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Cannabinoids for spasticity due to multiple sclerosis or paraplegia: A systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Objectives: Spasticity remains highly prevalent in patients with spinal cord injury and multiple sclerosis. To summarize the effects of cannabinoids compared with usual care, placebo for spasticity due to multiple sclerosis (MS) or paraplegia.

Methods: Searches of MEDLINE, EMBASE, CENTRAL and LILACS to March 2017 were performed to identify randomized controlled trials. The primary outcomes were spasticity and spasm frequency. The criteria were any patient with MS and spasticity affecting upper or lower limbs or both, and that had a confirmed diagnosis of MS based on validated criteria, or however defined by the authors of the included studies.

Results: 16 trials including 2597 patients were eligible. Moderate-certainty evidence suggested a non-statistically significant decrease in spasticity (standardized mean difference (SMD) 0.36 [confidential interval (CI) 95% −0.17 to 0.88; p = 0.18; I2 = 88%]), and spasm frequency (SMD 0.04 [CI 95% −0.15 to 0.22]). There was an increase in adverse events such as dizziness (risk ratio (RR) 3.45 [CI 95% 2.71–4.4; p = 0.20; I2 = 23%]), somnolence (RR 2.9 [CI 95% 1.98–4.23; p = 0.77; I2 = 0%]), and nausea (RR 2.25 [CI 95% 1.62–3.13; p = 0.83; I2 = 0%]).

Conclusions: There is moderate certainty evidence regarding the impact of cannabinoids in spasticity (average 0.36 more spasticity; 0.17 fewer to 0.88 more) due to multiple sclerosis or paraplegia, and in adverse events such as dizziness (419 more dizziness/1000 over 19 weeks), somnolence (127 more somnolence/1000 over 19 weeks), and nausea (125 more somnolence/1000 over 19 weeks).

1. Introduction

Spasticity can be considered disabling when it involves severe functional problems, and the management is essential to prevent further deterioration in function. If not managed in a timely manner, spasticity can lead to diminished activity, and problems with daily living activities (ADL) such as gait, feeding, washing, dressing and toileting.[1] Over time, spasticity may cause muscle pain, stiffness or spasms, trouble moving, impaired ability to stand and walk, difficulty eating and speaking, contracture leading to joint and bony deformity and even incontinence episodes [2]

Spasticity remains highly prevalent in patients with spinal cord injury (SCI) and multiple sclerosis (MS). In SCI patients, the lesion of the neurons in the spinal cord results in upper motor neuron syndrome with a prevalence of 65% to 78% in the first year post-injury,[3] and in MS, the same is caused by the demyelination of nerve fibers of spinal cord and is present in 84% of North American cases.[4]

The treatment of multiple sclerosis has changed over the last years.

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The existing options for the treatment of spasticity, such as baclofen, tizanidine, benzodiazepines, morphine, and botulinum toxin present great limitations requiring frequent administration of high doses, often causing incapacitating side effects, and having a large number of patients who are unresponsive to therapy.[5] Overall, the treatment of MS comprises three main groups: i) treatment of the acute attack; ii) prevention of future attacks by reducing triggers and use of disease-modifying therapies; and iii) symptomatic treatments of neurological difficulties such as spasticity, pain, fatigue, and bladder dysfunction. Thus, there is an urge for new treatment approaches, represented in the last decade by a number of publications regarding the use of cannabinoids and their effect in the endocannabinoid system.

The endogenous cannabinoids anandamide, 2-arachidonyl glycerol (2-AG) acts on specific cannabinoid receptors: CB1 receptors, present mostly in the CNS; and CB2 receptors, located in the CNS and extensively in the periphery (specially the immune system).[6] Cannabis sativa L. contains 60 or more cannabinoids, the most abundant of which are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[6] THC is a partial CB1 receptor agonist providing analgesia, muscle relaxation, anti-emesis, appetite stimulation and psychoactivity.[6] CBD has anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, antioxidant and antipsychotic activity and has been shown to reduce the anxiogenic and psychoactive effects of THC.[6] Both endogenous and exogenous cannabinoids have been shown to have an anti-spasticity effect in the recognized animal model of MS spasticity, and treatments that include THC and CBD have great potential for treating spasticity both in MS and SCI.[6]

There are a variety of new medications yet to be approved by governments that explore the effects of cannabinoids in the treatment of cancer pain, neuropathic pain, epilepsy, metabolic syndrome, inflammation, psychiatric disorders, spasticity in multiple sclerosis and spinal cord injury and other conditions, not to mention the possibility of using in-natura plant extracts.[7]

A recent systematic review of 79 trials addressing patient-important outcomes and including over 6000 patients reported that cannabinoids was associated with a reduction in spasticity as well as with improvements in nausea and vomiting due to chemotherapy, and weight gain in HIV infection, sleep disorders, and Tourette syndrome.[8] A more specific meta-analysis on chronic pain and psychiatric problems concluded that there is high-quality evidence supporting the use of marijuana or cannabinoids.[9]

We therefore undertook a systematic review of all randomized controlled trials (RCTs) comparing any type of cannabis extract or cannabinoid-based medication with usual care or placebo focusing on patient-important outcomes for multiple sclerosis and spinal cord injury patients with spasticity. The aim of this systematic review and meta-analysis is to look into more detail on the use of cannabinoids for these particular conditions. The intent to highlight specifically spasticity is due to the recent regulation of 1:1 THC:CBD oromucosal spray as a prescription medication in Brazil for patients with multiple sclerosis resistant to the current existing treatment.

2. Methods

The Cochrane Handbook for Intervention Reviews.[10] guided our choice of methods. This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement [11] and, the Quality of Reporting of Meta-analyses QUOROM [12]

2.1. Eligibility criteria

- Study design: RCTs.
- Participants: patients with spasticity due to MS or paraplegia (i.e. complications of paralysis of the legs and lower parts of the body) affecting upper or lower limbs or both, and that had a confirmed diagnosis of MS based on validated criteria, or however defined by the authors of the included studies, and regardless the subgroup of the disease such as relapsing remitting, primary progressive and secondary progressive MS.
- Interventions: cannabis plant, with any compounds such as delta-9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD), regardless the type of extracts (e.g. oil, hash, tinctures).
- Comparators: usual care, placebo or no intervention.
- Patient-important outcomes: the primary outcomes were spasticity, and spasm frequency and severity. Secondary outcomes were pain measured by any validated scale, bladder function; cognitive function; ADLs; and occurrence of any adverse events (dizziness, somnolence, nausea, dry mouth).

Eligible studies followed patients for a minimum of two weeks. We did not consider studies reported as conference abstracts due to the lack of complete information they contained.

2.2. Data source and searches

A previous review.[8] with similar inclusion criteria identified studies using cannabinoid treatment for different outcomes up to April 2015. We selected from the previous review [8] only the RCTs that analyses the use of cannabis-based medication for spasticity, and developed a search strategy (Appendix Figure A1) for MEDLINE, EMBASE, Cochrane Controlled Trials Register (CENTRAL) and LILACS up to March 20, 2017. The review authors scrutinised the reference lists of the identified relevant studies for additional citations. We consulted clinical specialists and contacted authors of included trials where appropriate to obtain unpublished data.

2.3. Selection of studies

After identifying all potentially eligible studies by the literature search and obtaining all of their full-text articles, teams of two reviewers independently evaluated these studies for eligibility. Disagreements were resolved through discussion with third party adjudication. We calculated the agreement, using kappa statistic, between reviewers for full-text screening.

2.4. Data extraction and risk of bias assessment

The following data were extracted independently by three pairs of reviewers using a pre-standardized form that included characteristics of the study design, participants, interventions, outcomes event rates and follow-up. Authors of the eligible studies were contacted by reviewers to identify missing data and confirm data accuracy. As there was multiple publication of the same study, we decided to quote all these references under results section.

The pairs of reviewers assessed risk of bias separately by using a modified version of the Cochrane Collaboration's tool [13] which includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the previously cited domains [14] A low risk of bias was designated for incomplete outcome data, loss to follow-up of less than 10% and a difference of less than 5% in missing data in intervention and control groups. If needed, reviewers discussed with a third party adjudication to resolve disagreements.

2.5. Certainty of evidence

Reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for certainty of evidence. Each outcome was rated high, moderate, low, or very low.[14] Detailed GRADE guidance was used to evaluate overall risk of bias,[15] imprecision,[16] inconsistency,[17] indirectness,[18] and publication bias [19] and results were summarized in an evidence profile.

