ACRE
Australian Centre for Cannabinoid Clinical and Research Excellence

PRESCRIBING GUIDANCE

THE USE OF CANNABIS MEDICINES FOR MANAGEMENT OF PAEDIATRIC AND ADULT EPILEPSY

About this document

Cannabis medicines are not first-line treatment. This Prescribing Guidance has been developed to provide practical information to assist NSW medical practitioners in their decision-making regarding the prescription of cannabis medicines for the management of drug-resistant paediatric and adult epilepsy. It:

- Acknowledges both the limitations of current published evidence pertaining to the use of cannabis medicines and the demands of patients with epilepsy for broader use.
- Notes that only one product is registered for use as a non-first line agent for specific epilepsy syndromes. The quality, safety or efficacy of unregistered cannabis medicines have not been evaluated by the Therapeutic Goods Administration (TGA).
- Provides generic information to assist prescribing for adult and young adult patients as they transition into adulthood.
- Details relevant considerations for prescribing cannabis medicines, including precautions and adverse events, drug interactions, dosing and monitoring outcomes.
- Presents information on cannabidiol and cannabidivarin, the cannabinoids examined in randomised controlled trials (RCT).
- Provides links to resources (including the TGA guidance)

Key points

- Epilepsy is classified as drug-resistant when two appropriate antiseizure medicines (ASM) utilised at an adequate dose have not provided sustained seizure control.
- The TGA's Guidance for the use of medicinal cannabis in the treatment of epilepsy in paediatric and adult patients in Australia[1] notes the evidence of efficacy for add-on cannabidiol in conjunction with best practice management of drug-resistant epilepsy in some epilepsy types. The majority of high-quality studies have been carried out using the purified cannabidiol product Epidyolex®.[2] However high quality, comparative data with best-practice management and use in the context of status epilepticus as a 'rescue' therapy is lacking.
- It is recommended that at least four TGA registered ASMs are trialled (or ketogenic diet, epilepsy surgery, neurostimulator) prior to the consideration of cannabidiol for severe drug-resistant epilepsy (e.g. Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS) or Tuberous Sclerosis Complex (TSC)).
- In NSW, expert clinical guidance and cannabis medicine prescribing advice for general practitioners, community pharmacists and rural health practitioners is available via the John Hunter Hospital Pharmacy Department. The John Hunter Hospital Pharmacy Department can be contacted by email via HNELHD-JHHPharmacy@health.nsw.gov.au.
  Public health practitioners working in metropolitan local health districts should consult their local medicines information services for clinical guidance and prescribing advice.

Current clinical trials

Clinical trials related to drug-resistant paediatric and adult epilepsy that are currently recruiting can be located via searching the Australian New Zealand Clinical Trials Registry and the Australian Epilepsy Clinical Trial Network.

Use of evidence-based therapies for paediatric and adult epilepsy

Evidence-based management options in accordance with clinical practice guidelines, where available, must be offered to paediatric and adult epilepsy patients prior to considering the therapeutic use of cannabidiol.

Useful resources for clinicians managing paediatric and adult epilepsy:

- eTG complete – Epilepsy and seizures (available through http://www.ciap.health.nsw.gov.au for NSW Health employees)[3]
- The Epilepsy Society of Australia.[4]

International resources include:

- American Academy of Neurology – Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy. 2018.[5]
- National Institute for Health and Care Excellence (NICE). Epilepsies in children, young people and adults NICE guideline. 2022.[6]

Best practice guidance for paediatric and adult epilepsy

Multidisciplinary care, including a neurologist is a core component of best practice management. The NICE. Epilepsies in children, young people and adults NICE guideline. 2022 [6] provides a comprehensive overview of best practice for children, young people and adults.

Prescribing cannabis medicines for the management of paediatric and adult epilepsy in patients

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

The prescriber

The patient's neurologist is highly recommended/essential to be involved for broader care options, and for ongoing involvement in the patient's care. All members of the treating team should be aware of the decision to prescribe cannabis medicines. Documentation in the patient's record allows early identification of adverse events and potential drug interactions. Follow up and assessment of efficacy and tolerability are essential.

The quality, safety or efficacy of unregistered cannabis medicines have not been evaluated by the TGA.

The patient

The patient or patient's Person Responsible (i.e. parent/s, carer) must give informed consent to treatment and consent documented. This advice includes:

- Most available cannabis medicines are unregistered and non-reimbursed (see products available for exceptions).
- The true likelihood of efficacy and side effects of this therapy are still being researched, but possible effects and side effects of treatment should be discussed including the unknown potential of long-term effects on the developing brain.
- Clear information about therapeutic goals and likely stopping criteria.

