Copyright

© Commonwealth of Australia 2017

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the Copyright Act 1968 or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.
# Table of contents

**Introduction** .......................................................................................................................... 1
  - Review method ......................................................................................................................... 1

**Caveats** .................................................................................................................................. 2

**Summary of the current evidence** ............................................................................................. 3
  - Key to grades—adapted from the Mayo Clinic ......................................................................... 3
  - Disability and disease progression ......................................................................................... 4
  - Pain ........................................................................................................................................ 4
  - Spasticity ................................................................................................................................. 5
  - Bladder function ....................................................................................................................... 6
  - Ataxia and tremor ...................................................................................................................... 6
  - Sleep ....................................................................................................................................... 7
  - Quality of life ............................................................................................................................ 7

**Adverse effects** ........................................................................................................................ 8

**Place in therapeutic hierarchy** .................................................................................................. 9

**Evidence on time to response** .................................................................................................. 9
  - Use of THC/CBD combinations or products ........................................................................... 10
  - Dosage forms, variations in route of administration and standardisation ......................... 10
    - Nabiximols ........................................................................................................................... 10
    - THC:CBD extracts ............................................................................................................... 10
    - Dronabinol .......................................................................................................................... 10
    - THC extracts ....................................................................................................................... 10
    - Nabilone .............................................................................................................................. 11
    - CBD extracts ...................................................................................................................... 11
    - Cannabis sativa ................................................................................................................... 11
  - Dose (including various cannabinoids in the product), dose ranges for which there is evidence, other pharmacological considerations for dosages ................. 11
    - Nabiximols ........................................................................................................................... 11
    - THC:CBD extracts ............................................................................................................... 11
    - Dronabinol .......................................................................................................................... 12
    - THC extract ....................................................................................................................... 12
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabilone</td>
<td>12</td>
</tr>
<tr>
<td>CBD extract</td>
<td>12</td>
</tr>
<tr>
<td>Cannabis sativa</td>
<td>12</td>
</tr>
<tr>
<td>Tolerance and persistence in treatment</td>
<td>13</td>
</tr>
<tr>
<td>Stopping rules</td>
<td>13</td>
</tr>
<tr>
<td>Identification</td>
<td>14</td>
</tr>
<tr>
<td>Screening</td>
<td>14</td>
</tr>
<tr>
<td>Eligibility</td>
<td>14</td>
</tr>
<tr>
<td>Included</td>
<td>14</td>
</tr>
<tr>
<td>NDARC Review</td>
<td>14</td>
</tr>
<tr>
<td>(see Appendix A)</td>
<td>14</td>
</tr>
<tr>
<td>Figure 1. PRISMA Chart</td>
<td>14</td>
</tr>
<tr>
<td>Appendix A</td>
<td>17</td>
</tr>
<tr>
<td>NDARC Review</td>
<td>17</td>
</tr>
<tr>
<td>References</td>
<td>18</td>
</tr>
</tbody>
</table>
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. 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

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.

<table>
<thead>
<tr>
<th>Evidence Grade</th>
<th>Cannabinoid used</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Cannabis sativa</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>Dronabinol</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>Nabiximols</td>
<td>Three reviews included two studies (two RCT) of moderate quality that reported nabiximols produced no change for patient disability or disease progression.</td>
</tr>
<tr>
<td>C</td>
<td>THC:CBD extracts</td>
<td>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.</td>
</tr>
</tbody>
</table>

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\(^15,16\).

<table>
<thead>
<tr>
<th>Evidence Grade</th>
<th>Cannabinoid used</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Cannabis sativa</td>
<td>One review included one study (one RCT) of low quality that reported cannabis sativa had a positive effect on pain.</td>
</tr>
<tr>
<td>B</td>
<td>Dronabinol</td>
<td>Six reviews included four studies (three RCT) of low to high quality that reported dronabinol had a positive effect in reducing pain.</td>
</tr>
<tr>
<td>B</td>
<td>THC extract</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>Nabiximols</td>
<td>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.</td>
</tr>
</tbody>
</table>
CH: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\(^ {7,18,19,20,21,22,23}\). 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\(^ {24,25,26}\).

