ACRE
Australian Centre for Cannabinoid Clinical and Research Excellence

PRESCRIBING GUIDANCE

PRESCRIBING CANNABIS MEDICINES FOR MANAGING SPASTICITY

About this document

This Prescribing Guidance has been developed to provide practical interim information to assist NSW medical practitioners in their decision-making around prescribing, managing and monitoring the use of cannabis medicines for the management of spasticity. The Prescribing Guidance:

- Provides a summary of standard, registered therapeutic options in the management of spasticity which should be used prior to considering the use of cannabis medicines.
- Details important considerations for prescribing cannabis medicines, including precautions and adverse events, drug interactions, dosing and monitoring outcomes.
- Presents information on delta-9-tetrahydrocannabinol (THC)-based cannabis medicines, as information on the use of other medicinal cannabinoids (other than THC) cannot be provided at this stage due to very limited evidence in the literature.
- Draws extensively on the Therapeutic Goods Administration (TGA) guidance documents and, as such, requires medical practitioners to review the TGA's guidance before making a decision to prescribe cannabis medicine products.
- This document refers to spasticity associated with conditions **other than multiple sclerosis**. For multiple sclerosis and spasticity, please refer to the Australian Government's *Guidance for the use of medicinal cannabis in the treatment of multiple sclerosis in Australia*[1].

Key Points

- Spasticity is defined as an abnormal, velocity-dependant increase in muscle tone caused by an interruption of the neural circuitry regulating muscle contraction. It is a symptom occurring in many neurological conditions including stroke, multiple sclerosis, hypoxic or traumatic brain injury, motor neurone disease and cerebral palsy[5]. Neuropathic pain may co-exist with spasticity, and if present should be managed appropriately. The treatment of neuropathic pain is different to the treatment of spasticity.
- The evidence for cannabinoids to treat spasticity in multiple sclerosis is weak, but reviews have suggested some modest benefit from THC:cannabidiol (CBD) combinations in some patients. The evidence base for cannabinoids in other causes of spasticity is even more limited.
- It is important that all standard, registered therapeutic options are exhausted or deemed inappropriate (due to adverse effects or contraindications) prior to the consideration of a cannabis medicine for the management of spasticity.
- Medical practitioners should review the guidance advice made available by the TGA before making a decision to prescribe cannabis medicine products for the management of spasticity.
- NSW-based medical practitioners can obtain further information and assistance with prescribing tailored to the patient-specific clinical context from the NSW Cannabis Medicines Advisory Service by email or by telephone (02) 4923 6200.

Current clinical trials

There are currently no Australian clinical trials recruiting for cannabis for spasticity.

Use of evidence-based therapies for spasticity

Spasticity does not always require intervention. It should only be treated pharmacologically when it is causing impairment of function or a risk of harm. Evidence-based management options include non-pharmacological therapies and centrally acting anti-spasticity medications, including baclofen and botulinum toxin type A.

Useful resources for clinicians managing spasticity:

- eTG complete[2] - Neurological and neuromuscular symptoms in palliative care.

Summary of best practice in the treatment of spasticity

Muscle spasticity can have a detrimental effect on a person's function, potentially impacting the ability to mobilise, dress, eat, meet personal hygiene needs and maintain bladder and bowel function.

Spasticity is a component of the upper motor neurone lesion, which is made up of positive symptoms (abnormal/exaggerated behaviours) and negative symptoms (performance deficits).

Clinicians should be aware that treating spasticity (a positive symptom) may unmask negative symptoms and have an overall detrimental effect on function. For example, increased muscle tone in the lower limbs may assist weight bearing when standing. Reversing this spasticity may unmask underlying weakness and impact ability to weight bear.

Spasticity should be assessed using a validated tool, for example the modified Ashworth scale[3].

Non-pharmacological management with physiotherapists and

occupational therapists should be initiated as first line therapy. If improvement is not sufficient and a decision is made to trial pharmacotherapy, oral medications should be considered first.

