashworth scale) and pain.
Meza 2017 Chile	Episte-monikos database (up to date not reported)	SRs (n = 25) Spasticity: 4 RCTs Pain: 3 RCTs	• Cannabinoids • Placebo	• Pain (VAS or NRS) • Bladder dysfunction (NRS) • Spasticity (Ashworth scale or NRS) • QoL • AEs	GRADE	Yes	• Cannabinoids do not reduce spasticity and pain (high-certainty evidence) • AEs were frequent (moderate-certainty evidence)
Mücke 2018 Germany	Cochrane Review (up to 7 November 2017)	Parallel, cross-over RCTs Pain: 4 RCTs QoL: 2 RCTs AEs: 3 RCTs Nervous system disorders: 3 RCTs Psychiatric disorders: 3 RCTs	• Herbal cannabis, plant-based cannabinoids (dronabinol: nabiximols), or synthetic cannabinoids (e.g. nabilone) • Placebo • Active comparators	• Pain • QoL • AEs	• Cochrane RoB • GRADE	Yes	Confidence in the effect estimate for pain was low.
Nielsen 2018 Australia	Overview	SR (n = 11) (AMSTAR criteria).	• Plant-based and pharmaceutical cannabinoids	• Pain • Spasticity	• SIGN • GRADE	No	• High-quality reviews find cannabinoids may have modest

Table 1. Systematic reviews on cannabis-based medicines for people with MS *(Continued)*

	(1980 up to 30 November 2016)	RCTs and non-randomised studies	• Placebo • Active comparators	• Quality of life • AEs			effects in MS for pain or spasticity. • AEs were mild to moderate
Torres-Moreno 2018 Spain	SR: yes (up to July 26, 2016)	Parallel and crossover RCTs (17 studies)	• Medicinal cannabinoids • Placebo	• Spasticity (Ashworth scale, MAS, or NRS scale) • Pain • Bladder dysfunction • AEs • Withdrawals due to AEs	• Cochrane RoB	Yes	• Limited efficacy of cannabinoids for spasticity, pain, and bladder dysfunction • Treatment can be considered as safe.
Whiting 2015 UK	SR: yes (up to April 2015)	Parallel and crossover RCTs Pain: 1 RCT Spasticity: 11 RCTs Non-randomised studies for AEs	• Cannabinoids • Usual care, placebo, or no treatment	• Spasticity (Ashworth scale or NRS) • QoL • AEs	• Cochrane RoB • GRADE	Yes	• Moderate quality evidence to support the use of cannabinoids for the treatment of spasticity. • Short-term AEs relatively common including serious AEs.

Abbreviations
AEs: adverse events; CI: confidence interval; MAS: modified Ashworth scale; NRS: Numeric Rating Scale; QoL: quality of life; RCTs: randomised controlled trials; RoB: risk of bias; SR: systematic review; VAS: Visual Analogue Scale; WMD: weighted mean difference.
* The Ashworth scale (Ashworth 1964) has been criticised 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

Search strategy for CENTRAL (the Cochrane Library online)

#1 MESH DESCRIPTOR Cannabis

#2 ((cannabi* or hash* or hemp or marijuana or marihuana or ganja 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

Search strategy for MEDLINE (PubMed)

#1"Cannabis"[Mesh]) OR "cannabi*"[Text Word] OR "hash*"[Text Word] OR hemp[Text Word] OR marijuana[Text Word] OR marihuana[Text Word] OR ganja[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]

#2"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"

#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]

#4 NOT (animals[mh] NOT (animals[mh] AND human[mh]))

Search strategy for Embase (EMBASE.com)

#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 ganja: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

Search strategy for 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 ganja) 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

Search strategy for 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]

Search strategy for Physiotherapy Evidence Database (PEDro)

Title & Abstract: "multiple sclerosis"
Therapy: cannabis; marijuana; marihuana; dronabinol; marinol; nabilone; cesamet; cannabidiol; nabiximols; dexanabinol; tetrahydrocannabinol; sativex
Subdiscipline: NA
Method: clinical trial

Search strategy for WHO International Clinical Trials Registry Platform (ICTRP)

Basic search: cannabis AND multiple sclerosis OR marijuana AND multiple sclerosis OR marihuana AND multiple sclerosis OR dronabinol AND multiple sclerosis OR marinol AND multiple sclerosis OR nabilone AND multiple sclerosis OR cesameAND multiple sclerosis OR cannabidiol AND multiple sclerosis OR nabiximols AND multiple sclerosis OR dexanabinol AND multiple sclerosis OR tetrahydrocannabinol AND multiple sclerosis OR sativex AND multiple sclerosis

