Australian Government
Department of Health
Therapeutic Goods Administration

Guidance
for the use of
medicinal cannabis
in the treatment of
multiple sclerosis
in Australia

Version 1, December 2017

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Introduction

A set of guidance documents has been made available to assist doctors and their patients who choose to prescribe medicinal cannabis in Australia under current access schemes. These have been developed based on reviews of available evidence for the use of medicinal cannabis in five different settings. Included is an overview addressing the evidence base for medicinal cannabis therapy generally as well as specific documents relating to medicinal cannabis in the treatment of palliative care, epilepsy, chemotherapy-induced nausea and vomiting (CINV), multiple sclerosis (MS) and chronic pain.

This document reflects the evidence supporting the use of medicinal cannabis in treating symptoms of MS, including pain, spasticity, bladder spasm, ataxia and tremor, adverse events, quality of life and disability and the recommendations of the Multiple Sclerosis Working Group.

Note: These guidance documents are based on evidence available at the time of publication and will be updated as new evidence emerges. Each document should be read in conjunction with the '*Guidance to the use of medicinal cannabis in Australia—Overview*'.

Review method

The Australian Government Department of Health commissioned a team from the University of New South Wales, University of Sydney and University of Queensland under the coordination of the National Drug and Alcohol Council (NDARC) to review the available evidence for the use of medicinal cannabis in the above five settings.

The researchers conducted a review of previously published reviews from multiple databases such as Medline, Embase, PsychINFO and EBM Reviews based on PRISMA[145]. PRISMA is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and is an evidence-based minimum set of items for reporting on randomised controlled trials (RCTs). These guidelines have been developed because of concern for low quality trials and aim to improve the quality of medical research, remove bias and improve transparency and accurate reporting of findings. Searches were guided by a specialist Librarian using specific search terms and were limited to studies published between 1980 and early 2017. Two reviewers independently examined titles and abstracts for relevance using Covidence Software and the Cochrane Risk of Bias Tool was used to assess studies, aiming to increase accuracy. The GRADE (grading of recommendations, assessment, development and evaluation) approach, an internationally recognised standard applying to weighting of evidence in scientific and medical literature was used to evaluate the quality of evidence.

In July 2017, the department also convened five separate Working Groups to consider the available evidence for the use of medicinal cannabis in the treatment of each of the settings. The five groups consist of individuals from a wide range of backgrounds and organisations, including senior staff from each state and territory Department of Health, fifteen healthcare professional organisations, clinical staff from twenty-nine hospitals and healthcare systems, fourteen outpatient or Primary Health Networks and eighteen consumer representative groups.

Caveats

It should be noted that there are significant limitations in our knowledge of the medicinal use of cannabis.

This document provides a guidance for health professionals in the use of an unapproved medicine, in the context of limited evidence of efficacy in the treatment of MS symptoms. There are few long-term studies and, other than for nabiximols (sativex), there are limited data to advise on dose, tolerance and safety in people with MS.

This document includes dosing suggestions for cannabinoids including delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD), their combinations and routes of administration.

Evidence of benefit from medicinal cannabis use is limited.

1. Guidance can only relate recommendations to the condition, drug and dose which have been studied. For example, evidence of efficacy in anorexia from one product and dose should not be extrapolated to pain control with the same product and dose.
2. There are limitations in how the evidence was obtained and reviewed.
3. Dose-response information is lacking, in particular for starting doses. This is particularly relevant when applying data from younger people to the elderly or people with cachexia, cognitive impairment and hepatic or renal disease.
4. Dose-response information for toxicity is also lacking, particularly for side effects which may overlap with distress symptoms and may occur at different doses and before efficacy is evident. Side effects which are reversible in younger people when ceasing the cannabinoid product may be irreversible in this setting.
5. There is no dose equivalence safety or efficacy data between products or between specific cannabinoids and current standard of care therapy.

