Interim Guidance regarding THC-based Medicinal Cannabis Treatment for Patients with Cannabis and/or other Substance Use Disorders

Date 4 August 2024

Foreword

The need for guidance.

The rapid expansion of medicinal cannabis treatment in Australia has resulted in (an estimated) >500,000 Australians having been prescribed a THC-based medicine[1,2] predominately for indications such as chronic pain, mental health and sleep disorders. International and Australian studies indicate that a considerable proportion (between 10-20%[3]) of these patients meet criteria of cannabis dependence – as many as 50-100,000 Australians prescribed THC-based medicines.

To minimise risks and optimise patient safety, clinicians should consider specific evidence-informed approaches when providing THC-based medicinal cannabis treatment to patients with cannabis dependence. There has been little to no guidance provided to date for clinicians, consumers or regulators on what is good clinical practice in this clinical context. In part this is because of the unique framework in Australia for prescription of medicinal cannabis – whereby medical/nurse practitioners prescribe specific preparations, concentrations and quantities with dosing instructions (like other medicines) and these are dispensed at a pharmacy. This contrasts with most international settings in which medical cannabis is available – whereby medical practitioners generally authorise a patient s access to medical cannabis – but allow patients to choose their own products and quantities at cannabis dispensaries[4].

The approaches described in this document are similar to those recommended for responsible prescribing of other medications that have the potential for 'iatrogenic dependence' or misuse – such as opioids and benzodiazepines[5,6]. It is timely that guidelines are developed to address this gap in the medicinal cannabis literature.

This interim guidance document has been developed by the Australian Medicinal Cannabis Association, with input from experienced medical practitioners, nurses, pharmacists and researchers who are AMCA members. Further consultation with a broader range of consumers, clinicians and academics will be sought in coming months, with a view to updating the document.

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[1] Based on estimates derived from AIHW National Household Survey 2022-23. Accessed June 2024 at https://www.aihw.gov.au/getmedia/b8b298cc-6d3f-4ab0-a238-9bd63f300c09/national-drug-strategy-household-survey-2022-2023.pdf?v=20240229072409&inline=true

[2] TGA Medicinal Cannabis SAP-B data portal accessible at https://www.tga.gov.au/medicinal-cannabis-special-access-scheme-category-b-data

[3] Dawson D, et al. The prevalence of cannabis use disorders in people who use medicinal cannabis: A systematic review and meta-analysis. Drug Alcohol Depend. 2024; 257:111263. doi: 10.1016/j.drugalcdep.2024.111263.

[4] https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/medical-use-cannabis.html; Ryan JE, McCabe SE, Boyd CJ. Medicinal Cannabis: Policy, Patients, and Providers. Policy Polit Nurs Pract. 2021 May;22(2):126-133. doi: 10.1177/1527154421989609.

[5] RACP Prescribing Drugs of Dependence in General Practice 2015. Accessed June 2024 at https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/drugs-of-dependence

[6] Black E, Khor KE, Demirkol A. Responsible Prescribing of Opioids for Chronic Non-Cancer Pain: A Scoping Review. Pharmacy (Basel). 2020 Aug 20;8(3):150. doi: 10.3390/pharmacy8030150.

Context for the Guidance

Target audience: This guidance document provides information for health care professionals (HCPs) (including medical and nurse practitioners, pharmacists), consumers and regulators involved with medicinal cannabis treatment under the Special Access Scheme-B (SAS-B) or Authorised Prescriber Scheme (APS) pathways administered by the TGA. It should be emphasized that HCPs must be familiar with - and comply with, relevant legislation and regulations regarding Schedule 8 medications- including MCS8 products.

Which medications? The guidance refers to the use of cannabinoid Schedule 8 medications that include delta-9-tetrahydrocannabinol (THC) – or Category 2 to 5 medicinal cannabis products within the TGA framework[7,8] (see Section 2.1, Table 5 for a description of TGA medicinal cannabis categories). For the remainder of this document, we use the abbreviation MCS8 (Medicinal Cannabis Schedule 8) to refer to THC-based medicinal cannabis products.

Cannabidiol-only (CBD) medicines (Category 1 within TGA framework) are registered as Schedule 4 medicines, have no abuse or addictive potential, and as such are not included in these guidelines.

Which clinical populations? The target clinical population for the guidance is patients who have a cannabis use disorder (either to prescribed or non-prescribed cannabis) and/or have a substance use disorder to another substance (e.g. opioids, benzodiazepines, alcohol). In most cases, the primary indication for MCS8 treatment is for the management of other medical conditions (e.g., pain, mental health, sleep, neurological conditions). To date, only a small number of patients are treated with MCS8 for the primary indication of treating cannabis or other substance use disorders[6].

In some instances, patients seeking MCS8 treatment may be dependent on other substances (e.g. opioids, benzodiazepines, alcohol) and not to cannabis. Some state/territory Health Departments require prescribing practitioners to obtain an S8 permit prior to prescribing THC based medicines to a drug dependent person (see Section 1.3). Patients with a substance use disorder to other drugs are at increased risk of developing CUD as part of MCS8 treatment, and the guidelines here also refer to good clinical practice in that context (i.e., patients dependent on other drugs, and seeking treatment with MCS8).

Guiding principles. The guidance is based upon a universal precaution framework – borrowed from responsible opioid prescribing[6,9] – whereby all patients seeking MCS8 should be screened for a potential substance use disorder, and treatment tailored accordingly. As such, the guidance here has implications for all patients and HCPs involved in MCS8 treatment.

This document does not attempt to provide general guidance for providing medicinal cannabis treatment outside of this clinical context. Readers are referred to relevant guidance documents[10].

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[7] Therapeutic Goods Administration. Scheduling basics Canberra: Department of Health; 2011. Available at www.tga.gov.au/industry/ scheduling-basics.htm [Accessed January 2014].
[8] https://www.tga.gov.au/news/media-releases/new-streamlined-process-medicinal-cannabis-applications
[9] Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med 2005;6(2):107–12.
[10] https://www.tga.gov.au/medicinal-cannabis-guidance-documents

Summary of clinical recommendations for HCPs

1. Assessment

1.1. History of presenting condition, including current and prior treatment approaches, and where relevant, liaise with other health care providers

1.2. History of cannabis and other substance use

- Quantity, frequency and type of cannabis used, duration of use, and estimate proportion of cannabis use that is for medical versus non-medical purposes
- Does the patient meet criteria for a CUD or other SUD (use DSM5 or ICD-11 checklists)
- Does the patient have risk factors for developing CUD with medicinal cannabis?
  - Male, age <40; poor psychological health; mental health indication, history other SUDs
  - Inhaled v oral route; daily use of high THC doses; long-term treatment (>3 months); frequent non-medical cannabis use

1.3. Investigations: Examine Safescript for history of MCS8 and other S8/S4D medication use. Consider role of urine drug screen for detecting recent cannabis or other substance use.

