

PRESCRIBING GUIDANCE PRESCRIBING CANNABIS MEDICINES FOR CHRONIC NON-CANCER PAIN

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 chronic non-cancer pain (CNCP). The Prescribing Guidance:

- Provides a summary of standard, registered therapeutic options in the management of CNCP 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.

Key Points

- The Australian Government's [Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia](#)¹ explains that for one patient with CNCP to get a clinically relevant improvement in pain (30% reduction in pain), 24 people need to be treated with a cannabinoid. However in terms of harm, only 6 patients need to be treated with a cannabinoid for one patient to have clinically relevant harm. Further, the review states that the clinical relevance of the evidence is limited by the small number of studies and their small samples. It also states that currently there is insufficient information to make a recommendation about the role of medicinal cannabis in the treatment of pain associated with arthritis and fibromyalgia.
- 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 CNCP.
- Medical practitioners should review the guidance advice made available by the [TGA](#) before making a decision to prescribe medicinal cannabis products for CNCP.
- 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

No clinical trials are currently recruiting in NSW for CNCP.

Use of evidence-based therapies for chronic non-cancer pain

Evidence-based management options in accordance with clinical practice guidelines, where available, must be offered to patients with CNCP prior to considering the therapeutic use of cannabis medicines. Medical professionals should note:

- A comprehensive sociopsychobiomedical assessment of the patient with CNCP is appropriate.
- The use of medications, including medicinal cannabis, is not the core component of therapy for CNCP.
- Patient education is a critical component of therapy for CNCP, particularly with respect to expectations of drug therapy.
- There is a need for larger trials of sufficient quality, size and duration across the wide variety of clinical presentations to examine the safety and efficacy of medicinal cannabis use in aspects of CNCP.

Useful resources for clinicians managing CNCP:

- [eTG complete](#)² 'Chronic pain: Overview', (available through www.ciap.health.nsw.gov.au for NSW Health employees).
- Royal Australian College of Physicians (RACP) 'Prescription Opioid Policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use'³.
- NSW Government's Agency for Clinical Innovation Pain [Management Resources](#).

Summary of best practice in the treatment of chronic non-cancer pain

Chronic pain is a complex condition with variable presentations. It may be associated with ongoing active pathology (e.g. rheumatoid arthritis). Usually however, the originating event is no longer active but pain persists because of lasting changes within the neurological system. Managing chronic pain requires a multimodal approach which in Australasia emphasises non-pharmacological approaches without

relying on pharmacological therapy alone. Patient engagement and education is vital.

Non-pharmacological approaches include:

- Physical techniques (passive or active).
- Mind–body techniques (e.g. biofeedback, Feldenkrais, mirror therapy, acupuncture).
- Mind-based techniques (e.g. cognitive behavioural therapy, hypnosis, relaxation/meditation, mindfulness, operant conditioning, acceptance and commitment therapies, psychoanalytic and psychodynamic therapies).
- Use of aids/orthotics and occupational therapy (e.g. home and workplace/work practice modification).
- Social/environmental interventions (e.g. community support groups, work retraining).
- Combinations of any or all of these approaches².

Functional improvement as well as a reduced pain score is the aim of management of CNCP. Pharmacological interventions including cannabis may make engagement and functional improvement more difficult and complicated.

Selection of analgesic medication will take into account the patient’s medical history, nature of pain (e.g. site, severity, type), factors that may affect patient compliance and tolerance. Maximal doses of an analgesic should be used before moving on to the next line of medications. The patient’s response should be assessed after 2 to 3 weeks of use.

Existing evidence does not support the long term efficacy and safety of pharmacological therapy, including opioid therapy, for CNCP. Patients are advised to try to reduce recreational drugs of addiction as part of engagement into a pain management plan. Information on a chronic management plan can be found at on NSW Health’s [Chronic Pain Management](#) page.

A chronic non-cancer pain management plan that has been agreed to by the patient, GP and pain management team should be in place before commencing pharmacological or non-pharmacological intervention.

