ACRE
Australian Centre for Cannabinoid Clinical and Research Excellence

PRESCRIBING GUIDANCE

THE USE OF CANNABIS MEDICINES FOR MANAGEMENT OF INSOMNIA

About this document

Cannabis medicines are not first-line treatment for the management of insomnia. At present these drugs remain 'unapproved' by the Australian Therapeutic Goods Administration (TGA), although they provide pathways for authorised prescribers to access them for patient use.[1] This Prescribing Guidance has been developed to provide practical information to assist medical practitioners in their decision-making regarding prescription of cannabis medicines for the management of insomnia. It:

- Acknowledges the limitations of current published evidence pertaining to the use of cannabis medicines. Management of insomnia is multifaceted although there are medicines that are registered for this setting. Cannabis medicines should only be considered when non-pharmacological strategies and registered medicines have been tried and proven unsuccessful in managing symptoms or medical condition. Due to limited evidence and the need to accumulate more information, where accessible, clinical trials provide the best framework for use of cannabis medicines in insomnia. It is anticipated that this guidance will be updated as further published research becomes available.
- Notes that the quality, safety or efficacy of unregistered cannabis medicines have not been evaluated by the TGA and using them off-label has specific medicolegal considerations.
- Provides links to resources that outline non-pharmacological and standard, registered therapeutic options in the management of insomnia 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.
- Acknowledges the need for high quality randomised controlled trials (RCTs) with larger cohorts to examine the safety and efficacy of cannabis medicines in insomnia, when current therapies including non-pharmacological have failed.
- Recognises the role of cannabis medicines in treating insomnia as an evolving area of research. Research on insomnia (as per DSM-5 criteria)[2] cannot be readily extrapolated to patients with other sleep disorders, or vice versa.

Key points

- Cognitive behavioral therapy for insomnia (CBTi) is first line treatment for long term insomnia. Approved treatments for short term insomnia include melatonin, orexin receptor antagonists, benzodiazepines, and gamma-aminobutyric acid type A (GABAA) receptor agonists (Z drugs).
- Cannabis medicines should only be used for the treatment of insomnia when approved treatments for insomnia have failed. Ideally, patients should be offered the opportunity to participate in a clinical trial.
- Only certain cannabis medicine products are likely to benefit insomnia.
- Based on the limited evidence, a compound containing a synthetic tetrahydrocannabinol analogue (nabilone) 0.5-1 mg, cannabidiol (CBD) 160 mg and a combination of tetrahydrocannabinol (THC):cannabinol (CBN):CBD 10:2:1 mg/mL 0.5-1.0 mL have been shown in small randomised control studies to improve insomnia symptoms in the short term.
- Patient consent, Therapeutic Goods Administration (TGA) and in limited circumstances state approvals

need to be obtained prior to prescribing cannabis medicines.
- Use a validated self-report insomnia questionnaire for regular monitoring.
- Patients using THC cannot drive.
- Potential benefit versus harm evaluation should include consideration of vulnerable populations and potential for drug interactions.
- Ceasing use of medical cannabis by slowly tapering the dose can reduce potential for withdrawal symptoms and rebound insomnia.

Current clinical trials

Clinical trials related to insomnia that are currently recruiting can be located via searching the Australian New Zealand Clinical Trials Registry and the Australian Epilepsy Clinical Trial Network.

First Line Treatment for insomnia

Key points
- Cognitive behavioral therapy for insomnia (CBTi) is first line treatment.
- CBTi is usually delivered by a clinical psychologist trained in insomnia.
- Licensed medications for insomnia are approved for short term use.