2. Patient Education and Informed Consent

2.1. Discuss risks of cannabis dependence and cannabis withdrawal arising from long-term MCS8 use, including factors that increase these risks (daily use, prolonged use, inhaled routes, higher THC doses)

2.2. Informed consent to treatment

2.3. Consider written patient agreement identifying conditions of treatment (e.g. dose escalations, replacing scripts, conditions for stopping MCS8 treatment, Safescript)

3. Tailor Treatment according to risk

3.1. Obtain and follow conditions of S8 permit as required by local Health Department.

3.2. Prescribing guidance

- THC/CBD ratios: Unclear as to whether adding CBD to THC alters potential for CUD
- Formulation: Inhaled routes more likely associated with increased CUD risk, although may be preferred for episodic use. Encourage oral routes for patients with regular THC use.
- Doses: patients with tolerance to cannabis usually require higher doses of THC, titrated upwards to achieve clinical effect. *For individuals with tolerance to cannabis, daily doses of up to 80mg oral or 500mg THC inhaled may be required.* Seek a second opinion from an experienced medicinal cannabis prescriber if prescribing higher doses.

3.3. Dispensing

- Consider interval dispensing (e.g. weekly / fortnightly supplies) for patients experiencing Difficulties managing their medication (e.g. running out early, dose escalations);
- Discuss safe storage of medications;
- Discuss potential for adverse events, drug-drug interactions (e.g. alcohol, sedating drugs).

4. Monitoring and clinical documentation

4.1. Regularly monitor and document effectiveness of medicinal cannabis in treating the primary condition – including symptom reduction and functional outcomes. Consider discontinuation of MCS8 treatment if no clinically significant improvement over time.

4.2. Regularly monitor safety (adverse events, DDIs)

4.3. Regularly monitor medication adherence, including regular examination of Safescript for evidence of the patient's S8 and S4D medication use. Monitor and document extent to which the patient is using the medication as prescribed and assess for aberrant medication behaviours (e.g. unauthorised dose escalations, non-recommended route; diversion to others; cannabis use for non-medical reasons; accessing MCS8 from other HCPs)

Contents

1. Background

1.1 What are cannabis use disorder and cannabis dependence?

1.1.1. Cannabis use disorder, cannabis dependence.

Cannabis use disorder is the term used in the Diagnostic and Statistical Manual of Mental Disorders (5th edition)[11] (DSM5) classification system and refers to a chronic bio-psycho-social condition signifying regular cannabis use despite clinically significant impairment arising from the use of cannabis. DSM5 identifies 11 diagnostic criteria within the preceding 12 months for a Substance Use Disorder (SUD) (Table 1), and recognises a continuum of severity – with Mild (2-3 criteria), Moderate (4-5) and Severe (6+) conditions.

Table 1. DSM-5 criteria for diagnosing a Substance Use Disorder[14]	
A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following 11 criteria, occurring within a 12-month period:	
Impaired control criteria	1. Substances are often taken in larger amounts or over a longer period than was intended
	2. There is a persistent desire or unsuccessful efforts to cut down or control substance use
	3. A great deal of time is spent in activities necessary to obtain the substance; use the substance; or recover from its effects
	4. Craving or strong desire or urge to use the substance
Social impairment criteria	5. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school or home (e.g. repeated absences from work or poor work performance related to substance use; substance-related absences, suspensions or expulsions from school; neglect of children or household)
	6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of substances (e.g. arguments with a spouse about consequences of intoxication; physical fights)
	7. Important social, occupational or recreational activities are given up or reduced because of substance use
Risky use criteria	8. Recurrent substance use in situations in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance use)
	9. Substance use is continued despite knowledge of having persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
Pharmacological criteria	10. Tolerance, as defined by either of the following: a. A need for markedly increasing amounts of the substance to achieve intoxication or desired effect b. A markedly diminished effect with continued use of the same amount of the substance
	11. Withdrawal, as manifested by either one of the following: a. The characteristic withdrawal syndrome for substance b. Substance is taken to relieve or avoid withdrawal symptoms
Current severity:	Mild: Presence of 2–3 symptoms Moderate: Presence of 4–5 symptoms Severe: Presence of 6 or more symptoms
In early remission:	After full criteria for SUD were previously met, none of the criteria for SUD have been met for at least 3 months but for less than 12 months (excepting cravings)
In sustained remission:	After full criteria for SUD were previously met, none of the criteria for SUD have been met at any time during a period of 12 months or longer (excepting cravings)

[11] Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright ©2013). American Psychiatric Association.

ICD-11 uses an alternative classification system of harmful cannabis use (6C41.2) and cannabis dependence (6C41.2), criteria for which are shown in Table 2 below.

Table 2. ICD-11 Cannabis Dependence[12]
A pattern of recurrent episodic or continuous use of cannabis is required for diagnosis, with evidence of impaired regulation of cannabis use that is manifested in two or more of the following:
1. Impaired control over cannabis use (i.e. onset, frequency, intensity, duration, termination, context);
2. Increasing precedence of cannabis use over other aspects of life, including maintenance of health, and daily activities and responsibilities, such that cannabis use continues or escalates despite the occurrence of harm or negative consequences (e.g. repeated relationship disruption, occupational or scholastic consequences, negative impact on health);
3. Physiological features indicative of neuroadaptation to cannabis, including tolerance to the effects of cannabis or a need to use increasing amounts of cannabis to achieve the same effect; withdrawal symptoms following cessation or reduction in use of cannabis; or repeated use of cannabis or pharmacologically similar substances to prevent or alleviate withdrawal symptoms
The features of dependence are usually evident over a period of at least 12 months, but the diagnosis may be made if use is continuous (daily or almost daily) for at least 3 months.

Where a person exhibits harms to their physical, mental health or social functioning, but without features of physiological dependence or impaired control over use, then an ICD-11 diagnosis of Harmful Cannabis Use may be more appropriate.

Whilst the criteria used to define cannabis dependence have minor differences to DSM5, Moderate to Severe CUD under DSM5 is broadly consistent with a diagnosis of cannabis dependence in ICD-11.

Both ICD-11 Dependence and DSM5 Mod-severe CUD correspond to the term 'drug dependence' in most state based therapeutic poisons regulations and have implications for approval, treatment and monitoring conditions in each Australian jurisdiction (see Section 1.3 for a summary of each jurisdictions prescribing and dispensing requirements for MCS8 to patients). HCPs are advised to become familiar with specific requirements in the jurisdiction in which they work.

Substance use disorder classification systems have historically been developed for drugs that are used outside of a medical context (e.g. alcohol, illicit drugs, non-medical use of prescription drugs). There is recognition within DSM5 that for some drug classes (e.g. opioids), the long-term and regular use of prescribed medications can be associated with features of physiological dependence – tolerance and withdrawal, that are normal physiological responses, and on their own, should not be included as criteria for SUD. Thus, where opioid medications *are used as prescribed* (dose, route of administration, duration) tolerance and withdrawal criteria are excluded from the diagnosis of prescription opioid use disorder (pOUD), and instead of 11 criteria, diagnosis of mild pOUD requires 2-3/9 criteria, moderate pOUD is 4-5/9 criteria, and severe pOUD is 6+ of 9 criteria.

