ACRE
Australian Centre for Cannabinoid Clinical and Research Excellence

PRESCRIBING GUIDANCE

PRESCRIBING CANNABIS MEDICINES FOR MANAGEMENT OF CHRONIC NON-CANCER PAIN (CNCP)

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, and monitoring the use of cannabis medicines for the management of chronic non-cancer pain (CNCP). The Prescribing Guidance:

- Provides a summary of standard, registered therapeutic options in the management of CNCP which should be used prior to considering the use of cannabis medicines.
- Details important considerations for prescribing cannabis medicines, including precautions and adverse events, drug interactions, dosing and monitoring outcomes.
- Presents information on delta-9-tetrahydrocannabinol (THC)-based cannabis medicines, as information on the use of other medicinal cannabinoids (other than THC) cannot be provided at this stage due to very limited evidence in the literature.
- Draws on the Therapeutic Goods Administration (TGA) guidance documents and, as such, requires medical practitioners to review the TGA's guidance before making a decision to prescribe cannabis medicine products.

Key points

- The TGA's Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia[1] explains that for one patient with CNCP to get a clinically relevant improvement in pain (30% reduction in pain), 24 people need to be treated with a cannabinoid. However, in terms of harm, only 6 patients need to be treated with a cannabinoid for one patient to have clinically relevant harm. Further, the review states that the clinical relevance of the evidence is limited by the small number of studies and their small samples. It also states that currently there is insufficient information to make a recommendation about the role of cannabis medicines in the treatment of pain associated with arthritis and fibromyalgia.
- All registered therapeutic options are exhausted or deemed inappropriate (due to adverse effects or contraindications) prior to the consideration of a cannabis medicine for CNCP.
- Medical practitioners should review the guidance advice made available by the TGA before making a decision to prescribe cannabis medicine products for CNCP.
- NSW-based medical practitioners can obtain further information and assistance with prescribing tailored to the patient-specific clinical context from the NSW Cannabis Medicines Advisory Service. The service can be contacted via email HNELHD-CMAS@health.nsw.gov.au.

Current clinical trials

Clinical trials related to chronic-non-cancer pain that are currently recruiting can be located via searching the Australian New Zealand Clinical Trials Registry.

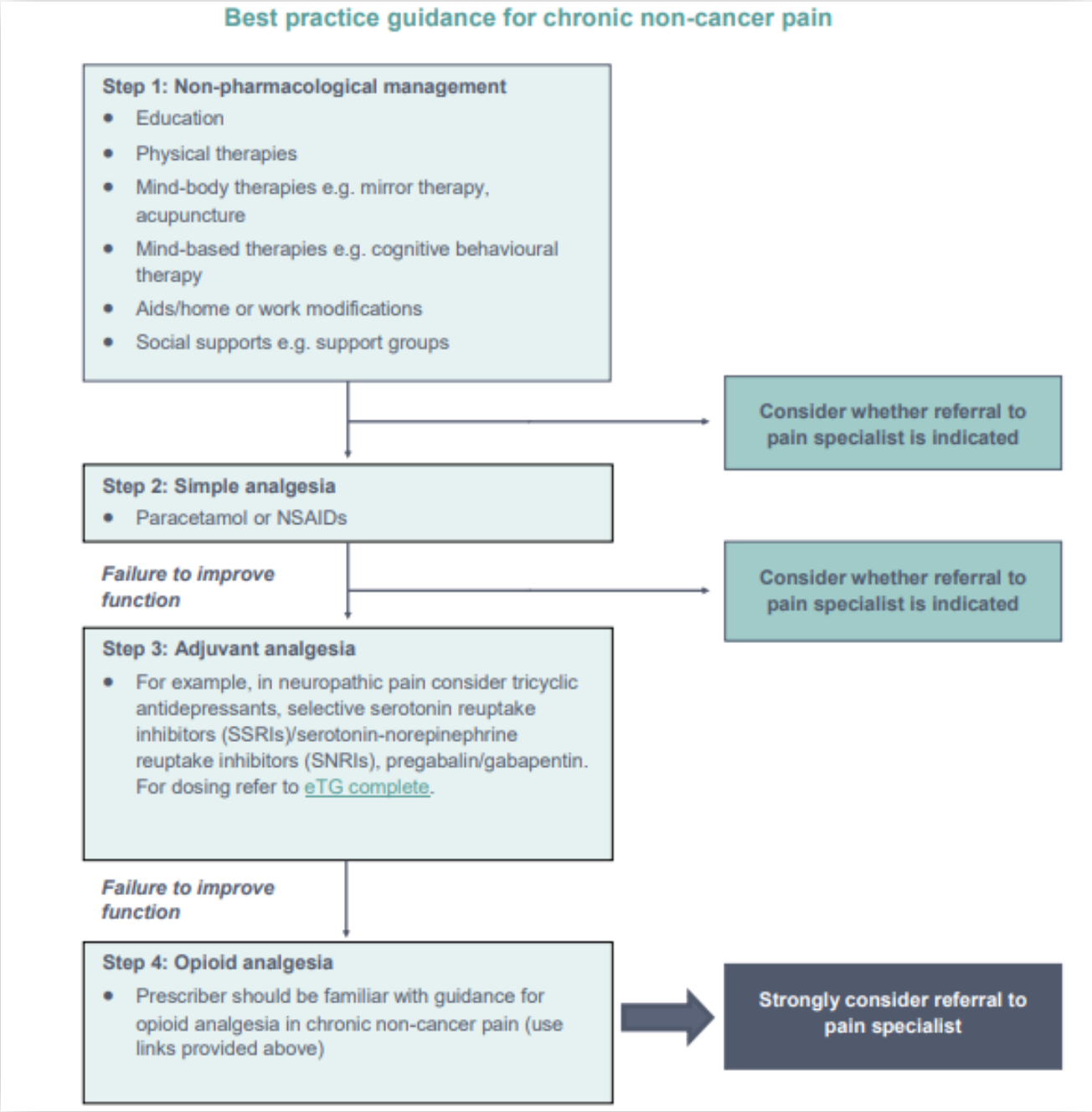
Use of evidence-based therapies for chronic non-cancer pain