Use of evidence-based therapies for insomnia and sleep disorders

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

Useful resources for clinicians managing insomnia:

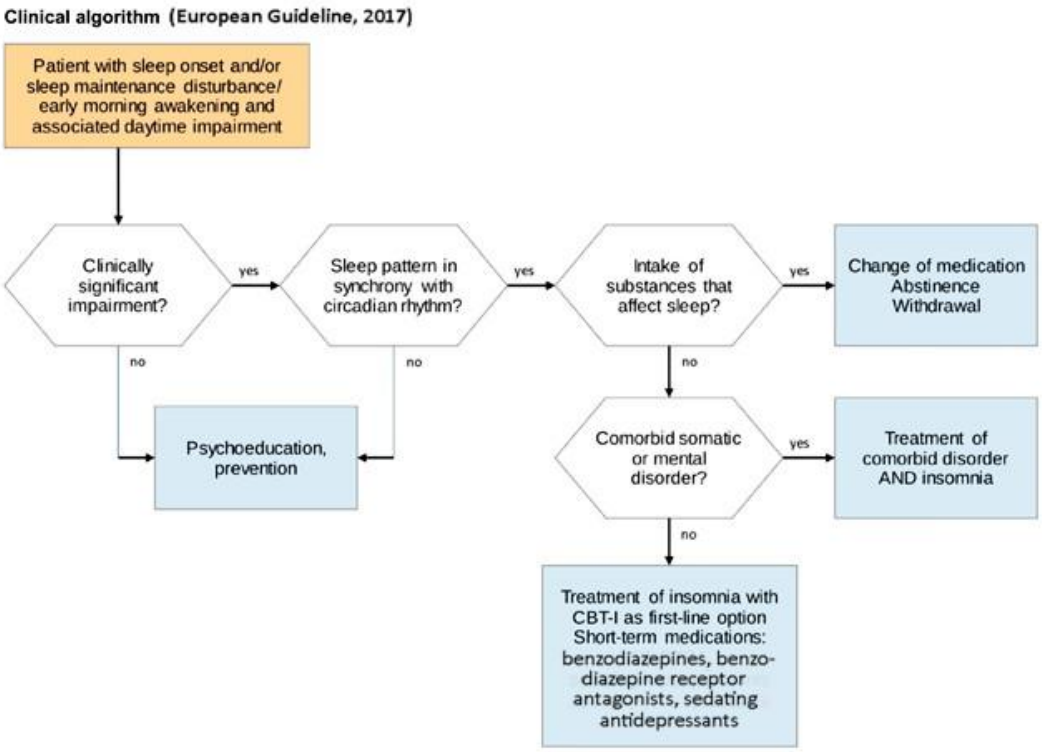
- eTG complete[3] – Insomnia in adults (available through http://www.ciap.health.nsw.gov.au for NSW Health employees)
- Ng L, et al. Management of insomnia in primary care. Australian Prescriber. 2021;44:124-8.4
- Qaseem A, et al. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Int Med. 2016;165(2):125-33.[5]
- Reimann D, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017;26:675-700.[6]
- De Crescenzo F, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. The Lancet. 2022;400(10347):170-184.[7]
- Royal Australian College of General Practitioners brief CBT-I guide: https://www.racgp.org.au/clinical-resources/clinical-guidelines/handi/handi-interventions/mental-health/brief-behavioural-therapy-insomnia-in-adults8
- International Directory of CBT-I providers: https://www.cbti.directory[9]

Best practice in treatment of insomnia

Insomnia is a common clinical problem characterised by dissatisfaction with sleep quantity or quality and associated with difficulty initiating or maintain sleep or early morning awakening. To meet the DSM-5 diagnostic criteria it must: cause significant distress or impairment, occur at least 3 nights per week, be present for at least 3 months, occur despite adequate opportunity for sleep, not be better explained by another sleep-wake disorder, not be attributable to effect of illicit substances or medication, and not be explained by coexistent medical disorders.[10]
Insomnia symptoms are frequently attributable to underlying causes which include situational disturbances, medical disorders, psychiatric conditions, and medications.[11] The situational disturbances include stress from work, financial issues, life events, and conflict. The medical conditions include those associated with dyspnoea, pain, discomfort, and disability. Other sleep disorders, menopause, and pregnancy may also contribute. Psychiatric issues that contribute to insomnia include mood disorders, anxiety, and substance abuse. Medications associated with insomnia include caffeine, ethanol, psychostimulants, beta blockers, alpha agonists, various antidepressants and anticonvulsants, antilipidemic drugs, dopamine agonists, thyroxine, quinolone antibiotics, theophylline, corticosteroids, and others. Sedative withdrawal can also cause insomnia.
Given this, it is essential that an underlying cause for insomnia symptoms be investigated and treated, if present. However, also treating insomnia in its own right is indicated even when comorbidities are present[5,12] as doing so often results in improved outcomes for comorbid conditions. Treatment strategies involve sleep hygiene advice and cognitive behavioural therapy. Pharmacological management using current approved drugs have a limited, short duration role. The sleep hygiene advice encourages behaviours that promote sleep including regular hours of sleep, avoidance of alcohol and caffeine before bedtime, and ensuring a comfortable sleeping environment. Sleep hygiene is not supported as a standalone treatment but may be beneficial in conjunction with CBT-I. The cognitive behavioural advice principles include sleep restriction, stimulus control, relaxation training, and cognitive therapy. These techniques are best administered by a clinical psychologist expert in insomnia management. Where such resources are not available, evidence-based online resources are available, using programmes such as Sleepio® and Shuti®.