As with all therapies, medical practitioners must exercise their professional judgment in determining whether medicinal cannabis products are an appropriate treatment for an individual patient. At this time, the use of medicinal cannabis should be considered only where conventional treatments have been proven unsuccessful in managing the patient's symptoms.

Summary of the current evidence

This document reviews the role of cannabinoids in treating the symptoms associated with multiple sclerosis, including:

- disability and disability progression;
- pain;
- spasticity;
- bladder function;
- ataxia and tremor;
- sleep; and
- quality of life.

A literature search for high quality systematic reviews was conducted on the use of cannabinoids to treat the symptoms of multiple sclerosis, with a cut-off date of November 30, 2016. A systematic review-of-reviews was conducted of studies that provided evidence on the use of cannabinoids as anti-emetics.

Overall, there is low to moderate quality evidence which suggests pharmaceutical-grade THC (dronabinol or THC extract) is effective for treating symptoms of pain.

THC:CBD (nabiximols, Sativex) may be effective for treating symptoms of pain and spasticity in MS, in certain patient populations.

Findings were mixed as to whether cannabinoids assisted in improving bladder function, sleep, patient quality of life, ataxia/tremor and disability/disease progression.

No studies included active alternatives (non-cannabinoid medicines) as comparators, which is an important limitation.

These results are based on 11 systematic reviews, which included 32 individual studies (see page 16).

Key to grades—adapted from the Mayo Clinic[1]

A Strong scientific evidence for this use
B Good scientific evidence for this use
C Unclear scientific evidence for this use
D Fair scientific evidence against this use (it may not work)
F Strong scientific evidence against this use (it likely does not work)

Disability and disease progression

Six reviews, with a total of 11 individual studies, reported data on measures of patient disability or disease progression[2,3,4,5,6]. Few studies evaluated the effect of cannabis sativa and nabiximols in slowing disability and disease progression. Where there was evidence it suggested that they had no effect. Likewise, findings were inconsistent for the use of dronabinol and THC:CBD extracts as therapies to slow disability or disease progression. The overall lack of evidence for an effect of cannabinoids on disease progression was emphasised by the Working Group.

Evidence Grade	Cannabinoid used	Outcomes
C	Cannabis sativa	One review included one study (one Randomised Control Trial - RCT) that reported evidence of low quality that cannabis sativa produced no change in patient disability or disease progression.
C	Dronabinol	Four reviews included four studies (two RCT) that provided very low to high quality evidence that reported inconsistent effects of dronabinol on disability and disease progression.
C	Nabiximols	Three reviews included two studies (two RCT) of moderate quality that reported nabiximols produced no change for patient disability or disease progression.
C	THC:CBD extracts	Six reviews included six studies (five RCT) of low to moderate quality that reported inconsistent effects of THC:CBD extracts on patient disability and disease progression.

Pain

Seven reviews, including 19 individual studies, reported data on measures of pain[8,9,10,11,12,13,14]. There was some evidence that THC, including dronabinol and THC extracts, was effective in reducing pain. Findings were more inconsistent for nabiximols and THC:CBD extract combinations, with some reports of positive outcomes for pain. Two reviews concluded that cannabinoids were probably effective for the treatment of painful spasticity[15,16].

Evidence Grade	Cannabinoid used	Outcomes
C	Cannabis sativa	One review included one study (one RCT) of low quality that reported cannabis sativa had a positive effect on pain.
B	Dronabinol	Six reviews included four studies (three RCT) of low to high quality that reported dronabinol had a positive effect in reducing pain.
B	THC extract	Three reviews included three studies (two RCT) of very low to low quality that reported THC extracts had a positive effect in reducing patient pain.
C	Nabiximols	Four reviews included eight studies (five RCT) of very low to moderate quality that reported inconsistent results of the effect of nabiximols in reducing patient pain.

C	THC:CBD extracts	Six reviews included seven studies (five RCT) of very low to high quality that reported inconsistent results of the effect of THC:CBD extracts in reducing pain.
C	Nabilone	Two reviews included one RCT of very low quality that reported a positive effect of nabilone in reducing pain.
C	CBD	Three reviews included two studies (2 RCT) of low quality that reported mixed results for the effectiveness of CBD in reducing pain.

