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NEUROLOGY OF SYSTEMIC DISEASES (J BILLER, SECTION EDITOR)

The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews

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Abstract

Purpose of Review Pharmaceutical cannabinoids such as nabiximols, nabilone and dronabinol, and plant-based cannabinoids have been investigated for their therapeutic potential in treating multiple sclerosis (MS) symptoms. This review of reviews aimed to synthesise findings from high quality systematic reviews that examined the safety and effectiveness of cannabinoids in multiple sclerosis. We examined the outcomes of disability and disability progression, pain, spasticity, bladder function, tremor/ataxia, quality of life and adverse effects.

Recent Findings We identified 11 eligible systematic reviews providing data from 32 studies, including 10 moderate to high quality RCTs. Five reviews concluded that there was sufficient evidence that cannabinoids may be effective for symptoms of pain and/or spasticity in MS. Few reviews reported conclusions for other symptoms.

Summary Recent high quality reviews find cannabinoids may have modest effects in MS for pain or spasticity. Future research should include studies with non-cannabinoid comparators; this is an important gap in the evidence.

Keywords Multiple sclerosis · Cannabinoid · Pain · Spasticity · Nabiximols · Dronabinol · Cannabis

Introduction

Multiple sclerosis is a chronic neuroinflammatory disease of the brain and central nervous system. It is characterised pathologically by demyelinating plaques within both grey and white matter, representing loss of both myelin sheath and supporting oligodendrocytes [1]. While remyelination may occur early in the history of the disease, over time this inflammatory process results in progressive neuroaxonal loss and increased disability.

The course of the condition varies in clinical form, with relapsing-remitting multiple sclerosis (RRMS) accounting for approximately 85% of cases [2]. The varied signs and symptoms of multiple sclerosis depend upon the site of lesions in the brain and spinal cord. Common symptoms and signs include spasticity, weakness, sensory disturbances, painful spasms, ataxia, tremor, optic neuritis and complex opthalmoplegias, fatigue and dysphagia [1]. There is considerable heterogeneity in the course of the disease and its symptoms [3] so treatment needs to be individualised to address the symptoms that patients report most adversely affect their quality of life [4].

Current drug therapies for multiple sclerosis can be grouped into two categories: disease-modifying and symptomatic therapies. Disease-modifying therapies aim to lessen the number, severity and duration of relapses, maintain remission and slow progression. These therapies are usually immunomodulatory and/or immunosuppressive treatments such as interferon beta, copaxone, fingolimod, natalizumab and alemtuzumab [5–7]. Symptomatic therapies that relieve the

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distressing and/or disabling symptoms of multiple sclerosis include anticonvulsants for neuropathic pain, anticholinergic drugs for bladder dysfunction and dysphagia, and botulinum toxin injections for spasticity [1]. The use of these symptomatic therapies may be limited by their toxicity [8].

Anecdotal reports that patients with multiple sclerosis experience symptomatic relief after smoking cannabis have prompted research using cannabinoids to manage symptoms [9]. Research is now also examining the potential for cannabinoids to slow disease progression as well as palliate spasticity and pain [10].

Neuropathic pain and pain in association with muscle spasms are common distressing symptoms in multiple sclerosis [11]. Animal models have suggested that cannabinoid (CB)-1 receptor activation may reduce neuropathic, visceral and inflammatory pain [12, 13]. Several preclinical studies have demonstrated that systemic administration of cannabinoid receptor ligands produce analgesia in acute and chronic pain models [14]. Research has also explored the role of CB2 receptors, which seem to mediate anti-hyperalgesia in inflammatory pain states, [15, 16] and reduce inflammation and neuropathic pain [17]. Cannabinoids, and the endocannabinoid system, have been demonstrated to have a role in reducing spasticity in animal models [18].

Multiple reviews on this topic have been conducted with varying conclusions. This systematic review of reviews synthesises moderate to high quality reviews assessing the effectiveness of cannabis and cannabinoids for treating multiple sclerosis. More specifically, the objectives are to identify the effectiveness of plant-based cannabinoids, and pharmaceutical cannabinoids (plant-derived or synthetically manufactured) in reducing disability and disability progression, pain, spasticity and improving quality of life in people with multiple sclerosis. These outcomes are patient-centred, short to medium term, and relevant to the daily lives and experiences of people living with multiple sclerosis.

Methods

Inclusion Criteria

Types of Participants

The review considered systematic reviews of studies that included participants with multiple sclerosis.

Types of Intervention

We included reviews of studies that evaluated plant-based and pharmaceutical cannabinoids: tetrahydrocannabinol; cannabidiol; combination tetrahydrocannabinol + cannabidiol; *Cannabis sativa*; and where evidence exists, other cannabinoids e.g. tetrahydrocannabinolic acid (thca), cannabidiolic acid, cannabidivarin, and the synthetic delta-9-tetrahydrocannabinol formulations (nabilone and dronabinol).