Search strategy for CLINICAL TRIALS.GOV

#1 "multiple sclerosis" OR "encephalomyelitis" OR "demyelinating disease*" OR "neuromyelitis optica" OR devic OR "optic neuritis" OR "transverse myelitis"

#2 cannabis OR hash* OR hemp OR cannabis OR marijuana OR marihuana OR ganja OR bhang OR dronabinol OR marinol OR nabilone OR cesamet OR cannabidiol OR nabiximols OR dexanabinol OR tetrahydrocannabinol OR sativex

Search strategy for European Union Clinical Trials Register

Basic search: cannabis AND multiple sclerosis OR marijuana AND multiple sclerosis OR marihuana AND multiple sclerosis OR dronabinol AND multiple sclerosis OR marinol AND multiple sclerosis OR nabilone AND multiple sclerosis OR cesameAND multiple sclerosis OR cannabidiol AND multiple sclerosis OR nabiximols AND multiple sclerosis OR dexanabinol AND multiple sclerosis OR tetrahydrocannabinol AND multiple sclerosis OR sativex AND multiple sclerosis

Search strategy for International Association for Cannabinoid Medicines (IACM) databank

Multiple sclerosis and controlled study

Appendix 2. Document for implementation of the RoB 2 tool

Pilot review cannabis for people with multiple sclerosis – RoB2 implementation

DOMAIN 1 - the randomisation process

SQ.1.3 (**Did baseline differences between intervention groups suggest a problem with the randomisation process?**)

if there are imbalance in baseline characteristics do not answer PY if the sample is small (i.e. less than 50 participants in the study) and differences are compatible with chance

DOMAIN 2 – Deviation from the intended intervention ASSIGNMENT

SQ 2.1 (Were participants aware of their assigned intervention during the trial?) and 2.2 (Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?): if the study is stated as double blind but is not reported that drugs and placebo were identical in taste and appearance, answer NI

If you are considering effect of assignment:

SQ 2.1 and 2.2: Answer always PY, independently on what is reported about the blindness of participants and personnel. Epidemiologic data show that the prevalence of cannabis use among the MS population is significantly higher than in the general population [1-3]. The AEs and the psychotropic effect of cannabis are easily recognisable [4]; for this reason, also if the study is double blind, is very likely that participants will be able to recognise the intervention actually received.

SQ 2.3 (If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?) answer PN if there were no protocol deviation, if cointerventions were anticipated in the protocol, withdrawals due to AEs is not an issue for assignment. Answer PN if has been specified in the protocol or in the methods section that cannabis has been added to usual practice, so that variation in co-intervention, as normally happen in usual practice, can happen without protocol. Answer PY if there were cointerventions not anticipated in the protocol, if they were different in frequency between the two groups.

Answer PY if there are the following potential deviations and are not anticipated in the protocol:

Trial personnel (carers or people delivering the interventions) undermine the implementation of the trial protocol in ways that would not happen outside the trial for what concern: rehabilitation treatment, concomitant antispastic medications (e.g. baclofen, tizanidine, dantrolene, benzodiazepines), dose/duration of allowed antispastic medication different from protocol; concomitant analgesic, antiepileptic (gabapentin or pregabalin) or antidepressant (duloxetine, amitriptyline) medications. Rehabilitation and antispastic medication are relevant for spasticity and PGIC, QoL; analgesics, antiepileptics and antidepressants are relevant for pain, PGIC, QoL.

Answer NI if no information is provided concerning the above-mentioned co-interventions. In the majority of the studies this information is not reported, so the answer will be often NI

For the outcomes AE, SAEs and withdrawn due to AEs, consider all the concomitant medication listed above but not rehabilitation.

S.Q 2.4 (If Y/PY to 2.3: Were these deviations likely to have affected the outcome?) answer PY only if there are the cointervention listed for SQ 2.3., that arose because of the experimental context and that could actually impact the outcome, but not otherwise.

S.Q 2.5 (If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?) consider only the possible deviations listed for SQ 2.3. Answer N/PN if they are not balanced

S.Q 2.6. (Was an appropriate analysis used to estimate the effect of assignment to intervention?) answer PY if: A): the number of participants analysed coincide with the number of randomised participants or to the number of randomised minus the number of participants lost at follow up or for which the outcome measure was not available. B) the method used for ITT is described and it is adequate. The question asks if participants were analysed according to the arm to which they were randomised **for what concern the intervention, not the availability of the outcome.** So, if participants are excluded from the analysis because they are missing, this does not introduce bias for this question.