2.6. Data synthesis and statistical analysis

We calculated pooled risk ratios (RRs) for dichotomous outcomes and standardized mean differences (SMD) for continuous variables with the associated 95% CIs using random-effects models with the Mantel-Haenszel statistical method. Absolute effects and 95% CI were calculated by multiplying pooled RRs and 95% CI by baseline risk estimates derived from the largest of included RCTs in the meta-analysis. For dealing with missing data, we used complete case as our primary analysis; that is, we excluded participants with missing data. If results of the primary analysis achieved statistical significance, we planned to conduct sensitivity analyses to test the robustness of those results; however, we were not able to because the primary outcomes did not reach a statistical significance.

Results were assessed by each study using different scales. Variability in results across studies was undertaken by using I^2 statistic and the P value obtained from the Cochrane chi square test. Our primary analyses were based on eligible patients who had reported outcomes for each study (complete case analysis).

We focused on publication bias through visual inspection of funnel plots for outcomes addressed in 10 or more studies. We used Review Manager (RevMan) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses.[20]

3. Results

3.1. Selection of titles

Our search strategy focusing on publications since the last review identified 124 potential citations (Fig. 1). After title and abstract screening, we assessed the full-text articles of 33 relevant citations. In addition, we identified seven potentially eligible publications in our search strategy, and one further study through contact with an expert in the field. We subsequently assessed the eligibility of 41 full-text articles and excluded 17 studies (Fig. 1). Twenty-four publications documenting 16 RCTs involving 2597 participants seven cross-over,[21–30] and nine parallel group [31–44] proved eligible. The inter-observer agreement for the full-text screening was rated as good (kappa 0.65).

3.2. Study characteristics

Table 1 describes study characteristics related to study design, country, number of participants, mean age, eligibility criteria, and follow-up. Thirteen studies [24,28–39,24,40,44] were conducted in Europe, one in the USA [22,26] one in Canada,[23,25] and one did not report the country where the RCT was conducted.[27] Randomized trial sample sizes ranged from 11 [23,25] to 630 [41–43]. Participants were typically aged between 40 and 60 years, and were followed for two to 19 weeks. Inclusion criteria usually included having multiple sclerosis,[21,28–34,36–38,40–43] or having spinal chord injury [23,25,35] with symptoms of spasticity,[21–26,28–30,32,33,36–40,43] and/or pain [21,27,29,31,34,35,38] and to abstain from any type of cannabinoids for 7 days prior to the entry and during the study.[21,22,32,35,40,44] Exclusion criteria were most commonly having a disease of clinical importance,[21,24,26,28–44] psychiatric disorders,[21–26,31–41] being pregnant or lactating,[23–25,32,35,36,40–43] or having hypersensitivity to cannabinoids,[23,25,31–36,39,40].

Table 2 describes study characteristics related to intervention, control group, and assessed outcomes. All of the RCTs compared a cannabinoid substance to placebo. Nine of them used an oromucosal spray that delivers 2,7 milligrams of THC and 2,5 milligrams of CBD on each pump [21,24,29,31–35,37–40,44] four of them used synthetic

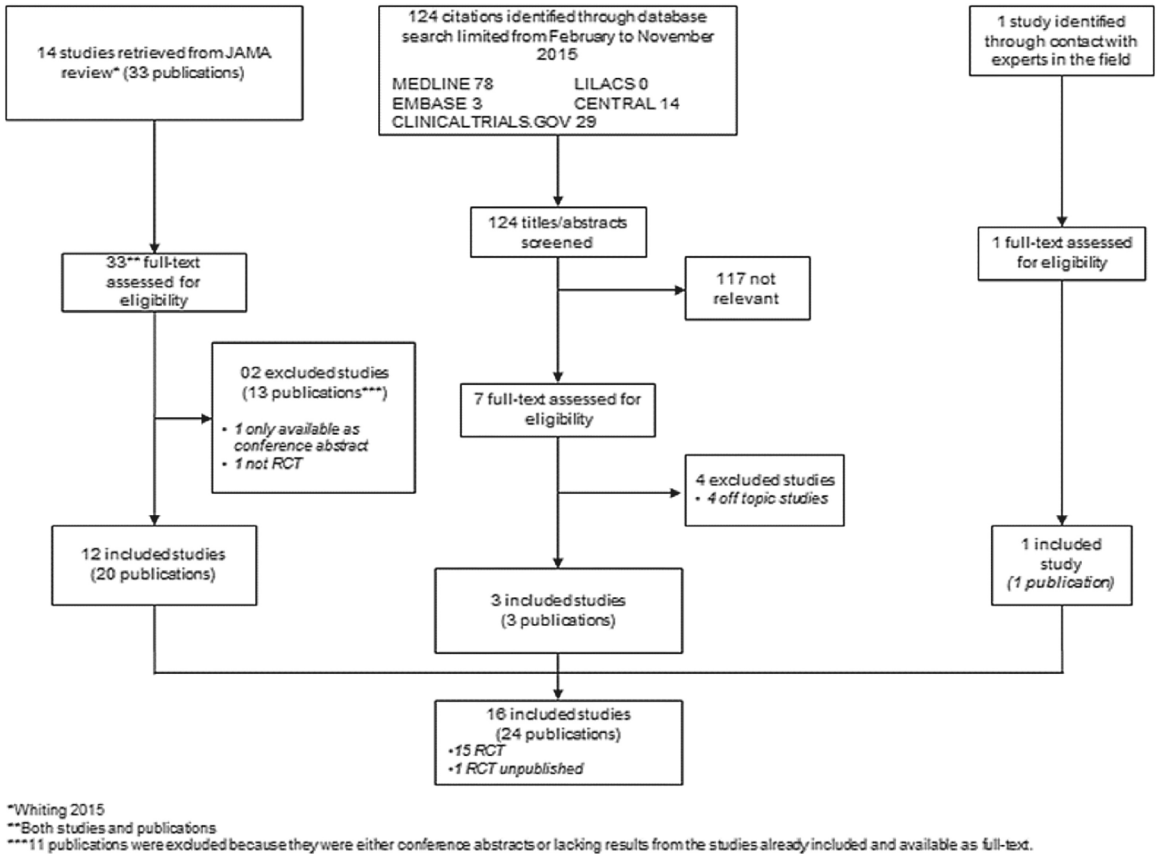

Fig. 1. Flow diagram of search results.

Table 1
Study characteristics related to population.

