ACRE
Australian Centre for Cannabinoid Clinical and Research Excellence

DRAFT PRESCRIBING GUIDANCE
PRESCRIBING CANNABIS MEDICINES FOR CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Introduction

The Australian Government's *Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia*[1] summarises the current evidence base for the use of cannabis products in the context of chemotherapy-induced nausea and vomiting (CINV). This review has shown that published evidence is of moderate quality at best. Further, interpretation of evidence should be done with the knowledge that the three most recently registered classes of anti-emetics for treatment of CINV have not been studied against medicinal cannabis. As these classes of drugs are significantly more safe and effective than earlier emesis agents, it is likely that medicinal cannabis products are inferior from an efficacy perspective to newer agents.

Initiation of cannabis medicines should only proceed after conventional treatments[2] have been tried and proved unsuccessful.

Current clinical trials

- **Cannabis Medicine Clinical Trial for Chemotherapy-Induced Nausea and Vomiting**
  A NSW Government funded placebo controlled trial evaluating an oral THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting in patients of any known malignancy receiving chemotherapy. See the Australian New Zealand Clinical Trials Registry for further information on the study.

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 for CINV in patients

Australian patients with CINV should first be treated according to the ASCO (2017)[2], MASCC/ESMO (2016) clinical practice guidelines, nationally accepted guidelines (eviQ) and other recognised locally-accepted treatment guidelines.

Pharmacokinetic and pharmacodynamic interactions between medicinal cannabis and antineoplastic agents are predicted but not fully elucidated. THC and CBD are substrates of the P450 system with significant inhibitory and inducing effects on some enzymatic pathways, depending on the cannabinoid. From a pharmacodynamic perspective, there is evidence that cannabinoids that bind to the CB2 receptor (including delta-9-THC) impact on T-cell function. Thus these drugs may be thus contraindicated in patients whose therapy involves immune modulation and activation of cytotoxic T-cells[5].

General information

Prior to considering cannabis medicines as a treatment option for CINV in patients, medical practitioners should review the following guidance advice on made available by the Therapeutic Goods Administration (TGA):

- *Guidance for the use of medicinal cannabis in Australia: Overview*
- *Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia*

Summary of best practice in management of CINV in patients

Antiemetic Guidelines for Chemotherapy-induced Nausea and Vomiting (based on ASCO Clinical Practice Guideline, 2017[2])

SEE NEXT PAGE FOR **'ANTIEMETIC GUIDELINES FOR CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING' DIAGRAM**.

Summary of Best Practice in management of CINV in patients

High-emetic risk antineoplastic agents: 4 drug combination of
- NK1 receptor antagonist
- 5HT3 receptor antagonist
- Dexamethasone
- Olanzapine

Moderate-emetic risk antineoplastic agents:
Carboplatin AUC ≥4mg/mL/min: 3 drug combination of
- NK1 receptor antagonist
- 5HT3 receptor antagonist
- Dexamethasone

All others: 2 drug combination of
- 5HT3 receptor antagonist
- Dexamethasone

High risk delayed nausea and vomiting:
- Continue dexamethasone

Low-emetic risk anti-neoplastic agents:
- 5HT3 receptor antagonist OR
- Dexamethasone

Minimal-emetic risk anti-neoplastic agents:
- Routine antiemetic prophylaxis not offered

Breakthrough N&V:
- Re-evaluate emetic risk and ensure adequate prophylactic antiemetic prescribed
- Assess disease status, concurrent illness, other medications
- Add olanzapine
- Add NK1 receptor antagonist
- Add lorazepam

Then:
- Consider dronabinol or nabilone
- Evidence is insufficient for any other medical cannabis product

High-emetic risk radiotherapy: both
- 5HT3 receptor antagonist
- Dexamethasone

Moderate-emetic risk radiotherapy:
- 5HT3 receptor antagonist
- AND/OR Dexamethasone

Low-emetic risk radiotherapy – Rescue as needed with:

Brain RT: dexamethasone

Head/neck/thorax/pelvis RT:
- 5HT3 receptor antagonist
- OR Dexamethasone
- OR Dopamine receptor antagonist

Chemotherapy + Radiotherapy:

Antiemetic regime as per highest chemotherapy emetic risk until chemo completed, then as per highest RT emetic risk

PRACTICE POINTS

Antineoplastic combinations:
Prescribe antiemetics based on the antineoplastic component with the highest emetic risk

Multi-day regimes:
Prescribe antiemetics appropriate for risk on every day of the cycle and for 2 days post cycle

Anticipatory nausea and vomiting:
- Prevention is better than cure
- Lorazepam
- Behavioural therapy with systematic desensitisation

Prescribing medicinal cannabis for the management of CINV 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.

Further advice and assistance is available to medical practitioners via the NSW Cannabis Medicines Advisory Service . The Service can be contacted 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 an oncologist, a specialist in palliative and supportive care, or a general physician/general practitioner in liaison with the patient's oncologist. It is important that all members of the treating team are aware of the decision to prescribe a cannabis medicine. It is also important that this information is communicated to other members of the care team in writing.