[12] International Classification Diseases Version 11. WHO. https://icd.who.int/browse/2024-01/mms/en#1129015467

There is currently debate whether similar modifications for prescription CUD diagnostic criteria (i.e. tolerance and withdrawal excluded) should be considered in circumstances where medicinal cannabis is used only as prescribed (dose, route of administration), with no use of non-prescribed (illicit cannabis) for any reason. In recent studies of CUD in medicinal cannabis patients, tolerance and withdrawal criteria are the most frequently reported individual criteria (see review[3]), such that the inclusion of these criteria may greatly impact on the prevalence of CUD in medicinal cannabis patients, and further research is required on this issue.

1.1.2. Cannabis withdrawal syndrome

Cannabis withdrawal syndrome (CWS) is the emergence of specific signs and symptoms within days of stopping or significantly reducing regular cannabis use. To meet DSM5 criteria for CWS, people must experience 3 or more of the signs or symptoms shown in Table 3.

Table 3. DSM-5 classification of Cannabis Withdrawal Syndrome[14]
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 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
D. The symptoms are not due to a general medical condition and are not better accounted for by another disorder

Symptoms are most severe in first 2 to 5 days after stopping, and generally subside over 1-4 weeks, although as with other SUDs, symptoms of anxiety, low mood and sleep disturbances can persist.

The overall prevalence of CWS in illicit cannabis users is estimated at approximately a third of people (32%) using less than daily , increasing to approximately half (46%) of people using cannabis daily[13]. Amongst a sample of Australian medical cannabis users[14], 35% met criteria for CWS, with the most common symptoms being sleep difficulty (47%), restlessness (32%), nervousness or anxiety (29%), depressed mood (25%).

1.2 Prevalence and predictors of CUD in patients prescribed medicinal cannabis.

Most research into CUD has focused upon people using illicit cannabis. Approximately 10% (CI 9-22%) of people who have used cannabis in the past year develop cannabis dependence

[13] Gorelick DA, Levin KH, Copersino ML, et al. Diagnostic criteria for cannabis withdrawal syndrome. Drug Alcohol Depend. 2012 Jun 1;123(1-3):141-7. doi: 10.1016/j.drugalcdep.2011.11.007.
[14] Mills L, Lintzeris N, O'Malley M, et al. Prevalence and correlates of cannabis use disorder among Australians using cannabis products to treat a medical condition. Drug Alcohol Rev. 2022 ;41(5):1095-1108. doi: 10.1111/dar.13444.

(moderate/severe CUD) and 22% (CI: 18-26%) meet criteria for CUD[15]. This rate increases to 30-50% in people using cannabis more regularly (daily or almost daily).

A recent systematic review of CUD in patients using medical cannabis[16] indicates broadly similar rates of CUD – estimated at 25% (CI: 18-33%) across studies for people with past year medical cannabis use, of which 11 -27% met criteria for moderate CUD, and 0-20% met severe CUD criteria across 14 studies. A recent study of people prescribed medicinal cannabis in Australia from the CAMS22 online survey[17] identified 15% of participants met criteria for moderate-severe CUD.

The recent systematic review of CUD in people using medical cannabis[12] highlighted that the following characteristics were associated with higher prevalence of CUD in people using medical cannabis:

- younger age (under the age of 30) had higher rates of CUD than older patients
- males had higher rates of CUD in some studies than females.
- frequency and quantity of medical cannabis use: daily medical cannabis use is associated with higher rates of CUD than people using cannabis less frequently, and CUD is associated with greater quantities of cannabis on days used
- route of administration: inhaled or smoked cannabis was associated with higher rates of CUD than oral routes.
- higher proportion of cannabis use for non-medical reasons (e.g. intoxication, social reasons) is associated with higher rates of CUD
- poor psychological health was associated with higher rates of CUD in several studies
- medical condition treated: patients using medicinal cannabis to treat mental health conditions (e.g. anxiety, depression, PTSD) had higher rates of CUD than other medical conditions. Chronic pain conditions had a variable impact – with some studies identifying chronic pain patients as having higher rates of CUD, whereas other studies (including Australian research[17, 18]) did not show this relationship in regression analyses.

The most common individual criteria of CUD subscribed by medicinal cannabis use are tolerance and withdrawal[17]. In the largest Australian study of people prescribed medicinal cannabis[18], the most common items reported were tolerance (28%), withdrawal syndrome (49%), cravings (23%) and ongoing medicinal cannabis use for longer than intended (17%).

[15] Leung J, et al. What is the prevalence and risk of cannabis use disorders among people who use cannabis? a systematic review and meta-analysis. Addict Behav. 2020;109:106479. doi: 10.1016/j.addbeh.2020.106479.
[16] Dawson D, et al. The prevalence of cannabis use disorders in people who use medicinal cannabis: A systematic review and meta-analysis. Drug Alcohol Depend. 2024 ;257:111263. doi: 10.1016/j.drugalcdep.2024.111263.
[17] Mills L et al. Prevalence and correlates of cannabis use disorder in people using prescribed medicinal cannabis in Australia. Submitted for review.
[18] Mills L, et al. Prevalence and correlates of cannabis use disorder among Australians using cannabis products to treat a medical condition. Drug Alcohol Rev. 2022 ;41(5):1095-1108. doi: 10.1111/dar.13444.

1.3 Relevant state and commonwealth regulatory requirements

1.3.1. Commonwealth TGA Framework

Two cannabis-based medicines - Sativex® (combined CBD and THC product) and Epidyolex® (CBD product) are licensed and registered with the TGA for specific indications (multiple sclerosis and specific paediatric epilepsies, respectively). All other medicinal cannabis products

- are unapproved (not licensed) medicines in Australia, that is, they have no stated clinical indication nor contraindications, dosing specifications, or adverse event profiles;
- must comply with the Australian Standard for Medicinal Cannabis (known as the Therapeutic Goods Standard for Medicinal Cannabis (TGO93) Order 2017[19]). TGO 93 sets out the testing, labelling and Good Manufacturing Practice (GMP) requirements for medicinal cannabis products, ensuring all products are of known cannabinoid composition and concentrations (from which doses can be estimated) and meet safety standards.

Medical or nurse practitioners can prescribe unlicensed medicinal cannabis products using one of two pathways:

- the Special Access Scheme B (SAS-B)[20], whereby prescribers must obtain an individual SAS-B permit approval from the TGA (through the online TGA portal) prior to prescribing to the patient, and pharmacies must have evidence of the SAS-B permit approval prior to dispensing to a particular patient.
- the Authorised Prescriber Scheme (APS), either by obtaining approval of their prescribing and treatment procedures by a Human Research Ethics Committee or specialist college, or by prescribing certain products for certain clinical conditions, as specified by the TGA through Established History of Use pathway[21]. Once an AP, the treating medical or nurse practitioner can prescribe to individual patients within the specified treatment conditions, without seeking individual patient SAS-B approvals from the TGA.