However, about 1 in 3 patients with insomnia have persistent symptoms despite cognitive behavioural therapy[13], making a case for pharmacological intervention. Current approved drugs for insomnia management can be effective aids in the short term but

are more limited in the longer term. This due to the development of tolerance and, in some cases, dependence. Drugs frequently used for insomnia management include benzodiazepines, $GABA_A$ receptor agonists, melatonergic drugs, sedating antidepressants, antihistamines, and orexin receptor antagonists.



From: Riemann D et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res 2017;26:675-700.[6]

The potential role for cannabis medicines in insomnia management

These limitations in current drug therapies for insomnia have encouraged the search for alternatives, with cannabinoids providing an interesting and promising new approach. Many studies of cannabis or cannabinoids in people with health problems (such as multiple sclerosis, post-traumatic stress disorder, or chronic pain) have noted better sleep quality, fewer sleep disturbances, or decreased time to fall asleep.[14] Such information provides the basis for further research into their potential for insomnia treatment.

As with other medical problems, the general practitioner provides the primary point of care for patients with insomnia. Where insomnia proves unresponsive to standard treatments, multidisciplinary care, including the patient's general practitioner, a sleep psychologist, and/or a sleep physician is appropriate and therapeutic approaches, including the use of cannabis medicines, may be considered.

Evidence for use of cannabis medicines in the treatment of insomnia

Key points

- Evidence for cannabis in the treatment of insomnia is very limited with no clear single cannabinoid beneficial for insomnia.

It is likely that different cannabinoids and combinations thereof exert differential effects on sleep.[15] A narrative review by Maddison et al.[16] describes published data related to the effects of cannabinoids on sleep and sleep architecture in healthy individuals, along with its effects on a number of sleep disorders. The following information is based on a literature review specific to insomnia in MEDLINE and Embase from inception to April 2022. Studies that reported on effects in other sleep disorders, insomnia as secondary outcome measures in the presence of primary co-morbid conditions, including but not limited to pain, cannabis use disorder, and cannabis withdrawal were excluded due to potential confounding effects. Reference lists of review articles were also searched. Exclusions included recreational use studies, observational studies, case-series, and case-reports.

In a small (n = 24) double-blind, randomised, placebo-controlled, crossover study involving 2-weeks of Zenivol® a product containing THC 20 mg/mL, CBN 2 mg/mL and CBD 1 mg/mL (0.5-1 mL oil taken sublingually one hour before sleep), a significant reduction in Insomnia Severity Index (ISI) was reported.[17] The product was well-tolerated; although 17/24 participants experienced at least one adverse event while taking Zenivol® the most frequently reported adverse events were dry mouth and dizziness.[18] The time to maximal concentration (Tmax) for CBD, CBN, THC, carboxy-THC (THC-COOH) was 4-6 hours. Based on this pharmacokinetic data, Walsh et al.[18] suggests that dosing 2-4 hours prior to desired bedtime in sleep onset insomnia and 1 hour before bed in sleep maintenance insomnia should be considered. However, product specific pharmacokinetic data is not necessarily extrapolatable to other cannabis medicine products (see Table 1).