Prescribing a cannabis medicine: important considerations

The following has been adapted from the TGA's Guidance for the use of medicinal cannabis in Australia: Patient information.[7]

Cannabis products

- A variety of cannabis products are available.
- There are up to 100 cannabinoids (chemical compounds) in the cannabis plant, many are active.
- Tetrahydrocannabinol (THC) is responsible for the psychosis seen with cannabis use.
- THC may contribute to the reduction of nausea, vomiting, pain and muscle spasms as well as improvements in sleep and appetite. It does have significant toxicity, however, particularly vomiting, altered mental status, seizures, hyperkinesis, psychosis, encephalopathy, coma, respiratory depression and cognitive dysfunction.
- Cannabidiol has neurologic effects including reduced seizure activity, sedation, and dizziness, however, psychosis has not been reported. It may be useful in the management of seizures and may have anxiolytic and antipsychotic effects for some people. Adding cannabidiol to a THC product in a patient with toxicity to reduce toxicity is unproven and may result in an increase in THC exposure. It is more appropriate to reduce the dose and/or frequency of THC.
- Different cannabis products can contain different ratios of cannabinoids and excipients which can significantly alter the pharmacokinetics.
- The majority of the high-quality epilepsy studies described in the medical literature used purified cannabidiol.
- other cannabinoids e.g. cannabidivarin are in research; it is anticipated that information on additional cannabinoids will be added to this guidance as high-quality trial data is published.

Oral route of administration

- Cannabidiol is a highly lipophilic drug that undergoes extensive first-pass metabolism.
- Oral cannabidiol bioavailability is low (~6%)[8], and variable. Systemic exposure to cannabidiol was observed to increase over fourfold when administered with a high fat/calorie meal. [9-10]
- Following oral administration, cannabidiol appears rapidly in the plasma with reported median or mean Tmax (time to maximum concentration) values ranging from 3 to 5 hours.[11]
- Steady-state plasma concentrations are achieved after ~2-4 days of twice-daily dosing.[11]
- Cannabidiol exhibits a multiphasic elimination profile and the reported estimates of terminal elimination half-life vary from 10 to 17 hours.
- While plasma exposure increases with increasing dose, when dosing in the range from 1500 mg to 6000 mg a less than dose-proportional increase has been observed.[10]
- 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 crossing the blood-brain barrier, rate and extent are influenced by route of administration and formulation.[12] Further research is needed to better understand the relationship between plasma concentration and therapeutic effect.
- A nonrandomised trial investigated transdermal cannabidiol gel[13]. Additional dose routes (nasal and inhaled) and formulations (nanoparticles) are currently being investigated.

Products available

Epidyolex®[11] (cannabidiol 100 mg/mL) oral liquid is registered (Schedule 4) for the indication of epilepsy, as adjunctive therapy for LGS, or DS (please refer to linked authority criteria associated seizures in patients ≥ 2 years of age in Australia (TSC in USA, Europe)).[14]

Some cannabinoids have different Scheduling than others, with cannabidiol available as TGA Schedule 3 as soon as a registered product is available for a specified indication. Not all cannabinoids have safety or efficacy evidence in epilepsy, for example, and may cause harms. The TGA Medicinal cannabis: Role of the TGA[15] and Over-the-counter access to low dose cannabidiol[16] webpages detail information on the Scheduling of cannabis medicines and the NSW Health cannabis medicines[17] webpage outlines state-specific regulatory information.

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[18] and the Therapeutic Goods (Microbiological Standards for Medicines) (TGO 100) Order[19] are available. The TGA has published a list of Medicinal cannabis products by active ingredients[20], 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 aforementioned list does not guarantee availability, product stability or shelf-life and security of supply.

The TGA has issued a warning about buying non-prescribed cannabis medicines online.[21] Self-prescription of unregulated local artisanal, homegrown or self-imported online cannabis products has potential risks and is strongly discouraged.[21-22]

This guidance focuses on purified cannabidiol and the oral route of administration based on existing RCT data, noting that other cannabinoids and routes of administration (e.g. transdermal, inhaled) may be evaluated in RCTs in the future.

Evidence for use

The following information has been adapted from the TGA's Guidance for the use of medicinal cannabis in the treatment of epilepsy in paediatric and young patients in Australia[1] published by the TGA in December 2017. Further information updates were obtained from a literature review in MEDLINE and Embase from January 2018 to January 2022.