Evidence on efficacy and tolerability of oral pharmacotherapies in spasticity (including cannabinoids) is limited[4].

Oral medications

- Baclofen - Centrally acting GABA analog. The most commonly used therapy for muscle spasticity. Withdrawal seizures and hallucinations may occur with abrupt discontinuation[5].
- Dantrolene - Alters release of calcium from muscle. Rare association with liver toxicity requires liver function tests at the beginning of treatment and every 3-6 months thereafter[5].
- Benzodiazepines (e.g. diazepam) - Recommended for muscle spasticity from motor neuron disease, however little data to support efficacy[11].
- Gabapentin - GABA analog. Side effect profile includes confusion[5].
- Clonidine - Limited to resistant cases, lack of robust evidence for efficacy in spasticity[5].
- Tizanidine - Imidazole derivative, with agonist action on alpha-2 adrenergic receptors in central nervous system. Not currently available in Australia[4].

Injected therapies

Injected therapies can be useful to manage focal areas of spasticity from a cerebral cause.

- Botulinum toxin - After injection into muscle causes blockade of the neuromuscular junction with resultant weakness (reducing muscle tone). Duration of effect is approximately 3 months[5]. Serious adverse effects such as dysphagia, dyspnoea or muscle weakness may rarely occur due to the spread of botulinum toxin.
- Phenol - May cause chronic altered sensation and pain. Other local skin reactions reported. Infrequently used since emergence of botulinum toxin[4].