Another small (n = 9) double blind study investigated a single night of THC 10, 20, 30 mg (powder in liquid carrier) in male patients with insomnia. A significant decrease in sleep onset latency, visually assessed by an experienced sleep observer, was reported. Pre- and post-sleep

adverse events included but were not limited to dry mouth and dizziness/grogginess. Temporal disorganisation and perceptual disturbances were reported pre-sleep. A greater number of adverse effects were observed with higher doses. Notably, a post-sleep hangover effect was reported with the 30 mg dose and the authors of the study suggest a 20 mg THC dose threshold in the context of insomnia.[19]

One study (n = 15) investigated the effect of single nights of CBD 40, 80 and 160 mg (powder in gelatine capsules) in comparison to placebo and nitrazepam as an active comparator in patients with self-reported difficulty falling and staying asleep.[20] Self-reported sleep duration was significantly improved, but not the time taken to fall asleep, when taking 160 mg of CBD compared to placebo. No differences in sleep quality or duration were reported when taking the 40 and 80 mg CBD doses compared to placebo. Symptoms indicative of morning hangover were not greater when taking any dose of CBD compared to placebo.

It is worth noting limitations of research published to date include a predominance of lower quality trial methodologies, high-risk of bias, lack of objective outcome measures and head-to-head studies with existing therapeutic strategies, and small cohorts, usually over a short duration. Further research is needed into which cannabinoid or combination thereof, route of administration, duration and dose to use in the treatment of insomnia. Additional considerations that would benefit from further research include the potential for use in combination with CBT-I, withdrawal/tapering, hangover effects, and falls risk. Systematic reviews on cannabis medicines and sleep disorders conclude that there is insufficient high-quality published research to guide use in clinical practice settings at this point in time.[21-22]

There are several randomised trials underway, therefore we anticipate as research outcomes are published this prescribing guidance will be updated.

Table 1 Randomised double-blind trials pertaining to cannabis medicines and insomnia

Population	Intervention	Participants (n =)	Outcomes
Insomnia (SOL 60-90 minutes), males 21 to 40 years (Cousens 1973)[19]	Single night-time dose THC 10, 20, 30 mg, placebo	9	Significantly decreased SOL 43, 62, 54 minutes, no alteration in WASO. Adverse events: Higher doses were associated with a greater number of adverse effects. <u>Pre- and post- sleep</u> Dizziness/grogginess, dry mouth, and funny taste. <u>Pre-sleep</u> Temporal disorganisation and perceptual disturbances. <u>Post-sleep</u> Residual 'hangover' effects the next day (perceptual disturbance, altered speed of thought) with the 30 mg dose.
Self-reported difficulty falling and staying asleep (SOL ≥ 60 mins) (Carlini 1981)[20]	Single dose CBD 40, 80, 160 mg capsules, nitrazepam 5 mg and placebo	15	Increased sleep duration with 160 mg (n = 10) based on self-reported measures.
Chronic insomnia symptoms (≥3 months), predominantly females, 53+/- 9 years (Walsh 2021)[18]	Sublingual cannabinoid extract (Zenivol®; ZTL-101 containing THC 10 mg, CBD 1 mg and CBN 0.5 mg) nightly for 2 weeks.	12 (ZTL-101); 12 (placebo)	Primary outcome: Significant reduction in ISI. Secondary outcomes: Reduction in self-reported SOL, actigraphy-derived WASO. Increased self-reported and actigraphy-derived TST, rested feeling on waking and SE. Adverse events: (n = 40 overall; n = 36 ZTL-101 and n = 1 withdrawal) mild, non-serious.

CBD = cannabidiol; THC = Delta-9-tetrahydrocannabinol; CBN = cannabinol; ISI = Insomnia Severity Index; actigraphy-derived and polysomnography measurements of sleep onset latency (SOL); WASO = wake after sleep onset; TST = total sleep time; SE = sleep efficiency.

Considerations for prescribing cannabis as a treatment for insomnia

Key points

- Two cannabis medicines are registered for use in Australia but these have not been investigated for the treatment of insomnia.
- Many unregistered medicinal cannabis products are available in Australia via the TGA Special Access and Authorised Prescriber Schemes, but the majority have not been investigated for the treatment of insomnia.
- Patient consent, TGA, and in limited circumstances state approvals, need to be obtained.
- High-quality research is necessary to determine which cannabis medicines are of potential benefit for insomnia and to quantify the adverse events.
- Patients should be aware of any opportunities to participate in a clinical trial of cannabis medicine for the treatment of insomnia.
- Patients need to be advised they cannot drive if using a medication containing THC.

