

REVIEW ARTICLE

Expert advice for prescribing cannabis medicines for patients with epilepsy—drawn from the Australian clinical experience

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There is international interest for consensus advice for prescribers working in the field of drug resistant epilepsy intending to trial potential therapies that are non-registered or off-label. Cannabinoids are one such therapy. In 2017, the New South Wales State Government (Australia) set up a cannabinoid prescribing guidance service for a wide variety of indications, based on known pharmacology together with the relevant new literature as it became available. Increasing interest in cannabis medicines use outside this State over the following 5 years together with a paucity of registration-standard clinical trials, lack of information around dosing issues, drug interactions and biological plausibility meant there remained a large unmet need for such advice. To address the unmet need in epilepsy, and until medicines were registered or regulator quality data were available, it was agreed to bring together a working group comprising paediatric and adult epilepsy specialists, clinical pharmacists, clinical pharmacologists and cannabis researchers from across Australia to develop interim *consensus advice* for prescribers. Although interim, this consensus advice addresses much of the current practice gap by providing an informed overview of the different cannabis medicines currently available for use in the treatment of epilepsy in paediatric and adult settings, with information on dose, drug interactions, toxicity, type of seizure and frequency of symptom relief. As such it supplements the limited evidence currently available from clinical trials with experience from front-line practice. It is expected that this consensus advice will be updated as new evidence emerges and will provide guidance for a subsequent Guideline.

KEYWORDS

cannabinoids, addiction medicine, epilepsy, neurology, prescribing, clinical pharmacology

1 | CONSENSUS ADVICE

The document complements the Australian regulator (Therapeutic Goods Administration (TGA)) Medicinal Cannabis Guidance¹ and provides more specific information around individualised dosing. Members of this team and other clinicians (in Acknowledgements) have also contributed to the Australian Centre for Cannabinoid Research Excellence (ACRE) NSW Cannabis Medicines Prescribing Guidance.²

2 | DEFINITIONS

CBD	Cannabidiol
THC	Tetrahydrocannabinol
ASM	Antiseizure medication
LGS	Lennox–Gastaut syndrome
DS	Dravet syndrome

Brief summary of current best evidence in the medical treatment of intractable epilepsy:

Epilepsy occurs in 1–2% of the population.³ Approximately 1/3 of people with epilepsy are considered drug resistant to standard anti-seizure medications (ASM). Many patients are interested to know if cannabis medicines are beneficial in epilepsy, particularly when standard ASM have failed to control their seizures.

Principles in the medical management of drug resistant epilepsy:

- (i) Accurate diagnosis. Epilepsy diagnosis is based primarily on a detailed clinical evaluation supported by investigations such as electroencephalography (EEG), video-EEG, magnetic resonance imaging, home video and genetics. This enables specific epilepsy syndrome classification and exclusion of the many mimics of epilepsy.
- (ii) Ideal treatment is with ASM monotherapy guided by seizure type and accurate epilepsy syndrome diagnosis.
- (iii) For drug-resistant epilepsy (DRE) patients, after failure of 2 appropriate ASM, alternative therapies should be considered (i.e., ketogenic diet; neurostimulation; epilepsy surgery) requiring referral to an epilepsy specialist centre.

2.1 | Evidence of efficacy related to cannabidiol/tetrahydrocannabinol and epilepsy

Over the past 5 years, a number of randomised, placebo-controlled and appropriately powered trials (RCT) have been published using cannabidiol (CBD) pharmaceutical products (all Epidyolex, 100 mg/mL oral liquid solution) in DRE patients with Lennox–Gastaut syndrome (LGS), tuberous sclerosis complex (TSC) and severe myoclonic epilepsy of infancy, also known as Dravet syndrome (DS).^{4–10} These short-term (14–16 wk) RCTs, important to note in a long-term disease, reported

that cannabinoids were more effective than placebo in reducing seizure frequency. Specifically, these studies demonstrated:

LGS (adults and children 2–55 y, 34% aged >18 y): Two trials^{6,7} of treatment with CBD at 10–20 mg/kg/d compared to placebo, led to a significant reduction in the median frequency of drop seizures, with ~42% reduction in the treatment group compared to ~17% in the placebo group.⁶

DS (age 2–18 y): The initial trial⁴ was a dose-ranging phase 2 study comparing 5, 10 and 20 mg/kg/d to placebo. The second trial⁵ with CBD dose at 20 mg/kg/d led to a reduction in convulsive seizure frequency of 39% compared to 13% in the placebo group. A third trial found similarly.⁹

TSC (age 1–65 y, 26% aged >18 y): treatment with CBD in 2 groups at 25 and 50 mg/kg/d was compared to placebo, with a significant reduction in the median frequency of seizures - 49% in the treatment group compared to 27% in the placebo group.⁸

These trials all reported similar efficacy comparing dosing levels over the 10–50 mg/kg/d range. On the downside, higher mg/kg doses were correlated with higher rates of serious adverse events. These data informed the recommended dosing information.