Cannabidiol Oral Solution (Epidyolex®, 100 mg/mL) has been evaluated in several RCTs in patients with drug-resistant epilepsy, including DS, LGS and TSC. Most of the RCTs were 14-16 weeks and, reported a reduction in seizure frequency compared to placebo (outcomes data is summarised in Table 1). Of note, more serious adverse events were observed with higher doses. RCTs have only been conducted using purified cannabidiol, and there is no established role for products containing other cannabinoids, including THC.[2]

Cannabidivarin has been assessed in a single RCT as add on therapy in patients with focal seizures. The

reported reduction in focal seizure frequency was similar in the treatment and placebo group.[23]

In addition to RCTs, there are a number of published open-label observational trials.[24-25] In an open-label trial involving a cohort of patients with DRE, a 36.5% decrease in monthly motor seizures was reported.[26]

Case series and/or open-label data are available in life-threatening infantile epilepsy, Aicardi syndrome and myoclonic-astatic epilepsy.[27-28] Cannabidiol (Epidyolex®, 100 mg/mL) was evaluated in an open-label case series (n = 7) in Febrile Infection-Related Epilepsy Syndrome (FIRES). Improvements in the frequency and duration of seizures were reported in 6 out of 7 patients.[29]

Table 1 Cannabinoid RCTs in DRE (Adapted from Lawson, et al.[2])*

Population	Intervention	No. Participants	Outcomes
DS aged 4–10 years[30]	CBD (100 mg/mL) 5 mg/kg/d (CBD5), 10 mg/kg/d (CBD10), 20 mg/kg/d (CBD20); 3-weeks	10 (CBD5); 8 (CBD10); 9 (CBD20); 7 (placebo)	Dose-proportional pharmacokinetics, elevated *N*-desmethylclobazam (except with concomitant stiripentol); well-tolerated.
DS aged 2–18 years[31]	CBD (100 mg/mL) 20 mg/kg/d (CBD20); 14-weeks	61 (CBD20); 59 (placebo)	Median change convulsive drop seizure frequency from baseline -38.9% (CBD20) and -13.3% (placebo). Secondary outcome 50% or more reduction in convulsive-seizure frequency: 43% (CBD20) and 27% (placebo).
DS aged 2–18 years[32]	CBD (100 mg/mL) 10 mg/kg/d (CBD10), 20 mg/kg/d (CBD20); 14-weeks	66 (CBD10); 67 (CBD20); 65 (placebo)	Percentage reduction convulsive seizure frequency from baseline 48.7% (CBD10), 45.7% (CBD20) and 26.9% (placebo). Secondary outcome at least a 50% reduction from baseline in convulsive-seizure frequency: 43.9% (CBD10), 49.3% (CBD20) and 26.2% (placebo).
LGS aged 2–55 years (30% >18 years)[33]	CBD (100 mg/mL) 10 mg/kg/d (CBD10), 20 mg/kg/d (CBD20); 14-weeks	73 (CBD10); 76 (CBD20); 76 (placebo)	Median reduction drop seizure frequency from baseline 37.2% (CBD10), 41.9% (CBD20) and 17.2% (placebo). Secondary outcome at least a 50% reduction from baseline in convulsive-seizure frequency: 36% (CBD10), 39% (CBD20) and 14% (placebo).
LGS aged 2–55 years (n = 30/86 CBD20, n = 28/85 placebo ≥18 years)[34]	CBD (100 mg/mL) 20 mg/kg/d (CBD20); 14-weeks	86 (CBD20); 85 (placebo)	Median reduction in monthly drop seizure frequency from baseline 43.9% (CBD20) and 21.8% (placebo). Secondary outcome 50% or more reduction in drop seizure frequency from baseline: 44% (CBD20) and 24% (placebo).
TSC associated seizures aged 1–65 years (n = 20/75 CBD25, n = 18/73 CBD50 and n = 20/76 placebo ≥18 years)[35]	CBD (100 mg/mL) 25 mg/kg/d (CBD25), 50 mg/kg/d (CBD50); 16 weeks	75 (CBD25); 73 (CBD50); 76 (placebo)	Percentage reduction in TSC-associated seizures 49% (CBD25), 48% (CBD50) and 27% (placebo). Secondary outcome at least a 50% reduction from baseline in convulsive-seizure frequency: 36% (CBD25), 40% (CBD50) and 22% (placebo).
Focal seizures 18–65 years[23]	CBDV 800 mg twice daily	81 (CBDV); 81 (placebo)	Reduction focal seizures 40.5% (CBDV) and 37.7% (placebo). 50% responders: 36% (CBDV) and 33% (placebo).