Before prescribing cannabis medicines for the management of insomnia

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

Current clinical trials

Clinical trials related to treatment of insomnia that are currently recruiting can be located via searching the Australian New Zealand Clinical Trials Registry. Suitable patients should be offered the opportunity to participate in an appropriate clinical trial.

Prescriber obligations

The prescriber should have 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 aware of the decision to prescribe cannabis medicines and 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 status of most cannabis medicines as unregistered medicines, prescribers should consider seeking advice from their medical indemnity insurers prior to prescribing.

Prescribers should adhere to TGA and state health department regulations regarding prescription of cannabis medicines.

Prescribers should ensure the Patient or the Patient's Responsible Person are fully informed prior to consenting to treatment.

Patient consent

The Patient or Patient's Responsible Person (i.e. parent/s, carer) must give informed consent to treatment and consent documented. 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 cannabis medicines are still being researched, but possible effects and side effects of treatment should be discussed.
- **Patients should be advised that they are not able to drive or operate heavy machinery while treated with cannabis medicines containing THC.** 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[23] and in the NSW Health's Prescribed Cannabis Medicines and Fitness to Drive Factsheet[24].
- The patient should be given clear information about therapeutic goals and likely stopping criteria.
- There is potential for dependence and withdrawal symptoms.

Which cannabis medicine product to prescribe?

- There are up to 100 cannabinoids (chemical compounds) in the cannabis plant, many are active and have active metabolites.
- THC is responsible for the intoxicating effects of cannabis and is one reason cannabis is used recreationally. THC may contribute to reduction of nausea, vomiting, pain, and muscle spasms and some describe improvements in sleep and appetite.
- Cannabidiol has effects on neurological function including seizure activity, sedation, and dizziness, however intoxication has not been reported. It may be useful in the management of seizures and may have anxiolytic and antipsychotic effects for some people.
- Different cannabis medicine products can contain different ratios of cannabinoids. These can bind to different receptors and are likely to elicit different effects.
- Consider the available evidence and products, and the patient's comorbidities and lifestyle requirements, to determine the most appropriate cannabis medicine to treat their insomnia.

TGA registered cannabis medicines

There are currently two registered cannabis medicines in Australia:

- Sativex®[25] oromucosal spray (THC 2.7mg/spray; CBD 2.5mg/spray) is registered (Schedule 8) for the indication of moderate to severe spasticity in patients with multiple sclerosis.
- Epidyolex®[26] (CBD 100 mg/mL) oral liquid is registered (Schedule 4) for the indication of epilepsy, as an adjunctive therapy for Lennox-Gastaut syndrome, or Dravet syndrome associated seizures in patients ≥ 2 years of age in Australia (please refer to linked authority criteria).

Neither of the registered products have been investigated for the treatment of insomnia.

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 & Drug Administration have approved the use of synthetic cannabinoid products, for specified indications, including:

- Marinol®[27] and Syndros®[28] – dronabinol* (anorexia in patients with Acquired Immune Deficiency Syndrome (AIDS) who have lost weight and treatment refractory nausea and vomiting associated with chemotherapy for cancer)

- Cesamet®[29] – nabilone* (treatment refractory nausea and vomiting associated with chemotherapy).

*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.

Unregistered cannabis medicines

The majority of cannabis medicines that are available in Australia are unregistered. A variety of unregistered cannabis medicines (that conform to the requirements of the Therapeutic Goods (Standard for Medicinal Cannabis) (TGO93) Order[30] and the Therapeutic Goods (Microbiological Standards for Medicines) (TGO 100) Order[31] are available. The TGA has published a list of Medicinal cannabis products by active ingredients[32], grouped into five categories:

- Category 1: CBD medicinal cannabis product (CBD ≥ 98%)
- Category 2: CBD dominant medicinal cannabis product (CBD ≥ 60% and < 98%)
- Category 3: Balanced medicinal cannabis product (CBD < 60% and ≥ 40%)
- Category 4: THC dominant medicinal cannabis product (THC 60% - 98%)
- Category 5: THC medicinal cannabis product (THC >98%)

However, inclusion of a cannabis medicine in the published TGA list does not guarantee availability. The information provided on the TGA website is self-declared from sponsors although the TGA will conduct routine compliance audits.