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

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

Useful resources for clinicians managing CNCP:

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



- NSW Government's Agency for Clinical Innovation Pain Management Resources[4].

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

Chronic pain is a complex condition with variable presentations. It may be associated with ongoing active pathology (e.g. rheumatoid arthritis). Usually, however, the originating event is no longer active but pain persists because of lasting changes within the neurological system. Managing chronic pain requires a multimodal approach, which in Australasia emphasises non-pharmacological approaches. Patient engagement and education is vital.

Non-pharmacological approaches include:

- Physical techniques (passive or active).
- Mind–body techniques (e.g. biofeedback, Feldenkrais, mirror therapy, acupuncture).
- Mind-based techniques (e.g. cognitive behavioural therapy, hypnosis, relaxation/meditation, mindfulness, operant conditioning, acceptance and commitment therapies, psychoanalytic and psychodynamic therapies).
- Use of aids/orthotics and occupational therapy (e.g. home and workplace/work practice modification).
- Social/environmental interventions (e.g. community support groups, work retraining). Combinations of any or all of these approaches[2].

Functional improvement as well as a reduced pain score is the aim of management of CNCP. Pharmacological interventions including cannabis medicines may make

engagement and functional improvement more difficult and complicated.

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

Existing evidence does not support the long-term efficacy and safety of pharmacological therapy, including opioid therapy, for CNCP. Patients are advised to try to reduce recreational drugs of addiction as part of engagement into a pain management plan. Information on a chronic management plan can be found at on NSW Health's Chronic Pain Management webpage[5].

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

An excellent resource, Reconsidering medication use for neuropathic pain[6], has been produced by Hunter New England Local Health District. In neuropathic pain, the first line agents (in 3 month trials) are tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors and anticonvulsants (pregabalin and gabapentin) used either alone or in combination.

The Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists (ANZCA) have published recommendations on chronic pain, neuropathic pain and low back pain[7]. These recommendations reference The International Association for the Study of Pain position statement on the use of cannabinoids to treat pain[8].

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

If the decision to proceed to cannabis medicine prescription is made, consider the information below.

The prescriber

The prescriber should have a key involvement in provision of care, including the patient's general practitioner in liaison with a specialist practitioner, and an ongoing relationship in the patient's journey. All members of the treating team should be are aware of the decision to prescribe a cannabis medicine documented in the patient's record. This enables awareness of adverse events and drug interactions early.