Author, year	Design of study – RCT	Location	Number of randomized participants	Mean age per studied group	Inclusion criteria	Exclusion criteria	Follow-up (weeks)
Langford, 2013 [34]	Parallel group	Europe	339	I: 48.42 P: 49.51	CNP due to MS, of at least 3 months duration; a sum score of at least 24 on a pain 0–10 point NRS on the last 6 days during the baseline period; analgesic regimen was to be stable for at least 2 weeks preceding the study entry day	Severe pain from other concomitant conditions (pain of a nociceptive, musculoskeletal – including spasms, peripheral neuropathic or psychogenic origin, or due to trigeminal neuralgia; history of significant psychiatric (other than depression associated with their underlying condition); renal, hepatic, cardiovascular, or convulsive disorders; sensitivity to cannabis or cannabinoids	14
Berman 2004 [47]	Parallel group	Europe	116	I:48.7 P:47.6	Aged 18 years or above; diagnosis of non-acute spinal cord injury with central neuropathic pain not wholly relieved by current therapy; CNP with a mean severity NRS score at least four during last seven days of the baseline period; relatively stable neurology during the preceding six months; stable medication regimen during the preceding four weeks; agreement, if female and of child bearing potential or if male with a partner of child bearing potential, to ensure that effective contraception was used during the study and for three months thereafter; had not used cannabinoids for at least the preceding seven days and willing to abstain during the study; clinically acceptable laboratory results at Visit 2; ability (in the investigator's opinion) and willingness to comply with all study requirements; agreement for the UK Home Office, their general practitioner, and their consultant if appropriate, to be notified of their participation in the study	History of significant psychiatric disorder other than depression associated with the underlying condition; history of alcohol or substance abuse; severe cardiovascular disorder (other than well controlled atrial fibrillation); autonomic dysreflexia; epilepsy; if female, pregnant, lactating or planning a pregnancy during the course of the study; significant renal or hepatic impairment; elective surgery or procedures requiring general anaesthesia during the study; terminal illness or considered inappropriate for placebo medication; other significant disease which may have either put the subject at risk because of participation in the study or may influence the result of the study or the subject's ability to participate in the study; regular levodopa use in the seven days leading to study entry; if male, receiving and unwilling to stop sildenafil for the duration of the study; known or suspected hypersensitivity to cannabinoids or the excipients of the study medications; known or suspected adverse reaction to cannabinoids; intention to travel internationally during the study; intention to donate blood during the study; participation in another research study in the 12 weeks leading to study entry; previous randomization into this study	7
Corey-Bloom, 2012 [22]	Cross-over	USA	37	51[a]	Spasticity and at least moderate increase in tone (score > 3 points on the modified Ashworth scale at the elbow, hip or knee)	Disease of clinical importance; use of other investigational drug; disease exacerbation; steroid treatment or use of cannabinoids in the 2 months preceding study entry; history of alcohol or drug abuse; depression; psychosis; schizophrenia	2
Zajicek, 2012 [36]	Parallel group	Europe	277	I: 51.9 P: 52	Patients aged 18–64 years with a diagnosis of MS according to the McDonald criteria who had stable disease for the previous 6 months and troublesome and ongoing muscle stiffness for at least 3 months before enrolment (as shown by a current disability score of at least 4 on an 11 point CRS	Patients with active sources of infection or taking immunomodulatory drugs that might affect spasticity (eg, b-interferon, but not azathioprine); fixed tendon contractures; severe cognitive impairment; history of psychosis; major illness; pregnancy and cannabis use in the 30 days before study start	12
Novotna, 2011 [37]	Parallel group	Europe	241	48.6[a]	MS of any subtype for at least 6 months with spasticity because of MS for at least 3 months, which was not wholly relieved with current anti spasticity medication; at least moderately severe spasticity, as defined by a score of ‡4 using a single spasticity 0–10 severity NRS at screening; at least a 20% reduction in their NRS spasticity score during the sensibility phase	Concomitant disease or disorder that had spasticity-like symptoms or that may have influenced the subject s level of spasticity, or who had a medical history that suggested that relapse/remission was likely to recur during the study which was expected to influence the subject s spasticity; current or previous use of cannabis or cannabinoid-based medications in the 30-day period prior to study entry; concurrent history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders; known or suspected history of alcohol or substance abuse, diagnosed dependence disorder or current non-prescribed use of any prescription drug	19
Collin, 2010 [38]	Parallel group	Europe	337	I: 48	Any disease subtype of MS of at least 6-months duration, and at least a 3-month history of spasticity due to MS, which was not	Subjects with symptoms of spasticity not due to MS; concurrent history of significant psychiatric, renal, hepatic, cardiovascular or	15

(continued on next page)

Table 1 *(continued)*

Author, year	Design of study – RCT	Location	Number of randomized participants	Mean age per studied group	Inclusion criteria	Exclusion criteria	Follow-up (weeks)
					wholly relieved with current therapy; sum of at least 24 in the 0–10 spasticity NRS in the 6-day baseline period; anti-spasticity regimen stable for at least 30 days preceding study entry	convulsive disorders	
Kavia, 2010 [39]	Parallel group	Europe	135	P: 47.1 I: 58.6	Stable dose of anti cholinergic medication for at least 14 days prior to study entry which remained unchanged throughout the study; to have had at least three incontinence episodes over five consecutive days during the baseline period	Symptomatic urinary tract infection or any other known cause for detrusor over activity; intermittent self-catheterization; history of use of cannabis or cannabis-derived medicines (street cannabis, dronabinol or nabilone) within 7 days of study entry; hypersensitivity to cannabinoids or any of the excipients of the medication; history of major psychiatric disorder (other than depression associated with underlying condition); severe personality disorder or history of alcohol or substance abuse; severe cardiovascular disorder, history of epilepsy or significant renal or hepatic impairment; and concomitant use of fentanyl, levodopa, or sildenafil citrate	10
Pooyania, 2010 [23]	Cross-over	Canada	11	P: 46.8 42.36	Subjects with SCI were eligible for the study if they were aged 18–65 years, the level of injury was at C5 (ASIA grade A–D) or below, and the injury occurred more than 1 year previously; stable neurologic level (ie, no change in ASIA neurologic level in the last 6 months); with moderate spasticity (Ashworth 3); spasticity medications had to be unchanged for at least 30 days before inclusion, and no botulinum toxin injections for more than 4 months	Patients were excluded if they had heart disease; a history of any active psychologic disorder; previously documented sensitivity to marijuana or other cannabinoid agents; severe liver dysfunction; cognitive impairment; major illness in another body area; if they were pregnant or a nursing mother; had a history of drug dependency; smoked cannabis less than 30 days before the onset of the study or were unwilling not to smoke during the study; fixed tendon contractures	
Conte, 2009 [24]	Cross-over	Europe	18	51.1[a]	Stable disease and no systemic corticosteroid therapy for at least 30 days before study entry; lower-limb spasticity; anti spastic agents (dose, frequency and route of administration) stable for at least 4 weeks before study entry; willing to comply with the protocol throughout the study	Disease modifying therapies prescribed in the 6 months before study; history of epilepsy of alcohol or substance abuse (cannabis-naive patients); major medical illnesses including renal, hepatic, cardiac, active thyroid disease, or diabetes mellitus; psychiatric or cognitive impairment that precluded safe participation in the study; concomitant therapy with antidepressants, psychoactive drugs or corticosteroids; female patients who were pregnant, lactating or planning pregnancy during the course of the study; patients suffering from acute or chronic pain	
Collin, 2007 [40]	Parallel group	Europe	189	I: 49.7	> 18 years old; diagnosis of MS and stable disease for at least 3 months; significant spasticity in at least two muscle groups; failure of current therapy (used for at least 30 days before the study and during it); not use cannabis or cannabinoids seven days before the entry and during the study; adequate contraception for subjects at child bearing age	Psychosis or severe psychiatric disorder other than depression; known substance abuse; severe cardiovascular condition; seizures; pregnancy; lactation; sensitivity to cannabinoids; planned travel abroad during the study	6
Wissel, 2006 [27]	Cross-over	Not reported	13	P: 47.8 Not reported	Patients with chronic upper motor neuron syndrome; suffer from disabling spasticity-related pain refractory to previous pain treatment	Painful muscle spasms alone	9
Vaney, 2004 [28]	Cross-over	Europe	57	I: 53.8	Clinically confirmed MS and clinically stable spasticity with at least one joint scoring higher than 2 on the Ashworth scale	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 (Beck Depression Index higher than 11); history of psychosis; use of cannabinoids during the week prior to inclusion; or significant cognitive impairment (Short Orientation Memory Concentration Test lower than 21)	3
Wade, 2004 [29]	Parallel	Europe	160	P: 56.1 I: 51	Clinically confirmed MS of any type; had been stable over the	Primary symptom rated at less than 50% of maximal severity;	10

(continued on next page)

Table 1 *(continued)*

Author, year	Design of study – RCT	Location	Number of randomized participants	Mean age per studied group	Inclusion criteria	Exclusion criteria	Follow-up (weeks)
	group				preceding four weeks with no relapse, confirmed clinically on entry to the study; stable regular medication; willing to abstain from alternative cannabinoid use for seven days prior to screening and throughout the study; volunteer one of the five target symptoms at a sufficient level of severity (spasticity, spasms, bladder problems, tremor or pain that was not obviously musculoskeletal)	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; had a planned visit abroad during the active study	
Zajicek, 2003 [43]	Parallel group	Europe	630	P: 50.4 I1: 50,5 I2: 50,2 P: 50,9	Patients aged 18–64 years with clinically definite or laboratory-supported multiple sclerosis who, in the opinion of the treating doctor, had stable disease for the previous 6 months, with problematic spasticity (Ashworth score of 2 in two or more lower limb muscle groups)	Ischemic heart disease and the upper age limit were imposed; patients with active sources of infection; taking medication such as beta interferon; fixed-tendon contractures; severe cognitive impairment; past history of psychotic illness; major illness in another body area; pregnancy; use of 9-THC at any time; use of cannabis in the 30 days before the start of the study	13
Killestein, 2002 [30]	Cross-over	Europe	16	46[a]	Progressive MS (primary and second); disease duration > 1 year; severe spasticity (mean Ashworth spasticity score of 2 or more in at least one limb) during screening, and Expanded Disability Status Scale score between 4 and 7.5	Disease of clinical importance; use of other investigational drug; disease exacerbation; steroid treatment or use of cannabinoids in the 2 months preceding study entry; history of alcohol or drug abuse; depression; psychosis; schizophrenia	4
Wade, 2003 [44]	Cross-over	Europe	21	48[a]	Neurological diagnosis and to be able to identify troublesome symptoms which were stable and unresponsive to standard treatments	History of drug or alcohol abuse, serious psychiatric illness (excluding depression associated with the neurological condition), serious cardiovascular disease or active epilepsy	10

I: intervention group; P: placebo; NRS: numerical rating scale; MS: multiple sclerosis; CNP: central neuropatic pain; SCI: spinal cord injury; CRS: category rating scale; THC: tetrahydrocannabinol; CBD: canabidiol

[a] Data for all sample size.