Spasticity

Early data in animal models of MS suggested improvement in spasticity from cannabinoids in humans.

Seven reviews, with a total of 20 individual studies, reported data on changes in patient measures of spasticity[17,18,19,20,21,22,23]. Findings were inconsistent for the use of nabiximols and THC:CBD extract combinations. There was some evidence from moderate quality studies that nabiximols reduced spasticity as reported by patient ratings. A number of reviews concluded that cannabinoids (particularly THC:CBD combinations) were probably effective in reducing spasticity[24,25,26].

Evidence Grade	Cannabinoid used	Outcomes
C	Cannabis sativa	Two reviews included two studies (two RCT) of low quality that reported cannabis sativa had reduced patient spasticity.
C	Dronabinol	Six reviews included five studies (five RCT) of low to high quality reported mixed findings on the effectiveness of dronabinol in reducing patient spasticity.
C	THC extract	Four reviews included two studies (one RCT) of very low to low quality that reported THC extracts reduced patient spasticity.
C	Nabiximols	Five reviews included seven studies (six RCT) of very low to moderate quality that reported inconsistent findings on the effectiveness of nabiximols in reducing patient spasticity.
C	THC:CBD extracts	Seven reviews included six studies (five RCT) of low to high quality that reported inconsistent findings on the effectiveness of THC:CBD extracts in reducing patient spasticity.
C	Nabilone	One review included two studies (two RCT) of very low to low quality that reported nabilone had a positive effect on spasticity.
C	CBD	One review included one low quality RCT that reported CBD likely did not have an effect on patient spasticity.

Bladder function

Four reviews, with a total of seven individual studies, reported the effects of cannabinoids on patient bladder function [27,28,29,30]. Evidence across all cannabinoids tested was insufficient or inconsistent. Two reviews concluded that nabiximols and THC extract were effective at reducing urinary incontinence or the number of bladder voids per day but these conclusions were based on a single study [31,32].

Evidence Grade	Cannabinoid used	Outcomes
C	Dronabinol	Two reviews included two studies (one RCT) of high quality that reported mixed results for dronabinol in improving bladder function.
C	THC extract	One review included one very low quality study (zero RCT) that reported THC had a positive effect in improving patient bladder function.
C	Nabiximols	Two reviews included two studies (two RCT) of moderate quality that reported nabiximols mixed effects on patient bladder functioning.
C	THC:CBD extracts	Two reviews included four studies (two RCT) of very low to high quality reported mixed findings on the effect of THC:CBD extracts on bladder functioning. High quality studies reported that there was no significant improvement in patients receiving THC:CBD.
C	Nabilone	Two reviews included one low quality RCT that reported nabilone had no effect on patient bladder functioning.

Ataxia and tremor

Four reviews, with a total of eight individual studies, reported changes to patient ataxia and tremor [33,34,35,36]. Evidence was based on small studies, and most cannabinoids had no significant effect of ataxia and tremor. Two reviews concluded that cannabinoids were probably ineffective or produced no significant benefit in treating patient tremor [37,38].

Evidence Grade	Cannabinoid used	Outcomes
D	Dronabinol	Three reviews included three studies (two RCT) of very low to high quality that reported dronabinol had mixed effects on patient ataxia and tremor.
D	Nabiximols	Three reviews included two studies (two RCT) of moderate quality reported that nabiximols had no effect on patient ataxia or tremor.
D	THC:CBD extracts	Three reviews included four studies (four RCT) of low to high quality reported mixed results of the effect of THC:CBD extracts on ataxia and tremor. The high quality RCT reported no significant changes to patient tremor in those receiving THC:CBD extracts.

D	Nabilone	One review included one low quality RCT that reported there was no effect of nabilone in reducing patient ataxia and tremor.