A Phase II RCT in a population of patients with focal seizures taking cannabidiol as an add-on therapy showed similar reductions in frequency between the treated and placebo group.¹⁰ The only other numerically large publication was from a multicentre USA-based collaboration with an open-label intervention in patients with various diagnoses and DRE on stable doses of ASM.¹¹ This study showed a reduction in monthly motor seizures of 36.5% after treatment of up to a maximum of 50 mg/kg/d of CBD. However, these publications provoked some critical commentary¹² related to the confounding effect of the known interaction between CBD and clobazam, an ASM often used in paediatric patients, and possibly responsible for the observed reduction in motor seizures in the open-label trial.

There is no class I, II or III evidence for the effectiveness of tetrahydrocannabinol (THC) or other cannabinoids to treat epilepsy in humans. There is no established role in the treatment of epilepsy for any preparation other than one containing pure CBD. However, for completeness, we undertook a search strategy (Box 1) to ensure we included all randomised controlled clinical trials in this area. We also referenced observational and noncontrolled studies where appropriate to strengthen our clinical advice.

From June 2018, the US Food and Drug Administration approved Epidyolex (CBD oral solution) for the treatment of seizures associated with these rare epilepsy syndromes. The Australian regulator, the TGA, have approved the use of CBD with the different trade name of Epidyolex in patients with LGS and DS, whilst Pharmaceutical Benefits Advisory Committee recommended Government subsidy for the use of Epidyolex only in DS.

The following recommendations made by the authors are independent of the regulatory decisions. These criteria have been adapted from the published clinical studies (Box 1, Appendix 1), Food and Drug Administration guidance and our own expert clinical practice. It is intended only as an interim guide for clinicians, to be updated once quality GRADE trials are undertaken.

BOX 1 Search strategy

Using Embase, we found 101 404 manuscripts on cannabinoids. After focus on epilepsy and applying the Cochrane highly sensitive search strategy for identifying controlled trials (reference: 3.6.2 Search filters for identifying randomized trials in Embase, Box 3.e), we found 370 manuscripts. This was reduced to 7 by a manual search.

Search terms excluded for cannabinoids—nabiximols, nabilone, dronabinol.

Embase revised search strategy (same 7 articles retrieved).