Types of Outcomes

This review considered the following eight key outcomes in trials of cannabinoids for symptom relief in multiple sclerosis [19•]:

- Disability and disability progression
- Pain
- Spasticity
- Bladder function
- Ataxia and tremor
- Sleep
- Quality of life
- Adverse effects

Inclusion Criteria

We included reviews of experimental and epidemiological study designs. These included randomised controlled trials, non-randomised controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies. Reviews were required to meet the minimum standards of describing a systematic search and providing study level data within the review (i.e. met the AMSTAR criteria 3 and 6, see Appendix 2). Review articles that were not published in English were considered for inclusion. Where these reviews used high quality methodology or provided research evidence that was not included in existing reviews we planned to obtain translations; however, no such reviews were identified.

Exclusion Criteria

We did not include reports of single studies, reviews of mechanisms of cannabinoid systems, or commentary articles and clinical overviews that did not describe a systematic review or assess and synthesise evidence at the individual study level.

Search Strategy

Eight databases (Medline, Medline In-Process & Other Non-Indexed Citations/Ovid; Embase/Ovid; PsycINFO/Ovid; EBM Reviews—Cochrane Central Register of Controlled Trials/Ovid) were searched with the terms below (and their corresponding subject headings in each database where specialised thesauri existed). The searches were limited to studies published from 1980 to the end of 2016 (a sample Medline search is reproduced, Appendix 1).

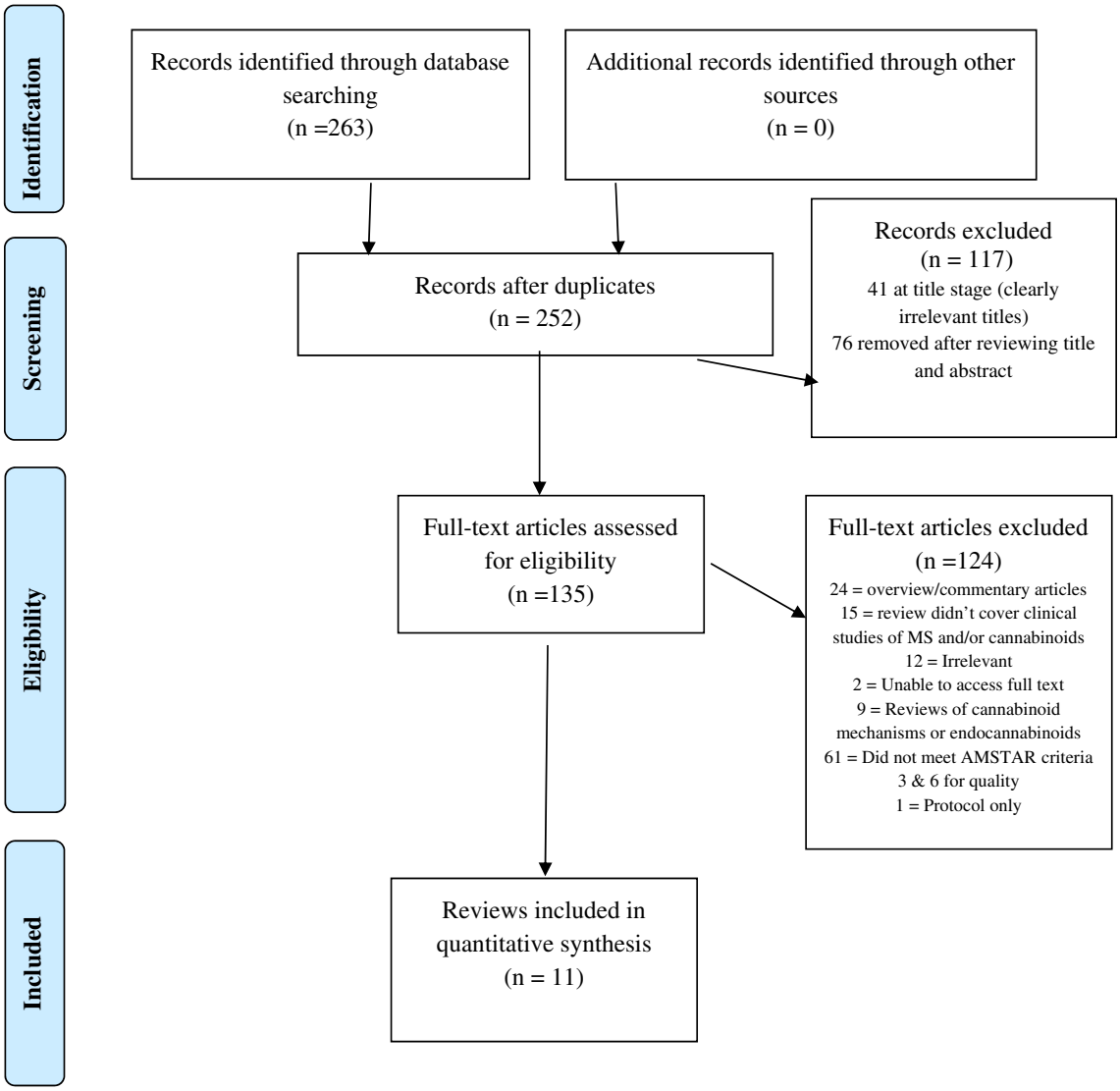

Fig. 1 PRISMA flow diagram for selection of reviews

Two reviewers independently examined titles and abstracts using Covidence software. Relevant review articles were obtained in full, and independently assessed for inclusion in the review by two reviewers. Reasons for exclusion were documented in Covidence. Inter-reviewer disagreement was resolved by consensus in all cases.