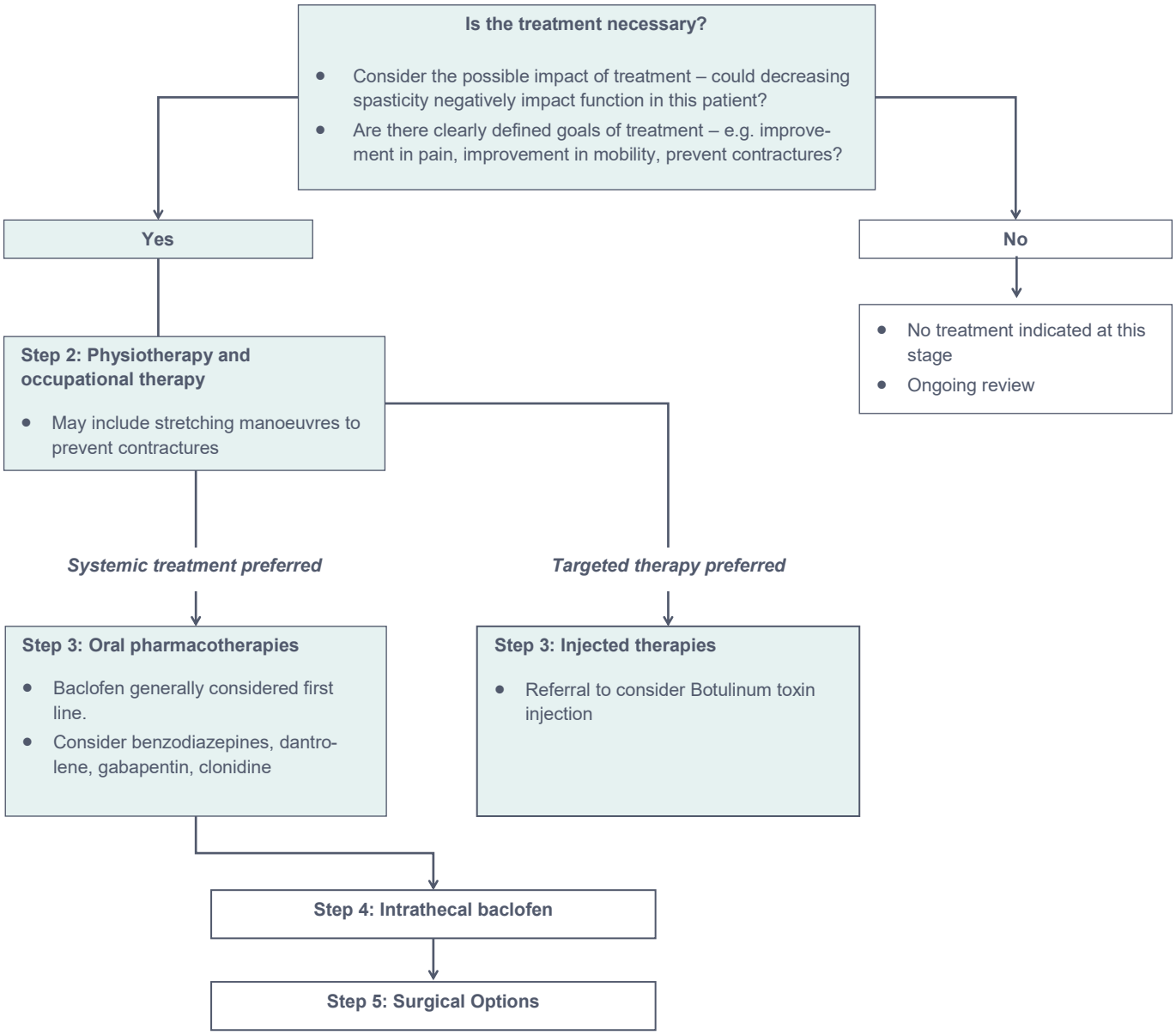
Intrathecal therapies

- Baclofen - balance potential improvements in function against potential harms including ongoing maintenance of pump, risk of infection etc[4]. There is some evidence for benefit in spasticity after spinal cord injury.

Surgery

- Reserved for refractory cases. Includes orthopaedic procedures to prevent contractures, and dorsal rhizotomy[4,5].

Best Practice Guidance for Spasticity



Prescribing cannabis medicines for the management of spasticity

If the decision to proceed to cannabis prescription is made, please consider the following information.

Working through the following information will assist medical practitioners in completing the regulatory paperwork required to prescribe cannabis medicines.

The Prescriber

The prescriber should have a key involvement in provision of care. As cannabinoids should be trialled when other non-pharmacological and evidenced based pharmacological therapies have failed, the prescriber should be a specialist, or a general practitioner in liaison with a specialist practitioner. It is important that all members of the treating team are aware of the decision to prescribe a cannabis medicine and that this information is communicated to other members of the care team in writing. The prescriber should have an ongoing therapeutic relationship with the patient.

Given the current status of cannabis medicines as unregistered medicines, prescribers should consider seeking advice from their medical indemnity insurers prior to prescribing.

The Patient

The patient must give informed consent to treatment. The consent process should include:

- This is an unregistered medicine (and costs may reflect this).
- The efficacy and side effects of this therapy are still being researched.
- However, they must be made aware of the likely effects and side effects of treatment.
- There will be restrictions on driving and operating heavy machinery.
- The patient should also be given clear information about therapeutic goals and likely stopping criteria.
- Potential for dependence or withdrawal.

Patients should be advised that they are not able to drive while treated with cannabis medicines.

Patients should be informed that measurable concentrations of THC can be detected in saliva for significant periods of time after administration. Further information is available from the Transport for NSW Centre for Road Safety and in NSW Health's Prescribed Cannabis Medicines and Fitness to Drive Factsheet.

Prescribing a cannabis medicine: Important considerations

The following has been adapted from the TGA's *Guidance for the use of medicinal cannabis in Australia: Patient information*[6]

Cannabis products

- A variety of products are available.
- There are up to 100 cannabinoids (chemical compounds) in the cannabis plant.
- Many of the studies described in the medical literature have used either smoked cannabis (which is not recommended on health grounds) or purified tetrahydrocannabinol (THC) or cannabidiol (CBD).
- THC is responsible for the psychoactive effects of cannabis and is the reason cannabis is used recreationally. THC may contribute to reduction of nausea, vomiting, pain and muscle spasms as well as improvements in sleep and appetite.
- CBD is psychoactive and causes sedation, but it appears non intoxicating. It may be useful in the management of seizures, pain, and may have anxiolytic and antipsychotic effects. Adding CBD to a THC product in a patient with toxicity to reduce toxicity is unproven. It is more appropriate is to reduce the dose and/or frequency of THC.
- Different cannabis products contain different ratios of THC to CBD.
- There are other cannabinoids under research including cannabigerol (CBG), tetrahydrocannabivarin (THCV), cannabinol (CBN) and cannabichromene (CBC).