Follow up and assessment of efficacy and toxicity is essential.

Given the current status of most 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:

- Most available cannabis medicines are unregistered and non-reimbursed (see products available for exceptions).
- The true likelihood efficacy and side effects of this therapy are still being researched, but possible effects and side effects of treatment should be discussed.
- 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 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[9] and in NSW Health's Prescribed Cannabis Medicines and Fitness to Drive Factsheet[10].

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[11].

Cannabis products

- A variety of cannabis products are available.
- There are up to 100 cannabinoids (chemical compounds) in the cannabis plant, many are active.
- Many of the studies described in the medical literature have used either smoked cannabis (which is not recommended on health grounds) or purified cannabidiol (CBD) or synthetic THC cannabis medicines.
- THC is responsible for the psychoactive effects of cannabis and is the reason cannabis is used recreationally. THC may contribute to reduction of nausea, vomiting, pain and muscle spasms as well as improvements in sleep and appetite.
- CBD has effects on neurological function including seizure activity, sedation, and dizziness, however psychosis has not been reported. It may be useful in the management of seizures, and may have anxiolytic and antipsychotic effects for some people. Adding CBD to a THC product in a patient with toxicity to reduce toxicity is unproven and may increase the THC exposure. It is more appropriate to reduce the dose and/or frequency of THC.
- Different cannabis products contain different ratios of THC to CBD.
- There are other cannabinoids under research including cannabigerol (CBG), tetrahydrocannabivarin (THCV), cannabinol (CBN) and cannabichromene (CBC).

Route of administration

Vaporising

- Rapid onset of action, usually within minutes.
- High blood concentrations of cannabinoids with shorter duration of effect than oral.
- Peak concentration in 30 minutes, effects last 2-4 hours. Useful for symptoms requiring rapid and intermittent relief.

Oral/oro-mucosal/oro-buccal administration

- Care with dosing with oral liquid.
- 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 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 CBD and CBN.
- Time of onset, duration of action and likelihood of depot occurrence are unknown although it is expected the time of onset will be slower than vaporised route and faster than oral. This route is therefore not recommended at this stage.

Products available

There are currently two registered cannabis medicines in Australia:

- Sativex®[8] oromucosal spray (for the indication of moderate to severe spasticity in patients with multiple sclerosis)
- Epidyolex®[9] (CBD 100 mg/mL) oral liquid (for the indication of epilepsy, as an adjunctive therapy for Lennox-Gastaut, or Dravet syndrome associated seizures in patients ≥ 2 years of age).

It is noted that some cannabinoids have different scheduling than others, with CBD available as Schedule 3 as soon as a registered product is available.

The U.S. Food and Drug Administration have approved the use of synthetic cannabinoid products, for specified indications, including:

- Marinol®[14] and Syndros®[15] - dronabinol* (anorexia in patients with Acquired Immune Deficiency Syndrome (AIDS) who have lost weight and treatment refractory or cancer chemotherapy associated nausea and vomiting)
- Cesamet®[16] - nabilone* (treatment refractory, cancer chemotherapy associated nausea and vomiting).

The cannabinoid composition of unregistered products can be generally grouped into THC-predominant, CBD-predominant, THC and CBD ~1:1 and other cannabinoids and ratios.

A variety of unregistered cannabis medicines (that conform to the requirements of the Therapeutic Goods (Standard for Medicinal Cannabis) (TGO93) Order and the Therapeutic Goods (Microbiological Standards for Medicines) (TGO 100) Order are available, including chewable tablets, crystals, flos/granulate for inhalation, lozenges, oral oils, oral solutions, oro-mucosal sprays, oral capsules, sublingual wafers, tinctures, topical balm, and transdermal patch dosage forms.

*Some cannabis products and dose forms may not be readily available onshore in Australia. Some synthetic cannabis medicine products that are available overseas may require importation and necessary permits via the Special Access Scheme.

Evidence for use

The following information has been adapted from the TGA's Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia[1] published by the TGA in December 2017 (see Table 1). Further information updates were obtained from a literature review in MEDLINE and Embase from January 2018 to December 2020. The Agency for Healthcare Research and Quality publish quarterly reports from a living systematic review on cannabis-based treatments for chronic pain[17].