<table>
<thead>
<tr>
<th>Evidence Grade</th>
<th>Cannabinoid used</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Cannabis sativa</td>
<td>Two reviews included two studies (two RCT) of low quality that reported cannabis sativa had reduced patient spasticity.</td>
</tr>
<tr>
<td>C</td>
<td>Dronabinol</td>
<td>Six reviews included five studies (five RCT) of low to high quality reported mixed findings on the effectiveness of dronabinol in reducing patient spasticity.</td>
</tr>
<tr>
<td>C</td>
<td>THC extract</td>
<td>Four reviews included two studies (one RCT) of very low to low quality that reported THC extracts reduced patient spasticity.</td>
</tr>
<tr>
<td>C</td>
<td>Nabiximols</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>THC:CBD extracts</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>Nabilone</td>
<td>One review included two studies (two RCT) of very low to low quality that reported nabilone had a positive effect on spasticity.</td>
</tr>
<tr>
<td>C</td>
<td>CBD</td>
<td>One review included one low quality RCT that reported CBD likely did not have an effect on patient spasticity.</td>
</tr>
</tbody>
</table>
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\(^ {31,32} \).

<table>
<thead>
<tr>
<th>Evidence Grade</th>
<th>Cannabinoid used</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Dronabinol</td>
<td>Two reviews included two studies (one RCT) of high quality that reported mixed results for dronabinol in improving bladder function.</td>
</tr>
<tr>
<td>C</td>
<td>THC extract</td>
<td>One review included one very low quality study (zero RCT) that reported THC had a positive effect in improving patient bladder function.</td>
</tr>
<tr>
<td>C</td>
<td>Nabiximols</td>
<td>Two reviews included two studies (two RCT) of moderate quality that reported nabiximols mixed effects on patient bladder functioning.</td>
</tr>
<tr>
<td>C</td>
<td>THC:CBD extracts</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>Nabilone</td>
<td>Two reviews included one low quality RCT that reported nabilone had no effect on patient bladder functioning.</td>
</tr>
</tbody>
</table>

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\(^ {37,38} \).

<table>
<thead>
<tr>
<th>Evidence Grade</th>
<th>Cannabinoid used</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Dronabinol</td>
<td>Three reviews included three studies (two RCT) of very low to high quality that reported dronabinol had mixed effects on patient ataxia and tremor.</td>
</tr>
<tr>
<td>D</td>
<td>Nabiximols</td>
<td>Three reviews included two studies (two RCT) of moderate quality reported that nabiximols had no effect on patient ataxia or tremor.</td>
</tr>
<tr>
<td>D</td>
<td>THC:CBD extracts</td>
<td>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.</td>
</tr>
</tbody>
</table>
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\textsuperscript{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\textsuperscript{43}.

<table>
<thead>
<tr>
<th>Evidence Grade</th>
<th>Cannabinoid used</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Dronabinol</td>
<td>Three reviews included two studies (one RCT) of moderate to high quality that reported mixed results, mostly indicating a positive effect on sleep.</td>
</tr>
<tr>
<td>C</td>
<td>THC extract</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>Nabiximols</td>
<td>One review included one moderate quality RCT that reported nabiximols had a positive effect on patient sleep quality.</td>
</tr>
<tr>
<td>C</td>
<td>THC:CBD extracts</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>CBD extract</td>
<td>One review included one low quality RCT that reported CBD had a positive effect on patient sleep quality.</td>
</tr>
</tbody>
</table>

Quality of life

Four reviews, with a total of 12 individual studies, reported on the effects of cannabinoids on patient quality of life\textsuperscript{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\textsuperscript{48}. Studies of other cannabinoids gave little or no evidence that they improved patient quality of life.