*CBD = cannabidiol, CBDV = cannabidivarin

Precautions

- Cannabis medicines, including cannabidiol should be avoided by patients who are pregnant, planning on becoming pregnant, or breastfeeding.[11, 38]
- Some products, such as Epidyolex® contain alcohol (79 mg/1 mL).[11] Alcohol content, particularly with higher product doses used for epilepsy, should be taken into account in children, pregnancy or patients with hepatic disease.

- Consider concomitant medication use and potential for pharmacokinetic and pharmacodynamic drug interactions (e.g. clobazam and valproate, see below).

Contraindications

- Any allergies to carrier oil (e.g. sesame) or other excipients.
- Elevated transaminases >3x upper normal limit (UNL) and bilirubin >2x UNL.[11]

For further information on recommended patient eligibility and exclusion criteria, please refer to Lawson et al. Expert advice for prescribing cannabis medicines for patients with epilepsy – drawn from the Australian clinical experience. British Journal of Clinical Pharmacology. 2022 .[2]

Adverse effects

Cannabidiol is associated with an increased rate of adverse events, including diarrhoea, vomiting, lethargy, fever, increased seizure frequency, respiratory tract infections, and reduction in appetite and weight. Adverse effects such as sedation and somnolence may decrease with continued treatment.[11]

Cannabidiol can cause hepatotoxicity and elevated liver transaminases.[11]

Higher doses have been observed to be associated with an increased frequency of adverse events. Patients with multiple comorbidities and polypharmacy may be at greater risk of adverse effects.

Drug interactions

The systemic exposure of the patient to cannabidiol 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® (cannabidiol)[11], 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.

Guidance for adult and young adult patients

Exclusions to driving and operating heavy machinery are likely with drug-resistant epilepsy. Adult and adolescent patients should be advised that there are considerations in relation to driving in epilepsy and workplace drug screening while treated with cannabis medicines.

Information on driving and epilepsy can be located on the NSW Government's How medical conditions, illness and injuries affect your license webpage.[36] See also the Prescribed Cannabis Medicines and Fitness to Drive Factsheet.[37]

See additional precautions and contraindications below.

Antiseizure medications

In patients administered clobazam in combination with cannabidiol, increased active metabolite *N*-desmethylclobazam (nCLB) concentrations were observed.[39-41] This is likely due to CYP2C19 inhibition by cannabidiol.[41] Higher nCLB concentrations were associated with a higher frequency of reports of sedation. Increased concentrations within normal therapeutic ranges of eslicarbazepine, rufinamide, topiramate and zonisamide were reported in an open-label safety study of cannabidiol.[39] A small increase in stiripentol concentration has been reported when combined with cannabidiol. The combination of cannabidiol and valproate has been reported to cause elevations in liver function tests.[42-43] The results of a systematic chart review of a paediatric cohort suggest that monitoring for thrombocytopenia should be considered when valproate and cannabidiol are combined.[44]

Phenytoin is largely metabolised by CYP2C9 which has been shown to be inhibited by cannabidiol in in-vitro studies. While no clinical studies have formally investigated this potential interaction, increased exposure to phenytoin, which has a narrow therapeutic index, may occur and dose reduction should be considered.[11]

UGT enzymes, including UGT2B7 are involved in the metabolism of lamotrigine. In-vitro, inhibition of UGT2B7 by cannabidiol has been observed. No clinical studies have formally investigated this potential interaction which could result in elevated plasma lamotrigine concentration when it is co-administered with cannabidiol.[11]

In a published case series, co-administration of cannabidiol with brivaracetam resulted in increased plasma brivaracetam concentrations.[45]
Clinical and therapeutic drug monitoring (where applicable and available) is recommended with the use of cannabidiol and ASM.

A brief reference summary table has been included

below, however potential drug interactions with cannabidiol are not limited to this (see Table 2).