Answer PN if only a per protocol analysis was undertaken, where participants were grouped according to the intervention they actually received, instead of to the intervention they were randomised to receive

DOMAIN 2 – Deviation from the intended intervention ADHERING (outcomes SAEs e AEs)

S.Q 2.3 (If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?), 2.4 (Were there failures in implementing the intervention that could have affected the outcome?),2.5 (Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?) answer to all these questions for adverse events and SAEs

Scenario 1.

SQ 2.1. and **SQ 2,2** answer PY If participants (personnel) were aware of their intervention (e.g. they have taken cannabis before randomisation, or all participants took cannabis in the first phase of the trial as in the Markova study)

SQ 2.3 answer PY if any variations in interventions (both if happened because of the experimental context and because of choice of the patients) are balanced between groups; (**question focussed on co-intervention)**

Answer PN if has been specified in the protocol or in the methods section that cannabis has been added to usual practice, so that variation in co-intervention, as normally happen in usual practice, can happen without protocol. Answer PN if important non-protocol deviations are balanced between groups, e.g., different percentages of participants in the two groups assuming analgesics drugs not accepted in the protocol,

SQ 2.4 answer PN if No additional failures of implementation were found that are likely to affect the outcome; deviation from the protocol in the implementation of the experimental intervention, due to inadequate behaviour of clinician delivering the intervention (**question focussed on experimental intervention delivered by clinician**)

SQ 2.5 answer PN if non-adherence to the intervention, including **imperfect compliance, cessation of the intervention (>95% completed), and cross over** (**focussed on patients behaviour**) to the other arm that could have affected the outcome, was not found; answer PY if there were cessation or cross to the other intervention

SQ 2.6 (If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?) the analysis of AEs and SAEs are always descriptive, so answer always PY or Y

DOMAIN 3 - Missing outcome data

S.Q 3.1 (Were data for this outcome available for all, or nearly all, participants randomised?) if continuous outcome data are dichotomised, it should be considered as dichotomous data. Therefore, the following rule applies: "If the observed number of events is much greater than the number of participants with missing outcome data, the bias would necessarily be small.

For continuous outcomes, we do not want users to consider 95% as a strict cut off.

Only the overall % of missing should be considered for this SQ. Not the imbalance between groups and reason for missing

For efficacy outcomes we suggest to use the following cut off:

PN: ≤90%

PY: ≥91%

For SAe and AEs answer PY if the safety population coincide with the randomised population

Answer always PY for the outcome withdrawn due to AEs

SQ 3.2 (If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?) PY if the analysis corrects for missing data. LOCF is not a correct analysis. Baseline Observation Carried Forward (BOCF) is correct-.

S.Q 3.3. (If N/PN to 3.2: Could missingness in the outcome depend on its true value?) (Could**in theory** missing data depend on its true value**?)** The place where dichotomised continuous outcome data are not treated as dichotomous data (see section 6.1.3 section 3) is for signalling question 3.3.

Answer PY if: for efficacy outcomes missingness could depend on the true value if there are at least **5% missing due to lack of efficacy independently if missing data are unbalanced or balanced between the groups**) because our OR come from a dichotomization of continuous outcome. Other reasons for withdrawn (AEs, withdrawn consent, other, should not be considered)

Answer PN if reasons are reported for missingness and all are unrelated to the outcome and to the intervention

Answer NI if reason for missingness is not reported,

S.Q 3.4 (If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?) (is likely that **actually** missing data depend on its true value?) answer PY if 1) proportion of missing data are unbalanced for lack of efficacy or adverse events; 2) if reasons for missing are reported and depend on the true value (i.e., lack of efficacy); 3) if reasons are different between the groups (e.g., more patients in the cannabis group dropped out for AE and more patients in the placebo group dropped out for lack of efficacy)

DOMAIN 4 - Measurement of the outcome

S.Q 4.1(Was the method of measuring the outcome inappropriate?)

AEs, answer PY if they are recorded on the basis of what patients reported

Answer PN if they information has been achieved by active surveillance (i.e., questionnaire with a list of possible AEs)

Withdrawn due to AE: answer always PN

Spasticity answer PY (Inappropriate) if the following instruments have been used:

1. The Ashworth scale and the Modified Ashworth scale are not considered ideal scales for assessing the severity of MS spasticity [5,6].
2. All spasticity outcome measured by electrophysiological tests e.g. (e.g., objective spasticity: the

answer PN (appropriate) if the following measures have been used

1. Reduction of 30% in the spasticity Numeric Rating Scale (NRS), over baseline. Both dichotomic measure (responders) and continuous measure (in our protocol = important outcome). The NRS is a discrete variable describing spasticity level with numbers from 0 to 10 [7].