Assessment of Methodological Quality

The full text reviews deemed eligible by two reviewers were assessed for quality by one reviewer and these quality ratings were checked by a second reviewer. Methodological quality ratings described the methodological quality across 11 predefined domains for each included review using the AMSTAR measurement tool to assess the methodological quality of systematic reviews [20] (Appendix 2). The AMSTAR tool documents assessed risk of bias at the review level.

To be eligible for inclusion, a review needed to meet criteria 3 and 6 of the AMSTAR tool. These criteria required that a review described a comprehensive search and described the characteristics of the studies included in the review. Those studies that did not meet criteria 3 and 6 are listed in Supplementary Table 1 with the other excluded studies. Details of reported potential conflicts of interests of review authors were extracted (see Supplementary Table 3). Details of AMSTAR scores for individual items are also reported in Supplementary Table 3.

Grading of Evidence

An evidence grade was given to each review using the Scottish Intercollegiate Guidelines Network (SIGN) grading

system [21]. To enable an assessment of the evidence contained in the reviews, we also rated the individual studies included in the review according to the GRADE criteria [22]. Where reviews reported an assessment quality metric for each study, this was considered in the assessment. As per the GRADE rating, randomised controlled trials (RCTs) were considered high quality evidence, downgraded RCTs (for reasons of bias, sample size or other issues around design) were considered moderate quality evidence, double-downgraded RCTs (e.g. downgraded two levels from high to low quality because of multiple concerns with study design or bias) or observational studies were considered low quality evidence, and triple-downgraded RCTs, downgraded observational studies, case series or case studies were considered very low quality evidence (see Supplementary Table 4).

Data Collection

Data were extracted from reviews using a standardised data extraction tool implemented in a custom-built Microsoft Access database. The data extracted included details about the interventions, populations, study methods and outcomes of interest. Data extraction tools were piloted and reviewed by the study authors before the results of the extraction were finalised.

Data Synthesis

Review findings were synthesised to highlight when multiple reviews arrived at the same or different conclusions and to describe the strength of the evidence in each case. We synthesised findings by generating a set of statements that represented the findings according to their quality and the similarity in review conclusions.

Results

Results are presented grouped by cannabinoid types. Where reviews did not identify studies that reported on outcomes measure for a specific cannabinoid product, the gaps in the evidence are also indicated in Table 2.

Description of Reviews

Eleven reviews met the eligibility criteria (see Fig. 1; Table 1). Two Cochrane reviews were identified that focused on ataxia and tremor [23] and spasticity [24]. The remaining nine systematic reviews focused on multiple sclerosis [25, 26], movement disorders more broadly [27, 28•, 29], or included studies of multiple sclerosis as part of more comprehensive reviews of the therapeutic uses of cannabinoids [30••, 31–33].

Five reviews were graded as 1+ in the SIGN grading system. This represents 'well-conducted meta-analyses, systematic reviews, or randomised control trials with a low risk of bias'. Six reviews had a SIGN grading of 1− comprising 'meta-analyses, systematic reviews, or randomised control trials with a high risk of bias'. Quality as rated with the AMSTAR scale ranged from 2 to 10 out of a possible 11, with a mean score of 6. The review covered studies published between 1981 and 2013, and the reviews themselves were published between 2006 and 2016. The reviewed studies assessed a range of cannabinoids including tetrahydrocannabinol (THC), cannabidiol (CBD), THC:CBD formulations, pharmaceutical cannabinoids (dronabinol and nabilone), smoked *Cannabis sativa* plant material and oral cannabinoid extracts (Table 2).

Evidence was examined on eight pre-specified outcomes. Details by outcome domain are provided below. A summary of the review evidence on the eight outcomes is presented in Table 2.

Quality of the Evidence Contained in the Reviews

Overall, 32 published reports were identified from the 11 systematic reviews. Of these, four provided very low quality evidence, 17 provided low quality evidence, 9 provided moderate quality evidence and two publications from one larger RCT (> 300 people) judged to have a low risk of bias provided high quality evidence (see Appendix 3).

Disability and Disability Progression

Six reviews reported data relating to disability or disease progression using different scales and outcome measures [24, 25, 29, 30••, 31, 33] (see Supplementary Table 5). Overall, the effects of cannabinoids on disability and disease progression were mixed. Reviews did not report conclusions on this outcome, or focus on disability and disease progression as the primary outcome.

Pain

Seven reviews reported on a range of cannabinoids for the treatment of pain in patients with multiple sclerosis [24, 26, 28•, 29, 30••, 31, 33] (see Supplementary Table 6). Although the effects were mixed, reviews presented evidence that most cannabinoids reduced pain on at least some measures.