1.3.2. State and Territory frameworks.

Separate to the Commonwealth framework, states and territories have their own legislation and regulations that govern the use of drugs and therapeutics. These are summarised for MCS8 products in Table 4 below (as at the time of writing, and readers are recommended to review their local requirements as conditions may change over time).

Table 4. MCS8 permit requirements by State and Territory Health Departments

State/ territory	*Legislative requirements*
New South Wales[21]	An approval from NSW Ministry of Health is required to prescribe or supply any Schedule 8 medicine to • a drug dependent person (this includes people dependent to S8 drugs, illicit drugs or in Opioid Dependence Treatment)

[19] https://www.tga.gov.au/resources/resource/guidance/conforming-therapeutic-goods-standard-medicinal-cannabis-tgo-93-order-2017

[20] https://www.tga.gov.au/products/unapproved-therapeutic-goods/medicinal-cannabis-hub/medicinal-cannabis-access-pathways-and-usage-data#:~:text=Authorised%20Prescriber%20Scheme%20(AP)&text=To%20become%20an%20AP%2C%20a,college%20to%20prescribe%20the%20product.

[21] https://www.health.nsw.gov.au/pharmaceutical/doctors/Pages/guides-legislation-medical-practitioners.aspx

	• or a child aged under 16 years. Applications for MCS8 products can be made using a specific application form[22].
Victoria[23]	Medical and nurse practitioners are required to gain a Treatment Permit from the department before prescribing a Schedule 8 medicine to a patient with a history of drug dependence (including for Schedule 8 medicinal cannabis products).
South Australia[24]	A section 18A authority to prescribe a MCS8 (drug of dependence) is required: • after 2 months of treatment or before commencing treatment where the person has already been prescribed a Schedule 8 drug for a period exceeding 2 months • before commencing treatment for any person the medical practitioner reasonably believes is dependent on drugs. A section 18A authority is not required for patients aged 70 years or older, nor for Notified Palliative Care Patients (although notification must be made to the Drugs of Dependence Unit).
Queensland[25]	No state based approval for prescribing MCS8 medications is required. Conditions for prescribing and dispensing MCS8 medications are described in the document "Prescribing and dispensing unapproved medicinal cannabis"
Western Australia[26]	All medical practitioners in WA are eligible to prescribe medicinal cannabis products. For most patients, a general practitioner may initiate treatment. For some patients, including those with a history of drug dependency, children and young adults, the support of a suitable specialist will be required. Before prescribing MCS8, authorisation is required from the Department of Health, for each individual patient. Details of prescribing requirements are available in the Schedule 8 Medicines Prescribing Code.
Tasmania[27]	An authorisation under Section 59E of the Tasmanian Poisons Act 1971 is required prior to issuing a prescription for a MCS8. Section 59E authorisation is required for each individual patient.
Australian Capital Territory	Medicinal Cannabis products that contain controlled medicines (Schedule 8 Medicines) require an ACT Chief Health Officer approval. Prescribers are advised to contact the ACT Health Department for further information.
Northern Territory	Prescribers must comply with NT regulations regarding S8 medicines, and prescribers are advised to contact NT Health for further information.

Whilst there are some minor differences between jurisdictions, all require treating doctors to obtain an S8 approval or authority from their local Health Department when prescribing S8 medications to patients considered to be drug dependent (generally consistent with ICD11 and DSM5 criteria in Section 1). This includes prescribing an S8 medication even if the patient is

[22] https://www.health.nsw.gov.au/pharmaceutical/Documents/cannabis-application.pdf
[23] https://www.health.vic.gov.au/drugs-and-poisons/medicinal-cannabis-regulatory-framework
[24]https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/conditions/medicines/medicinal+cannabis/medicinal+cannabis+patient+access+in+south+australia
[25] https://www.health.qld.gov.au/__data/assets/pdf_file/0032/1256756/fs-prescribing-dispensing-unapproved-medicinal-cannabis.pdf
[26] https://www.health.wa.gov.au/articles/a_e/cannabis-based-products
[27] https://www.health.tas.gov.au/health-topics/medicines-and-poisons-regulation/medicinal-cannabis/information-about-medicinal-cannabis-prescribers-tasmania#what-approvals-are-required

dependent on another drug class. For example, in most jurisdictions, a treating doctor must obtain an S8 authority if they plan to prescribe THC (an S8 medicine) to a patient in opioid dependence treatment with methadone or buprenorphine. Local Health Department can apply conditions on the nature of the S8 THC approvals that prescribers must adhere to.

Most jurisdictions facilitate application for an S8 permit with their Health Department as part of the TGA SAS-B application process, and doctors receive approvals from both the Commonwealth TGA and local Health Department. Other jurisdictions have separate TGA SAS-B and state based S8 application and approval pathways. Patients prescribed under TGA Authorised Prescriber conditions should seek approvals from their state Health Departments as required. Prescribers should be familiar with procedures in the jurisdiction in which they work.

1.4. Universal precautions: a framework to minimise risks of medicinal cannabis for patients and the community.

In response to growing concerns regarding harms associated with prescribed opioid medications, a framework of universal precaution' was developed in an attempt to optimise patient and community safety regarding the use of opioids[28]. This framework involved the following approaches when treating all patients with opioid medications for chronic pain - hence the term universal precautions rather than assuming that opioid medication problems only occur in some patients. The key elements of universal precautions for prescribing opioid medications are:

- Informed consent. Discuss the potential risks and benefits of opioid medications with each patient (ideally before opioid treatment is commenced), the risk and consequences of developing an opioid use disorder and/or opioid withdrawal. Use of opioid medications should only be considered after patients have been informed of these risks and benefits, and consent to treatment is documented.
- Assess all patients being prescribed opioids to identify those who already have an opioid use disorder or are at risk of developing an opioid use disorder – ideally before prescribing opioid medications. For opioid medications, commonly identified risk factors for developing an OUD include: male gender, younger age, history of depression, other substance use disorders.
- Adjust how opioid treatment is delivered according to the level of individual patient risk. Opioid treatment for patients at increased risk of developing, or who have developed an OUD may be modified with regards to
    - type, duration and doses of opioid medications prescribed, with preference for abuse deterrent formulations or safer opioids (e.g. buprenorphine),
    - the frequency with which medications are dispensed at a pharmacy (interval dispensing), reducing the risk of unauthorised dose escalation by the patient,
    - avoiding unnecessary dose escalations, with greater emphasis upon non-opioid strategies to address pain;

[28] Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med. 2005 Mar-Apr;6(2):107-12. doi: 10.1111/j.1526-4637.2005.05031.x. PMID: 15773874.