Please note: Participant-reported frequency and severity of painful spasms, e.g., Penn Spasm Frequency Scale [8] is an appropriate measure of spasticity, but in our protocol is reported as "Outcome of limited importance".

Pain: answer PY (inappropriate) if the following instruments have been used

1. Verbal rating scale (VRS) consisting of a series of verbal pain descriptors, has been shown to lack sensitivity to detect changes in pain intensity when compared with VAS or NRS-PI [9]

Answer PN (appropriate) if the following instruments have been used

1. Multidimensional (composite) pain outcome measures, e.g., the McGill Pain Questionnaire (MPQ, SF-MPQ); the Neuropathic Pain Scale (NPS); the Neuropathic Pain Symptom Inventory (NPSI) [9, 10]
2. The Multidimensional Pain Inventory (MPI) and the Brief Pain Inventory (BPI) both provide
3. The Numeric Rating Scale-Pain Intensity (NRS-PI) over baseline. Both dichotomic measure (responders 50% reduction) and continuous measure (in our protocol = important outcome). The NRS is a discrete variable describing pain level with numbers from 0 to 10 [9, 10].
4. The visual analogue scale (VAS), a continuous variable on a 10 cm line representing “no pain” to “worst imaginable pain” [9, 10].

Please note: Pain relief of 30% or greater in a composite neuropathic pain scale or in the 0-10 NRS-PI should not be considered inappropriate, but in our protocol is reported as “Outcome of limited importance”.

S.Q 4.2 (Could measurement or ascertainment of the outcome have differed between intervention groups?) this information is very rarely reported in the studies; however, we judged that the answer is PN for all the outcomes

S.Q 4.3 (If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?) : answer PY for the all the outcomes also if the study is classified as double blind and it is reported that drug and placebo were identical in taste and appearance. The AEs of cannabis are very specific [4] and make easily recognisable the type of intervention received for provider. Also, participants who have taken cannabis in the past for therapeutic or recreational purpose can easily recognise the AE and the psychotropic effects.

S.Q 4.4 (If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?): answer always PY for the outcomes spasticity, pain, SGIC, QOL, AEs and withdrawn due to AEs. Answer PN for SAEs

S.Q 4.5. (**If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?)** Answer PN for the outcomes: spasticity, pain, SGIC, QOL, AEs and withdrawn due to AEs. This decision was based on the results from the Wright study [11] which reports that there was no evidence that unblinding to Sativex in people with multiple sclerosis led to bias in the assessment of the treatment difference between Sativex and placebo for patient-reported outcomes or adverse events.

DOMAIN 5 - Selection of the reported result

S.Q 5.1 (Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?) the question is focussed in knowing whether the analysis was done in accordance to a “prespecified analysis plan; not for what concern the statistical analysis plan, but for what concern the description of the outcome in the protocol, which should be published before the study was completed

Answer PY if the outcome is mentioned in the protocol and the protocol was published before the study is completed; or if the outcome was added after the first protocol registration (i.e., in the amendment) but the reason was reported and it was justified (e.g. a new more valid scale was published)

Answer NI if the prespecified analysis plan is not available

Answer PN if the outcome is not prespecified in the protocol or if it was added after the first registration of the protocol

N.B. in Clinical trial.gov we should look at the date when the protocol (not results) where first registered.

In EUTRACT the date of first registration can be found in the registration number

For AEs, SAEs and withdrawn due to AEs answer always PY also if they are not mentioned in the protocol

S.Q 5.2 (Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?)

1) the cut off of 30% and 50% reduction both for spasticity and pain should be considered as two different outcomes, not as two different ways to measure the same outcome. We are interested only in 30% reduction in spasticity and 50% reduction in pain, as reported in our protocol [12]. Answer PN if these outcomes are reported in the protocol and in the results section. No matter if they report in the protocol other cut off level whose results are not shown in the results, because we are not interested in the other cut off. If 30% reduction in spasticity or 50% reduction in pain are described in the protocol but results are not reported in the paper, RoB2 will not be assessed for this outcome. Risk of bias of MA will be covered in the RoB ME tool a tool to assess for missing evidence

2) follow up assessment: we are interested in the longest available FU, not in a particular FU time (e.g. 12 weeks or 16 weeks).

Answer PN if the longest FU period reported in the protocol is the same as the longest FU reported in the paper.