The effectiveness of cannabis medicines in CNCP is assessed in trials by a number of end points including percentage pain reduction, overall physical function, quality of life and sleep[1].

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

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

Overall, there is some data suggesting a limited benefit of cannabis medicines in the management of CNCP[1,18,19]. However, the data is derived from studies of low- or very low-quality[20]. A systematic review has shown the effect size for pain reduction is modest, with an estimated number needed to treat (NNT) to reduce pain by 30% of 24, and number needed to harm (NNH) of 6[21]. Studies also suggest a modest improvement in sleep patterns, but no apparent improvement in overall physical function or quality of life[1,19].

Most data regarding the use of cannabis medicines in CNCP derives from studies in neuropathic pain[22,23]. The evidence for

the use of cannabis medicines in other forms of CNCP such as arthritic and mixed pain syndromes is limited and further research is needed to make conclusive statements[24]. A small randomised controlled trial in fibromyalgia suggests an improvement in composite symptoms (which include mental health domains), as measured by the fibromyalgia impact questionnaire (FIQ), with a THC rich cannabinoid oil[25]. There has been very limited, low-quality research into the use of CBD products for pain.

Most evidence on cannabis medicines in CNCP is derived from use as adjuvant medications. As such it is not recommended that cannabis medicines be used in place of guideline-based treatments for chronic pain[1].

Precautions

The following has been adapted from the TGA's Guidance for the use of medicinal cannabis in Australia: Overview [26].

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

Cannabis medicines are associated with an increased rate of adverse events in CNCP studies such as dizziness, drowsiness, fatigue, nausea, dry mouth and hallucinations[18]. Patients using cannabis medicines were 2-3 times more likely to drop out of trials due to adverse effects[27]. Older patients with multiple comorbidities and polypharmacy may be a greater risk of adverse effects.

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

The cessation of long-term (of more than several months) use of THC-based medicines may also be associated with the experience of discontinuation effects.

Drug interactions

While some cannabis medicines contain only one active ingredient, others contain THC and/or CBD in varying ratios as well as other cannabinoids or compounds extracted from cannabis plant material. The systemic exposure of the patient to the cannabinoids THC and CBD will be influenced by the formulation, dose administered, route of administration and the frequency of administration.

Current information sources for drug interactions with cannabinoids are drug interaction databases, the product information on Epidyolex® (CBD)[13], Cesamet® (nabilone)[16], Marinol® (dronabinol)[14], and Sativex® (THC and CBD)[12], recently published case reports, in-vitro studies and clinical trial outcomes in the primary literature.

As part of cannabinoid drug interaction assessment, patient variables that also need to be considered include but are not limited to polypharmacy, patient age, hepatic function, comorbidities and genetic polymorphisms. Diet (fed or fasted state, components of food) is a variable that can influence bioavailability of oral oils. Many of these factors are confounders in case reports in the published literature. Lack of formal causality analysis in many case reports also limits the interpretation of described outcomes.

Pharmacokinetic drug-drug interactions

Plasma THC and CBD concentrations may be increased or decreased when co-administered with medications that inhibit or induce enzymes involved in the metabolism of THC and CBD.

Enzyme Inhibition or Induction

The cytochrome P450 (CYP) enzymes CYP2C9 and CYP3A4 play a significant role in the metabolism of THC[28]. Pharmacogenetic data also supports CYP2C9 being a significant contributor to THC metabolism[29].

CBD is primarily metabolised by CYP2C19 and also CYP3A4[27]. Other CYP enzymes including CYP1A1, CYP1A2, CYP2C9, CYP2D6 and CYP3A5 may also play a role in CBD metabolism[30,31].

Induction or inhibition of these CYP enzymes may affect the pharmacokinetics of THC and CBD. Co-administration of ketoconazole (a strong CYP3A4 inhibitor) was observed to significantly increase plasma THC and CBD concentrations. Co-administration of rifampicin (a strong CYP3A4 and CYP2C19 inducer) resulted in decreased plasma THC and CBD concentrations. However, when omeprazole (a CYP2C19 inhibitor) was co-administered with THC, no changes in plasma THC concentration were observed[32].