Route of administration

Smoking

- Rapid onset of action, usually within minutes.
- High levels of blood THC with shorter duration of effect.
- Peak concentration in 30 minutes, effects last 2-4 hours.
- Significant individual variability due to unknown quantity of THC in product and loss of active agent in side stream/combustion during smoking.
- Smoking is well known to be harmful and not recommended on health grounds.

Vaporising/oro-mucosal/buccal routes

- Rapid absorption and high blood concentrations.
- Fewer contaminants and reduced "side stream" (when vaporised).
- Peak concentration in 15-30 minutes, effects last 2-4 hours.
- Useful for symptoms requiring rapid and intermittent relief.
- Titration of dosing may be easier with oro-mucosal sprays than oral formulations.
- Sprays may be easier for those with difficulty swallowing.

Oral administration

- Oils or liquid capsules are available.
- Slow onset of action with first effects at 30-90 minutes, peak effect at 2-4 hours.
- Effects can last 8-24 hours.
- Useful for symptoms requiring relief over longer periods of time (similar to controlled release medications).

Topical

- Cannabinoids are highly lipophilic compounds and this may facilitate permeation into the skin. However, the degree of water solubility (or polarity) of these compounds will also influence the rate and extent of transfer across the skin.
- THC is relatively less well absorbed than cannabidiol and cannabinol.
- Time of onset, duration of action and likelihood of depot occurrence are unknown and this route is therefore not recommended at this stage.

Evidence for Use

This document refers to spasticity associated with conditions **other than multiple sclerosis**. For multiple sclerosis and spasticity, please refer to the Australian Government's *Guidance for the use of medicinal cannabis in the treatment of multiple sclerosis in Australia*[1].

A 2017 Cochrane Review of symptomatic treatments in motor neuron disease reported that (based on one RCT) delta-9-tetrahydrocannabinol (THC) is probably ineffective at treating muscle cramps[7]. A 2018 randomised control trial of 60 patients with motor neurone disease found a small but significant improvement in Modified Ashworth Scale scores for patients treated with nabiximols (Sativex®) compared to placebo. Patients on nabiximols (Sativex®) experienced a higher incidence of adverse events, but none were severe or resulted in withdrawal from the study[8].

There have been some small published studies of THC:CBD and THC in spasticity from spinal cord injuries, which have shown some improvement in spasticity. There are no larger RCTs in this area[9,10].

Precautions

The following has been adapted from the TGA's *Guidance for the use of medicinal cannabis in Australia: Overview*[11].

Cannabis medicine products containing THC are generally **not appropriate** for patients who:

- Have a previous psychotic or concurrent active mood or anxiety disorder.
- Are pregnant, planning on becoming pregnant, or breastfeeding.
- Have unstable cardiovascular disease.

Any allergies to potential carrier oils (e.g. sesame, canola, sunflower) should be noted as products available in Australia often contain oils. This may influence product selection.

Consider concomitant medication use and potential for pharmacokinetic and pharmacodynamic drug interactions (see below).

Adverse effects

The following has been adapted from the TGA's *Guidance for the use of medicinal cannabis in the treatment of palliative care patients in Australia*[12].

Patients and prescribing clinicians should be aware of possible adverse events such as somnolence, nausea and dizziness. Adverse events such as confusion, pain, diarrhoea or hallucinations may impact the overall aims of the palliative medicine and reduce quality of life, and should be evaluated on a case-by-case basis.

