ACRE
Australian Centre for Cannabinoid Clinical and Research Excellence

PRESCRIBING GUIDANCE

PRESCRIBING CANNABIS MEDICINES FOR THE MANAGEMENT OF DEMENTIA

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 dementia. The Prescribing Guidance:

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

- Dementia is a chronic condition characterised by progressive decline in cognitive function and functional ability with the greatest burden of care related to behavioural disturbance with agitation and aggression. There is pre-clinical research occurring in the area of treatment of dementia and management of behavioural disturbance with cannabinoids and some families may enquire about the role of cannabis medicines for their loved one.
- There is currently a very limited evidence base for cannabis medicines in the treatment, or behavioural management of patients with dementia or Alzheimer's disease.
- The TGA's *Guidance for the use of medicinal cannabis in the treatment of palliative care patients in Australia*[1] notes that 'unclear scientific evidence' was found in a study in the use of medicinal cannabis in Alzheimer's disease patients. In this study, no significant difference was noted between the use of medicinal cannabis (dronabinol 2.5 mg twice a day) in comparison to a placebo in decreasing pain, increasing caloric intake or decreasing mood disorders.
- Furthermore, the TGA's *Guidance for the use of medicinal cannabis in Australia: Patient Information*[2] advises that medicinal cannabis is not appropriate for people with active or previous psychotic or active mood or anxiety disorders.
- The Australian clinical guidelines for the management of dementia do not address the use of cannabinoids in dementia. Emphasis is on behavioural management, with some medications.
- 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 dementia.
- 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 dementia.
- 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 NSW-based clinical trials for the management of dementia symptoms with cannabis medicines. The following is an Australian trial based in Western Australia:

- **Medicinal cannabis and dementia: Effects on behavioural symptoms among older residential care recipients.**

  Led by The University of Notre Dame, Australia, this research project will investigate the effects of medicinal cannabis oil among those living within a residential aged care facility and have received a medical diagnosis of dementia. Using a cross-over N-of-1, randomised double blind trial, participants will receive either an oil-based placebo or medical cannabis oil in the form of purified THC/CBD. See the Australian New Zealand Clinical Trials Registry for further information on the study.

Use of evidence-based therapies in dementia

Evidence based therapies are summarised in the eTG complete[3] section 'Dementia'.

General information

Dronabinol, a synthetic THC, has been the most studied cannabinoid in dementia. It is currently not readily available in Australia and prescribers should consider this when prescribing a similar medicinal

cannabis agent and extrapolating from dosages recommended in studies. A small (N=6) open-label pilot study[5] showed reduction in night-time motor activity and agitation with daily dronabinol 2.5 mg. One retrospective chart review (N=40) demonstrated a reduction in agitation and aggression scores but was at high risk of bias[6]. A small double blind placebo crossover trial (N=15) using 6 weeks of dronabinol 2.5 mg BD described decreased disturbed behaviour, but was reported in such a way that data could not abstracted for systematic review[7]. Another randomised, double-blind, placebo controlled study (N=50) using THC 1.5 mg three times daily for 3 weeks showed no improvement in neuropsychiatric symptoms, agitation, quality of life or activities of daily living vs placebo[8].

The current evidence base is limited by small study size, limits in study design and reporting and inconsistent effects. The current limited evidence does not support a therapeutic effect of cannabis medicines for management of behavioural disturbance in dementia.

Best Practice Guidance for Management of Alzheimer's Disease

Step 1. Non-pharmacological measures

- Should be provided for all patients
- Family education and support
- Home environment adaptations
- Access to spectacles/hearing aids
- Provide contact details for local Dementia Behaviour Management Advisory Service (DBMAS), which has a 24-hour helpline
- Aged Care Assessment referrals where necessary
- Monitor for common symptoms e.g. constipation and delirium
- Support with appointing enduring guardian and power of attorney (where appropriate)

Step 2a. Behavioural management

- Mainstay is non pharmacological
- Where pharmacology is needed, follow guide-lines for prescription of:
- Risperidone,
- Olanzapine or
- Oxazepam

Step 2b. Cognitive management

Consider addition of drugs which may slow cognitive decline:

- Cholinesterase inhibitors: donepezil, galantamine and rivastigmine
- N-methyl-D-aspartate antagonist: memantine

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

Summary of best practice in the treatment of dementia

The following information is based on information from eTG complete[3]. More detailed information and prescribing guidelines regarding dose, frequency and sequential drug choices should be sought before prescribing.

Dementia is a clinical syndrome that is characterised by a progressive deterioration in cognition with resulting decline in function.

While cholinesterase inhibitors or memantine may be helpful for the treatment of cognitive impairment caused by Alzheimer's disease, the care and management of the patient with dementia predominantly involves non-pharmacological measures, such as family education and support, and adjustment of the environment.

Psychotropic medications may be required for behavioural symptoms where non-pharmacological measures fail to control severe symptoms. Caution should be taken prescribing drugs in this population due to the high rates of side effects and drug-drug interactions.

Prescribing cannabis medicines for the management of dementia

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. The prescriber may be a general physician or geriatrician, 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, or in the case of a patient without capacity the guardian or next-of-kin, must give informed consent to treatment. The consent process should include:

- This is an unregistered medicine (and costs may reflect this).
- The efficacy of this therapy is still being researched.
- They must be made aware of the likely effects and side effects of treatment – with particular mention made on the increased risks in the elderly and for those on multiple medications.
- There will be restrictions on driving and operating heavy machinery.
- The patient/guardian/next-of-kin should also be given clear information about therapeutic goals and likely stopping criteria.
- The 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*[2].

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 has effects on neurological function including seizure activity, sedation, and dizziness, however psychosis has not been reported. 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.

Precautions

The following has been adapted from the TGA's *Guidance for the use of medicinal cannabis in Australia: Overview*[4].

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*[1].

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.

Based on the available studies, 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®[9](THC) and Sativex®[10](THC and CBD combination). 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, however this occurred at concentrations significantly higher than the maximum observed in clinical trials.
- In patients on clobazam, increased active metabolite N-desmethylclobazam (nCLB) concentrations were noted[11]. likely due to CYP2C19 and CYP3A4 inhibition by CBD[12]. Higher nCLB concentrations were associated with a higher frequency of reports of sedation[11].
- 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 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).
- 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 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 – adapted from Dronabinol (Marinol®) product information[9] (for treatment of anorexia):

- Starting dose 2.5 mg once daily or BD.
- Monitor for side effects.
- In view of likely multiple medications already prescribed and likelihood that the patient is elderly there is the potential for multiple drug interactions and side effects.
- 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.

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. dementia) 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 x, 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[15].

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-5 Diagnostic Criteria for Cannabis Withdrawal Syndrome[16]

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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