Initiating, monitoring, and ceasing cannabis medicines for the treatment of insomnia

Key points:

- Patient response to cannabis medicines varies widely, and responses and side effects show both intra and interindividual variation, dose, regimen, route of administration, concomitant medicine use and patient factors all contribute. Start with a low dose and titrate slowly.
- Regular follow-up and monitoring response to treatment using validated insomnia questionnaire such as the Insomnia severity index (ISI).
- Gradually taper over 4 to 8 weeks ceasing cannabis to prevent withdrawal symptoms such as rebound insomnia and mood disturbance.

Dosing

- Start at low dose and frequency.
- Titrate to effect whilst monitoring for side effects.
- Patient response to these medications varies widely.
- Lower doses should be considered in older patients due to higher rates of polypharmacy and comorbidities, including hepatic impairment.
- As lipophilic foods may increase bioavailability, doses should be taken consistently with or without food.
- The following is an example only – doses should be individualised.

There is very limited high-quality data on which to base cannabinoid dosing recommendations in insomnia. One small study used a sublingual product (Zenivol®; THC 20 mg/mL, CBN 2 mg/mL, and CBD 1 mg/mL) at night for a two-week period. The starting dose was 0.5 mL and was optionally increased to 1.0 mL after 3 nights.[18] Further high quality randomised controlled trials are needed to guide optimal dose, frequency, and route of administration. The authors of another trial suggested that doses greater than 20 mg of THC may be associated with a hangover effect.[19]

When taking CBD alone, one trial identified that 160 mg improved sleep duration while 80 mg did not.[20]

Dosing based on very limited clinical trial data cannot be readily extrapolated to other unregistered oral products, other routes of administration or indications.

Route of administration

Existing evidence utilised oral or oro-mucosal dosing only. Effects are likely to be variable in terms of time of onset of action, time to peak effect, and duration of effect with other routes of administration.

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

Pharmacokinetics and pharmacodynamics

- Cannabinoids are lipophilic and undergo extensive first pass metabolism.
- Oral cannabinoid bioavailability is low, variable and increases with a high fat meal. [33,34, 35,50]
- Following oral administration, CBD appears rapidly in the plasma with reported time to maximum concentration values usually 3 - 5 hours.[26]
- Steady-state plasma CBD concentrations are achieved after ~2-4 days of twice daily dosing.[26]
- Dose and frequency adjustments may be required over time due to auto-inhibition of metabolism, active metabolite accumulation in fat with chronic dosing, and active metabolites with longer half-lives.
- Although cannabidiol is highly lipophilic and can cross the blood brain barrier, rate and extent is influenced by route of administration and formulation.[36] Further research is needed to better understand the relationship between plasma concentration and therapeutic effect.

- The pharmacokinetics and pharmacodynamics of THC are very similar to those of CBD when administered by the same route. [50]

Monitoring outcomes

Monitoring should initially involve reviewing the patient weekly in person, and via phone if required in the interim between clinical reviews. 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 with a validated tool, for example the Insomnia Severity Index[17] or a sleep diary to determine sleep efficiency (proportion of time spent asleep relative to the time spent trying to sleep).

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[37] when these events occur to enable patterns of toxicity and contributing factors to be elucidated, to support future prescribing information.

3. Monitoring

CBD may cause hepatocellular injury. Liver function biochemistry should be monitored prior to initiation and periodically as clinically indicated. Drug serum or plasma concentration monitoring is generally only indicated when medications have specific characteristics (e.g. a narrow therapeutic index), 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.

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 rebound and/or withdrawal effects.