Table 2 Cannabidiol drug interaction brief reference summary

Drug	Publication type examples	Reported outcomes
Brivaracetam	Case series[45]	Increased plasma brivaracetam concentrations.
Citalopram and escitalopram	Open-label trial[46]	Elevated citalopram concentration.
Clobazam	Open-label trials, phase II randomised trial[39-41]	Increased active metabolite nCLB concentrations. Sedation.
Everolimus and sirolimus	Paediatric case report and retrospective review[47-48]	Increased everolimus and sirolimus concentrations.
Lithium	Case report[49]	Elevated lithium concentration.
Methadone	Case report[50]	Raised methadone concentration. Sleepiness and fatigue.
Eslicarbazepine, rufinamide, topiramate, zonisamide	Open-label trial[39]	Increased concentrations within normal therapeutic ranges.
Stiripentol	Open-label trial, phase II randomized trial[42-43]	A small increase in stiripentol concentrations.
Tacrolimus	Case reports and/or series[51-52]	Altered tacrolimus concentrations.
Tamoxifen	Case report[53]	Reduction in tamoxifen active metabolite concentration.
Valproate	Open-label trial, phase II randomised trial, systematic chart review[39,42-44]	Elevated liver function tests. Thrombocytopenia.
Warfarin	Case reports[54-56]	Elevated INR Recent published case report indicated no interaction – Potential dose threshold.

Dosing in general

Dosing in general (2 years of age and older):

- Start at low dose and frequency.
- Titrate to effect (seizure control) whilst monitoring for side effects.
- Patient response to these medications varies widely.
- Favour lower doses in older patients (>65 years old) due to higher rates of polypharmacy and comorbidities, including hepatic impairment.

The following is an example only – doses should be individualised. Dosing advice can only be provided on cannabidiol-based cannabis medicines. Information on the use of other medicinal cannabinoids (other than cannabidiol) cannot be provided at this stage due to limited evidence in the literature. Dosing guidance is based on Epidyolex® Product Information[11] and may not be able to be extrapolated to unregistered oral products, other routes of administration or indications.

Example for cannabidiol – adapted from Epidyolex® Product Information[11]:

- The starting dose is 5 mg/kg/day cannabidiol in two divided doses for one week.
- Slow titration to effect, increasing weekly by 5 mg/kg/day in two divided doses, in conjunction with monitoring for side effects.
- The initial target maintenance dose is 10 mg/kg/day in two divided doses. The maximum recommended dose is 20mg/kg/day in LGS and DS and 25-50 mg/kg in TSC.
- Higher rates of adverse events have been associated with doses greater than 20-50 mg/kg/day.
- As lipophilic foods may increase bioavailability, doses should be taken consistently with or without food.
- Dose adjustments are required for patients with moderate or severe hepatic impairment. Use in severe hepatic impairment should only occur following a potential benefit versus harm assessment.[11]
- Serum transaminases and total bilirubin levels should be obtained at baseline and regularly monitored (1, 3, 6 months and as clinically indicated) during treatment.

Monitoring outcomes

Monitoring should initially involve regularly reviewing the patient in person or via telehealth, every 2-4 weeks or more frequently if required for the first 2-3 months.

There are three areas of outcomes that should be considered:

1. **Seizure control**
   A pre-defined measure of success should be negotiated with the patient prior to commencement of therapy. This can be

measured by using a common tool, for example a seizure diary or video or ambulatory electroencephalogram as clinically appropriate.

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 due to pharmacokinetic and pharmacodynamic interactions. Doses of these medicines should be adjusted as appropriate. Significant adverse events observed with unregistered medicines must be reported to the TGA. Although some of the adverse events are well known (e.g. diarrhoea, somnolence) it is still important to notify the TGA[57] when these events occur to enable patterns of toxicity and contributing factors to be elucidated, to support future prescribing information.
3. **Pathology monitoring**
   Monitoring is generally only indicated when medications have specific characteristics (e.g. a narrow therapeutic index), where patients have specific morbidity affecting drug clearance or activity, where the consequences of undertreatment cannot be recognised clinically and can be serious (e.g. seizure), and/or if toxicity is suspected. Cannabidiol may cause hepatocellular injury. Liver biochemistry should be monitored prior to initiation and periodically as clinically indicated.

Cessation and withdrawal

If there is no significant seizure benefit from 3 months following initiation cessation is recommended.

For non-urgent cessation of Epidyolex®, reduce the dose by 10% per day over 10 days until cessation. If immediate urgent cessation is required, follow standard safety measures consistent with rapid anticonvulsant drug withdrawal. In light of drug interactions with ASM, dose adjustments may be required following cannabidiol cessation.

There is no recognised withdrawal syndrome associated with cessation of short-term cannabidiol in healthy volunteers.[58]

Further Information

- In NSW, expert clinical guidance and cannabis medicine prescribing advice for general practitioners, community pharmacists and rural health practitioners is available via the John Hunter Hospital Pharmacy Department. The John Hunter Hospital Pharmacy Department can be contacted by email via HNELHD-JHHPharmacy@health.nsw.gov.au.
  Public health practitioners working in metropolitan local health districts should consult their local medicines information services for clinical guidance and prescribing advice.
- 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.

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