It is possible that other drugs which are inhibitors or inducers of the enzymes CYP3A4, CYP2C9 and CYP2C19 may affect the pharmacokinetics of THC and CBD. Care should be taken when prescribing such medications, during dose modifications or when discontinuing these medications in patients taking cannabinoids. For further information on drugs which are CYP inhibitors and inducers please refer to resources such as the Australian Medicines Handbook.

Cannabinoids are also subject to UDP-glucuronosyltransferase (UGT)-dependent glucuronidation by UGT enzymes. CBD undergoes direct conjugation by UGT enzymes while UGT enzymes play an important role in metabolism of THC metabolites THC-OH and THC-COOH[28,33]. CBD is a substrate of the UGT enzymes UGT1A7, UGT1A9 and UGT2B7. No formal drug-drug interaction studies with UGT inhibiting drugs have been reported. However, caution should be taken if CBD and drugs which inhibit UGT1A7, 1A9 and 2B7 enzymes are co-administered. Dose reduction may be required[13].

THC and CBD may affect plasma drug concentrations of co-administered medications.

In-vitro studies have also indicated that, besides being substrates of CYP enzymes, CBD and THC may also act as inhibitors of CYP enzymes.

A recent review compared in-vitro inhibition parameters to physiologically achievable cannabinoid concentrations and concluded that CYP2C9, CYP1A1/2, CYP1B1, CYP2D6, CYP2C19, CYP2B6 and CYP2J2 are likely to be inhibited by THC and CBD while CYP3A4/5/7 are potentially inhibited by

CBD. However, it should be noted that contradictory in vitro results reporting both activation and inhibition of CYP2C9 have been reported[34]. Product Information for Epidyolex® suggests there may be inhibitory effect at clinically relevant concentrations on 2C8, 2C9, 2D6 and 2C19 and possible dual inhibition/induction effect for 1A2 and 2B6[13,35].

CBD may also inhibit UGT1A9 and UGT2B7. An in-vitro study using ethanol as a substrate reported that CBD produced significant reduction of UGT1A9 and UGT2B7 activity. UGT enzymes are involved in glucuronidation of a range of drugs. Inhibition of these enzymes will reduce excretion of drugs that are substrates. However, the clinical relevance of any inhibition by cannabinoids has not been assessed. Since many commonly used medications undergo glucuronidation (including paracetamol, ibuprofen, tapentadol, canagliflozin, sorafenib, regorafenib, propofol, valproic acid, mycophenolate), CBD should be used with caution in patients who are stabilised on medications which undergo glucuronidation and when commencing these medications. Patients should be carefully monitored for side effects[35].

In vitro studies have shown Sativex® has broad CYP450 enzyme inhibition effects. Although these effects may occur at concentrations higher than those observed with the registered dose of Sativex®, in practice many patients are using doses of other unregistered products that exceed the registered dose of Sativex®. Monitoring is recommended to detect possible clinical implications of elevated drug concentrations[12].

In summary, caution should be exercised when considering prescribing cannabis products with medications that undergo significant metabolism by CYP2C19, CYP2C9 and CYP1A2 or by UGT enzymes due to the possibility of altered disposition[34]. Narrow therapeutic index (NTI) drugs which are metabolised by these enzymes should be closely monitored. While in-vitro and animal studies provide some preliminary information, well-designed clinical trials are needed to fully evaluate the clinical significance of enzyme induction and inhibition drug interactions. Route of administration, dose and duration of dosing may also influence whether significant interactions due to enzyme inhibition or induction occur.

Patients should also be informed of the possibility of drug-drug interactions when cannabinoids are co-administered with other medications, particularly with NTI drugs.

Smoking cannabis may increase the clearance of medicines metabolised by the P450 system, particularly 1A1 and 1A2.

CYP1A1 and CYP1A2 enzyme activity is increased by both cannabis and tobacco smoking and the induction effect between both tobacco and cannabis smoking is additive. Mechanism for induction of enzymes is thought to be due to the polycyclic aromatic hydrocarbons produced by pyrolysis. Dose adjustments for drugs metabolised by these enzymes may be required. Rapid downregulation of CYP1A enzymes occurs on smoking cessation and dose reduction of CYP1A metabolised drugs may be necessary even in the first few days after smoking cessation[36].