Serious adverse events (SAEs) have been described clinically, such as psychosis and cognitive distortion requiring external assistance, but the severity, time course and further details are not recorded. SAEs are also likely where there are concomitant medications prescribed that are metabolised by, induced or inhibited by enzymes in the P450 system, or where there are similar pharmacodynamic effects.

Based on the available studies, commonly reported adverse events in the use of medicinal cannabis products in the palliative care setting include:

- nausea (21% of patients)
- somnolence (20% of patients)
- dizziness (16% of patients)
- asthenia (13% of patients)
- tiredness/fatigue (12% of patients)
- vomiting (11% of patients)
- anaemia (11% of patients)
- confusion (10% of patients)
- pain (10% of patients)
- diarrhoea (8% of patients)
- headache (8% of patients)
- dyspnoea (8% of patients)
- hallucinations (5% of patients)
- In a small (15 patient) study, 11 had anxiety symptoms.

The cessation of long-term (of more than several months) use of THC-based medicines may also be associated with the experience of discontinuation effects.

Drug Interactions

The current available information on drug interactions with cannabinoids is mainly sourced from the product information on Marinol®[13] (THC) and Sativex®[14] (THC and CBD combination). Drug interactions with cannabidiol have been summarised in the literature[15,16].

Ongoing reports of potential interactions to the TGA is vital to improve the data in this area.

Pharmacokinetic interactions

- THC and CBD are metabolised by the cytochrome P450 enzyme system. CBD has significant inhibitory effect on this system, in addition.
- In vitro studies have shown Sativex® has CYP450 enzyme inhibition effects.
- In patients on clobazam, increased active metabolite N-desmethylclobazam (nCLB) concentrations were noted[16] likely due to CYP2C19 and CYP3A4 inhibition by CBD[17]. Higher nCLB concentrations were associated with a higher frequency of reports of sedation[16] .
- If concomitant drug treatment with CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin, fluoxetine) is started or stopped, a new dose titration may be required. If concomitant drug treatment with strong enzyme inducers (e.g. rifampicin, carbamazepine, St John's wort) is started or stopped, a new dose titration may be required.
- Monitor for potentially increased delta-9-THC-related adverse reactions when co-administered with inhibitors of CYP2C9 (e.g. amiodarone, fluconazole) and inhibitors of CYP3A4 enzymes (e.g. ketoconazole, itraconazole, clarithromycin, ritonavir, erythromycin, grapefruit juice).
- delta-9-THC is highly bound to plasma proteins and might displace and increase the free fraction of other concomitantly administered protein-bound drugs. Although this displacement has not been confirmed *in vivo*, monitor patients for increased adverse reactions to narrow therapeutic index drugs that are highly protein-bound (e.g. warfarin, cyclosporine, amphotericin B) when initiating treatment or increasing the dosage of delta-9-THC.
- Based on in vitro data an inhibition of p-glycoprotein at the intestinal level by CBD cannot be excluded. Therefore, caution is recommended upon concomitant treatment with digoxin and other substrates for p-glycoprotein.

Pharmacodynamic interactions

Sedation

- Care should be taken with hypnotics, sedatives and drugs with potential sedating effects as there may be an additive effect on sedation and muscle relaxing effects. This may include opioids, benzodiazepines, anticholinergics and antihistamines.
- Cannabis medications may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly. In general, alcoholic beverages should be avoided.

Cardiac toxicity

- Additive hypertension, tachycardia, possibly cardiotoxicity with amphetamines, cocaine, atropine or other sympathomimetic agents.

Psychiatric effects

- Case reports of hypomania when cannabis is co-administered with fluoxetine and also disulfiram.

Musculoskeletal

- Care should be taken when co-administering Sativex® with antispasticity agents since a reduction in muscle tone and power may occur, leading to a greater risk of falls.

Dosing

In general:

- Start at low dose and frequency.
- Titrate to effect whilst monitoring for side effects.
- Patient response to these medications varies widely.
- Favour lower doses in the elderly who may be at higher risk of CNS and cardiac adverse effects.