<table>
<thead>
<tr>
<th>Evidence Grade</th>
<th>Cannabinoid used</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Cannabis sativa</td>
<td>Two reviews included two low quality RCTs that reported some patients experienced improvement in overall quality of life, however clinical measures were not significant.</td>
</tr>
<tr>
<td>C</td>
<td>Dronabinol</td>
<td>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.</td>
</tr>
</tbody>
</table>
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.

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.

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 cannabinoids49. Koppel et al50 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 alone51. 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 al52. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{59,60,61} A number of studies had maintenance phases for patients after titrating to their effective cannabinoid dose.\textsuperscript{52,63,64,65,66} 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 nabiximols), 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

<table>
<thead>
<tr>
<th>Cannabinoid product</th>
<th>Preparation</th>
<th>Administration</th>
<th>Standardised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabiximols</td>
<td>Liquid</td>
<td>Oromucosal spray</td>
<td>Yes</td>
</tr>
<tr>
<td>THC:CBD extracts</td>
<td>Liquid</td>
<td>Sublingual spray</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Capsule</td>
<td>Oral</td>
<td>Yes</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Capsule</td>
<td>Oral</td>
<td>Yes</td>
</tr>
<tr>
<td>TH extract</td>
<td>Liquid</td>
<td>Spray</td>
<td>Yes</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Capsule</td>
<td>Oral</td>
<td>Yes</td>
</tr>
<tr>
<td>CBD</td>
<td>Liquid</td>
<td>Spray</td>
<td>Yes</td>
</tr>
<tr>
<td>Cannabis sativa</td>
<td>Cigarette</td>
<td>Smoked</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{117,118,119,120}. Effective sublingual sprays administered 2.5mg THC and 2.5mg CBD up to 48 times per day\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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

Identification
Records identified through database searching (n = 263)
Additional records identified through other sources (n = 0)

Screening
Records after duplicates removed (n = 256)
Records excluded (n = 117)
41 at title stage (clearly irrelevant titles)
76 removed after reviewing title and abstract

Eligibility
Full-text articles assessed for eligibility (n = 139)
Full text reviews that met eligibility criteria (n = 77)

Included
Studies included in qualitative synthesis (n = 11)

Excluded from data extraction
65 = did not meet AMSTAR criteria
3 and 6 for quality
1 = protocol only

Full-text articles excluded (n = 62)
24 = overview/commentary articles
15 = review didn’t cover clinical studies of MS and/or cannabinoids
12 = irrelevant
2 = unable to access full text
9 = reviews of cannabinoid mechanisms or endocannabinoids
### Table 1: Evidence for cannabis and cannabinoids for the treatment of symptoms of multiple sclerosis

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

NDARC Review

This review is a comprehensive ‘review of reviews’\textsuperscript{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\textsuperscript{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\textsuperscript{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.
References