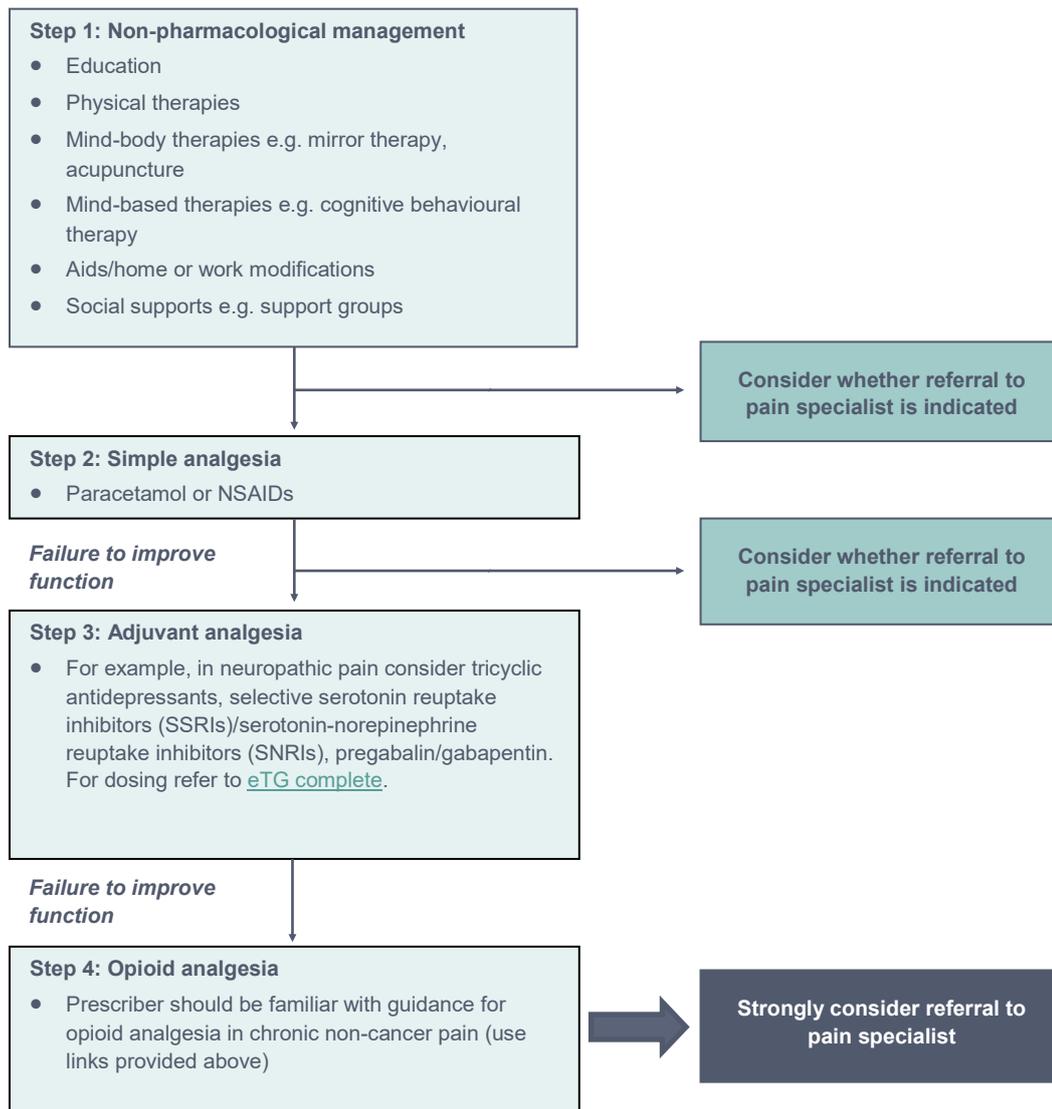
An excellent resource, *Reconsidering drug therapy for neuropathic pain, CRPS and fibromyalgia*⁴, has been produced by Hunter New England Local Health District. Relevant points from this document include:

- In neuropathic pain, the first line agents (in 3 month trials) are tricyclic antidepressants, serotonin and noradrenalin reuptake inhibitors and anticonvulsants (pregabalin and gabapentin) used either alone or in combination.
- In fibromyalgia, there is modest evidence of treatment effect from duloxetine 60 mg daily and pregabalin 600 mg daily in a trial of up to 12 weeks’ duration.

It is expected that these medications are ceased after 12 weeks if no benefit is seen.

NSW Health has a listing of [Pain Management Services in NSW](#) available on their website.

Best practice guidance for chronic non-cancer pain



Prescribing medicinal cannabis for the management of chronic non-cancer pain in patients

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 medicinal cannabis.

The Prescriber

The prescriber should have a key involvement in provision of care. The prescriber may be a pain 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 – it is important 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 advice that:

- This is an unregistered, non-reimbursed medicine.
- 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 medicinal cannabis.