The following is an example only – doses should be individualised for patient and indication. Dosing advice can only be provided on THC-based cannabis medicines. Information on the use of other medicinal cannabinoids (other than THC) cannot be provided at this stage due to limited evidence in the literature.

Example for THC:CBD – from Sativex® oromucosal spray Product Information[14]. Note that this Product Information was developed for the indication of spasticity in multiple sclerosis.

- Initially one spray per day, slow titration over two weeks.
- The mean number of sprays required for symptom relief was 4.81 per day (i.e. THC 12.5 mg/CBD 12.98 mg in divided doses daily).

Monitoring Outcomes

Monitoring should initially involve reviewing the patient weekly in person, and via phone if required in the interim between clinical reviews.

There are three areas of outcomes that should be considered:

1. ***Symptom control***

   A pre-defined measure of success should be negotiated with the patient prior to commencement of therapy. This can be measured by using a validated tool, for example by the Palliative Care Symptom Assessment Scale.

2. ***Drug adverse events***

   Careful monitoring of patients for adverse events and the need for a change in dosage is important. Adverse events may become apparent after commencement or after change in dose.

   Adverse events may be related to other concurrent medications. Doses of these medicines should be adjusted as appropriate.

   Significant adverse events observed with unregistered medicines must be reported to the TGA (including dependence and withdrawal symptoms). Although some of the adverse events are well known (e.g. psychosis, anxiety) it is still important to notify the TGA when these events occur to enable patterns of toxicity and contributing factors to be elucidated, to support future prescribing information.

3. ***Pathology monitoring***

   Drug concentrations of drugs where there is a potential or actual drug-drug interaction may be important.

   Cannabidiol may cause hepatocellular injury. Patient's liver function biochemistry should be monitored prior to initiation and periodically as clinically indicated.

Cessation and withdrawal

The cessation of long-term (of more than several months) use of THC based medicines may be associated with the experience of discontinuation effects. These can be categorised as relapse and/or withdrawal effects.

Relapse refers to a worsening of the underlying condition (e.g. spasticity) for which THC is being prescribed.

The cessation of heavy (e.g. daily or almost daily) and prolonged (of several months or more) cannabis use can be associated with a withdrawal syndrome in up to 15 to 40% of long term cannabis users[18,19]. The features of cannabis withdrawal as defined in DSM5 are shown in Table 1, with sleep problems (e.g. vivid dreams, insomnia), depressed mood and irritability/anxiety most commonly reported. Symptoms tend to emerge within 2-3 days of last THC use, peak within 4 to 14 days, with some residual symptoms persisting for 2-6 weeks[20].

For those looking to discontinue THC based medication, a gradual dose taper over 4 to 8 weeks is generally recommended to minimise the severity of cannabis withdrawal symptoms.

There is no effective pharmacotherapy for managing cannabis withdrawal at this time, and supportive care is recommended. Consider a referral to Alcohol and Drug Service or Addiction Medicine specialist for patients experiencing difficulties with withdrawal.

It should be noted that there is no recognised withdrawal syndrome associated with cessation of CBD.

Criterion A	Cessation of cannabis use that has been heavy and prolonged
Criterion B	3 or more of the following seven symptoms develop within several days of Criterion A: 1. Irritability, anger or aggression 2. Nervousness or anxiety 3. Sleep difficulty (insomnia) 4. Decreased appetite or weight loss 5. Restlessness 6. Depressed mood 7. Physical symptoms causing significant discomfort from at least one of the following: stomach pain, shakiness/tremors, sweating, fever, chills, headache
Criterion C	The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
Criterion D	The symptoms are not due to a general medical condition and are not better accounted for by another disorder

Table 1. DSM-5Diagnostic Criteria for Cannabis Withdrawal Syndrome[21]

Further Information

- NSW-based medical practitioners can obtain further information and assistance with prescribing tailored to the patient-specific clinical context from the NSW Cannabis Medicines Advisory Service by email or by telephone (02) 4923 6200.
- Information on the NSW Prescribing Pathways for unregistered cannabis medicines is available from the NSW Government's Centre for Medicinal Cannabis Research and Innovation.
- Information on NSW-based regulatory requirements around applying for and supplying Schedule 8 cannabis medicines, including requirements of the prescriber, dispensing and storage is available from the NSW Government's Pharmaceutical Services page on Cannabis Medicines.