- the level and frequency of monitoring for non-medical use of medications or other substances (e.g. more frequent clinical reviews, urine drug tests),
- the use of real-time prescription monitoring systems to monitor medication use from other HCPs
- the use of individual patient agreements regarding medication use, with clarity regarding conditions by which medications may be discontinued (e.g. persistent non-medical use).

— Preventing and/or managing opioid withdrawal when it emerges. Discontinuation of opioids or rapid dose reductions can be associated with an opioid withdrawal syndrome, which in turn can be distressing for the patient, impair function and quality of life, and has been associated with increased mortality (both suicide and overdose following relapse to opioid use). Strategies to prevent or manage opioid withdrawal include patient education, gradual dose tapers rather than sudden opioid cessation, opioid rotation (allowing a reset to a lower opioid equivalent dose), or in patients unable to discontinue opioid medications due to their opioid use disorder – treatment for opioid dependence with methadone or high dose buprenorphine products.

These universal precaution principles can inform clinical approaches to also prevent and/or manage individual patient and community harms linked to THC-based medicines – particularly in those patients at risk of developing, or who already have CUD.

1.5 Is medicinal cannabis treatment contraindicated in patients with a cannabis or other substance use disorder?

Several randomized controlled trials establish an evidence base for the safety of MCS8 medications in patients with CUD[29,30,31]. The safety and efficacy of nabiximols (a sublingual THC:CBD formulation) in the treatment of CUD – demonstrating 'high dose' nabiximol treatment (daily doses in the range of 50 to 80mg) are safe in this patient population (comparable rate and profile of adverse events to placebo arm) and effective in reducing cannabis withdrawal severity and illicit cannabis use.

Most medicinal cannabis products remain unregistered in Australia – and as such have no formal indications or contraindications. Responsibility for the conditions of medicinal cannabis treatment rests with the prescribing doctor and dispensing pharmacist. Hence, whilst there are no formal contraindications, it is sensible to consider a cannabis use or other substance use disorder as a precaution, that warrants:

- careful patient assessment,
- consumer information as part of the informed consent process, including written patient consent

[29] Allsop DJ, Copeland J, Lintzeris N, et al. (2014) Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. JAMA Psychiatry. 71(3):281-91.
[30] Lintzeris N, Bhardwaj A, Mills L, et al. Nabiximols for the Treatment of Cannabis Dependence: A Randomized Clinical Trial. JAMA Intern Med. 2019. 179(9):1242-53. doi: 10.1001/jamainternmed.2019.1993.
[31] Trigo JM, Soliman A, Quilty LC, et al. Nabiximols combined with motivational enhancement/cognitive behavioral therapy for the treatment of cannabis dependence: A pilot randomized clinical trial. PLoS One. 2018 Jan 31;13(1):e0190768. doi: 10.1371/journal.pone.0190768.

- modification of how treatment is delivered (doses, formulations, dispensing arrangements),
- monitoring, communication with other HCPs and clinical documentation

by HCPs involved in delivering medicinal cannabis treatment.

Whilst the risks of MCS8 treatment may be considered less severe than other S8 (e.g. opioids, stimulants) or S4D (e.g. benzodiazepines) medications (e.g. medicinal cannabis is extremely unlikely to cause overdose deaths as seen with opioids), it can nevertheless be associated with harms to the patient and community that warrant risk mitigation by treating clinicians. For medicinal cannabis treatment, particular risks include:

- development or worsening of cannabis use disorder
- cannabis-related acute toxicity[32] (including symptoms such as agitation, psychosis, palpitations, chest pain, hypertension, tachycardia, anxiety, vomiting and headaches)
- onset or aggravation of pre-existing psychiatric conditions (e.g. anxiety, psychosis[33]) and/or psychosocial dysfunction (e.g. relationship or employment problems).
- drug-drug interactions that can lead to poor clinical outcomes (most notably with other sedatives such as opioids, benzodiazepines)
- concerns regarding diversion of medicinal cannabis products to people not prescribed medicinal cannabis – including diversion to the black market or use by children.

[32] Dines AM, Wood DM, Galicia M, et al. Presentations to the Emergency Department Following Cannabis use--a Multi-Centre Case Series from Ten European Countries. J Med Toxicol. 2015; 11(4):415-21. doi: 10.1007/s13181-014-0460-x.
[33] Vallersnes OM, Dines AM, Wood DM, et al. Psychosis associated with acute recreational drug toxicity: a European case series. BMC Psychiatry. 2016 ;16:293. doi: 10.1186/s12888-016-1002-7..

2. Pharmacology of cannabis-based medicines

A detailed description of the pharmacology of cannabis-based medicines is beyond the scope of this document, and readers are referred to texts that comprehensively review this subject. The following principles however are pertinent to understanding the clinical recommendations made in the guidance document.

2.1. Cannabinoid composition: THC and CBD

Two of the principal cannabinoids in medicinal cannabis are THC and CBD – each having distinct pharmacological properties. The two cannabinoids can be used in isolation or in combination. The TGA classification system for medicinal cannabis products into 5 categories based on their THC and CBD profiles (Table 5). As previously described, this guidance document refers to the use of THC-based medicines (Schedule 8) medications, not the use of CBD (Schedule 4 with no abuse or addictive properties). Throughout this document, the abbreviation MCS8 refers to Category 2 to 5 products (irrespective of their CBD content). TGA SAS-B and APS data indicate that the majority of approvals are for MCS8 (Category 2-5) products, with Category 1 (CBD only) accounting for xx%

Table 5: TGA Categories of medicinal cannabis products		
MC Category	*Description*	*TGA Schedule*
Category 1	CBD medicinal cannabis product (CBD ≥98%)	Schedule 4
Category 2	CBD dominant product (CBD ≥60% and <98%)	Schedule 8
Category 3	Balanced product (CBD <60% and ≥40%)	Schedule 8
Category 4	THC dominant product (THC 60–98%)	Schedule 8
Category 5	THC medicinal cannabis product (THC >98%)	Schedule 8

2.2. Oral and inhaled routes of administration

Medicinal cannabis products are available in a variety of routes of administrations – with the most commonly used routes involving oral (including liquid, solution, oil, capsules) and inhaled (herb flower, liquid, vaporized capsules) products. TGA SAS-B MCS8 product approval data (to June 2024) indicates 51.6% approvals were for oral, and 48.5% approvals were for inhaled products.

A key issue in understanding the role of inhaled versus oral products is their pharmacokinetic profiles[34]. Although there will be variation between products, in general:

- oral routes of administration result in a slower onset and time to peak effects, but more prolonged duration of action – with peak effects around 1-3 hours after a dose, and effects lasting for 6-12 hours (depending on numerous factors such as the size of the dose, hepatic metabolism, drug-drug interactions, age of patient)

[34] Grotenhermen F. Pharmacokinetics and Pharmacodynamics of Cannabinoids. Clin Pharmacokinet 2003; 42 (4): 327-360

- inhaled routes of administration result in a much faster onset and time to peak action, but shorter duration of action, typically peak effects within 5 to 15 minutes, with effects lasting for 1-3 hours (again depending on a range of dose, product and individual patient factors).