The prescriber should have already established or will have an ongoing therapeutic relationship with the patient. Follow up, assessment of efficacy, side effects, and pharmacovigilance 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:

- This is an unregistered medicine (and costs may reflect this).
- The efficacy of this experimental therapy is still being researched.
- Awareness 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*[3].

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), purified tetrahydrocannabinol (THC) or cannabidiol (CBD)
- Tetrahydrocannabinol (THC) is responsible for the psychoactive effects of cannabis and is the main 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. However it may also worsen these symptoms.
- Cannabidiol (CBD) is not psychoactive and may be useful in the management of seizures, pain, and may have anxiolytic effects. Cannabidiol may be helpful because it inhibits metabolism of other drugs used in these situation
- Different cannabis products contain different cannabidiol components, and different ratios of THC to CBD.
- There are other cannabinoids under research for CINV 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" or combustion during smoking
- Smoking is well known to be harmful and not recommended on health grounds

Vaporising

- 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 relief

Oral administration and oro-mucosal sprays

- 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

- THC is not well absorbed through the skin
- Cannabidiol and Cannabinol are better absorbed topically and more likely to be available in topical preparations.
- Time of onset and duration of action are unknown and therefore would not be recommended for first line use.

Evidence for use

The following has been adapted from the *Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia*[1].

There is an absence of reliable evidence of the efficacy of medicinal cannabis in the treatment of CINV according to relative emetogenicity of chemotherapeutic regimens, or against currently available antiemetic regimens.

SEE NEXT PAGE FOR **'SUMMARY OF EVIDENCE FOR CANNABIS AND CANNABINOIDS FOR THE TREATMENT OF NAUSEA AND VOMITING' TABLE**.

Cannabinoid product	Condition	Preparation	Administration	Standardised
Dronabinol	CINV*	Capsule	Oral	Yes
	Cancer-associated N&V	Capsule	Oral	Yes
	CINV*	Capsule	Oral	Yes
Nabilone	Cancer-associated N&V*	Capsule	Oral	Yes
	CINV*	Capsule	Oral	Yes
	CINV*	Dissolved formula	Intramuscular injection	Yes
THC	CINV*	Liquid	Oromucosal spray	Yes
Nabiximols/THC:CBD	CINV*	Cigarette	Inhalation	Not specified

Table 1. Summary of evidence for cannabis and cannabinoids for the treatment of nausea and vomiting.
See *Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia*[1].

*No studies of these medicinal cannabis products have been performed against the most recently approved antiemetics, considered the most efficacious available in adequately designed and performed randomised clinical trials.

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 nabiximols (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.

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 *Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia*[1].

Patients and prescribing clinicians should be aware of possible adverse events such as somnolence, nausea and dizziness from cannabinoid products. Common adverse events such as confusion, pain, diarrhoea or hallucinations may impact the therapeutic goal (control of nausea) and reduce quality of life, and should be evaluated on a case-by-case basis.

Serious adverse events have been described clinically, such as psychosis and cognitive distortion requiring external assistance, but the severity, time course and further details are not recorded.

Details of the incidence and severity of adverse events with most medicinal cannabis products are lacking, as reported in the literature.

Based on the available studies, the most commonly reported adverse events in the use of medicinal cannabis in nausea and vomiting include in order of frequency:

- dysphoria and or depression (13% of patients)
- hallucinations (6% of patients)
- paranoid delusions (5% of patients)
- drowsiness (proportion not reported)
- dry mouth (proportion not reported).

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)[7,8].

Ongoing reports of potential interactions to the TGA are 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.
- 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) is started or stopped, a new dose titration will 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 will 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, cyclosporin, 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, opioids, benzodiazepines, anticholinergics and antihistamines as there may be an additive effect on sedation and muscle relaxing effects.
- 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 are examples only – doses should be individualised for patient and indication.

Please refer to Table 1 of the TGA *Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia* [1] for a summary of existing evidence for cannabis and cannabinoids.

Example for THC – adapted from Dronabinol (Marinol®) product information (for treatment of chemotherapy-induced nausea and vomiting)[7]:

- Starting dose 2.5 mg/m^2 once daily, given 1-3 hours prior to chemotherapy
- Monitor for side effects
- The dosage can be titrated to clinical response based upon initial response, as tolerated, in increments of 2.5 mg/m^2
- Maximum dosage is 15 mg/m^2 per dose up to 4 times per day
- Adverse reactions are dose related and psychiatric symptoms increase significantly at maximum dosage

Example of dosing for THC:CBD product — using Sativex® oro-mucosal spray in chemotherapy induced nausea and vomiting[8].

- Slow titration over two weeks, initially one spray per day
- 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

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.

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 for the prevention or management of nausea and vomiting in Australia. https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-prevention-or-management-nausea-and-vomiting-australia
2. Hesketh PJ et al Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology* 35, no. 28 (October 2017) 3240-3261.
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