References

1. Department of Health Therapeutic Goods Administration. Guidance for the use of medicinal cannabis in the treatment of multiple sclerosis in Australia. 2017. https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-treatment-multiple-sclerosis-australia (accessed 28 Feb 2018)
2. eTG complete. https://tgldcdp.tg.org.au/viewTopic?topicfile=palliative-care-neurological-neuromuscular-symptoms&guidelineName=Palliative%20Care&topicNavigation=navigateTopic (accessed 20 May 2019))
3. Modified Ashworth Scale. https://www.med-iq.com/files/noncme/material/pdfs/DOC%201--Modified%20Ashworth%20Scale.pdf (accessed 8 March 2018)
4. MS Australia. Spasticity and multiple sclerosis. 2009. www.msaustralia.org.au (accessed 28 Feb 2018)
5. Satkunam LE. Rehabilitation medicine: 3. Management of adult spasticity. CMAJ, Nov 2003; 169: 1173-1179.
6. Department of Health Therapeutic Goods Administration. Guidance for the use of medicinal cannabis in Australia: Patient information. https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-australia-patient-information. (accessed 28 Feb 2018)
7. Ng L, Khan F, Young CA, Galea M. Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD011776. DOI:

10.1002/14651858.CD011776.pub2.

8. Riva N, Mora G, Sorarù G et al. Safety and efficacy of nabiximols on spasticity symptoms in patients with motor neuron disease (CANALS): a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Neurology, 2018. http://dx.doi.org/10.1016/S1474-4422(18)30406-X

9. Pooyania S et al. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. Archives of Physical Medicine & Rehabilitation. 2010. 91(5):703-7.

10. Wade DT et al. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clinical Rehabilitation. 2003. 17(1):21-9.

11. Department of Health Therapeutic Goods Administration. Guidance for the use of medicinal cannabis in Australia: Overview. 2017. https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-australia-overview (accessed 28 Feb 2018)

12. Department of Health Therapeutic Goods Administration. Guidance for the use of medicinal cannabis in the treatment of palliative care patients in Australia. 2017. https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-treatment-palliative-care-patients-australia (accessed 28 Feb 2018)

13. Marinol Product Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf (accessed 28 Feb 2018)

14. Sativex Product Information. https://www.tga.gov.au/sites/default/files/auspar-nabiximols-130927-pi.pdf (accessed 28 Feb 2018)

15. Sarah Melton. Stirring the Pot: Potential Drug Interactions With Marijuana - Medscape - Jun 08, 2017 https://www.medscape.com/viewarticle/881059. (accessed 28 Feb 2018)

16. Gaston, T. E., Bebin, E. M., Cutter, G. R., Liu, Y., Szaflarski, J. P. and the UAB CBD Program. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia. 2017. 58: 1586–1592. doi:10.1111/epi.13852.

17. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015. 56(8):1246-51.

18. Gorelick DA, Levin KH, Copersino ML, et al. Diagnostic criteria for cannabis withdrawal syndrome. Drug Alcohol Depend. 2011. 123(1-3):141–147. doi:10.1016/j.drugalcdep.2011.11.007

19. Lintzeris N, Driels J, Elias N, Arnold J, McGregor I, Allsop DJ. Findings from the Cannabis as Medicine Survey (CAMS-16): an online survey of medical cannabis use in Australia. MJA. 2018. 209(5):211-216. PMID: 30092752

20. Hesse M., and Thylstrup,B. Time-course of the DSM-5 cannabis withdrawal symptoms in poly-substance abusers. BMC Psychiatry. 2013. 13:258

21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). 2013. Arlington, VA