Sleep

Three reviews, with a total of six individual studies, reported effects of cannabinoids on patient sleep quality[39,40,41,42]. There was evidence from one study that nabiximols were effective at improving sleep quality. One review noted the studies included indicated a positive effect of cannabinoids on sleep quality [43].

Evidence Grade	Cannabinoid used	Outcomes
C	Dronabinol	Three reviews included two studies (one RCT) of moderate to high quality that reported mixed results, mostly indicating a positive effect on sleep.
C	THC extract	One review included three studies (two RCT) of very low to low quality that reported mixed effects of THC extracts on patient sleep and sleep quality.
C	Nabiximols	One review included one moderate quality RCT that reported nabiximols had a positive effect on patient sleep quality.
C	THC:CBD extracts	Three reviews included four studies (three RCTs) of low to high quality that reported mixed (mostly positive) effects of THC:CBD extracts on patient sleep quality.
C	CBD extract	One review included one low quality RCT that reported CBD had a positive effect on patient sleep quality.

Quality of life

Four reviews, with a total of 12 individual studies, reported on the effects of cannabinoids on patient quality of life [44,45,46,47]. Findings were inconsistent across the cannabinoids. There was some moderate quality evidence that nabiximols were more effective than placebo at improving patient global impression of change. One meta-analysis reported the mean number of patients reporting improved global impression of change scores was greater for nabiximols than placebo [48]. Studies of other cannabinoids gave little or no evidence that they improved patient quality of life.

Evidence Grade	Cannabinoid used	Outcomes
C	Cannabis sativa	Two reviews included two low quality RCTs that reported some patients experienced improvement in overall quality of life, however clinical measures were not significant.
C	Dronabinol	Three reviews included two low to high quality RCTs that reported mixed findings. The high-quality study reported that there was no significant change in patient general health scores.

B	Nabiximols	One review included five RCTs of moderate quality that reported inconsistent results. The average number of patients who reported an improvement on global impression of change was greater for nabiximols than placebo.
C	THC:CBD extracts	Four reviews included three RCTs of low to high quality that reported mixed results. The high-quality study reported no significant difference between cannabinoids and placebo for measures of patient quality of life.
C	Nabilone	Two reviews included two RCTs of very low to moderate quality that reported mixed results. There was some evidence that nabilone improved patient global impression, however sample sizes were very small.

Recommendation

There is some evidence that dronabinol or THC extracts may be effective at reducing pain associated with multiple sclerosis. There is also some evidence (although inconsistent) that nabiximols and other THC:CBD extracts may reduce muscle spasticity and improve patient quality of life.

Recommendations are limited by lack of quality evidence. Currently available studies demonstrate no evidence of an effect of cannabinoids on MS disease activity or disability progression. There have been no studies comparing cannabinoids against current standard treatments for multiple sclerosis.

Adverse effects

Commonly reported adverse events in trials in MS included dizziness, somnolence dysphoria, euphoria, feeling 'high', diarrhoea, and vertigo. Most reviews classified these adverse events as mild or well tolerated.

Acute administration of cannabis to elderly or particularly sensitive patients should be considered carefully, and psychotic or 'particularly vulnerable' patients should avoid the chronic use of cannabinoids[49]. Koppel et al [50] also noted that cognitive impairment is likely to be of concern. Some patients who have neurologic conditions may have pre-existing cognitive dysfunction, which may increase their susceptibility to cannabinoids' toxicities.

Combined extracts of THC and CBD may attenuate side effects associated with THC alone[51]. The incidence of side effects varies greatly and depends on the amount of cannabis needed to limit spasticity.

In a meta-analysis of adverse events associated with medical cannabinoid use, Wang et al[52]. reported that the most frequently reported adverse events were nervous system disorders. Serious adverse events included 21 instances of relapse of multiple sclerosis, serious convulsion, and severe dizziness.

Recent reviews have suggested as many as 10 per cent of adults who use cannabis develop psychological dependence and that percentage may be higher in younger age groups[53]. There is no evidence to provide guidance on drug-drug interactions. If cannabinoids are to be used in conjunction with other therapies, clinicians and patients should be aware of common adverse events associated with cannabinoid use and consider whether these events are likely to interfere with quality of life.