Two reviews of medium quality (AMSTAR score 4 and 5 out of 11) concluded that there was an evidence that THC and THC:CBD/nabiximols were efficacious or probably efficacious in reducing pain or painful spasm in multiple sclerosis [28•, 29]. Some reviews concluded that there was insufficient evidence or mixed findings [24, 26, 33]. One review cited a non-significant meta-analysis of 3 studies (565 participants)

Table 1 Overview of reviews characteristics

Review ID	Title	Type of review	Aim of review	Types of evidence considered by the review, and sample size reported^	Year studies published	SIGN grade	Funding/COIs	AMSTAR score
Andrzejewski 2016	Cannabinoids in the treatment of movement disorders: a systematic review of case series and clinical trials	Systematic review	To assess the use of exogenous cannabinoids in the treatment of movement disorders.	Two randomised, double-blind placebo-controlled crossover study ($n = 14$ [Fox 2004] and $n = 57$ [Vaney 2004]), one case series ($n = 8$ [Clifford 1983]), one randomised double-blind parallel group (1, $n = 337$ Collin 2010) and one double-blind RCT (1, $n = 667$ Wade 2004)	2003–2010	1−	Not reported	2
Whiting 2015	Cannabinoids for medical use: a systematic review and meta-analysis	Systematic review	To conduct a systematic review of the benefits and adverse events of cannabinoids.	Parallel RCT (Collin 2007 [$n = 189$], Collin 2010 [$n = 337$], Langford 2013 [$n = 339$], Van Amerongen 2014 [$n = 24$], Wade 2004 [$n = 160$], Zajicek 2003 [$n = 657$], Zajicek 2012 [$n = 279$]) or crossover RCT (Corey-Bloom 2012 [$n = 37$], Killestein 2002 [$n = 16$], Leocani 2014 [$n = 43$], Vaney 2004 [$n = 57$])	2003–2010	1+	Declared funding/no apparent COI	10
Koppel 2014	Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders	Systematic review	To determine the efficacy of medical marijuana in several neurologic conditions.	Double-blind RCTs (Kavia 2010 [$n = 135$], Zajicek 2003 [$n = 630$], Wade 2004 [$n = 160$], Vaney 2004 [$n = 57$], Freeman 2006 [$n = 522$], Zajicek 2012 [$n = 224$], Rog 2005 [$n = 66$], Collin 2010 [$n = 265$], Zajicek 2005 [$n = 502$], Corey-Bloom [$n = 37$], Svendsen 2004 [$n = 24$], Greenberg 1994 [$n = 20$]), (Killestein 2002 [$n = 16$], Collin 2010 [$n = 337$], Fox 2004 [$n = 14$], Fox 2002 [$n = 15$]) Randomised double-blind controlled trial (Ungerleider 1987 [$n = 13$]); Open label study (Centzone 2009 [$n = 20$]), Open label follow-up post RCT (Wade 2006 [$n = 137$])	1987–2012	1−	Declared funding with no apparent COI	4
Jawahar 2013	A systematic review of pharmacological pain management in MS	Systematic review	To systematically review pain management strategies for the reduction of non-spastic and non-trigeminal neuralgic pain in MS patients.	Double-blind placebo-controlled RCTs (Rog 2005 [$n = 66$], Wade 2004 [$n = 160$], Double-blind crossover RCT (Svendsen 2004 [$n = 24$])	2004–2013	1+	No funding/-possible COI	6
Zhornitsky 2012	Cannabidiol in humans—the quest for therapeutic targets	Systematic review	To examine the randomised and crossover studies that administered CBD to healthy controls and clinical patients.	Clinical trials: Killestein 2002 ($n = 16$), Zajicek 2003 [$n = 630$], Freeman 2005 ($n = 255$), Brady 2005 ($n = 15$) Wade 2003 ($n = 20$), Notcutt 2004 ($n = 34$),	2002–2006	1−	Not reported/no apparent COI	3
Karst 2010	Role of cannabinoids in the treatment of pain and (painful) spasticity	Systematic review	To review the most current and relevant data available on the antinociceptive properties of cannabinoids for their potential or already established use in clinical settings.	For the clinical trials, we included non-randomised, observational, and randomised, double-blind, placebo-controlled trials (RCTs) in clinical and experimental settings. RCT: Petro and Ellenberger 1981 ($n = 9$), Ungerleider 1987 ($n = 13$), Martyn 1995 ($n = 1$), Killestein 2002 ($n = 16$), Zajicek 2003 ($n = 630$), Wade 2003 ($n = 24$), Wade 2004 ($n = 160$), Svendsen 2004 ($n = 24$), Vaney 2004 ($n = 57$), Zajicek 2005 ($n = 502$), Rog 2005 ($n = 66$), Wade 2006 ($n = 13$), Rog 2007 ($n = 63$), Collin 2007 ($n = 189$), Conte 2009	1981–2009	1−	No funding	5

Table 1 (continued)