P-glycoprotein inhibition (P-gp)

Drug efflux transporters such as P-gp plays a significant role in absorption and clearance of some drugs. In vitro and animal studies have observed that CBD and THC interact with P-gp. An in-vitro study indicated that CBD may significantly inhibit P-gp mediated drug transport and influence absorption and disposition of other drugs which are P-gp substrates[37]. A study which administered the P-gp substrate risperidone and THC to mice demonstrated that THC exposure increased P-gp expression in various brain regions important to risperidone's antipsychotic action, reversing the neurobehavioural effects of risperidone. When clozapine (which is not a P-gp substrate) was co-administered with THC, the behavioural effects of clozapine were not affected[38]. However, not all in-vitro studies have demonstrated an effect of THC or CBD on P-gp[34].

Further research is needed to confirm the clinical presence and relevance of transporter interactions. Until this research is undertaken, caution is recommended when CBD or THC is co-administered with drugs that are P-gp substrates, including NTI drugs, such as digoxin[12].

Protein binding

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 NTI drugs that are highly protein-bound (e.g. warfarin, ciclosporin, amphotericin B) when initiating treatment or increasing the dosage of THC. This may be relevant when blood concentrations are being interpreted; care is needed as although the total drug may be changed, the free fraction may be stable[14].

Clinical reports of pharmacokinetic drug-drug interactions

Antiepileptic drugs (AED)

In patients administered clobazam in combination with CBD, increased active metabolite N-desmethylclobazam (nCLB) concentrations were observed[39,40]. This is likely due to CYP2C19 inhibition by CBD[41]. Higher nCLB concentrations were associated with a higher frequency of reports of sedation[39]. Increased concentrations within normal therapeutic ranges of rufinamide, topiramate and zonisamide were reported in an open label safety study of CBD[39]. A small increase in stiripentol concentration has been reported when combined with CBD. The combination of CBD and valproate has been reported to cause elevations in liver function tests[42,43]. Although there was a 25% to 32% increase in 7-COOH-CBD exposure, the mechanism may not be completely pharmacokinetic. The results of a systematic chart review of a paediatric cohort suggest that monitoring for thrombocytopenia should be considered when valproate and CBD are combined[44]. Clinical and therapeutic drug monitoring (where applicable) is recommended with the use of CBD and AED.

Phenytoin is largely metabolised by CYP2C9 which has been shown to be inhibited by CBD in in-vitro studies. While no clinical studies have formally investigated this potential interaction, increased exposure to phenytoin, which has a NTI, may occur and dose reduction should be considered[13].

UGT enzymes, including UGT2B7 are involved in the metabolism of lamotrigine. In-vitro, inhibition of UGT2B7 by CBD has been observed. No clinical studies have formally investigated this potential interaction which could result in elevated plasma lamotrigine concentration when it is co-administered with CBD[13].

In a published case series, co-administration of CBD with brivaracetam resulted in increased plasma brivaracetam concentrations[45].

Additive effects may occur when cannabinoids are co-administered with other medication.

Anticoagulant, antiplatelet and thrombolytic agents

Case reports have noted elevated INR in patients taking warfarin following use of various cannabinoids and dose forms. A clinically significant interaction between CBD and warfarin via CYP2C9 inhibition is predicted[46-51]. Based on in vitro evidence, THC and CBD may inhibit platelet aggregation and may theoretically increase the bleeding risk when used with antiplatelets and anticoagulants[52]. There has also been a case report of cerebral haemorrhage following administration of recombinant tissue plasminogen activator for ischaemic stroke in a patient with heavy cannabis use[53].

Immunosuppressants

A paediatric case report of increased everolimus concentration with CBD[54] is consistent with the results of a retrospective review, where increased mTOR inhibitor (everolimus and sirolimus) concentrations were observed in 19 of 25 patients taking CBD. However, coadministration of other drugs (including clobazam) that interact with CYP enzymes may have confounded the observed outcomes in some of the patients[55].

Altered tacrolimus concentrations have been described in case reports and/or series when combined with CBD only or predominant products[56,57] and THC containing products[58,59], although a large degree of intra-individual variability with the NTI drug tacrolimus limits the interpretation of these observations. Everolimus has been proposed to interact via CYP3A4[54] and tacrolimus via CYP3A and/or P-gp[57,59]. Concentration monitoring is advised and dose reduction may be required. Independent effects of cannabis medicines on the immune system also need to be considered.