Patients and prescribing clinicians should be aware of likely adverse events such as dizziness, somnolence, dysphoria and diarrhoea. Clinicians considering cannabinoid therapy for patients should consider the individual's capacity for using cannabinoids for long periods of time.

Place in therapeutic hierarchy

It is difficult to evaluate where cannabinoids could usefully be placed in the therapeutic hierarchy because all trials have compared cannabinoids to placebo rather than other therapies. Several reviews concluded that cannabinoids may be effective or beneficial for the treatment of spasticity or pain associated with multiple sclerosis but made no recommendations about their place in the therapeutic hierarchy [54,55,56,57,58].

To determine the relative efficacy of cannabinoids as treatments for spasticity or pain, trials would need to compare cannabinoids to standard first and second-line treatments used to treat multiple sclerosis.

Recommendation

In the absence of evidence comparing cannabinoids to first line treatments for pain and spasticity in MS, including baclofen, dantrolene, and benzodiazepines, there is no basis for using cannabinoids as a monotherapy or first line treatment. If pain and spasticity are not properly controlled by standard therapies, doctors may discuss with their patients the use of nabiximols or dronabinol as an adjunctive therapy.

Evidence on time to response

Treatment duration in randomised controlled trials and open label clinical trials was a median of four weeks (range one day to 52 weeks). Three studies evaluated cannabinoids for up to two years [59,60,61]. A number of studies had maintenance phases for patients after titrating to their effective cannabinoid dose [62,63,64,65,66]. None of the reviews made statements about typical time to response.

Recommendation

In the absence of strong evidence for dosing and particular preparations of cannabis or cannabinoids in the treatment of symptoms of multiple sclerosis (other than nabixomols), it is recommended that any treating physician who elects to initiate cannabinoid therapy should re-evaluate patients after four to six weeks for evidence of response to treatment.

Use of THC/CBD combinations or products

The majority of studies (21) evaluating the use of cannabinoids in treating symptoms of multiple sclerosis used THC/CBD combinations.

Nabiximols (THC:CBD), trade name Sativex, were most commonly tested. There was some evidence that they may be effective for reducing patient pain and spasticity and may improve sleep and quality of life. THC:CBD or nabiximols were the only cannabinoid products that studies assessed all the identified outcomes used to evaluate effectiveness.

Dosage forms, variations in route of administration and standardisation

Cannabinoid product	Preparation	Administration	Standardised
Nabiximols	Liquid	Oromucosal spray	Yes
THC:CBD extracts	Liquid	Sublingual spray	Yes
	Capsule	Oral	Yes
Dronabinol	Capsule	Oral	Yes
THC extract	Liquid	Spray	Yes
Nabilone	Capsule	Oral	Yes
CBD	Liquid	Spray	Yes
Cannabis sativa	Cigarette	Smoked	Not specified

Nabiximols

Nabiximols were administered as a standardised oromucosal liquid spray. Studies using nabiximols addressed all eight outcomes identified as indicators of effectiveness and safety for treatment for symptoms of multiple sclerosis[67,68,69,70,71,72,73,74,75,76,77].

THC:CBD extracts

THC:CBD extracts were administered as either a standardised oromucosal liquid spray or an oral capsule. Studies using THC:CBD extracts addressed all eight outcomes identified as indicators of effectiveness and safety for treatment of symptoms of multiple sclerosis[78,79,80,81,82,83,84,85,86,87].

Dronabinol

Dronabinol was administered in a standardised oral capsule form. Studies using dronabinol addressed all eight outcomes identified as indicators of effectiveness and safety for treatment of symptoms of multiple sclerosis[88,89,90,91,92,93,94,95,96].

THC extracts

THC extracts were administered in standardised liquid form either as an oromucosal or sublingual spray. Studies using THC extracts did not address disability/disease progression and

quality of life outcomes as indicators of effectiveness and safety for the treatment of symptoms of multiple sclerosis[97,98,99].