Review ID	Title	Type of review	Aim of review	Types of evidence considered by the review, and sample size reported^	Year studies published	SIGN grade	Funding/COIs	AMSTAR score
				(*n* = 18), Centzone 2009 (*n* = 20), Collin 2010 (*n* = 337)				
Mills 2007	Treatment for ataxia in multiple sclerosis	Cochrane review	To assess the efficacy and tolerability of both pharmacological and non-pharmacologic treatments of ataxia and tremor in patients with MS.	Blinded, randomised trials (RCTs), which were placebo-controlled or compared two or more treatments, were included. One parallel (Wade 2004, [*n* = 160]) and two crossover studies (Fox 2004 [*n* = 14], Killestein 2002 [*n* = 16]) were reviewed	2002–2004	1−	Not reported	9
Lakhan 2009	Whole plant cannabis extracts in the treatment of spasticity in M: a systematic review	Systematic review	To systematically evaluate the effectiveness of combined THC and CBD extracts on MS-related spasticity in order to increase understanding of the treatment's potential effectiveness, safety and limitations.	Only randomised, placebo-controlled, human studies of shorter treatment periods (under 6 months) were included. Crossover RCT (Killestein 2002 [*n* = 16], Wade 2003 [*n* = 24], Vaney 2004 [*n* = 57], Parallel RCT(Zajicek 2003 [*n* = 395], Collin 2007 [*n* = 184], Wade 2004 [*n* = 154])	2002–2007	1+	No funding	7
Shakespeare 2003	Anti-spasticity agents for multiple sclerosis	Cochrane review	To assess the absolute and comparative efficacy and tolerability of anti- spasticity agents in MS patients.	Double-blind, randomised controlled trials (RCTs) of treatment duration longer than 7 days which are either placebo-controlled or comparing two or more agents were analysed. Killestein 2002 [*n* = 16] reported a crossover study, Wade 2003 reported a crossover study [*n* = 160]	2002–2003	1+	Not reported	9
Wang 2008	Adverse effects of medical cannabinoids: a systematic review	Systematic review	To create an evidence base for cannabis-related adverse events and to facilitate future cannabis research initiatives.	Randomised controlled trials evaluating the safety and efficacy of cannabis if adverse events were quantified. Observational studies in which cannabis represented the main exposure were included, provided the outcome of interest was adverse events. Case reports were included if they described adverse events in people exposed to cannabis. Studies on MS: Parallel RCTs (Collins 2007 [*n* = 189], Rog 2005 [*n* = 66], Wade 2004 [*n* = 160], Zajicek 2003 [*n* = 630, Zajicek 2005 [*n* = 611] and Crossover RCT (Wade 2003 [*n* = 611], Killestein 2002 [*n* = 16], Petro and Ellenberger 1981 [*n* = 9], Svendsen 2004 [*n* = 24], Vaney 2004 [*n* = 57])	1981–2007	1+	Funding not reported, author MW possible COI (speaker fees and consultancy)	6
Ben Amar 2006	Cannabinoids in medicine: a review of their therapeutic potential	Systematic review	To report on the most current data available on the therapeutic potential of cannabinoids.	Double-blind crossover RCT (Petro and Ellenberger 1981 [*n* = 9], Ungerleider 1987 [*n* = 13], Martyn 1995 [*n* = 1], Killestein 2002 [*n* = 16], Wade 2003 [*n* = 18], Fox 2004 [*n* = 14], Vaney 2004 [*n* = 50]) Single-blind placebo-controlled (Clifford 1983 [*n* = 8]) Double-blind parallel RCT (Greenberg 1994 [*n* = 10], Zajicek 2003 [*n* = 630], Wade 2004 [*n* = 160], Svendsen 2004 [*n* = 24])	1981–2004	1−	Not reported	2

^Note that reported sample size differed for the same study between reviews

Table 2 Summary of study level evidence on the safety and efficacy of cannabis and cannabinoids in the treatment of multiple sclerosis