Table 2
Study Characteristics related to description of intervention and control, and outcomes.

Author, year	No. of randomized patients in intervention and control	Description of intervention	Description of control	Measured outcomes
Langford, 2013 [34]	I:167	Pump-action oromucosal spray of THC/CBD, each 100 μcl actuation of active medication delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. Patients were restricted to a maximum of 12 sprays per 24-h period	Placebo spray	Pain NRS 30% responder; 50% responder; NPS; Sleep quality NRS; BPI-SF; Breakthrough analgesia; PDI; Spasticity NRS; Bladder NRS; Spasm severity NRS; Tremor NRS; Fatigue NRS; EQ-5D Health state index; EQ-5D Health status VAS; SF-36: Physical functioning, Role physical, Bodily pain, General health, Vitality, Social functioning, Role emotion, Mental health
	P: 172			
Berman 2004 [47]	I:56	Pump-action oromucosal spray of THC/CBD, each 100 μcl actuation of active medication delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. The maximum permitted dose of study medication was eight actuations in any three-hour period, and 48 actuations in any 24 h period	Placebo spray	Mean Central Neuropathic Pain 11-Point NRS Scores; Mean Percentage of Days on Which Escape Medication Was Used; Mean Spasm Severity Numerical NRS Score; Percentage of Days on Which Spasm Was Experienced; Mean Spasticity Severity NRS Scores; Percentage of Days on Which Spasticity Was Experienced; Modified Ashworth Scale Score; Mean Short Orientation Memory Function Concentration Test Score; Mean Spitzer Quality of Life Index Scor; Mean Caregiver Strain Index Score; Patient Global Impression of Change; Mean Brief Pain Inventory Scor; Mean Sleep Disturbance NRS Score; Adverse Events
	P:60			
Corey-Bloom, 2012 [22]	I: 37	Cannabis cigarretes contained about 4% delta-9-tetrahydrocannabinol (delta-9-THC)	Placebo cigarretes	Change in spasticity as measured by patient score on the modified Ashworth scale; VAS for pain; physical performance (using a timed walk); and cognitive function (PASAT)
	P:37			
Novotna, 2011 [37]	I: 124	Pump-action oromucosal spray of THC/CBD, each 100 μcl actuation of active medication delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. Subjects were restricted to a maximum of 12 sprays in any 24-h period	Placebo spray	Primary efficacy end-point was the change in spasticity (0–10 NRS) from the point of randomization to the end of treatment. Secondary efficacy end-points: spasm frequency, sleep disruption, Barthel Activities of Daily Living, Physician Global Impression of Change, Subject Global Impression of Change and Carer Global impression of Change in Function
	P: 117			
Zajicek, 2012 [36]	I: 143	Capsules containing 2.5 mg THC and standardised on CBD (0.8–1.8 mg). The maximum allowable total daily dose was 25 mg THC	Placebo capsules	Primary outcome: an 11 point CRS to evaluate perceived change in muscle stiffness after 12 weeks of treatment compared with the premedication phase; Secondary outcome measures included further equivalent CRSs measuring perceived relief from body pain, muscle spasms and sleep disturbance compared with pretreatment
	P: 134			
Collin, 2010 [38]	I: 167	Pump-action oromucosal spray of THC/CBD, each 100 μcl actuation of active medication delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. The maximum permitted dose of studymedication was eight actuations in any 3-h period,and 24 actuations in any 24-h period	Placebo spray	Numerical rating scale (0–10 NRS); Modified Ashworth scale;Barthel ADL index and; timed 10-metre walk
	P: 170			
Kavia, 2010 [39]	I:67	Pump-action oromucosal spray of THC/CBD, each 100 μcl actuation of active medication delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa	Placebo spray	Primary endpoint was the reduction in daily number of urinary incontinence episodes from baseline to end of treatment (8 weeks). Other endpoints included incidence of nocturia and urgency, overall bladder condition, daytime frequency, Incontinence Quality of Life, Patient's Global Impression of Change and volume voided
	P: 68			
Pooyania, 2010 [23]	I: 5	Nabilone	Placebocapsules	Primary outcome: Ashworth Scale for spasticity in the most involved muscle group, in either the upper or lower extremities, chosen by the subject and clinician. Secondary outcomes: the sum of the Ashworth Scale in 8 muscle groups of each side of the body measured by the clinician; Spasm Frequency Scale and visual analog scale, reported by the subject; Wartenberg Pendulum Test, in order to quantify severity of spasticity; and the Clinician's and Subject's Global Impression of Change
	P:6			
Conte, 2009 [24]	I: 9	Pump-action oromucosal spray of THC/CBD, each 100 μcl actuation of active medication delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. The maximum permitted dose was 8 sprays in 3 h and a total dose of 48 sprays over 24 h	Placebo spray	Clinical assessment:VAS and Asworth Scale/Neurophysiologic assessment: RIII reflex M wave and H reflex (Stimulation techniques, Recording techniques, Measurements, Statistical analysis)
	P:9			

(continued on next page)

Table 2 *(continued)*

Author, year	No. of randomized patients in intervention and control	Description of intervention	Description of control	Measured outcomes
Collin, 2007 [40]	I: 124 P: 65	Pump-action oromucosal spray of THC/CBD, each 100 µcl actuation of active medication delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa	Placebospray	Change from baseline in the severity of spasticity based on a daily diary assessment by the subject on a 0–10 NRS; Ashworth Scale and Motricity Index in muscles affected by spasticity; mean daily spasm score; and patient global impression of change
Wissel, 2006 [27]	I: 13 P: 13	Nabilone	Placebo capsules	11-Point-Box-Test, Ashworth-Score, Rivermead-Motor-Assessment and Barthel-Index as secondary outcome measures at baseline
Vaney, 2004 [28]	I: 28 P: 29	A whole-plant cannabis extract containing 2.5 mg THC and 0.9 mg CBD	Placebo capsules	Primary outcome: Ashworth scale of muscle tone applied bilaterally to elbow flexors and extensors, wrist flexors and extensors, hip flexors, extensors and adductors, knee flexors and extensors, and foot plantar flexors and extensors; RMI and 10-m timed walk for people able to walk; 9HPT; The Nottingham Extended ADL Index (NEADL) recorded at the initial point referring to the month before admission; EDSS, PASAT; digit span of the WAIS R intelligence scale.
Wade, 2004 [29]	I: 80 P: 80	Pump-action oromucosal spray of THC/CBD, each 100 µcl actuation of active medication delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. Guidelines were given for increments up to a maximum of 120 mg THC and 120 mg CBD per day with no more than 20 mg of each in any 3-h period	The placebo spray with peppermint flavour	100 mm VAS for the primary target symptom, and for any other of the five target symptoms that were troublesome; Barthel ADL index, the RMI, the short Orientation-Memory-Concentration Test, the Adult Memory and Information Processing Battery test of attention adapted for patients with MS, GNDS,the Beck Depression Inventory, the Fatigue Severity Scale and VAS to rate sleep: quality, amount and feelings on awakening; diary records using a VAS of spasm frequency, feeling of intoxication, and severity of each of the target symptoms on one nominated day each week; and, where appropriate: The modified Ashworth Scale of Spasticity measured at wrist, elbow, knee and ankle and summed across all joints,a tremor ADL questionnaire, the 9HPT of manual dexterity, a questionnaire on disability arising from urinary incontinence and the time in seconds to walk 10m.
Zajicek, 2003 [43]	I: 417 P: 213	Synthetic 9-THC (Marinol) or a cannabis extract capsules, containing 2.5 mg of THC and 1.25 mg of cannabidiol	Placebo capsules	Primary outcome: change inspasticity related to multiple sclerosis, using the Ashworthscore of spasticity. Secondary outcome measures included the RMI, a timed 10 m walk, and four selfcompletionquestionnaires—the United Kingdomneurological disability score, the Barthelindex, the general health questionnaire (GHQ-30), anda series of nine CRS
Wade, 2003 [29]	I: 21 P: 21	Whole-plant extracts of delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), 1:1 CBD:THC	Placebo spray	VAS to provide a daily record of subjective intoxication, alertness, appetite, happiness, relaxation,optimism, energy, general well-being, sleep and feeling refreshed; Short Orientation-Memory Concentration (SOMC) test, the Barthel ADL Index, RMI, GNDS; Ashworth scale for spasticity;9HPT of manual dexterity;10-m timed walk; NRS of fatigue, pain, spasticity, bladder urgency and urinaryincontinence, and frequency of muscle spasms and nocturia
Killestein, 2002 [30]	I: 16 P: 16	Capsules containing Dronabinol or C. sativa plant extract (standardized THC content = 20 ou 30% CBD and < 5% other cannabinoids)	Placebo capsules with sesame oil	Safety, tolerability, and efficacy of oral delta-THC and Cannabis Sativa plant extract