Nabilone

Nabilone was administered in a standardised oral capsule form. Studies using nabilone did not address disability/disease progression and change to sleep outcomes as indicators of effectiveness and safety for the treatment of symptoms of multiple sclerosis[100,101,102,103].

CBD extracts

CBD extracts were administered as a standardised liquid sublingual spray. Studies using CBD extracts addressed four of the eight identified outcomes as indicators of treatment effectiveness and safety, namely changes to pain, spasticity, sleep, and adverse events[104,105].

Cannabis sativa

Cannabis sativa was administered in a herbal cigarette and was unlikely to be a standardised product. Studies using cannabis sativa addressed five of the eight identified outcomes as indicators of treatment effectiveness and safety, namely change to disability/disease progression, pain, spasticity, quality of life, and adverse events[106,107].

Recommendation

For patients who may benefit from the use of cannabinoids in treating pain or spasticity from multiple sclerosis, it is recommended that a physician who elects to initiate cannabinoid therapy use standardised products, and pharmaceutical-grade nabiximols, dronabinol, or THC extract produced with GMP (good manufacturing practice) which have the greatest evidence for efficacy based on the review.

Dose (including various cannabinoids in the product), dose ranges for which there is evidence, other pharmacological considerations for dosages

Nabiximols

Studies reported patients receiving nabiximols received the standardised oromucosal spray which delivers 2.7mg THC and 2.5mg CBD per spray. Patients were able to administer between 12 and 48 sprays per 24 hours. In studies where there was evidence of effectiveness, doses ranged between 12 and 48 sprays per day[108,109,110,111,112,113,114,115].

The Mayo Clinic reports that, to treat symptoms of multiple sclerosis, 2.5–120 mg in divided doses (eight sprays within three hours, up to 48 sprays in 24 hours) has been used for 6 to 14 weeks[116].

THC:CBD extracts

Studies reported patients receiving THC:CBD extracts received either capsule or sublingual sprays. Dosages for capsules ranged from 2.5mg and up to 12.5mg of THC, and 0.8mg and up to 2.5mg of CBD. Capsules were given two to four times per day. Dosages for sublingual

sprays administered 2.5mg THC and 2.5mg CBD, up to 48 times per day. In studies where there was evidence for effectiveness, capsule doses ranged between 2.5mg and 12.5mg of THC, and 0.8mg to 1.8mg CBD, administered two to four times per day[117,118,119,120]. Effective sublingual sprays administered 2.5mg THC and 2.5mg CBD up to 48 times per day[121,122,123].

The Mayo clinic reports that, to treat symptoms of multiple sclerosis, cannabis extracts with THC:CBD combinations ranging between 2.5–120mg has been taken by mouth daily for two to 15 weeks[124].

Dronabinol

Studies reported patients receiving dronabinol in standardised capsule form. Dosage ranged from 2.5–15mg, received between one and four times per day. Where there is evidence for effectiveness, dose ranges were between 2.5mg and 15mg, administered between one and four times per day[125,126,127,128,129,130].

The Mayo Clinic reports that to treat multiple sclerosis symptoms, 2.5mg of dronabinol is taken by mouth daily, increasing to a maximum of 10mg daily for three weeks[131].

THC extract

One study reported patients received 2.5mg of THC as a sublingual spray, up to 48 times per day. This dose was reported to be effective[132].

Nabilone

Studies reported patients received nabilone as a standardised capsule. Dosage ranged from 0.5mg–1.0mg, and in one study 0.03mg/kg. Dosage ranged between one and two capsules a day, and in one study, was administered every second day. Where there was evidence of effectiveness, dosages ranged between 0.5mg–1.0mg, and were administered one to two times per day, or in one case study, every second day[133,134,135].

CBD extract

Two studies reported that patients received CBD extract as a sublingual spray. They received 2.5mg of CBD per spray and were able to administer up to 48 sprays per day. There was evidence that this dosage range and schedule were effective[136,137].