A key principle of therapeutics when stabilizing doses for patients with physiological dependence (tolerance and withdrawal) on drugs of dependence (opioids, benzodiazepines, THC) is to attempt to stabilize the patient on long-acting rather than short-acting medications. Examples include the use of long-acting methadone or extended-release opioid formulations rather than short-acting immediate-release opioids, or the use long-acting benzodiazepines to stabilize benzodiazepine dependence (e.g. diazepam or clonazepam rather than alprazolam or temazepam).

The rationale here is that long-acting formulations produce less variation between peak and trough plasma levels: high peak plasma levels can be associated with intoxication, whereas trough levels can be associated with reduced clinical effect (e.g. worsening of pain symptoms), withdrawal and increased cravings. As such, oral formulations may have benefits for patients who require cannabinoid activity for extended periods of time. For patients seeking cannabinoid activity for short durations, shorter acting inhaled routes of administration may be preferable. In practice, many patients will benefit from a combination of oral and inhaled products.

2.3. Dosing schedules in patients with tolerance to THC

There is considerable variation in THC doses used between patients, and it is beyond the scope of this document to review this literature. Some key principles relevant to this context are:

For patients without significant tolerance to cannabis (no recent history of regular cannabis use, no evidence of cannabis withdrawal symptoms), the general therapeutic principle for prescribing THC-based medicines is to start with low doses, and incrementally titrate the dose according the patient's experience of effectiveness (symptom relief) and side effects (symptoms such as intoxication, cognitive impairment, palpitations or tachycardia, anxiety, confusion).

A common dosing schedule for cannabis naïve patients is to commence with between 1 to 2.5mg oral THC once or twice a day, with small dose increments (of 1 to 2.5mg every one to three days) as required and tolerated. In general, most patients can be effectively treated for a range of conditions with THC doses in the range of 10 to 20mg per day[35].

Dosing schedules usually need to be adapted for patients with physiological dependence on THC (tolerance, withdrawal).

- In patients with a clear history of tolerance, initial doses of oral THC in the range of 5mg to 10mg once or twice a day may be required, increasing incrementally according to the patient's experience (see discussion above). Doses in the range of 30 to 60mg per day are often required. Most patients will not require nor benefit from doses of greater than 80mg oral per day. It is recommended that a second opinion from an experienced medicinal cannabis prescriber be sought if requiring higher doses.

[35] Vickery AW, Roth S, Ernenwein T, et al A large Australian longitudinal cohort registry demonstrates sustained safety and efficacy of oral medicinal cannabis for at least two years. PLoS one. 2022;17(11):e0272241

- In patients without a clear history of established tolerance, we recommend commencing with low THC doses, reviewing the patient frequently and increasing the dose according to clinical effects.

Dosing schedules usually need to be adapted for patients with physiological dependence to THC due to factors such as physical or mental health conditions (e.g. liver disease, past history of psychosis), the potential for drug-drug interactions (e.g. use of other sedating drugs such as opioids, benzodiazepines, antipsychotics, gabapentoids, alcohol), patient age. Clinicians should review patients with these conditions more frequently to adjust doses as required.

3. Clinical Guidance for providing treatment with MCS8 products for patients with cannabis or other substance use disorders.

3.1 Assessment

Assessment includes history from the patient and others (as appropriate), physical and mental state examination, and investigations as indicated.

3.1.1 History of presenting condition for which medicinal cannabis is being considered

In general, treatment with unapproved (unlicensed) medicines such as medicinal cannabis is usually considered a second line treatment – that is, introduced when conventional therapies are ineffective, inaccessible (*e.g.,* due to cost) or have unwanted side effects. As such, an assessment of the underlying condition(s) for which MCS8 is being considered is essential, including:

- diagnosis, duration, severity of condition, how it impacts on patient, what the patient is seeking (patient goals);
- a history of current and prior treatment approaches, the effectiveness and acceptability (*e.g.,* side effects, cost, beliefs) to the patient and treatment providers. This usually involves communication (ideally with patient consent) with HCPs previously or currently involved in the patient's care; and
- whether the patient has used cannabis products previously to manage the condition, whether this has been prescribed or non-prescribed, and how cannabis impacted on the condition.

3.1.2. History of cannabis and other substance use, including medical and non-medical use

3.1.2.a. Pattern of recent cannabis use: Has the patient been using cannabis in the past 1 to 12 months? If so, establish:

- type of cannabis used and how used: the most commonly used types of cannabis products include oral preparations (e.g. liquids, solutions or oils, capsules, gummy bears) and cannabis plant matter / flower. Establish how inhaled products are usually consumed (smoked in joints, bongs, or vaporiser). Inhalable e-liquids, hashish, concentrates, and resins are being increasingly used in Australia in recent years.
- quantity and frequency of use (days used in past 28 days), how much is typically consumed on an average use day. Ask the patient to estimate the potency or strength of cannabis products if known
- for how long this pattern of use has extended.

- establish how much of the patient's cannabis use is for medical reasons (to help manage health condition) and how much is non-medical – this can be estimated as a % of medical and % non-medical (totaling 100%). In most studies of medicinal cannabis users in Australia,[36,37,38] the majority of patients report previously using illicit cannabis prior to commencing medical cannabis use, albeit many people may have not used cannabis for extended periods of time (*e.g.,* years) prior to commencing medical cannabis use.
- enquire from the patient to identify any 'good things' and 'not so good things' about their cannabis use.

3.1.2.b. Past history of cannabis use. Establish what age the patient first used cannabis, and whether they ever had a period of regular use (use more than weekly), and when regular cannabis use began (and/or ended).

For those with a history of regular cannabis use, assess whether there have been any substantial breaks from using (*e.g.,* one month or more), whether the patient experienced cannabis withdrawal symptoms upon trying to stop.

3.1.2.c. History of other substance use disorders. Patients with SUDs to one substance are more likely to develop a SUD to another substance. A diagnosis of drug dependence to other drugs (e.g. opioids) may also have important medico-legal ramifications with regards to the need for S8 permits, and co-ordination across treatment providers.

3.1.2.d. Diagnosing CUD / Cannabis Dependence and Risk Screening

We recommend using a formal checklist (e.g. DSM5 or ICD-11 criteria) for diagnosing CUD or dependence. From a medico-legal perspective, as THC is a Schedule 8 medicine, prescribers need to assess the patient for a diagnosis of moderate-severe CUD (DSM5) or ICD-11 Dependence, and to document this clearly in the medical record.