No.: number; THC: tetrahydrocannabinol; CBD: cannabidiol; I: intervention group; P: placebo; CRS: category rating scale; 9HPT; The nine-hole peg test; GNDS: The Guy's Neurological Disability scale; NRS:numerical rating scale; ADL:Activities Daily living; PASAT: Paced auditory serial addition test; RMI: Rivermead mobility index;BPI: breaf pain inventory; SF: short form; EDSS: expanded disability status scale; WAIS R: Wechsler adult intelligence scale review.

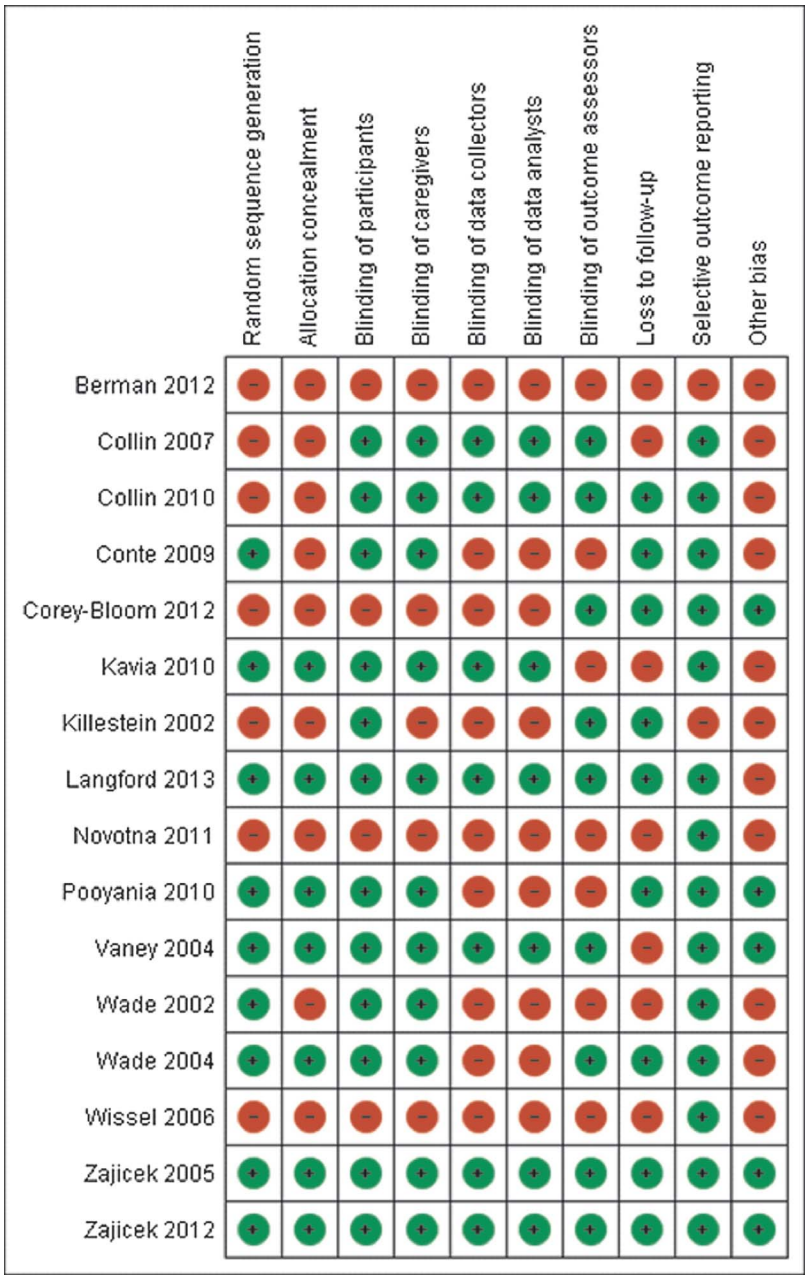

Fig. 2. Risk of bias assessment.

cannabinoids in capsules (one used dronabinol,[30] one used marinol,[41–43] two used nabilone,[23,25,27]), three used cannabis extracts in capsules [22,28,30] and one used cannabis cigarettes.[22,26] The most commonly described outcomes were spasticity,[22–29,31–38,42–44] pain,[22,26,31,34–36] functionality,[22,26–29,31,34,35,41–44] and urinary symptoms,[29,31,34,39,44].

3.3. Risk of bias assessment

Fig. 2 describes the risk of bias assessment for the RCTs. The major issue in the bias assessment was the risk of bias related to conflict of interest in the majority of the RCTs (68.7%). Others were problems with random sequence (43.75%), concealment of randomization (56.25%), blinding of data collectors (56,2%), data analysts (56.2%), outcome assessors (43.75%), the extent of missing outcome data (43.75%). The CAMS study [41–43] was the only one that was rated as low risk of bias for all assessed domains (Fig. 2).

3.4. Outcomes

3.4.1. Spasticity

Results from seven RCTs [21–23,25,26,28,29,32,35,40,44] found a not statistically significant different between cannabinoids and placebo related to spasticity (Std. Mean Difference (SMD) 0.36 [Confidential interval (CI) 95% −0.17 to 0.88; p = 0.18; I^2 = 88%]). Certainty in evidence was rated down to low because of inconsistency, indirectness, risk of bias, missing outcome data [35] lack of blinding of participants,[22,26,35] and outcome assessors [23,25,35,44] and random sequence and allocation concealment,[22,26,32,35,40,44] (Fig. 3, Table 3).

3.4.2. Spasm frequency

Results from six RCTs [21,23,25,28,29,32,35,40,44] found no statistically significant difference between cannabinoids and placebo related to spasm frequency (SMD 0.04 [CI 95% −0.15 to 0.22; p = 0.70; I^2 = 2%]). Certainty in evidence was rated down to moderate because of indirectness, risk of bias, due to missing outcome data [35] and lack of

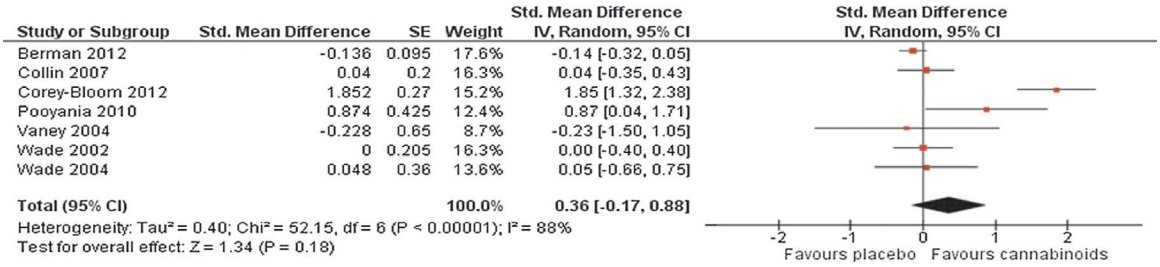

Fig. 3. Pooled analysis of spasticity comparing cannabinoids and placebo.

blinding of participants [35] and outcome assessors [23,25,35,44] and random sequence and allocation concealment,[32,35,40,44] (Fig. 4, Table 3).

3.4.3. Spasm severity

Results from three RCTs [23,25,35,44] found no statistically significant difference between cannabinoids and placebo related to spasm severity (SMD −0,14 [CI 95% −0.63 to 0.36; p = 0.59; I^2 = 0%]). Certainty in evidence was rated down to moderate because of indirectness, risk of bias, missing outcome data [35] lack of blinding of participants,[35] and outcome assessors [23,25,35,44] and random sequence and allocation concealment,[26,44] (Fig. 5, Table 3).