Cannabis sativa

Two studies reported the use of cannabis sativa as a herbal cigarette. Dosages could not be accurately reported, but THC content ranged between 1.54 per cent and four per cent. Where there was evidence for effectiveness, one study reported that patients smoked one cigarette with four per cent THC content[138].

The Mayo Clinic reports cannabis extract capsules of 15–30mg have been taken by mouth, in 5mg increments, based on tolerance, for 14 days. Cannabis extracts such as Cannador have been taken by mouth for two to four weeks[139].

Tolerance and persistence in treatment

In the studies included in the review, treatment with cannabinoids appeared to be well tolerated but patients receiving them were more likely to withdraw from trials for any reason and due to adverse events. In a systematic review and meta-analysis of the use of cannabinoids to treat neurological disorders, 6.9 per cent of patients receiving cannabinoids stopped treatment because of adverse events compared to 2.2 per cent of patients who received placebo[140]. In longer-term treatment, two open-label extension studies were associated with withdrawal rates of up to 25 per cent[141]. Comparison to standard treatments for pain and spasticity in multiple sclerosis is needed to determine whether patients are significantly more likely to withdraw from cannabinoids than other multiple sclerosis treatments.

Recommendation

If treatment is likely to be long term, it is important that any side-effects from cannabinoids are not greater than the side effects experienced with other medications. This requires their response to treatment to be regularly assessed. Measures of tolerability include experience of adverse event and patient assessment of treatment efficacy.

Stopping rules

There is no current high quality evidence in multiple sclerosis symptom clusters.

There is little information on dose-response. Starting doses should be low, and the dose increased in response to lack of efficacy until toxicity outweighs any benefit.

In the absence of strong evidence for dosing and specific preparations of cannabis or cannabinoids in the treatment of multiple sclerosis symptoms it is recommended that any treating physician who elects to initiate cannabinoid therapy should re-evaluate the effectiveness and adverse effects of the cannabinoid medication after 12 weeks of therapy.

Information on pharmacovigilance should be collected by the prescribing doctor. This will help refine guidance documents and provide additional data.

NDARC Review

(see Appendix A)