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

The cessation of heavy (e.g. daily or almost daily) and prolonged (several months or more) cannabis use can be associated with a withdrawal syndrome in up to 15 to 40% of long term recreational cannabis users.[38-39] 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.[40] The effects of withdrawal from long-term medicinal cannabis use remains to be elucidated. However as with other medicines bind to G-protein coupled receptors, the effects on the endogenous cannabinoid system is expected to take several weeks to reset.

When discontinuing a 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.

There is no recognised withdrawal syndrome associated with cessation of CBD.[41]

Precautions

Key points:

- Adverse effects of cannabis medicines include sedation, dizziness, and blood pressure effects.
- Avoid using cannabis medicines in patients with co-morbid previous psychotic or concurrent active mood or anxiety disorder, unstable cardiovascular disease, pregnancy, breastfeeding or in those planning a pregnancy.
- THC and CBD are metabolised by Cytochrome P450 (e.g., CYP3A4, CYP2C9 and CYP2C19) and can be affected by inducers and inhibitors of this enzyme. Clinical, laboratory and therapeutic drug monitoring (where relevant) are the mainstays of management of potential pharmacokinetic and pharmacodynamic drug interactions with cannabis medicines. Dose adjustments may be required.

General precautions

Cannabis medicines, including cannabidiol should be avoided by patients who are pregnant, planning on becoming pregnant or breastfeeding.[26,42]

Cannabis medicine products containing THC are generally not appropriate for patients who:

- Have a history of psychotic or concurrent active mood or anxiety disorder.
- Have unstable cardiovascular disease.[43]

Consider concomitant medication use and potential for pharmacokinetic and pharmacodynamic drug interactions (see below).

Use in special populations.

Older patients

Older patients with multiple comorbidities and polypharmacy may be a greater risk of adverse effects,

including but not limited to falls. Consider use of lower doses.

Renal failure
Limited data on cannabidiol in renal impairment suggests that metabolism is not affected.[44]

Hepatic considerations
Due to the significant liver metabolism of cannabinoids, dose adjustments are likely to be needed in moderate to severe hepatic impairment.[45]

Adolescents and young adult patients
Cannabis medicine products containing THC have the potential to impact neurocognitive functioning in patients under 25 years of age.[46-47]

Contraindications

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.

Avoidance or cessation of CBD should be considered in those with elevated transaminases >3x upper normal limit (UNL) and bilirubin >2x UNL[26]. However doses used for insomnia are significantly lower than for epilepsy.

Adverse effects

Somnolence, sedation, dizziness, psychosis (with THC) and bidirectional effects on blood pressure are potential adverse effects of cannabinoids. Therefore, care is needed in individuals at risk of falls. In randomised controlled trials of cannabinoids in insomnia, the most common adverse effects observed include dizziness, dry mouth, headaches, and feeling abnormal.[48] Altered taste, temporal disorganisation, and perceptual disturbances have also been reported.[19]

Tolerance to somnolence and sedation may occur with chronic use.[26-27,29]

Higher doses (THC 30 mg) have been observed to be associated with an increased frequency of adverse events, including hangover effects.[19]

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

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)[26], Cesamet® (nabilone)[29], Marinol® (dronabinol)[27], and Sativex® (THC and CBD)[25], 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.

Potential pharmacodynamic drug interactions with cannabis medicines

- Sedatives
- Alcohol
- Opioids
- Cardiovascular drugs
- Neuro-psychiatric drugs
- Anti-spasticity agents
- Cancer immunotherapies

For comprehensive information on cannabidiol drug interactions, please refer to Cannabidiol drug interaction considerations for prescribers and pharmacists[49], particularly the quick reference summaries in Tables 4 and 5. For detailed information on other cannabinoids, including but not limited to THC, please refer to the NSW Guidance on cannabis medicine drug interactions document.

Further Information

- 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 cannabis medicines, including requirements of the prescriber, dispensing and storage is available from the NSW Government's Pharmaceutical Services page on Cannabis Medicines.
- NSW-based general practitioners, community pharmacists, and rural health practitioners can contact the NSW Health cannabis medicines information service via John Hunter Hospital Pharmacy Department HNELHD-

JHHPharmacy@health.nsw.gov.au. Public health practitioners working in metropolitan local health districts should consult their local medicines information services.

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