3.4.4. Pain

Results from five RCTs [21,22,26,29,31,34,35,44] found no statistically significant difference between cannabinoids and placebo related to pain (SMD −0.02 [CI 95% −0.39 to 0.35; p = 0.90; I^2 = 0%]). Certainty in evidence was rated down to moderate because of indirectness in all studies (Fig. 6, Table 3).

3.4.5. Cognitive function

Results from three RCTs [22,26,28,44] found no statistically significant difference between cannabinoids and placebo related to cognitive function (SMD 0.55 [CI 95% −3.33 to 4.43; p = 0.78; I^2 = 0%]). Certainty in evidence was rated down to moderate because of indirectness, risk of bias, lack of blinding of participants [22,26] and outcome assessors [44] and random sequence and allocation concealment,[22,26,44] (Fig. 7, Table 3).

3.4.6. Daily activities

Results from three RCTs [21,29,44] found no statistically significant difference between cannabinoids and placebo related to daily activities (SMD 0.01 [CI 95% −1.21 to 1.24; p = 0.98; I^2 = 0%]). Certainty in evidence was rated down to moderate because of indirectness in all studies (Fig. 8, Table 3).

3.4.7. Motricity

Results from four RCTs [21,22,26,29,32,40] found no statistically significant difference between cannabinoids and placebo related to motricity (SMD 0.34 [CI 95% −0.60 to 1.27; p = 0.48; I^2 = 0%]). Certainty in evidence was rated down to moderate because of indirectness in all studies (Appendix Figure A2).

3.4.8. Bladder function

Results from one RCT [21,29] found no statistically significant difference between cannabinoids and placebo related to bladder function (SMD −0.06 [CI 95% −19.13 to 19.01; p = 0.99; I^2 not applicable]). Certainty in evidence was rated down to moderate because of indirectness in all studies (Appendix, Figure A3).

3.5. Adverse events

3.5.1. Dizziness

Results from 14 RCTs [21,22,24,26,28–44] found a statistically significant difference favoring placebo over cannabinoids (RR 3.45 [CI 95% 2.71–4.40; p < 0.00001; I^2 = 23%]). Certainty in evidence was rated down to moderate because of risk of bias, lack of random sequence [30,37] and allocation concealment [22,24,26,30,37,44] lack of blinding,[21,29,37,39,44] missing outcome data,[28,37] and, indirectness in all studies (Fig. 9, Table 4).

3.5.2. Somnolence

Results from 11 RCTs [21,28,29–38,40,44] found a statistically significant difference favoring placebo over cannabinoids (RR 2.90 [CI 95% 1.98–4.23; p < 0.00001; I^2 = 0%]). Certainty in evidence was rated down to moderate because of risk of bias, lack of random sequence [32,33,35,37,30,38] and allocation concealment [24,27,30,32,33,40,41,44] lack of blinding,[21,24,29,30,35,37,44] missing outcome data [28,37] selective outcome reporting,[30] and, indirectness in all studies (Fig. 9, Table 4).

3.5.3. Headache

Results from 12 RCTs [21,22,24,26,28,29–32,34–37,39,40,44] found no statistically significant difference comparing cannabinoids to placebo (RR 1.10 [CI 95% 0.79–1.54; p = 0.57; I^2 = 7%]). Certainty in evidence was rated down to moderate because of risk of bias, lack of random sequence [22,26,30,32,35,37,40] and allocation concealment [21,22,24,26,30,32,37,40,44] lack of blinding,[21,24,26,29,30,35,37,39,44] missing outcome data,[28,37,39,44] selective outcome reporting,[30] and, indirectness in all studies (Fig. 9, Table 4).

3.5.4. Nausea

Results from 11 RCTs [21,22,24,26,28,29,31–40,44] found a statistically significant difference favoring placebo over cannabinoids (RR 2.25 [CI 95% 1.62–3.13; p < 0.00001; I^2 = 0%]). Certainty in evidence was rated down to moderate because of risk of bias, lack of random sequence [22,26,32,33,35,37,38,40] and allocation concealment [21,22,24,26,29,32,33,35,37,38,40] lack of blinding,[21,22,24,26,29,35,41,42,44] missing outcome data,[37,39] and, indirectness in all studies (Fig. 9, Table 4).

3.5.5. Dry mouth

Results from 10 RCTs [28,31–38,40–44] found a statistically significant difference favoring placebo over cannabinoids related to dry mouth (RR 2.82 [CI 95% 2.06–3.85; p < 0.00001; I^2 = 0%]). Certainty in evidence was rated down to moderate because of risk of bias, lack of random sequence [30,32,33,35,37,38,40] and allocation concealment [30,32,33,35,37,38,40,44] lack of blinding,[30,35,37,44] missing outcome data,[30,37] selective outcome reporting.[30] and, indirectness in all studies (Fig. 9, Table 4).

More than 10 studies addressed adverse events; visual inspection of the funnel plot did not suggest publication bias (Appendix Figure A4).

3.5.6. The cannabinoids in multiple sclerosis (CAMS) study

The CAMS study [41–43] was the largest study approaching cannabinoids versus placebo for spasticity; however there was no statistically significant difference regards improvement in spasticity between both studied groups (RR 1.47 [CI 95% 0.99–1.28], 209 patients]). The study also reported the following non statistically-significant difference outcomes: spasm frequency (RR 1.29 [CI 95% 0.92–1.80], 231 patients); daily activities (energy) (RR 1.02 [CI 95% 0.69–1.51], 249 patients); and pain (RR 2.14 [CI 95% 1.31to 3.49], 178 patients).

Table 3
GRADE evidence profile of continuous outcomes: cannabinoids for spasticity in multiple sclerosis or spinal cord injury patients.

Quality assessment						Illustrative comparative risks (95% CI)		Certainty in estimates OR Quality of evidence
No of participants (studies) Range follow-up time in weeks	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Assumed risk	Corresponding risk	
						Placebo	Cannabinoids	
Spasticity								
550 (7) 2–10	Serious limitation[1]	Serious limitation[2]	Serious limitation[3]	No serious limitation	Undetectable	The std. mean in change in spasticity was −0.136 (SE 0.095)[a]	The std. mean in changes in spasticity in the intervention group was on average 0.36 more (0.17 fewer to 0.88 more)	Low
Spasm Frequency								
520 (6) 2–10	Serious limitation[1]	No serious limitation	Serious limitation[3]	No serious limitation	Undetectable	The std. mean in change in spasm frequency was 0 (SE 0.096)[b]	The std. mean in changes in spasm frequency in the intervention group was on average 0.04 more (0.15 fewer to 0.22 more)	Moderate
Spasm Severity								
142 (3) 8–10	Serious limitation[4]	No serious limitation	Serious limitation	No serious limitation	Undetectable	The std. mean in change in spasm severity was 0.015 (SE 0.295)[a]	The std. mean in changes in spasm severity in the intervention group was on average 0.14 fewer (0.63 fewer to 0.36 more)	Moderate
Cognitive Function								
107 (3) 4–10	Serious limitation	No serious limitation	Serious limitation	No serious limitation	Undetectable	The std. mean in change in cognitive function was 0.692 (SE 2.285)[c]	The std. mean in changes in cognitive function in the intervention group was on average 0.55 more (3.33 fewer to 4.43 more)	Moderate
Daily Activities								
180 (2) 10	No serious limitation	No serious limitation	Serious limitation	No serious limitation	Undetectable	The std. mean in change in daily activities was 0.05 (SE 0.74)[d]	The std. mean in changes in cognitive function in the intervention group was on average 0.01 more (1.21 fewer to 1.24 more)	Moderate
Pain								
665 (5) 2–14	No serious limitation	No serious limitation	Serious limitation	No serious limitation	Undetectable	The std. mean in change in pain was 0.031 (SE 0.205)[e]	The std. mean in changes in pain in the intervention group was on average 0.02 fewer (0.39 fewer to 0.35 more)	Moderate
Motricity								
399 (4) 2–10	No serious limitation	No serious limitation	Serious limitation	No serious limitation	Undetectable	The std. mean in change in motricity was 0.417 (SE 0.525)[d]	The std. mean in changes in motricity in the intervention group was on average 0.34 more (0.60 fewer to 1.27 more)	Moderate
Bladder Function								
160 (1) 10	No serious limitation	No serious limitation	Serious limitation	No serious limitation	Undetectable	The std. mean in change in bladder function was −0.064 (SE 9.73)[d]	The std. mean in changes in bladder function in the intervention group was on average 0.06 fewer (19.13 fewer to 19.01 more)	Moderate

SE = standard error; std. = standardized.

