

PRESCRIBING GUIDANCE

PRESCRIBING CANNABIS MEDICINES FOR NAUSEA IN PALLIATIVE CARE PATIENTS

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 nausea in palliative care patients. The Prescribing Guidance:

- Provides a summary of standard, registered therapeutic options in the management of nausea in palliative care patients 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.
- Chemotherapy-induced nausea and vomiting (CINV) is considered separately. Please refer to ACRE's separate 'Prescribing Cannabis Medicines for chemotherapy-induced nausea and vomiting' Prescribing Guidance.

Key Points

- The TGA's [Guidance for the use of medicinal cannabis in the treatment of palliative care patients in Australia](#)¹ has identified little evidence for symptom benefit from cannabinoid medicines in the management of nausea in palliative care patients.
- In an Australian meta-analysis, there were no significant differences in outcomes between palliative care patients who received medicinal cannabis or placebo.
- 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 nausea in palliative care patients.
- Medical practitioners should review the guidance advice made available by the [TGA](#) before making a decision to prescribe medicinal cannabis products for the management of nausea in

palliative care patients.

- 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 nausea in palliative care patients.

Use of evidence-based therapies for nausea in advanced cancer

[Caresearch – Palliative Care Knowledge Network](#)² has [resources](#) available to assist doctors provide evidence-based care for patients with nausea related to advanced cancer.

The [eTG complete](#)³ is another useful resource (available through [www.ciap.health.nsw.gov.au](#) for NSW Health employees)

Summary of best practice in management of nausea in palliative care patients with advanced cancer

The following information is based on information from both the [Caresearch](#)² website and [eTG complete](#)³. More detailed information and prescribing guidelines regarding dose, frequency and sequential drug choices should be sought from these sources.

Nausea in the palliative care population is often multifactorial, can be acute or chronic, and can occur with or without vomiting. Nausea and vomiting can cause severe discomfort and interfere with oral drug administration. Nausea may arise from the gastrointestinal tract, be centrally mediated, be drug related, and can be associated with anxiety or a learned response to chemotherapy (i.e. anticipatory nausea).

Where possible the underlying causes of the nausea should be considered and reversible causes treated, always considering the context of the patient's care goals and the ceilings of care desired by the patient.

It is important to treat nausea symptoms while waiting for resolution of any reversible underlying cause.

Management

Check for reversible causes and treat appropriately:

- Metabolic – renal/hepatic failure, hypercalcaemia
- Sepsis – especially respiratory and urosepsis
- Gastrointestinal dysmotility
 - Consider constipation and manage
 - Consider bowel obstruction (may be functional or inoperable, refer to [eTG complete](#) for guidance)
 - Consider gastroparesis and the use of a prokinetic agent
- Gastrointestinal reflux disease or gastritis – consider an H2 receptor antagonist or a proton pump inhibitor (PPI)
- Medication and treatment side effects – including opioids, chemotherapy, radiotherapy
- Anxiety/depression – consider both pharmacological and non-pharmacological management
- Anticipatory nausea – associated with chemotherapy
- Food odour/consistency issues
 - Consider offering smaller meals more frequently
 - Reduce food odours
 - Trial liquid or puree food

The main classes of anti-emetics are:

- Dopamine antagonists (e.g. metoclopramide, haloperidol, domperidone, levomepromazine, other atypical antipsychotic medicines)
- Antihistamines (e.g. cyclizine, promethazine)
- 5HT3 antagonists (e.g. ondansetron)
- Other agents (e.g. steroids, benzodiazepines, anticholinergics)

Select anti-emetics with a spectrum of action based on the underlying cause of the nausea:

Gastrointestinal causes

These may include abdominal disease, drug side effects, radiotherapy, chemotherapy, gastroparesis, gastro-oesophageal reflux disease or gastritis, and constipation. Consider treating with:

- Metoclopramide
- Domperidone
- Histamine H2 receptor antagonist
- Proton pump inhibitor
- Ondansetron (for chemotherapy/radiotherapy side effects)

Central nervous system or vestibular causes

Central nausea can be caused by drugs (e.g. chemotherapy, opioids, anti-infective agents, digoxin), or metabolic dysfunction (e.g. hypercalcaemia or uraemia) which affects the chemoreceptor trigger zone. Vestibular dysfunction may also be caused by labyrinthitis or metastatic disease and invasion of the base of skull. Consider treating with:

- Haloperidol
- Metoclopramide
- Prochlorperazine
- Promethazine
- Cyclizine

Intracranial causes

Raised intracranial pressure and brain metastases can both cause nausea. Consider treating with:

- Dexamethasone
- Haloperidol

If commencing dexamethasone, consider gastroprotection with ranitidine or a PPI.