The patient's history of previously prescribed / dispensed THC-containing medicines and other medications of note (*e.g.,* opioids, benzodiazepines) should be explored using Safescript systems. THC (S8) medications should be recorded in each state's Safescript system. Whilst checking Safescript is not mandatory for medical practitioners or pharmacists in most parts of Australia, it is certainly strongly recommended for all patients when a HCP plans to initiate prescribing or dispensing of any S8 medication, and to check at regular intervals, according to the level of concerns.

In addition to assessing whether a patient has a current diagnosis of CUD, clinicians should also seek to identify patients who could be considered *at risk* of developing a cannabis use disorder, and who may require risk mitigation strategies in how MCS8 treatment is delivered. Risk factors for developing a CUD include:

1. History of cannabis use disorder in the past;

[36] Lintzeris N, Driels J, Elias N, et al. Medicinal cannabis in Australia, 2016: the Cannabis as Medicine Survey (CAMS-16). Med J Aust. 2018 Aug 3;209(5):211-216. doi: 10.5694/mja17.01247.
[37] Mills L, Arnold JC, Suraev A, Abelev SV, Zhou C, Arkell TR, McGregor IS, Lintzeris N. Medical cannabis use in Australia seven years after legalisation: findings from the online Cannabis as Medicine Survey 2022-2023 (CAMS-22). Harm Reduct J. 2024 May 28;21(1):104. doi: 10.1186/s12954-024-00992-1.
[38] Erridge S, Leung O, Holvey C, et al. An observational study of clinical outcome measures in patients treated with cannabis-based medicinal products on the UK Medical Cannabis Registry. Neuropsychopharmacol Rep. 2023 Dec;43(4):616-632. doi: 10.1002/npr2.12403.

2. History or current substance use disorder to other substances (e.g. alcohol, opioids, benzodiazepines, stimulants);
3. Patients reporting high proportion of non-medicinal cannabis use. Patients reporting that more than 20% of their cannabis use is for non-medical reasons may be considered at higher risk of developing CUD;
4. Younger patients with chronic mental health conditions (e.g. anxiety, depression, PTSD);
5. Few alternate treatment strategies for underlying condition: an over-reliance upon medicinal cannabis to treat underlying health condition.

At present, there are no validated risk screening tools for CUD in patients treated with MCS8, and these issues should be assessed clinically.

Whilst such patients may not be actively cannabis dependent (and for example may not require a S8 Health Department permit, HCPs should carefully consider how they provide medicinal cannabis treatment to reduce risks of developing CUD subsequent to treatment with MCS8.

3.1.3. Examination and investigations

Consider relevant examination (physical, mental state) and investigations for the underlying health conditions of the patient.

Biological assays (*e.g.,* urine drug screens, saliva or hair tests) to identify recent cannabis or other substance use can be of assistance in some circumstances. THC is quickly metabolised and largely excreted as the inactive metabolite THC-COOH in the urine. THC-COOH can be detected and remain positive in the urine for 5-7 days after episodic use and may remain positive for weeks (indeed months) following regular cannabis use. Saliva (hours) and hair (weeks to months) tests detect different periods of use – however are not reimbursed (Medicare) and can be difficult to access and arrange.

3.2. Patient education and informed consent

Patients embarking on medicinal cannabis treatment should be provided with information regarding the risks of cannabis dependence and cannabis withdrawal with long-term use of MCS8 products, and to include these issues in shared clinical decision making with patients. Patients should be informed that the risk of cannabis dependence / withdrawal increases with:

1. Prolonged regular use of medicinal cannabis (probably beyond 3 months, and certainly beyond 12 months);
2. Use of higher doses is likely to increase the risks of developing tolerance and withdrawal, and other features of dependence. The patient should be warned against unauthorised dose escalations.
3. Daily use of cannabis increases the risk of dependence. The patient should consider taking drug holidays where possible (days or weeks without MCS8 use),
4. Inhaled or oral cannabis formulations. There is uncertainty as to whether inhaled or oral THC products are associated with increased rates of adverse events or dependence.
    - There is increased likelihood that tolerance will develop more rapidly if the patient has elevated plasma levels of THC throughout the day. Hence, the use of short-acting THC products episodically (*e.g.,* for sleep at night, or in response to episodic pain episodes)

may have lower risk of dependence than longer-acting oral products used throughout the day.

- The use of drugs that have a rapid onset of effect and higher peak plasma concentrations (*e.g.,* as seen with inhaled cannabis) are likely to be associated with higher rates of dependence than drugs with slower onset of effects and lower peak plasma concentration. This means that if a patient is using regular medicinal cannabis over a 24-hour period, then oral products in general are associated with less risk of dependence or rebound withdrawal, compared with multiple doses (e.g. 4 to 6 times a day) of inhaled products.

5. Over-reliance on medicinal cannabis for symptom management can be associated with the risks of dose escalation (quantity, concentration and frequency of use) in response to deteriorations in the treated condition. Non-cannabis-based strategies for relieving symptoms such as psychological approaches, physical therapies, and non-cannabis medications are important ways of reducing the severity or risk of cannabis dependence.

Medical and nurse practitioners should document that the risks of dependence and withdrawal have been communicated with the patient. A standardised template for commencing medicinal cannabis is worth considering for HCPs[39].

Medical practitioners should also inform patients of their medico-legal requirement to notify their relevant health department where they seek to prescribe an S8 medication (THC) to a person considered drug dependent.

3.3. Prescribing and dispensing THC-based medicinal cannabis

3.3.1 Cannabinoid composition: THC:CBD

THC is the cannabinoid in medicinal cannabis that is associated with dependence and potential medication misuse. There is little evidence to suggest that the addition of CBD to THC impacts upon the development of dependence to THC. There is some evidence that combining CBD with THC can improve treatment outcomes (*e.g.,* in some pain contexts), and as such may enable lower doses of THC to be used. However, at this time we cannot make recommendations as to whether THC:CBD combinations lower the risk of dependence to cannabis (THC) products.

3.3.2 Formulations

As described previously (Section 2.2), there may be advantages and disadvantages of different formulations. The key issues are the rapidity of onset (Tmax), peak concentration (Cmax) and duration of effects of each formulation. In general, oral formulations have a slower onset, lower peak concentration and longer duration of effect, and should be encouraged where the patient requires cannabinoid effects over extended periods of time - the equivalent of using a extended-release opioid compared to a short-acting opioid formulation. However, for patients only seeking episodic cannabinoid effects (*e.g.,* nighttime for sleep, in response to specific acute pain symptoms, or acute episodes of anxiety), then short-acting THC-based medicinal cannabis (*e.g.,* inhaled) products may be preferred as a strategy to reduce sustained plasma levels of THC and the development of physiological dependence. Increasingly, many patients are using combinations of long-acting (oral) and short-acting (inhaled) THC-based products

[39] See example of template in Appendix 1 from RACGP (2019) Position Statement: Medicinal use of cannabis products https://www.racgp.org.au/advocacy/position-statements/view-all-position-statements/clinical-and-practice-management/medical-cannabis

over a 24-hour period. This is most likely appropriate for many individuals using high doses of THC – where a combination or oral and inhaled products are often preferred.