#	Searches	Results	Type	Actions	Annotations
1	exp cannabinoid/	78473	Advanced	Display Results More ▾	□
2	cannabinoid.mp.	34910	Advanced	Display Results More ▾	□
3	1 or 2	86055	Advanced	Display Results More ▾	□
4	cannabis.mp.	60216	Advanced	Display Results More ▾	□
5	marjuana.mp.	20477	Advanced	Display Results More ▾	□
6	cannabindivarin.mp.	185	Advanced	Display Results More ▾	□
7	tetrahydrocannabinol.mp.	14927	Advanced	Display Results More ▾	□
8	cannabidiol.mp.	7564	Advanced	Display Results More ▾	□
9	medical cannabis.mp.	3514	Advanced	Display Results More ▾	□
10	4 or 5 or 6 or 7 or 8 or 9	72434	Advanced	Display Results More ▾	□
11	3 or 10	101404	Advanced	Display Results More ▾	□
12	exp epilepsy/	277898	Advanced	Display Results More ▾	□
13	epilep*.mp.	287283	Advanced	Display Results More ▾	□
14	12 or 13	320537	Advanced	Display Results More ▾	□
15	11 and 14	3024	Advanced	Display Results More ▾	□
16	Randomized controlled trial/	693483	Advanced	Display Results More ▾	□
17	Controlled clinical trial/	465126	Advanced	Display Results More ▾	□
18	random\$.ti.ab.	1754800	Advanced	Display Results More ▾	□
19	randomization/	92969	Advanced	Display Results More ▾	□
20	intermethod comparison/	27832	Advanced	Display Results More ▾	□
21	placebo\$.ti.ab.	339793	Advanced	Display Results More ▾	□
22	(compare or compared or comparison).ti.	585532	Advanced	Display Results More ▾	□
23	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	2434325	Advanced	Display Results More ▾	□
24	(open adj label).ti.ab.	93782	Advanced	Display Results More ▾	□
25	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti.ab.	257769	Advanced	Display Results More ▾	□
26	double blind procedure/	193923	Advanced	Display Results More ▾	□
27	parallel group\$.ti.ab.	28717	Advanced	Display Results More ▾	□
28	(crossover or cross over).ti.ab.	115630	Advanced	Display Results More ▾	□
29	((assign\$ or match or matched or allocation) adj\$ (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti.ab.	372699	Advanced	Display Results More ▾	□
30	(assigned or allocated).ti.ab.	439028	Advanced	Display Results More ▾	□
31	(controlled adj\$ (study or design or trial)).ti.ab.	400532	Advanced	Display Results More ▾	□
32	(volunteer or volunteers).ti.ab.	270018	Advanced	Display Results More ▾	□
33	human experiment/	563136	Advanced	Display Results More ▾	□
34	trial.ti.	355890	Advanced	Display Results More ▾	□
35	or/16-34	5704872	Advanced	Display Results More ▾	□
36	(random\$ adj samp\$ adj\$ (cross section\$ or questionnaire\$1 or survey\$ or database\$1)).ti.ab. not (comparative study/ or controlled study/ or randomi\$ed controlled\$.ti.ab. or randomly assigned\$.ti.ab.)	8920	Advanced	Display Results More ▾	□
37	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi\$ed controlled\$.ti.ab. or control group\$1).ti.ab.)	294950	Advanced	Display Results More ▾	□
38	((case adj control\$) and random\$) not randomi\$ed controlled\$.ti.ab.	19326	Advanced	Display Results More ▾	□
39	(Systematic review not (trial or study)).ti.	196512	Advanced	Display Results More ▾	□
40	(nonrandom\$ not random\$).ti.ab.	17617	Advanced	Display Results More ▾	□
41	Random field\$.ti.ab.	2630	Advanced	Display Results More ▾	□
42	(random cluster adj\$3 samp\$).ti.ab.	1401	Advanced	Display Results More ▾	□
43	(review.ab. and review.pt.) not trial.ti.	955497	Advanced	Display Results More ▾	□
44	we searched.ab. and (review.ti. or review.pt.)	39857	Advanced	Display Results More ▾	□
45	update review.ab.	119	Advanced	Display Results More ▾	□
46	(databases adj\$4 searched).ab.	47625	Advanced	Display Results More ▾	□
47	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset\$1).ti. and animal experiment/	1134734	Advanced	Display Results More ▾	□
48	Animal experiment/ not (human experiment/ or human/)	2385275	Advanced	Display Results More ▾	□
49	or/36-48	3870261	Advanced	Display Results More ▾	□
50	35 not 49	5066600	Advanced	Display Results More ▾	□
51	15 and 50	370	Advanced	Display Results More ▾	□
52	from 51 keep 4, 44, 87, 108, 194, 196...	7	Advanced	Display Results More ▾	□

2.2 | Patient eligibility criteria for use of cannabis medicines: Recommendation

Although some community proponents recommend general use for epilepsy, based on literature to date and our clinical experience,

the following proposed restricted criteria are for the following indications:

- Severe, drug resistant epilepsy; and
- Diagnosis of DS, LGS or TSC.

- Previous treatment with 4 TGA registered ASM (or the ketogenic diet, epilepsy surgery, neurostimulator) including specific unsuccessful ASM trials:
 - LGS: valproate; lamotrigine; clobazam; rufinamide.
 - DS: valproate; topiramate; clobazam; stiripentol.
 - TSC: vigabatrin.

2.3 | LGS

People with LGS are eligible for treatment with CBD if:

- (i) Clinical diagnosis of LGS not controlled by standard ASM.
- (ii) Age >2 years.
- (iii) EEG showing a pattern of slow (<3.0 Hz) generalised spike-and-wave complexes and/or GPFA.
- (iv) At least 2 types of generalized seizures for at least 6 months
- (v) Drop seizures must be present for this diagnosis, with at least 2 drop seizures each week over a sustained period. Drop seizure is defined as epileptic seizure (atonic, tonic) involving the entire body, trunk, or head that could lead to a fall.