Chemotherapy or radiotherapy-induced nausea

Chemotherapy-induced nausea and vomiting (CINV) is considered separately. Please refer to ACRE's separate 'Prescribing Cannabis Medicines for chemotherapy-induced nausea and vomiting' Prescribing Guidance.

Anxiety or anticipatory nausea

This is usually associated with patients who have previously experienced severe chemotherapy induced nausea and vomiting. Treatment with lorazepam may be useful. Non-pharmacological treatment of anxiety and anticipatory nausea should also be considered.

Refractory nausea and vomiting

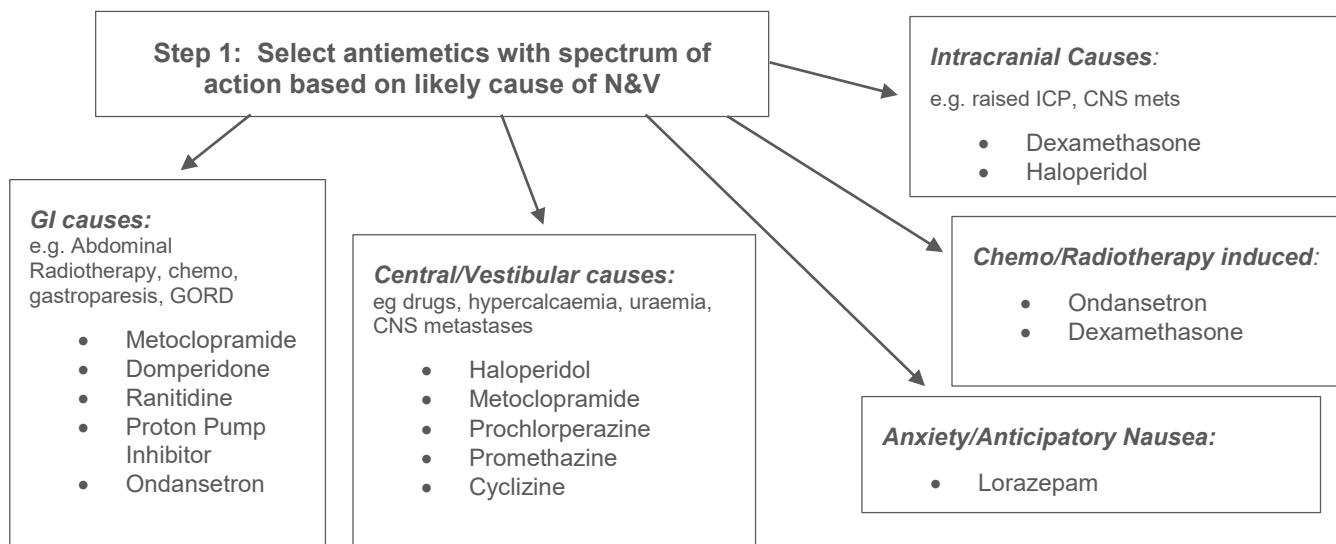
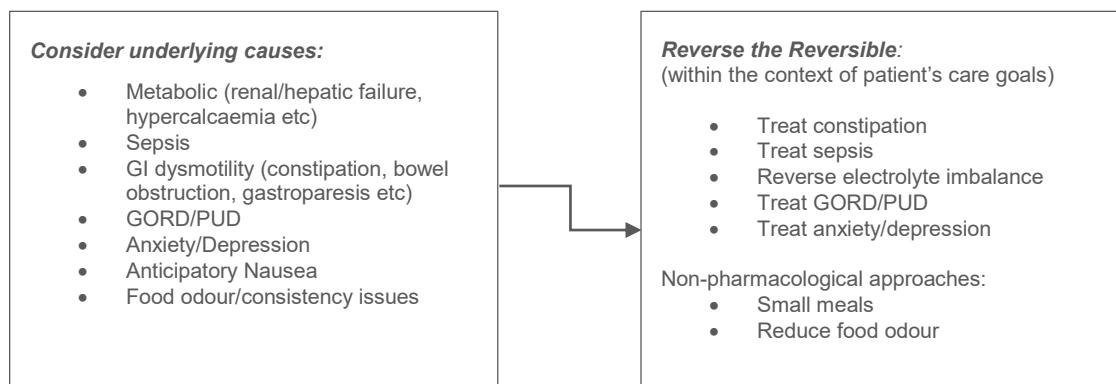
In view of the multifactorial nature of nausea and vomiting in the palliative patient, and the likelihood of progression of underlying disease then some cases require multiple antiemetics. When combining drugs attempt to target different elements of the emetogenic process and be mindful of drug interactions.

Levomepromazine is a phenothiazine neuroleptic drug with antipsychotic, analgesic, hypnotic and anti-emetic properties. Levomepromazine exerts its effects by blocking a variety of receptors including adrenergic, dopamine, histamine, muscarinic and serotonin receptors. Currently use in Australia requires an application to the Special Access Scheme. Advice should be sought from a Palliative Care Specialist Physician prior to use.