Answer PY if in the longest FU available in the paper is shorter than the longest FU described in the protocol. Unlike the previous case concerning cut off, where we were interest in a specific cut off, here we will extract data on the longest FU available, and we will answer PY (risk of bias) in the case the FU results reported in the paper are shorter that the FU results described in the paper.

3) Quality of life: we give the preference to specific scales; if both specific and generic scales are mentioned in the protocol and, in the study, the specific scale results are reported, answer PN (no matter if the generic scale's results are not reported) If in the protocol both specific and generic scales are mentioned but, in the study, the generic scale results only are reported, answer PY. We will put the generic scale results in MA but it will be at risk of bias

S.Q 5.3 (**Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?)** answer could be NI because the statistical analysis plan is very rarely reported in the protocol. However, if the study seems to be well done, if authors are known and we trust in them, we can answer PN if there is correspondence between the methods and the results section in the published paper for what concern the type of analysis undertaken

OVERALL JUDGMENT: in case we'll have many domains with some concern, we will not downgrade the judgment to high risk of bias, but the final judgment will remain some concern.

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HISTORY

Protocol first published: Issue 10, 2019

CONTRIBUTIONS OF AUTHORS

GF conceived the review

GF, SM, FB and KD drafted the protocol

FB and GF selected the studies for inclusion

FB, GF, SM and MC extracted data

GF, FB, SM, KD and MC assessed Risk of bias of the included studies

KD performed data analysis

GF drafted the manuscript of the review. All review authors contributed to writing and revising the final report.

DECLARATIONS OF INTEREST

GF: none

SM: none

FB: She 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

MC: none

KD: She is employed as statistical editor by Cochrane

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Internal sources

- Fondazione Istituto Neurologico Carlo Besta - Milan, Italy

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External sources

- No source of support supplied, Other

  No source of support supplied
- New Source of support, Other

  No source of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Title. We changed the review title to "Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis" to clearly state that this review is about cannabis and cannabinoids for MS symptoms only.

2. Dealing with missing data. In the protocol we had planned to evaluate methods for monitoring and detecting adverse events in included studies. This has been removed since we assessed this aspect using version 2 of the Cochrane risk of bias tool (RoB2).

3. Dealing with missing data. We did not perform a sensitivity analysis to assess effects of missing data on critical and important outcomes since this bias was assessed as low risk for most studies in this review using version 2 of the Cochrane 'Risk of bias' tool (RoB2). Moreover, a sensitivity analysis on harms outcomes is unlikely to be plausible (i.e. assuming that participants who contributed to missing outcome data had adverse events).

4. Assessment of clinical heterogeneity. To evaluate the presence of clinical heterogeneity, we had planned to assess differences in characteristics of included participants, e.g. MS course, disease duration, baseline severity of spasticity or chronic neuropathic pain across trials using information reported in the 'Characteristics of included studies' table. However, this was not possible because most studies included grouped data as relapsing and progressive forms of MS, data on disease duration were not available, and studies measured baseline severity of spasticity and pain with different instruments.

5. Data synthesis. We had planned to combined dichotomous outcomes from parallel-group and cross-over trials according to the method of Becker 1993 combining lnORs from parallel trials with marginal cross-over lnORs. This was not possible because data were not available.

6. Subgroup analyses. We did prespecify subgroup analyses of number of participants reporting spasticity or pain reduction over baseline for study design and duration of follow-up, baseline severity score, different cannabinoids and co-therapies, to assess whether treatment effects varied across subgroups. However, we did not conduct subgroup analyses for the following reasons. First, the variation in treatment effect on spasticity and pain tended to be explained by outlying single studies rather than variation across all the studies. Second, less than 10 studies for subgroup analyses as planned were available leading to imbalance in studies when defined by subgroups. Third, there was a predominance of parallel group studies and short duration of follow-up.

7. Sensitivity analysis. In the protocol we had planned a sensitivity analysis on the exclusion of trials that we judged to be at high risk of bias or to raise some concerns in at least one domain of RoB2. However, since we judged all included trials at high risk of bias or with some concerns we did not seek to conduct this sensitivity analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Analgesics [therapeutic use]; *Cannabinoids [adverse effects]; *Cannabis; *Chronic Pain [drug therapy]; Dronabinol [adverse effects]; *Multiple Sclerosis [complications] [drug therapy]; *Neuralgia [drug therapy] [etiology]; Plant Extracts [therapeutic use]; Quality of Life

MeSH check words

Adolescent; Adult; Female; Humans; Male; Middle Aged; Young Adult