[a] Baseline risk estimates for spasticity come from control arm of Berman 2004 study (largest randomized trial in the meta-analysis).

[b] Baseline risk estimates for spasm frequency come from control arm of Pooyania 2010 study (largest randomized trial in the meta-analysis).

[c] Baseline risk estimates for spasm frequency come from control arm of Corey-Bloom 2012 study (largest randomized trial in the meta-analysis).

[d] Baseline risk estimates for spasm frequency come from control arm of Wade 2004 study (largest randomized trial in the meta-analysis).

[e] Baseline risk estimates for spasm frequency come from control arm of Langford 2013 study (largest randomized trial in the meta-analysis).

[1] Some studies did not provide blind of adjudication. Two of seven studies were ranked as high risk of bias for both allocation sequence and allocation concealment.

[2] There was a substantial heterogeneity (I^2 = 88%) provided per the different scores used in the included studies (i.e., modified Ashworth scale; NRS).

[3] There was no substantially difference related to the mean age throughout the seven included studies as well as the majority of the exclusion criteria such as psychiatric disorder other than depression; pregnant or lactating; drug or alcohol abuse as well as inclusion criteria (e.g., diagnosis of MS and stable disease).

[4] One study was ranked high risk of bias in all of the evaluated categories, two failed to provide blinding adjudication.

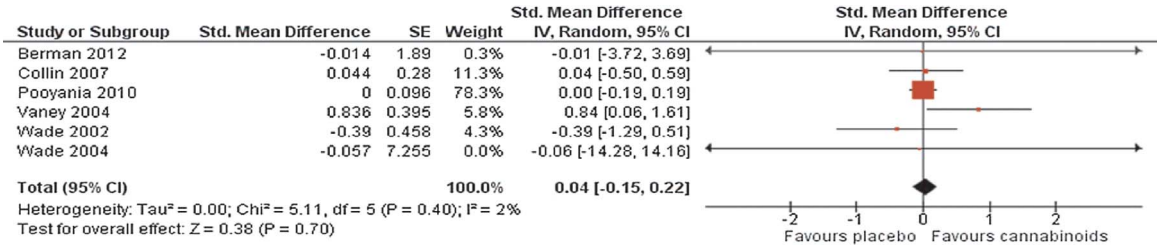

Fig. 4. Pooled analysis of spasm frequency comparing cannabinoids and placebo.

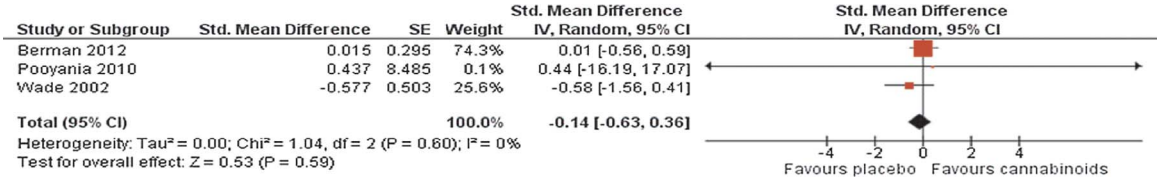

Fig. 5. Pooled analysis of spasm severity comparing cannabinoids and placebo.

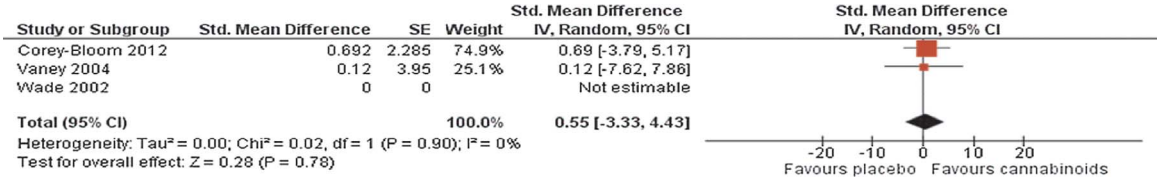

Fig. 6. Pooled analysis of pain comparing cannabinoids and placebo.

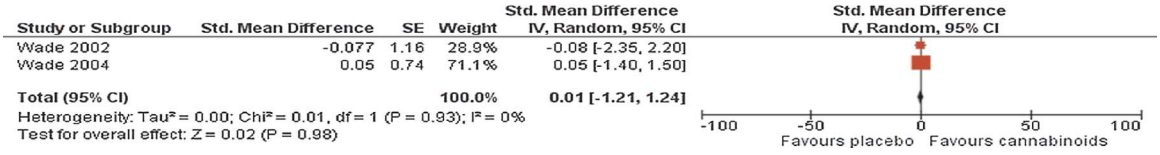

Fig. 7. Pooled analysis of cognitive function comparing cannabinoids and placebo.

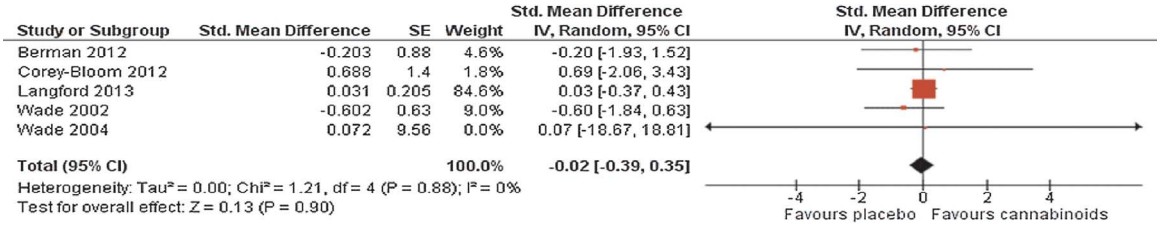

Fig. 8. Pooled analysis of daily activities comparing cannabinoids and placebo.

4. Discussion

4.1. Main findings

Based on the GRADE approach, meta-analysis of moderate certainty evidence from 16 eligible placebo-controlled trials including 2597 patients suggested a non-statistically significant improvement in spasm frequency and severity, cognitive function, daily activities, and motricity with cannabinoid use. Low certainty evidence showed a possible reduction in spasticity, although the association did not reach statistical significance either. Moderate certainty evidence also indicated a non-statistically significant deterioration in pain and bladder function.

Cannabinoid users experienced an approximately three-fold increased risk of dizziness, somnolence and dry mouth, and an approximately two-fold increased risk of nausea, relative to placebo. These adverse events are significantly more tolerable than those related to the use of the current spasticity therapy, such as respiratory depression, ataxia and hallucinations. A statistically significant difference favoring placebo over cannabinoids in relation to headaches was found as well.

4.2. Strengths and limitations

Strengths of this review include a broad search; evaluation of eligibility, risk of bias, and data abstraction independently and in duplicate; use of the GRADE approach in rating the quality of evidence; and focus on both absolute and relative effects of the intervention on patient-important outcomes.

Potential limitations are related to the data available for this subject on the current literature. Trials often had outcomes reported incompletely, inadequate random sequence, and a fail of blinding due to the nature of the intervention, but for some studies also avoidable lack of blinding (outcome adjudication).