2.4 | DS

People with DS are eligible for treatment with CBD if:

- (i) Clinical diagnosis of DS not controlled by standard ASM.
- (ii) Age >2 years.
- (iii) A minimum of 4 convulsive seizures per month on average over a 3-month baseline.

2.5 | TSC

People with TSC are eligible for treatment with CBD if:

- i. Clinical diagnosis of TSC not controlled by standard ASM.
- ii. Age >1 year.
- iii. A minimum of 8 seizures per month on average over a 3-month baseline.

2.6 | Exceptional cases

Patients who do not meet the above criteria may be put forward by the responsible clinician to a local clinical or hospital drug review committee for consideration as an exceptional case. As examples, this may include a child younger than 2 years; a severe epilepsy with prolonged and/or frequent hospitalization or intensive care unit admissions; or a dangerous seizure type. CBD could also be considered where case series data on CBD efficacy is available (e.g. life-threatening infantile epilepsy; febrile infection-related epilepsy syndrome; Aicardi

syndrome; myoclonic-astatic epilepsy). In Australia, there is an Ethics review pathway set up for epilepsy clinicians using cannabis to be identified as *authorised prescribers*.¹³ This enables expertise to develop and auditable clinical practice to be available wider for publication.

Patient exclusion criteria for use of cannabis medicines:

These criteria are based on a combination of trial specified criteria and input of the consensus group.

- Clinically significant illness in the 4 weeks prior to prescribing other than epilepsy.
- Clinically significant abnormal laboratory values, at baseline.
- Impaired hepatic function at baseline defined as any of the following:
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× above upper limit of normal (ULN).
 - ALT or AST > 3 × ULN and (total bilirubin >2 × ULN or international normalized ratio >1.5).
 - ALT or AST > 3× ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, and/or eosinophilia (>5%).
- Clinically relevant abnormalities in the ECG.
- History of alcohol or substance abuse within the last 2 years.
- Patient is currently using, or has in the recent past used, recreational or medicinal cannabis or synthetic cannabinoids.
- Female patient is of child-bearing potential or male patient's partner is of child-bearing potential; unless willing to ensure that they or their partner use highly effective contraception for the duration of the treatment and for 3 months after cessation. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., <1%/y) when used correctly.
- Female patient who is pregnant, lactating or planning pregnancy during the course of treatment and for 3 months thereafter.
- Patient has been part of a clinical trial involving another investigational medicinal product in the previous 6 months.
- Patient has been taking felbamate for <1 year prior to screening.
- Patient's risk of drug interactions with the addition of CBD cannot be managed by dose reductions of other drugs and clinical and/or therapeutic drug monitoring.

2.7 | Prescribing of cannabis medicines: Regulatory issues

If the decision to proceed to cannabis prescription is made, prescribers should be cognisant of local regulatory guidance.

The Australian TGA Special Access Scheme, Authorised Prescriber programmes and regulatory requirements are provided here as additional advice; this is available online.

Here it is recommended that prior to considering cannabis medicines, the prescriber should review the TGA's information on [accessing medicinal cannabis products](#),¹ access pathways (the Special Access Scheme and the Authorised Prescriber Scheme), ACRE [Cannabis Medicines Prescribing Guidance](#)² and the appropriate [State and Territory regulatory requirements](#).

The treating clinician should have an ongoing therapeutic relationship with the patient. Follow up and assessment of efficacy is essential.

The patient and/or legal guardian must give informed consent to treatment. The consent process should include noting that:

- This is an unregistered medicine with costs potentially borne by the patient/family.
- The efficacy and side effects with different dosages and combinations are still being researched.
- There are restrictions on driving and operating heavy machinery, care should be taken with tasks requiring alertness and cognitive awareness - these are likely to be general exclusions anyway for people with seizure history.
- Cannabis salivary or blood exposure may also have relevance to occupational drug screening.
- Therapeutic goals and likely stopping criteria should be set.
- There is a potential for dependence or withdrawal with some cannabinoids.

Adult and adolescent patients should be informed that measurable concentrations of THC can be detected in saliva for significant periods of time after administration. A useful Australian reference is the guidance in the [Transport for NSW Centre for Road Safety](#) and in [NSW Health's Prescribed Cannabis Medicines and Fitness to Drive Factsheet](#). It is also noted that in most circumstances, patients with epilepsy are unable to drive.