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](#)⁵.

Cannabis products

- A variety of cannabis 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 has effects on neurological function including seizure activity, sedation, and dizziness, however psychosis has not been reported. 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 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), tetrahydrocannabinol (THCV), cannabiol (CBN) and cannabichromene (CBC)

Route of administration

Smoking

- Rapid onset of action, usually within minutes.
- High concentrations 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 cannabiol.
- 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

The following has been adapted from the TGA's [Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia](#)¹ (see Table. 1 over page)

Most evidence on medicinal cannabis use in CNCP is derived from studies where cannabinoids were adjuvant interventions. Cannabinoids should not replace current approved first-line treatments for pain including non-pharmacological therapies.

To determine the role of medicinal cannabis in treating CNCP, trials would need to compare cannabinoids to first and second-line treatment, and no therapy.

Cannabinoid used (studies)	Outcome	Effect	Evidence Grade
Nabiximols (13)	30% reduction in pain	No significant evidence of effect	High
	50% reduction in pain	No significant evidence of effect	High
	Change in pain scores	Favours nabiximols	Moderate
Dronabinol (5)	30% reduction in pain	No significant evidence of effect	Moderate
	50% reduction in pain	No significant evidence of effect	Low
	Change in pain scores	No significant evidence of effect	Moderate
Nabilone (4)	30% reduction in pain	Favours nabilone	Very low
	50% reduction in pain	No significant evidence of effect	Very low
	Change in pain scores	No significant evidence of effect	Very low
Cannabis sativa (6)	30% reduction in pain	Favours cannabis sativa	Very low
	50% reduction in pain	No studies	--
	Change in pain scores	No significant evidence of effect	Very low
THC extract (4)	30% reduction in pain	No studies	--
	50% reduction in pain	No studies	--
	Change in pain scores	Favours THC extract	Moderate
THC:CBD extract (1)	30% reduction in pain	Favours THC:CBD extract	Moderate
	50% reduction in pain	No studies	--
	Change in pain scores	No significant evidence of effect	Low
CBD extract (0)	30% reduction in pain	No studies	--
	50% reduction in pain	No studies	--
	Change in pain scores	No studies	--
Ajulemic acid (1)	30% reduction in pain	Favours Ajulemic acid	Low
	50% reduction in pain	No significant evidence of effect	Very low
	Change in pain scores	No significant evidence of effect	Very low
Any cannabinoid (34)	30% reduction in pain	Favours cannabinoids	Moderate
	50% reduction in pain	Favours cannabinoids	Moderate
	Change in pain scores	Favours cannabinoids	Moderate

Table 1. Summary of randomised trials of efficacy of cannabinoids in CNCP from [Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia](#)¹

Precautions

The following has been adapted from the TGA's [Guidance for the use of medicinal cannabis in Australia: Overview](#)⁶.

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](#)⁷.

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.

Based on the available studies, the most 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

Clinicians considering cannabis medicine therapy for CNCP patients should consider the individual's risks in using these products for long periods of time.

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® (THC) and Sativex® (THC and CBD combination). Drug interactions with cannabidiol have been summarised in the literature^{10,11}.

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

Pharmacokinetic interactions

- delta-9-tetrahydrocannabinol (THC) and cannabidiol (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-desmethyloclobazam (nCLB) concentrations were noted¹¹ likely due to CYP2C19 and CYP3A4 inhibition by CBD¹². Higher nCLB concentrations were associated with a higher frequency of reports of sedation¹¹.
- 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. 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 are examples 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 – adapted from Dronabinol (Marinol®) Product Information⁸ (for treatment of anorexia):

- Starting dose 2.5 mg once daily or BD.
- Monitor for side effects.
- If tolerated, and further therapeutic effect desired, slowly increase dose.
- Higher doses are variably tolerated:
 - 10 mg twice daily has been tolerated in about half of the patients in appetite stimulation studies. It is likely that there will be less tolerance in older patients or those with significant physiological compromise.
 - In light of current evidence, generally there should be a maximum dose of 30 mg of tetrahydrocannabinol per day. Beyond this dose, the risk of adverse effects may increase.

Example for THC:CBD – from Sativex® oromucosal spray Product Information⁹. Note that this PI 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. CNCP) 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^{13,14}. The features of cannabis withdrawal as defined in DSM5 are shown in Table 2, 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 weeks¹⁵.

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 2. DSM-5 Diagnostic Criteria for Cannabis Withdrawal Syndrome¹⁶

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.

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