Olanzapine is an atypical antipsychotic which has been shown to have affinity for multiple neurotransmitter receptors, including those in the chemoreceptor trigger zone. Olanzapine has been shown to be effective in the context of chemotherapy induced nausea and vomiting and may be considered for second or third line use. Advice should be sought from a Palliative Care Specialist Physician prior to use.

SEE NEXT PAGE FOR 'BEST PRACTICE GUIDANCE FOR MANAGEMENT OF NAUSEA IN PALLIATIVE CARE PATIENTS WITH ADVANCED CANCER FLOW DIAGRAM'

Prescribing medicinal cannabis for the management of nausea in palliative care patients with advanced cancer



Step 2: Refractory Nausea

- Consider combination of antiemetics listed above
- Consider other agents: (seek specialist Palliative Care Advice)
- Levomepromazine (requires SAS approval)
- Olanzapine (see RCT in references)

Step 3:

All evidence based established treatment approaches as documented above should be trialled *prior* to consideration of cannabis medicines products.

Prescribing medicinal cannabis for the management of nausea in palliative care patients with advanced cancer

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 palliative care physician, an oncologist or a general practitioner in liaison with a specialist practitioner. Where the GP has a particular qualification in palliative care (e.g. Clinical Diploma in Palliative Care) it may be useful to provide this information. 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. Follow up and assessment of efficacy is essential.

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](#)⁴.

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 (in

conjunction with CBD), 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 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 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 cannabidiol.
- 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 palliative care patients in Australia](#)¹.

Five studies examined the use of medicinal cannabis for symptom control in patients with advanced cancer. Three studies were of moderate quality, and two of low quality. In a meta-analysis, there were no significant differences in outcomes between patients who received medicinal cannabis or placebo (see Table 1).

Thus, considering the evidence, a **THC-only product could be considered as the first cannabinoid to be added to a patient's treatment as this is where the best evidence of effect lies** (although this is small), noting that there is also evidence of potential

harm (due to side-effects) and lack of efficacy. Where a doctor chooses to use an alternative product to THC-only products, good clinical reasoning must be given, giving weight to the evidence above and understanding of cannabinoid pharmacology.

The TGA's Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia notes

a single study using nabiximol (Sativex®) showing a positive effect, however the study was at high risk of bias.

The Australian product information for nabiximols (Sativex®) notes some patients experience nausea and vomiting when administered this product.

Nausea is noted as a common side effect from dronabinol.

Evidence Grade	Cannabinoid used	Outcomes
C - Unclear scientific evidence for this use	Dronabinol, THC:CBD, THC	There was a non-significant effect of medicinal cannabis to reduce cancer pain.
D - Fair scientific evidence against this use (it may not work)	Dronabinol, THC:CBD, THC	There were no significant differences between medicinal cannabis and placebo in effects on patients' weight, caloric intake, appetite, nausea and vomiting, sleep, depressed mood, or quality of life. There were also no significant differences between medicinal cannabis and placebo in development of cognitive impairment or dizziness during treatment.
C - Unclear scientific evidence for this use	Cannabis sativa	All cancer and anti-cancer treatment symptoms (e.g. nausea, vomiting, mood disorders, fatigue, weight loss) were improved after initiating cannabis therapy. The lack of controlled studies restricts the conclusiveness of this finding and the clinical relevance is also unknown.
C - Unclear scientific evidence for this use	Dronabinol	Patients receiving dronabinol reported an increase in appetite and a decrease in nausea, however the treatment effects decreased as the disease progressed. The lack of controlled studies restricts the conclusiveness of this finding.
C - Unclear scientific evidence for this use	Nabilone	Patients receiving nabilone reported decreases in pain scores, morphine use, nausea, anxiety, overall distress, and borderline significant improvement in appetite. The lack of controlled studies restricts the conclusiveness of this finding.

Table 1. Extract from Symptom Control in Cancer, in [Guidance for the use of medicinal cannabis in the treatment of palliative care patients in Australia](#)¹. For additional information visit the TGA's Summary of Evidence [here](#).

Precautions

The following has been adapted from the TGA's [Guidance for the use of medicinal cannabis in Australia: Overview](#)⁵.

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 Events

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](#)¹.

Patients and prescribing clinicians should be aware of possible adverse events such as somnolence, nausea and dizziness. Adverse events such as confusion, pain, diarrhea 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.

Based on the available studies, the most commonly reported adverse events in the use of cannabis medicine 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®⁶ (THC) and Sativex®⁷ (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

- 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 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 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 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

information⁶ (for treatment of anorexia):

- Starting dose 2.5mg 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 physiologic 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 Information⁷. 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. nausea in palliative care) 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 (see over page), 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: <ol style="list-style-type: none"> 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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