ACRE
Australian Centre for Cannabinoid Clinical and Research Excellence

DRAFT PRESCRIBING GUIDANCE
PRESCRIBING CANNABIS MEDICINES FOR THE MANAGEMENT OF DEMENTIA

Introduction

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 medicinal cannabis therapy for their loved one.

The Australian Government'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 2.5mg 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 in not appropriate for people with active or previous psychotic or active mood or anxiety disorders.

There is currently a very limited evidence base for medicinal cannabis in treatment of or behavioural management of patients with dementia or Alzheimer's disease.

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.

Treatments for which the evidence base is greatest should be used prior to consideration of medicinal cannabis therapy for dementia.

Current clinical trials

There are currently no clinical trials for the management of dementia symptoms with medicinal cannabis being undertaken in Australia.

Up to date information can be obtained from the NSW Cannabis Medicines Advisory Service by email or by telephone (02) 4923 6200.

Use of evidence-based therapies in dementia

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

General information

Dronabinol, a synthetic Delta-9-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 2.5mg. 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 2.5mg 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 1.5mg 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 medicinal cannabis for management of behavioural disturbance in dementia.

Medical practitioners should review the following guidance advice on made available by the Therapeutic Goods Administration (TGA) before making a decision to prescribe medicinal cannabis products:

- *Guidance for the use of medicinal cannabis in Australia: Overview*

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 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.

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 guidelines 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

Prescribing medicinal cannabis 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 medicinal cannabis.

Further advice and assistance is available to medical practitioners via the NSW Cannabis Medicines Advisory Service by email or by telephone (02) 4923 6200.

The Prescriber

The prescriber should have a key involvement in provision of care. The prescriber may be a general physician or geratrician, 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 or will 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 under investigation.
- 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 infor-

mation 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 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*[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).
- Tetrahydrocannabinol (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.
- Cannabidiol (CBD) is not psychoactive and 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. 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 toxins and reduced "side stream"
- Peak concentration in 15-30 minutes, effects last 2-4 hours
- Useful for symptoms requiring rapid and intermittent relief

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)
- Titration of dosing may be easier with oro-mucosal sprays than oral formulations
- Sprays may be easier for those with difficulty swallowing

Topical

- Cannabinoids are lipophilic and therefore are likely to be well absorbed across the skin.
- THC is relatively less well absorbed than cannibidiol and cannibinol.
- 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].

Medicinal cannabis 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 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.

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

- 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, however this occurred at concentrations significantly higher than the maximum observed in clinical trials.
- 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 co-administered with fluoxetine and also disulfiram.

Musculoskeletal

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

Dosing

Prescribers who are unfamiliar with these products should consider contacting the NSW Cannabis Medicines Advisory Service by email or by telephone (02) 4923 6200.

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.

Example for THC – adapted from Dronabinol (Marinol®) product information[9] (for treatment of anorexia):

- Starting dose 2.5mg 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

No other medicinal cannabinoid could be recommended due to very limited evidence in the literature.

Monitoring Outcomes

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 **must** be reported to the TGA (including dependence and withdrawal symptoms)

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

NEED FURTHER INFORMATION AND ASSISTANCE?

Further advice and assistance is available to all NSW-based medical practitioners through the NSW Cannabis Medicines Advisory Service.

The Service can be contacted by email or by telephone (02) 4923 6200.

References

1. Department of Health Therapeutic Drug Administration. Guidance for the use of medicinal cannabis in the treatment of palliative care patients in Australia. https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-treatment-palliative-care-patients-australia
2. Department of Health Therapeutic Drug 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
3. eTG Complete https://tgldcdp.tg.org.au/etgcomplete (accessed 28 Feb 2018)
4. Department of Health Therapeutic Drug Administration. Guidance for the use of medicinal cannabis in Australia: Overview, December 2017. https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-australia-overview
5. Walther S et al; Delta-9-tetrahydrocannabidiol for nighttime agitation in severe dementia. Psychopharmacology (2006) 185: 524–528
6. Woodward MR et al; Dronabinol for the Treatment of Agitation and Aggressive Behavior in Acutely Hospitalized Severely Demented Patients with Noncognitive Behavioral Symptoms. Am J Geriatr Psychiatry 2014; 22:415
7. Volicer L et al; Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. Int. J. Geriat. Psychiatry, 12, 913-919, 1997.
8. Van den Elsen GAH et al; Tetrahydrocannabinol for neuropsychiatric symptoms in dementia, a randomized controlled trial. Neurology Jun 2015, 84 (23) 2338-2346
9. Marinol Product Information https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf (accessed 28 Feb 2018
10. Sativex Product Information https://www.tga.gov.au/sites/default/files/auspar-nabiximols-130927-pi.pdf (accessed 28 Feb 2018)