Figure 1. PRISMA Chart

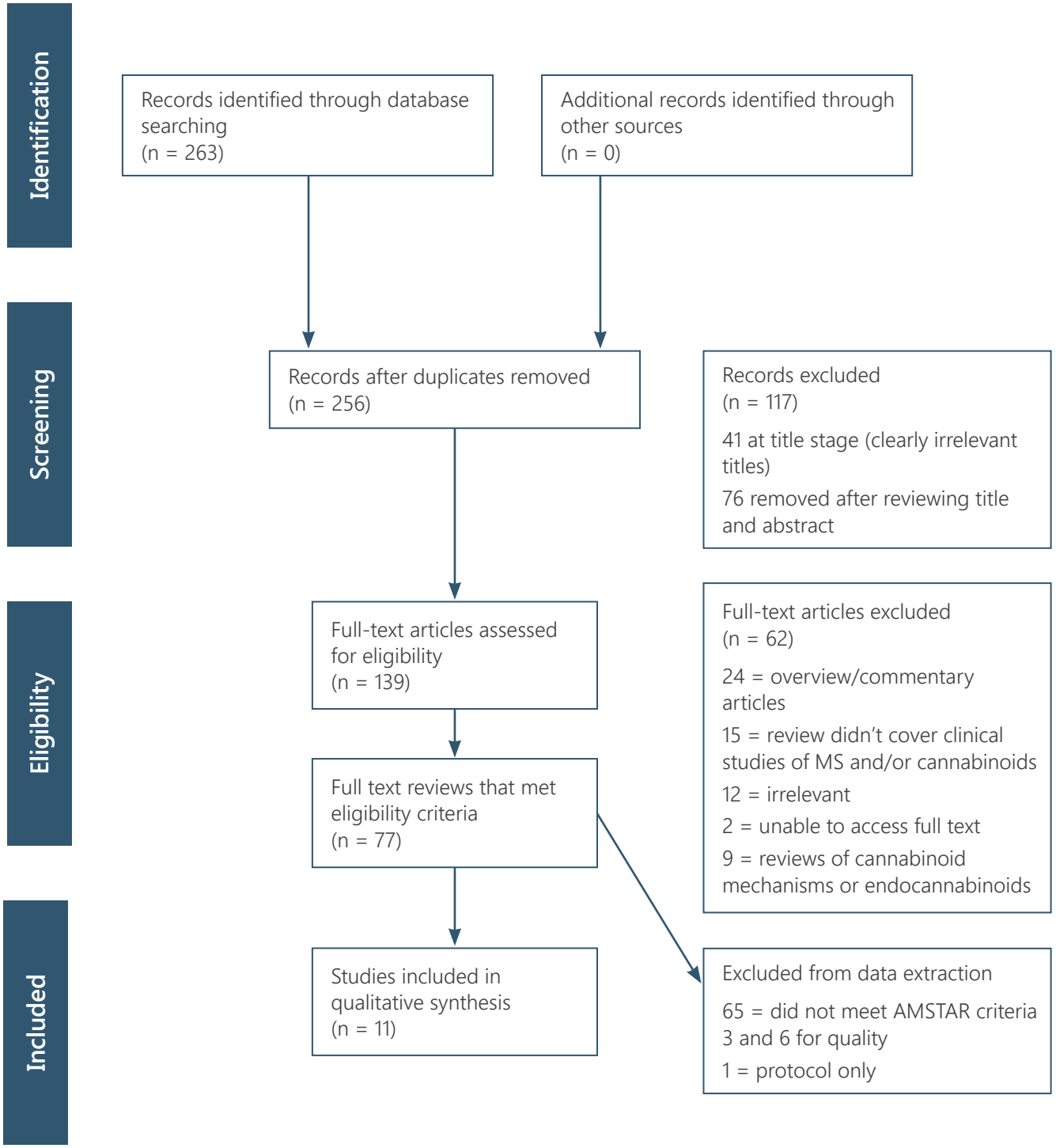

Table 1: Evidence for cannabis and cannabinoids for the treatment of symptoms of multiple sclerosis

	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 quality	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 study (1 RCT)
Findings		Positive effect	Positive effect	Positive effect		Mixed effect		AEs > comparator
Quality of evidence		Very low to low quality	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

	Disability and disease progression	Pain	Spasticity	Bladder function	Ataxia and tremor	Sleep	Quality of life	Adverse events
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 quality	Very low to low quality	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

Appendix A

NDARC Review

This review is a comprehensive 'review of reviews'[142] of high quality systematic reviews assessing the effectiveness of cannabinoids in treating the symptoms of multiple sclerosis. The objectives are to identify the cannabinoids used, including plant and pharmaceutical formulations, and assess their ability to improve patient experiences of disability, pain and spasticity, as well as improved quality of life. The review also considers tolerability and safety data, as reported by patient study withdrawals and reported adverse events. Each included review had to address at least one of the outcomes defined on the basis of clinical experience, namely:

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

Papers describing mechanisms of cannabinoid action, commentaries and clinical overviews that did not present the results of studies were not included in the review.

Review quality was assessed using the AMSTAR measurement tool of methodological quality of systematic reviews[143]. The AMSTAR tool documents assessed risk of bias at the review level. To identify reviews conducted methodologically, and to minimise bias at the review level in study selection, each identified review was required to meet criterion three and six of the AMSTAR tool at a minimum. This reflects reviews that were conducted with a comprehensive search, and those that, at a minimum, describe the characteristics of the included studies.

Each individual study included in the review was also graded according to the GRADE criteria[144]. RCTs were considered high quality evidence, but may be downgraded to moderate or low quality due to bias, sample size, or other issues around sample size. Observational studies were considered to be low to very low quality evidence, and case series or case studies were considered to be very low quality evidence.

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