7. Ibid.

8. Ben Amar, Systematic review

9. Karst et al, Role of cannabinoids

10. Shakespeare et al, Anti-spasticity agents

11. Whiting et al, Cannabinoids for Medical Use


15. Karst et al, Role of cannabinoids

16. Koppel et al, Systematic review

17. Ben Amar, Systematic review

18. Karst et al, Role of cannabinoids

19. Lakhan et al, Whole plant cannabis extracts in the treatment of spasticity

20. Shakespeare et al, Anti-spasticity agents

21. Whiting et al, Cannabinoids for Medical Use

22. Zhornitsky, S., Cannabidiol in humans

23. Koppel et al, Systematic review

24. Lakhan et al, Whole plant cannabis extracts in the treatment of spasticity

25. Whiting et al, Cannabinoids for Medical Use

26. Koppel et al, Systematic review

27. Ben Amar, Systematic review

28. Karst et al, Role of cannabinoids

29. Whiting et al, Cannabinoids for Medical Use

30. Koppel et al, Systematic review

31. Whiting et al, Cannabinoids for Medical Use

32. Koppel et al, Systematic review

33. Ben Amar, Systematic review

34. Koppel et al, Systematic review


37. Koppel et al, Systematic review

38. Mills et al, Treatment for ataxia in multiple sclerosis

39. Ben Amar, Systematic review

40. Karst et al, Role of cannabinoids

41. Whiting et al, Cannabinoids for Medical Use

42. Mills et al, Treatment for ataxia in multiple sclerosis

43. Zhornitsky, S., Cannabidiol in humans

44. Ben Amar, Systematic review

45. Karst et al, Role of cannabinoids

46. Whiting et al, Cannabinoids for Medical Use

47. Mills et al, Treatment for ataxia in multiple sclerosis

48. Whiting et al, Cannabinoids for Medical Use

49. Ben Amar, Systematic review

50. Koppel et al, Systematic review

51. Lakhan et al, Whole plant cannabis extracts in the treatment of spasticity


54. Ben Amar, Systematic review

55. Karst et al, Role of cannabinoids

56. Lakhan et al, Whole plant cannabis extracts in the treatment of spasticity

57. Whiting et al, Cannabinoids for Medical Use

58. Koppel et al, Systematic review
75 Rog et al, Oromucosal δ9-tetrahydrocannabinol/cannabinidiol
81 Killestein et al, Immunomodulatory effects
Guidance for the use of medicinal cannabis in the treatment of multiple sclerosis in Australia


Zajicek et al., *Cannabinoids for treatment of spasticity*

Zajicek et al., *Cannabinoids in multiple sclerosis (CAMS) study*

Zajicek et al., *Multiple sclerosis and extract of cannabis*

Killestein et al, *Immunomodulatory effects*


Zajicek et al., *Cannabinoids for treatment of spasticity*

Zajicek et al., *Cannabinoids in multiple sclerosis (CAMS) study*


Brady et al., *An open-label pilot study of cannabis-based extracts*

Notcutt et al, *Initial experiences with medicinal extracts of cannabis*

Wade et al, *A preliminary controlled study*


Turcotte et al., *Nabilone as an adjunctive to gabapentin*


Notcutt et al, *Initial experiences with medicinal extracts of cannabis*

Wade et al, *A preliminary controlled study*


Rog et al, *Oromucosal 89-113*

The Mayo Clinic. *Marijuana (cannabis sativa)—dosing*

Freeman, et al, *The effect of cannabis on urge incontinence*

Killestein, et al, *Immunomodulatory effects*

Vaney, et al, *Efficacy, safety and tolerability of an orally administered cannabis extract*

Zajicek, et al., *Multiple sclerosis and extract of cannabis*

Brady et al, *An open-label pilot study of cannabis-based extracts*
Notcutt et al., Initial experiences with medicinal extracts of cannabis
Wade et al., A preliminary controlled study
The Mayo Clinic. Marijuana (cannabis sativa)—dosing
Freeman et al., The effect of cannabis on urge incontinence in patients with multiple sclerosis
Killestein, et al, Immunomodulatory effects
Clifford, Tetrahydrocannabinol for tremor in multiple sclerosis
Svendsen et al., Does the cannabinoid dronabinol reduce central pain?
Ungerleider et al., Delta-9-THC in the treatment of spasticity
The Mayo Clinic. Marijuana (cannabis sativa)—dosing
Brady et al., An open-label pilot study of cannabis-based extracts
Turcotte et al., Nabilone as an adjunctive to gabapentin
Wissel et al., Low dose treatment with the synthetic cannabinoid Nabilone
Martyn et al, Nabilone in the treatment of multiple sclerosis
Notcutt et al., Initial experiences with medicinal extracts of cannabis
Wade et al, A preliminary controlled study
Corey-Bloom et al., Smoked cannabis for spasticity in multiple sclerosis
Corey-Bloom et al., Smoked cannabis for spasticity in multiple sclerosis
The Mayo Clinic. Marijuana (cannabis sativa)—dosing
Koppel et al, Systematic review