	Disability and disease progression	Pain	Spasticity	Bladder function	Ataxia and tremor	Sleep	Quality of life	Adverse events
Cannabis sativa (smoked)	1 study (1 RCT)	1 study (1 RCT)	2 studies (2 RCT)	No studies	No studies	No studies	2 studies (2 RCT)	2 studies (2 RCT)
Findings	No change	Positive effect	Positive effect				Mixed effect	AEs > comparator
Quality of evidence	Low quality	Low quality	Low quality				Low quality	Low quality
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence				Insufficient evidence	Insufficient evidence
Dronabinol	4 studies (2 RCT)	4 studies (3 RCT)	5 studies (5 RCT)	2 studies (1 RCT)	3 studies (2 RCT)	2 studies (1 RCT)	2 studies (2 RCT)	8 studies (6 RCT)
Findings	No change/negative effect	Positive effect	Mixed effect	Mixed effect	No change	Mixed effect (mostly positive)	Mixed effect	AEs > comparator
Quality of evidence	Very low to high	Low to high quality	Low to high quality	High quality	Very low to high quality	Moderate to high quality	Low to high quality	Very low to high quality
Conclusion	Inconsistent evidence	Some evidence of positive effect	Inconsistent evidence	Inconsistent evidence	Unlikely to have an effect	Insufficient evidence	Insufficient evidence	Mild AEs likely
THC extract	No studies	3 studies (2 RCT)	2 studies (1 RCT)	1 study (No RCT)	No studies	3 studies (2 RCT)	No studies	1 studies (1 RCT)
Findings		Positive effect	Positive effect	Positive effect		Mixed effect		AEs > comparator
Quality of evidence		Very low to low	Very low to low quality	Very low quality		Very low to low quality		Low quality
Conclusion		Some evidence of effect	Insufficient evidence	Insufficient evidence		Insufficient evidence		Mild AEs likely
Nabiximols	2 studies (2 RCT)	8 studies (5 RCT)	7 studies (6 RCT)	2 studies (2 RCT)	2 studies (2 RCT)	1 study (1 RCT)	5 studies (5 RCT)	10 studies (7 RCT)
Findings	No change	Mixed effect	Mixed effect	Mixed effect	No change	Positive effect	Mixed findings	AEs > comparator
Quality of evidence	Moderate quality	Very low to moderate quality	Very low to moderate quality	Moderate quality	Moderate quality	Moderate quality	Moderate quality	Very low to moderate quality
Conclusion	Insufficient evidence	Inconsistent evidence	Inconsistent evidence	Insufficient evidence	Unlikely to have an effect	Insufficient evidence	Some evidence of positive effect	Mild AEs likely
THC:CBD extracts	6 studies (5 RCT)	7 studies (5 RCT)	6 studies (5 RCT)	4 studies (2 RCT)	4 studies (4 RCT)	4 studies (3 RCT)	3 studies (3 RCT)	8 studies (6 RCT)
Findings	Mixed effect	Mixed findings	Mixed findings	Mixed findings	No change	Mostly positive effect	Mixed findings	AEs > comparator
Quality of evidence	Low to high quality	Very low to high quality	Low to high quality	Very low to high quality	Low to high quality	Low to high quality	Low to high quality	Low to high quality
Conclusion	Inconsistent evidence	Inconsistent evidence	Inconsistent evidence	Inconsistent evidence	Unlikely to have an effect	Some evidence of effect	Inconsistent evidence	Mild AEs likely
Nabilone	No studies	1 study (1 RCT)	2 studies (2 RCT)	1 study (1 RCT)	1 study (1 RCT)	No studies	2 studies (2 RCT)	3 studies (3 RCT)
Findings		Positive effect	Positive effect	Positive effect	No change		Mixed effect	AEs > comparator
Quality of evidence		Very low	Very low to low quality	Very low quality	Low quality		Very low to moderate quality	Very low to low quality
Conclusion		Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence		Insufficient evidence	Mild AEs likely
CBD extract	No studies	2 studies (2 RCT)	1 study (1 RCT)	No studies	No studies	1 study (1 RCT)	No studies	1 study (1 RCT)
Findings		Mixed effect	Mixed findings			Positive effect		AEs > comparator
Quality of evidence		Low quality	Low quality			Low quality		Low quality
Conclusion		Insufficient evidence	Insufficient evidence			Insufficient evidence		Insufficient evidence

Quality rating (Per GRADE approach in Cochrane Handbook V5.1)

High, randomised trials; or double-upgraded observational studies

Moderate, downgraded randomised trials; or upgraded observational studies

Low, double-downgraded randomised trials; or observational studies

Very low, triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports

with a pooled effect size for cannabinoids of 0.08 (95% CI − 0.74 to 0.89) [26], though noted positive results were observed when only studies of central pain were considered. The highest quality review (AMSTAR score of 10) did not report conclusions for the outcome of pain in multiple sclerosis, although it concluded that cannabinoids may reduce spasticity [30••] which is associated with pain.

Spasticity

Seven reviews examined the effects of cannabinoids on spasticity in multiple sclerosis [24, 25, 28•, 29, 30••, 31, 33] (see Supplementary Table 7). Many reported outcomes on the Ashworth Score, a measure of spasticity on a 5-point scale using subjective clinical assessments of tone ranging from 0—'no increases in tone' to 4—'limb rigid in flexion or extension [abduction/adduction]' [34].

In general, results were inconsistent between studies identified in the reviews, with many reporting positive effects on some, but not all measures of spasticity. Reviews reported that many studies did not find an effect of cannabinoids on spasticity using the Ashworth scale, one of the most widely used measures for this outcome. Positive effects were reported, however, on patient-rated measures of spasticity.

One review conducted a meta-analysis of outcomes of spasticity measured on the Ashworth scale [30••]. This meta-analysis demonstrated a trend towards an improvement (reduced score on the Ashworth scale) but did not detect a statistically significant effect, either when cannabinoid types were examined alone or when all studies were considered together. In a total of 1134 participants, the mean difference was − 0.12 units on a five-point scale (95% CI − 0.24 to 0.01). A meta-analysis of three studies found nabilone and nabiximols were associated with a greater average improvement on spasticity measured with a numerical rating scale (mean difference, − .76, [95% CI − 1.38 to − .014]). From these results, the authors concluded that there was moderate quality evidence to suggest cannabinoids may reduce spasticity [30••].

Three other reviews also concluded favourably on the use of cannabinoids to treat spasticity. Ben Amar [33] concluded that cannabinoids objectively showed a small noticeable beneficial effect on spasticity, and Koppel et al. [28•] concluded that THC:CBD extracts are effective, and THC/nabiximols are probably effective in treating painful spasticity. A similar conclusion was reached by Lakhan and Rowland [25] in their review of whole plant extracts. Karst et al. [29] concluded there was evidence of efficacy but a narrow therapeutic index limiting use. Overall, most reviews found evidence that THC and THC:CBD products may reduce spasticity or concluded that it generally favoured cannabinoids to treat spasticity based on the results of individual studies or trends towards significant effects [25, 28•, 29, 30••, 33].