3.3.3 Doses

Doses of THC vary according to a range of factors and can include: nature and severity of the underlying condition being treated, adverse effects, patient sensitivity to THC and CBD, other medications (*e.g.,* drug-drug interactions), and the patient's level of tolerance to THC.

In cannabis-naïve patients, most guidelines recommend commencing with low doses of THC (*e.g.* ,1-2.5mg oral) and titrating the dose according to the desired effect and side effects. Often daily doses in the range of 10-20mg are sufficient for treating a number of conditions (*e.g.,* pain, sleep)[38].

However, in the context of a patient with tolerance to cannabis, higher doses are required to achieve the same clinical effect. In studies of cannabis dependent patients, daily doses of sublingual THC (nabximols THC:CBD combinations) in the range of 50 to 80mg THC daily were well tolerated by patients, with comparable adverse effects compared to placebo. This is equivalent to higher oral doses (due to bioavailability), suggesting that in patients with established physiological dependence (tolerance), oral doses in the range of 60 to 100mg THC daily may be considered appropriate. For the purposes of establishing a clear level, we recommend that doses of up to 80mg oral THC per day may be considered safe and appropriate in patients with established tolerance to cannabis. When initiating treatment, always commence with low doses (*e.g.,* 5-10mg oral daily) and titrate the dose upwards accordingly.

It is difficult to translate oral THC doses to doses of inhaled flower. Whilst the bioavailability of inhaled THC is higher than oral THC, it is difficult to make dose conversions from oral to flower products. In general, many cannabis-dependent patients using illicit cannabis frequently report using between 1 to 4 grams daily, albeit the THC concentration is often unreliable and uncertain (may vary from 5 to 25% THC). Clinicians should not aim to match the amount (in grams) of illicit cannabis use reported by patients directly to the same amount of medicinal cannabis herb flower – given potential differences in THC content and the uncertainty of self-report in many patients. It is recommended to commence with approximately one third to one half the amount of herb flower reported used by patients, and increase the dose according to clinical response.

Clinical experience suggests that there are probably few patients that require cannabis flower doses of more than 500mg inhaled THC per day (equivalent to up to 2 grams daily of a 25% THC flower) for extended periods of time (higher doses may be required when initially stabilising a patient). Patients requiring such high doses of THC flower will most likely benefit from a combination of oral and flower products, thereby reducing the amount of cannabis flower to less than 500mg THC daily.

A second opinion (e.g. from a medical practitioner skilled in cannabinoid medicine, addiction medicine specialist or addiction psychiatrist) should be considered where patients are seeking more than 500mg inhaled THC per day or 80mg oral THC per day on an ongoing basis.

3.3.4 Dispensing issues

Where there are concerns regarding CUD (or the risk of CUD), or where there are examples of aberrant medication use (*e.g.,* unauthorised dose escalations resulting in patients running out early, or patients repeatedly losing their prescriptions), then the prescribing HCP and pharmacist should consider interval dispensing – whereby the patient attends their pharmacy at regular intervals (*e.g.,* weekly, fortnightly) rather than receiving medications for extended

periods (*e.g.,* monthly supplies). This reduces the risk of unauthorised dose escalations and the patient running out of medicine early.

Patients should be instructed regarding the safe use and storage of MCS8 products, as they can cause toxicity in cannabis naïve individuals (e.g., severe intoxication, confusion, anxiety, agitation, tachycardia, palpitations, vomiting, dehydration) particularly in vulnerable groups (*e.g.,* children, elderly).

All cannabis-based medications should be dispensed with relevant warnings regarding driving and the need to keep them away from children. Pharmacists play an important role in discussing safety matters with patients.

3.4 Monitoring patients and clinical documentation

Patients with a CUD or other SUD should be reviewed regularly (e.g., weekly at the beginning of treatment when titrating doses, and every 1 to 3 months thereafter) to assess:

- the effectiveness of medicinal cannabis in treating the primary condition – including symptom reduction (*e.g.,* severity of pain, mood or sleep problems) and functional outcomes (general activity, ability to participate in activities, quality of life).
- safety (adverse events, DDIs) of medications.
- medication adherence (is the patient using the medication as prescribed) and any aberrant medication behaviours, including (a) unauthorised dose escalations, (b) non-recommended route of administration (*e.g.,* joints, bongs rather than vaporisers), (c) diversion to others (giving or selling medication); (d) use of prescribed cannabis for non-medical reasons; (e) accessing medicinal cannabis from other sources. Regular use of Safescript systems is encouraged by prescribers and pharmacists.

3.5 Discontinuing THC-containing medicines

A considerable proportion of patients using cannabis regularly and for extended periods of time (more than a few weeks) may experience cannabis withdrawal upon attempts at markedly reducing or stopping cannabis use – estimated at least one third of long-term patients prescribed MCS8.

To minimise the severity and onset of cannabis withdrawal, the following strategies are recommended:

1. Patient education regarding he potential for CWS, likely symptoms, onset and duration;
2. Gradual taper and reduction of cannabis dose over weeks. reducing the dose by 25% every 1-4 weeks may be appropriate based upon the treatment history. Dose tapering may not be required with oral daily doses of THC <10mg.
3. Discuss coping strategies for common withdrawal symptoms (sleep hygiene, relaxation strategies, diet and hydration, exercise, coping with cravings);
4. There is currently a limited role for using other medications in treating cannabis withdrawal. There may be a role for low-dose and time-limited anxiolytic or hypnotic medications (*e.g.,* benzodiazepines, z-drugs), although these should be used cautiously;

5. Consider specialist referral (to an addiction medicine specialist or addiction psychiatrist) for patients not coping with dose reductions.

3.6 Communicating with other health professionals

Every effort should be made to communicate with other health care professionals involved in the patient care, particularly if other HCPs are also involved in treating the patient's underlying health conditions, and if they are prescribing S8 or S4D medications (*e.g,.* benzodiazepines). Whilst this should usually be done with patient consent, HCPs are allowed to communicate with other HCPs for patient safety issues (*e.g.,* where both are prescribing S8 medications) without patient consent.

4. Seeking support

HCPs should seek support from relevant specialists and other service providers particularly to assist in the management patients with complex presentations, or with conditions that are beyond their expertise. A second opinion from a colleague or specialist should be considered when providing treatment with unclear evidence, for patients experiencing safety concerns (e.g. side effects, persistent aberrant medication behaviours), or requiring higher than usual doses.

HCPs should consult their local Health Departments regarding regulatory requirements when prescribing MCS8 products.

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39. See example of template in Appendix 1 from RACGP (2019) Position Statement: Medicinal use of cannabis products https://www.racgp.org.au/advocacy/position-statements/view-all-position-statements/clinical-and-practice-management/medical-cannabis