Psychotropic drugs and theophylline

The estimated clearance of chlorpromazine was faster in regular users of tobacco, cannabis and the combination than in non-users[36].

A potential drug-drug interaction between CBD and lithium was highlighted in a case report. An elevated lithium concentration was observed[60].

Increased clearance of theophylline has been observed with regular smoking of cannabis (> twice per week) with no effect observed with occasional use. The increased clearance is postulated to be caused by aromatic hydrocarbons produced by pyrolysis[61].

Analgesics

Raised methadone concentrations and increased sleepiness and fatigue were reported with concomitant use of methadone and CBD in a paediatric case report[62]. CYP2B6 plays a major role in methadone metabolism and CBD is reported in an in-vitro study to be an inhibitor of this enzyme.

A retrospective study in patients receiving buprenorphine as opioid maintenance therapy observed that cannabis use decreased the formation of norbuprenorphine and elevated buprenorphine concentrations, probably by inhibition of CYP3A4. This may result in enhanced or altered opioid activity and risk of intoxication[63].

Pharmacodynamic drug interactions

While pharmacokinetic drug interactions are more easily detected due to changes in measured plasma drug concentrations, identifying pharmacodynamic interactions with cannabis medicines is much more complex. Identifying the mechanism of interaction may also be complicated by the possibility of both pharmacokinetic and pharmacodynamic interactions occurring concurrently.

Sedation

Cannabis has significant pharmacodynamic effects including sedation and cognitive impairment and these can be potentiated when co-administered with medications with similar effects or biological targets[64].

Care should be taken when cannabinoids are co-administered with central nervous system depressants including hypnotics, sedatives and drugs with potential sedating effects as there may be an additive effect on sedation and muscle relaxing effects. This group includes commonly used drugs such as opioid, benzodiazepine, anticholinergic and antihistamine therapies.

Alcohol

Studies evaluating the interaction of alcohol and cannabis have been conducted, with some reporting pharmacokinetic effects and others evaluating pharmacodynamic effects. Pharmacokinetic studies have reported conflicting results with some studies reporting no significant effect of alcohol on the pharmacokinetics of THC and others reporting significant increases in THC, CBD and metabolite levels. Pharmacodynamic studies reported psychomotor performance impairment when THC and alcohol were used concomitantly[65].

Cannabinoids and opioids

Several studies have reported that cannabis enhanced the analgesic effects of opioids, enabling lower opioid dosing. Vaporised cannabis administered to patients with chronic pain on opioid therapy was observed to increase analgesic effect with no significant differences in observed mean plasma opioid concentrations, suggesting this is a pharmacodynamic interaction. However, opioid delivery to the brain is influenced by ATP-binding cassette transporters and a pharmacokinetic interaction cannot be excluded[33].

A systematic review on the opioid sparing effect of cannabinoids reported that pre-clinical studies provided robust evidence of the opioid sparing effects of cannabinoids while only one of the nine clinical studies identified provided very low-quality evidence of this effect. The authors concluded that prospective high-quality clinical trials were required to determine the opioid sparing effect of cannabinoids[66].

A recent review of the therapeutic potential of opioid/cannabinoid combinations in humans noted that, while there is a groundswell of public advocacy supporting using cannabis and cannabinoids to replace opioid analgesics and to reduce the use of opioids, the current controlled clinical data does not support these uses when treating opioid use disorder or chronic pain[67].

Cardiovascular effects

Acute use of smoked THC can increase cardiac output, induce tachycardia, produce peripheral vasodilation, orthostatic hypotension and alter platelet aggregation. The tachycardic effect is presumed to be based on vagal inhibition and can be attenuated by beta blockers. With continued use, tolerance can develop to orthostatic hypotension and increased heart rate replaced by normal or slowed heart rate. Tolerance is mainly attributed to pharmacodynamic changes possibly due to receptor downregulation and/or desensitisation[68]. CBD may reduce heart rate and blood pressure[69].

Haemodynamic monitoring is advised following cannabis medicine initiation and dose titration, particularly when combined with medications with similar cardiac or blood pressure altering effects. Cannabinoids may have a bidirectional effect on blood pressure and may also cause hypotension.

Cannabinoids may interact with drugs that act on the heart and circulation. These drugs include amphetamines, adrenaline, atropine, beta blockers and antidepressants. Additive

tachycardia may occur when cannabinoids and atropine are taken together[68].