Bladder Function

Four reviews considered evidence on the effects of cannabinoids on bladder function in multiple sclerosis [28•, 29, 31, 33] (see Supplementary Table 8). In most of these reviews, this was not the primary outcome, and few reviews reported conclusions on the clinical use of cannabinoids for this indication. One review concluded that there was evidence that THC:CBD oromucosal spray was probably effective, whereas oral cannabinoid extracts and THC were probably not effective in reducing bladder symptoms [28•].

In general, the reviews provided some evidence, including positive findings from high quality RCTs, that THC and THC:CBD had positive effects on bladder symptoms. The latter included fewer voids, reduced frequency of nocturia and improved incontinence-related quality of life measures. These effects were not consistently observed across studies in the reviews and positive findings from smaller studies were not confirmed in larger, high quality studies.

Ataxia and Tremor

Four reviews considered evidence on the effects of cannabinoids on ataxia and tremor with use of dronabinol, nabilone, nabiximols and THC:CBD extracts [23, 27, 28•, 33] (see Supplementary Table 9). In most reviews this was not a primary outcome so few reported on the clinical use of cannabinoids for this indication. One review concluded that THC and oral cannabinoid extracts were probably ineffective, and nabiximols were possibly ineffective for tremor [28•]. A second review stated that no conclusions could be made of the efficacy of cannabinoids on the treatment of movement disorders, with studies failing to demonstrate a significant effect on tremor. [27]. Studies identified in reviews were generally small and not likely to have had the power to detect anything but very large effects.

Sleep

Three reviews reported on the effects of cannabinoids on measures of sleep [29, 31, 33] (see Supplementary Table 10). Sleep was also not a primary outcome in any review and no review reported a conclusion on the clinical use of cannabinoids to improve sleep in people with multiple sclerosis.

Quality of Life

Four reviews examined the effect of cannabinoids on overall quality of life or other measures of general functioning in patients with multiple sclerosis [23, 29, 30••, 33] (see Supplementary Table 11). Reviews provided evidence of mixed findings on the effect of cannabinoids on quality of life,

with reviews reporting data from studies that found both positive and negative effects on quality of life. One review reported that cannabinoids can lead to a moderate improvement in general well-being [33].

Adverse Effects

Eight reviews reported data on adverse effects (AEs) of cannabinoids in treating multiple sclerosis [25, 26, 28•, 29, 30••, 31–33] (see Supplementary Table 12). This included one systematic review of the adverse effects of therapeutic cannabinoids, from which we extracted data on studies in patients with multiple sclerosis [32].

Most reviews identified similar AEs from cannabinoids that were most frequently described as 'mild' to 'moderate'. They included dizziness, dry mouth, euphoria, diarrhoea, and difficulty concentrating. Adverse effects were consistently rated as more common in study participants who received cannabinoids than placebo. Most reviews did not draw conclusions on whether any of these adverse effects precluded clinical use.

No specific cannabinoid was identified as having a more serious adverse effect profile than another. Whiting et al. [30••] noted that no cannabinoid or route of administration was associated with any specific adverse event. Their meta-analyses of adverse events over a range of cannabinoids and medical conditions found that an adverse event was around three times more likely to occur with a cannabinoid than placebo (OR 3.03, 95% CI 2.42–3.80). There was a slightly greater odds of a serious adverse event (OR 1.41, 95% CI 1.04–1.92), and three times the odds of patients withdrawing due to adverse events with patients receiving cannabinoids rather than placebo (OR 2.94, 95% CI 2.18–3.96). They noted the lack of long-term follow-up data on adverse events.

Karst et al. [29] concluded that the risk to benefit profile was not optimally balanced with existing cannabinoid products. Koppel et al. [31] noted that adverse effects were a concern in patients with multiple sclerosis. One specific concern raised was the potential cognitive impairing effects of cannabinoids in patients with pre-existing cognitive dysfunction [28•]. Other reviews expressed caution about use of cannabinoids in the elderly and persons with a psychosis [33].

Review findings were inconsistent on the effect of the addition of CBD to THC on the adverse effect profile of THC. Some reviews identified evidence of an attenuation of adverse effects related to THC, while other reviews identified greater adverse effects from THC:CBD combinations than THC [25, 31]. Adverse effects with oral THC/dronabinol were dose dependent. One review identified that at least 10 mg of THC was reported as required to reduce spasticity and adverse effects were observed with doses of 15 mg and above [29]. Reviews were not able to compare side effects of cannabinoids with those of other active treatments because of a lack of such studies.

General Conclusions of the Reviews

One recent high quality review [30••] concluded that there was sufficient evidence to support the clinical use of nabiximols, nabilone, THC/CBD capsules, and dronabinol in treating symptoms of multiple sclerosis (see Supplementary Table 13). This review received an AMSTAR score of 10 and reported on 7 studies in patients with multiple sclerosis involving a total of 1218 participants.