Another limitation of this review is the fact that most of the patients are using others concurrent active drugs such as interferon beta 1-b, glatiramer, and corticoids which can introduce bias in the true effects of

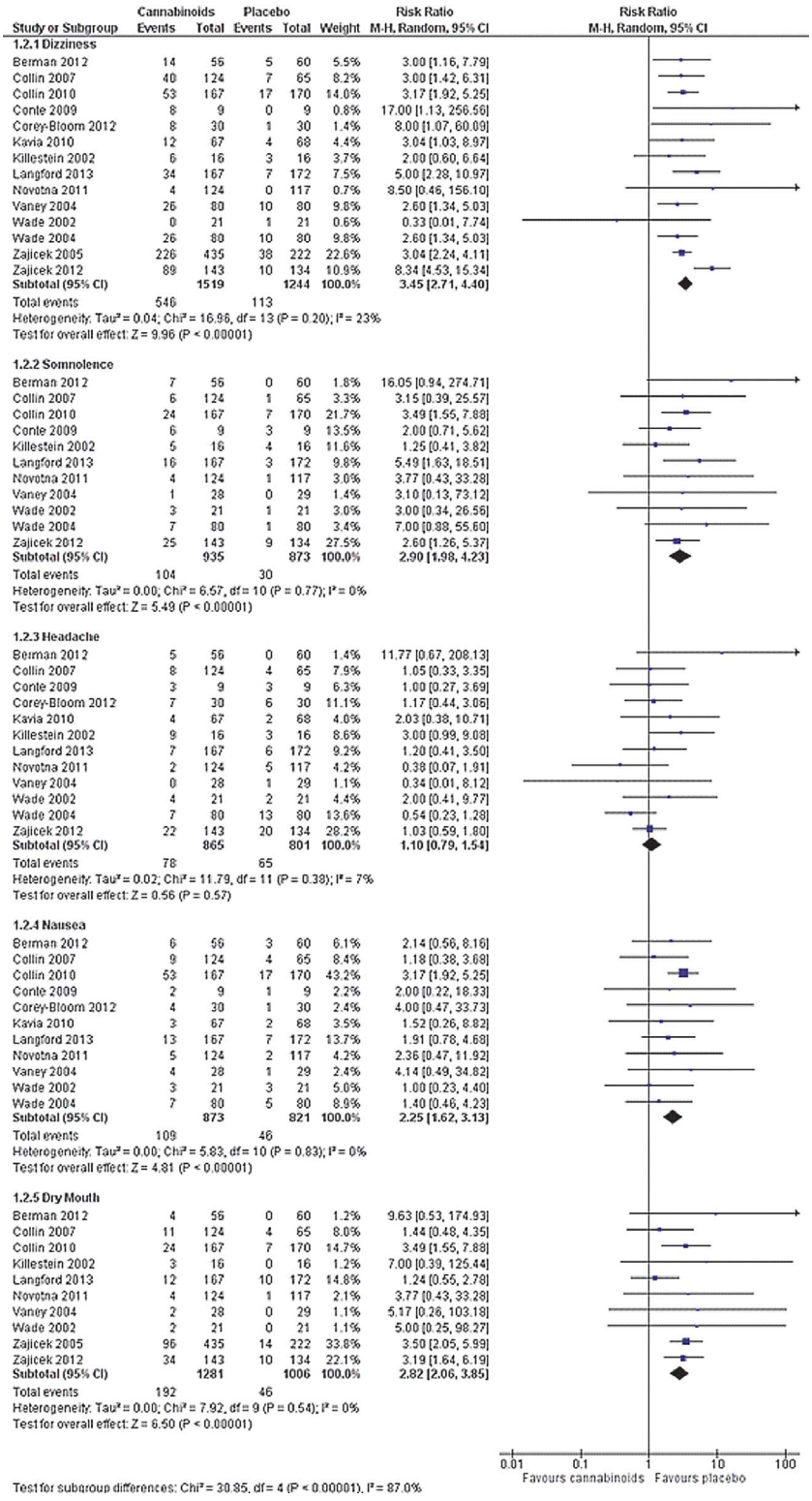

Fig. 9. Pooled analysis of adverse events comparing cannabinoids and placebo.

cannabinoids. The results of trials purporting beneficial effects of a new intervention could not ignore the effects of concurrent treatments.

Although this review presents some limitations, the issue is whether one should dismiss these results entirely or consider them bearing in mind the limitations. The latter represent our view of the matter.

4.3. Relation to prior work

A recent systematic review by Whiting and colleagues [8] reviewed the literature from inception to April 2015, finding 79 studies with 6462 participants. The review reported moderate certainty, non-statistically significant improvements in spasticity due to multiple sclerosis, and chronic neuropathic or cancer pain with cannabinoid use [8] Another review covering literature from 1948 to March 2015 via MEDLINE [9] supported these findings, with six trials (n = 325 patients) for chronic pain, six trials (n = 396 patients) for neuropathic pain, and 12 trials (n = 1600 patients) for multiple sclerosis-related spasticity supporting the potential efficacy of marijuana and cannabinoid

Table 4
GRADE evidence profile of adverse events: cannabinoids for spasticity in multiple sclerosis or spinal cord injury patients.

Quality assessment						Summary of findings					Certainty in estimates OR Quality of evidence
No of participants (studies) Range follow-up time in weeks	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Study event rates		Relative risk (95% CI)	Anticipated absolute effects over 19 weeks		
						Without Cannabinoids	With Cannabinoids		Without Cannabinoids	With Cannabinoids	
Dizziness											
2763 (14) 2–19	Serious limitation[1]	No serious limitation	Serious limitation[2]	No serious limitation	Undetectable	113/1244	546/1519	3.45 (2.71–4.40)	171 per 1000[a]	419 per 1000 (292 more to 581 more)	Moderate
Somnolence											
1808 (11) 2–19	Serious limitation[1]	No serious limitation	Serious limitation[2]	No serious limitation	Undetectable	30/873	104/935	2.90 (1.98–4.23)	67 per 1000[b]	127 per 1000 (65 more to 216 more)	Moderate
Headache											
1666 (12) 2–19	Serious limitation[1]	No serious limitation	Serious limitation[2]	No serious limitation	Undetectable	65/801	78/865	1.10 (0.79–1.54)	149 per 1000[b]	15 per 1000 (32 fewer to 80 more)	Moderate
Nausea											
1694 (11) 2–19	Serious limitation[1]	No serious limitation	Serious limitation[2]	No serious limitation	Undetectable	46/821	109/873	2.25 (1.62–3.13)	100 per 1000[c]	125 per 1000 (62 more to 213 more)	Moderate
Dry Mouth											
2287 (10) 2–19	Serious limitation[1]	No serious limitation	Serious limitation[2]	No serious limitation	Undetectable	192/1281	46/1006	2.82 (2.06–3.85)	63 per 1000[a]	114 per 1000 (66 more to 179 more)	Moderate

[a] Baseline risk estimates for dizziness and dry mouth come from control arm of Zajicek 2005 study (largest randomized trial in the meta-analysis).
[b] Baseline risk estimates for somnolence and headache come from control arm of Zajicek 2012 study (largest randomized trial in the meta-analysis).
[c] Baseline risk estimates for nausea come from control arm of Collin 2010 study (largest randomized trial in the meta-analysis).
[1] The large sample of studies include many that were ranked as high risk of bias in some of the categories analyzed.
[2] The sample of studies often included very similar populations.

treatment for these indications.

In 2016 two articles sought to shed light on the understanding of the management of spasticity in MS patients. One of them [45] is the largest multicentre observational study to date evaluating THC-CBD oromucosal spray effectiveness and tolerability in daily clinical practice, carried out in a routine outpatient setting. The other is a narrative review [46] that describes findings from both randomized controlled phase III trials and recent studies on everyday clinical practice. Intending to expand and complement the comprehension on the subject, we engaged on a systematic and meta-analytic approach on this present review. Worthy of note is that both articles showed conclusions in line with our own findings, considering that spasticity is tremendously impactful on the patients and that it is currently being poorly managed. The reasons behind the inadequate approach of this ailment range from the lack of convincing evidence regarding the effectiveness and efficacy of the currently available therapy and it's AEs (which are more severe and frequent than cannabis based medicine showed to be), to the questionable reliability of the most widely used scale (Ashworth Scale) used to assess spasticity from the healthcare professional perspective. The studies also reinforced the importance of patient reported data such as VAS and NRS. Finally, THC-CBD oromucosal spray was interpreted as a safe and useful option for the management of spasticity resistant to available medication in MS patients.

Our update systematic review with 16 additional RCTs involving 2597 participants identified moderate-certainty evidence supporting a similar non-statistically significant improvement in spasm frequency and severity, and low certainty evidence supporting a reduction in spasticity. However, our results contrasted previous findings regarding cannabinoid effects on pain, where moderate-certainty evidence suggested a non-significant deterioration in multiple sclerosis or paraplegia.

4.4. Implications for clinical practice and for research

There is moderate certainty evidence regarding the impact of cannabinoids in spasticity (average 0.36 more spasticity; 0.17 fewer to 0.88 more) due to multiple sclerosis or paraplegia, and in adverse events such as dizziness (419 more dizziness/1000 over 19 weeks), somnolence (127 more somnolence/1000 over 19 weeks), and nausea (125 more somnolence/1000 over 19 weeks) and, dry mouth (114 more somnolence/1000 over 19 weeks). Further large-scale RCTs exploring the effectiveness of cannabinoids for spasticity and chronic pain in this patient population, as well as for other indications, are warranted.

Funding and conflicts of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctim.2017.08.010.

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