Tachycardia has been described in case reports and series when tricyclic antidepressants were coadministered with smoked cannabis*[14,70-73].

Acute coronary syndrome (ACS) has been observed in case reports involving concomitant use of sildenafil with smoked cannabis*[74-77]. Cannabis inhibition of sildenafil metabolism by CYP3A4 may have played a role[76]. Another case report highlighted the adverse haemodynamic effects of cannabis due to its effect on the sympathetic and parasympathetic nervous system, the effect of cannabis smoking on elevating carboxyhaemoglobin and the resulting increased oxygen demand not being met, which may lead to plaque rupture. It was also noted that since ACS has been reported in the presence of normal coronary arteries, coronary vasospasm may be a mechanism. Reduced blood pressure produced by sildenafil may also contribute to these symptoms[75,77].

Neuro-psychiatric effects

Case reports have described hypomania and/or mania in patients taking disulfiram, following use of smoked cannabis*[78,79]. The alcohol content of some cannabis medicine dose forms may also precipitate disulfiram reactions[15].

A patient developed mania following the combination of fluoxetine and smoked cannabis[80].

THC may induce a transient increase in psychomimetic symptoms measured using the positive scale of the Positive and Negative Syndrome Scale (PANSS). In healthy volunteers who reported psychomimetic effects following inhaled (vaporised) THC, olanzapine was reported to reduce the effects of THC on the positive subscale. Haloperidol has also been reported to reduce psychomimetic effects[81].

Pre-treatment of fifteen occasional cannabis users with the cholinesterase inhibitor rivastigmine was observed to attenuate the effect of THC on cannabis-induced impairment of verbal memory[82].

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[12].

Cancer immunotherapies and cannabis medicine products

Cancer immunotherapies such as programmed cell death protein-1 (PD-1), programmed death-ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors are now used in a variety of different malignancies[83]. Evidence regarding their potential interactions with cannabis medicine products is limited but biologically plausible. A small retrospective observational trial performed in 2019 suggests that medicinal cannabinoids may reduce the response rate of non-small cell lung cancer patients to the PD-1 inhibitor nivolumab[84]. This is supported by a small prospective observational study in 2020 showing that medical cannabinoids may reduce progression free survival and overall survival of Stage 4 cancers treated with checkpoint inhibitors[85]. Given the small size of these studies their results should be interpreted with caution, and decisions regarding the use of cannabis medicines in patients on immunotherapies should be made on a case-by-case basis.

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 older patients 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®)[11] Product Information (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 older 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 THC per day. Beyond this dose, the risk of adverse effects may increase.

Example for THC:CBD – from Sativex®[9] oro-mucosal spray Product Information. 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).

*Smoking is not recommended as a route of administration in Australia due to the harmful effects of smoking.

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 Agency for Clinical Innovation –Pain Management Network - Assessment resources[86].

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

Monitoring is generally only indicated when medications have specific characteristics (e.g. a NTI), where there is an established therapeutic range, where the consequences of undertreatment cannot be recognised clinically and can be serious (e.g. seizure) and/or if toxicity is suspected. CBD may cause hepatocellular injury. Patient's liver function biochemistry should be monitored prior to initiation and periodically as clinically indicated.

Cessation and withdrawal

The cessation of long-term (of more than several months) use of THC based medicines may be associated with the experience of discontinuation effects. These can be categorised as relapse and/or withdrawal effects.

Relapse refers to a worsening of the underlying condition (e.g. CNCP) for which THC is being prescribed.

The cessation of heavy (e.g. daily or almost daily) and prolonged (of several months or more) cannabis use can be associated with a withdrawal syndrome in up to 15 to 40% of long term cannabis users[87,88]. The features of cannabis withdrawal as defined in DSM-5 are shown in Table 2, with sleep problems (e.g. vivid dreams, insomnia), depressed mood and irritability/anxiety most commonly reported. Symptoms tend to emerge within 2-3 days of last THC use, peak within 4 to 14 days, with some residual symptoms persisting for 2-6 weeks[89].

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.

Table 2. DSM-5 Diagnostic criteria for cannabis withdrawal syndrome[90].

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

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. The service can be contacted via email HNELHD-CMAS@health.nsw.gov.au .
- 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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