Four other reviews similarly concluded that there are possibly or probably beneficial effects on some outcomes (such as pain, spasticity and bladder symptoms) [25, 28•, 29, 33]. A further four reviews concluded that there was insufficient evidence to make any recommendations [23, 24, 27, 31]. The scope of these latter reviews was often narrower (e.g. limited to a specific symptom such as ataxia, or to a specific cannabinoid, such as cannabidiol). One review was focused on adverse effects as opposed to clinical efficacy [32].

No reviews made a recommendation on where cannabinoids would fit in the therapeutic hierarchy in treating different symptoms of multiple sclerosis, i.e. whether cannabinoids should be used as first line or later line treatments only after other treatments had been tried. No review recommended their use as a monotherapy.

Discussion

We reviewed the findings of 11 systematic reviews of evidence on the potential benefits of cannabinoids for multiple sclerosis. Recent high quality reviews supported the clinical use of cannabinoids for spasticity and pain in multiple sclerosis. The findings were inconclusive on use to treat other common symptoms (e.g. bladder control, ataxia and tremor). Some positive findings appear to support clinical use of cannabinoids in spasticity, although the magnitude of the effect was generally small. Few reviews could conduct meta-analyses because the measures used and outcomes examined were not standardised.

Reviews identified potentially negative effects in a small number of studies, often of low quality. A potential negative effect of cannabinoid use on disease progression warrants further research especially as many of the positive studies only measured short-term outcomes (i.e. up to 12 weeks).

Beneficial effects on bladder function and sleep were identified by some reviews. Because these symptoms were rarely the primary focuses of reviews, no reviews offered clinical recommendations on the use of cannabinoids for these indications. Future research may evaluate the effects of cannabinoids in patients who report that these are their symptom of greatest concern.

One challenge in studying the effects of cannabinoids on multiple sclerosis is that patients have heterogeneous

symptom profiles. This may make it difficult to find an effect on secondary outcome measures when symptoms are not found in all study participants. The seriousness of adverse effects may also vary with patients' presenting symptoms. For example, those with cognitive impairment may be more susceptible to potential cognitive effects of cannabinoids [28•].

A further challenge identified in the systematic reviews was a lack of harmonisation across the studies in the outcome measures used. This makes synthesis of findings challenging. Finally, the cannabinoid products evaluated were considered suboptimal. Newer cannabis products may have different risk-benefit profiles.

There are some limitations with the current review. Some of the evidence considered in the reviews came from well-conducted RCTs, including some with large samples sizes. This was supplemented by weaker evidence from studies with smaller sample sizes and subject to possible biases from weak study design. Different reviews reported on different outcome measures relating to symptoms of multiple sclerosis. In some cases, this explained why reviews came to different conclusions on the efficacy of cannabinoids despite including the same studies.

Some reviews argued that the risk versus benefit decision for patients with multiple sclerosis may need to be made at the individual rather than the population level. Their use may depend on which symptoms are most problematic for the patient, and on how the adverse effects of cannabinoids affect their quality of life. Most adverse events and most benefits reported in systematic reviews are likely to be noted within a short period of time. This facilitates individualised decision-making by means of a time-limited therapeutic trial. One study reported that benefits of cannabinoids are generally observed in the first 4 weeks of the study [35]. If so, a trial of 4–6 weeks may enable patients and their physicians to assess whether their symptoms will respond to cannabinoids. If benefits are not observed in this time, there is little benefit expected from continued use [35].

Few reviews drew any conclusions on use with symptoms other than pain or spasticity and some which reported benefits in spasticity found detriments in other domains, complicating general statements about the risk/benefit ratio of cannabinoids for individuals.

Further Research

One area in which further research is required is the possible role of cannabidiol in disease progression. One review reported that the THC:CBD combination may have adverse effects and showed more disease progression compared with THC alone [31]. Further, few studies used active comparators, and no review commented on if cannabinoids could be considered as a monotherapy. Given that there are other treatments with considerable efficacy for multiple sclerosis, studies with active comparators will be critical in further informing clinical decision-making about the use of cannabinoids.

Conclusions

In conclusion, reviews identified evidence that would support a trial of cannabinoids for pain or spasticity in a patient with multiple sclerosis. Effect sizes are generally small suggesting only modest effects may be expected. Adverse events were generally mild to moderate, although caution is warranted in specific populations of patients with multiple sclerosis with greater vulnerability to adverse effects from cannabinoids.

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Compliance with Ethical Standards

Conflict of Interest SN, MF and LD have all been investigators on untied investigator-driven educational grants funded by Reckitt Benckiser. MF and LD have received untied educational grant from Mundipharma for post-marketing surveillance studies of new opioid medications. SN, MF and LD have been investigators on untied investigator-driven educational grants funded by Indivior and Reckitt-Benckiser. NB is a member of the medical cannabis expert panel for New South Wales Health. WH provided evidence to parliamentary committees on medical uses of cannabis in Australia and the United Kingdom and is a member of the Australian Advisory Council on Medical Uses of Cannabis. SN, WH, MF, MW and LD have previously published manuscripts on the topic of therapeutic use of cannabis. Other authors declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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