2.8 | Prescribing a cannabis medicine: Other important considerations

2.8.1 | Choice of products

The principles of choosing the appropriate cannabinoid product for treating people with epilepsy involves the following:

- (i) Differences between registered plant derived cannabis medicines; synthetic cannabis medicines, and unregistered hemp-derived products.
- (ii) Differences between paediatric and adult prescribing.
- (iii) Cannabinoid, excipient and contaminant content.

(i) Differences between registered plant derived cannabis medicines; synthetic cannabis medicines; unregistered hemp-derived products and medicinal cannabis

The plant derived cannabis medicines Epidyolex (CBD oral solution) and Sativex (nabiximols) are the only medicines currently approved by any national government regulatory agency for medical prescription. Synthetic THC cannabinoids, dronabinol and nabilone also have regulatory approval for nonepilepsy indications, but not in Australia.

There are many nonapproved, nonregulated hemp-derived products that are being *prescribed* by physicians in other international jurisdictions. In Australia, a registered medical practitioner can currently

prescribe an unregistered product for epilepsy through the TGA *access schemes*.¹ This approves drugs made in a current Good Manufacturing Practice (GMP) facility to ensure batch-to-batch consistency and a stable and known shelf life and meeting a minimum chemical safety standard (Therapeutic Goods Order 93).

The TGA's *Guidance for the use of medicinal cannabis in Australia*¹ state that allergies to potential carrier oils (e.g. sesame, canola, sunflower) should be noted as products available in Australia often contain oils.

The rationale for choosing a regulated medicine over an unregulated product is very clear:

1. Manufacturing process

A regulatory compliant (and regulatory inspected) facility according to current GMP protects patients. Under GMP, approved medications must adhere to strict specifications that ensure batch-to-batch consistency and a stable and known shelf life.

2. Quality control

Quality control enables the product to meet national regulatory agency standards for quality (including purity, stability and batch-to-batch consistency). Each batch of product is tested against the manufacturing product specification as agreed by the regulators at product approval. This ensures that approved medicines contain consistent concentrations of cannabinoids and other product ingredients listed on the label, including impurities and degradants. It also allows for specific product removal from the market or individual batch recall if safety concerns are identified.

3. Scientific evidence

This includes extensive preclinical testing programme including animal toxicity and efficacy with dosing/safety/dependency evaluation in adult volunteers. It also requires regulatory compliant placebo-controlled clinical trials in large groups of patients to determine safety, efficacy and recommended dosing. Public disclosure of clinical trials is required. These are usually detailed in either Product Information or an Investigator Brochure.

4. Pharmacovigilance

Specific mechanisms exist to capture adverse event reporting both pre-marketing and post-marketing. This enables faster feedback to prescribers ensuring earlier identification and communication of potential side effects. It also allows for specific product removal from the market if unacceptable safety risks are identified, thereby protecting public health. In Australia, this is the responsibility of clinicians and the TGA.

5. Reimbursement

This includes potential eligibility for reimbursement in national health services, such as the PBS in Australia, if the product is cost-effective.

The above principles underlie the current TGA Special Access Scheme which states that unapproved products should not be considered substitutes for medicines that have been approved by a national regulatory system. This aims to ensure that patient safety and public health are actively protected. Rigorous regulatory approval process for medicines is undertaken in an effort to establish the efficacy, safety and quality of a medicine before use by the general public in order to ensure patient safety and public health.

(ii) Differences between paediatric and adult prescribing

No long-term safety information exists on the use of CBD. There is more (albeit unstandardised) information on recreational marijuana use (containing both THC and CBD). The preclinical and epidemiological data of neurodevelopmental effects¹⁴ on the foetus, child and adolescent brain is sufficient to suggest that THC use should be contraindicated in the paediatric (and even young adult) age range.

Epidyolex and several other TGA-listed, unregistered products have either nil or a sufficiently low (<2%) THC component.

(iii) Cannabinoid content, excipients and contaminants

The considerations related to GMP and quality control have been discussed above. The problem with contaminants in unregulated products has been evaluated in several reviews.¹⁵ It is important to note that some formulations contain alcohol and other excipients. For example, each 1 mL of Epidyolex contains 79 mg alcohol. Thus, the maximum recommended single dose of CBD (10 mg/kg) will increase the concentration of ethanol in the body by about 13 mg/L. For an adult weighing 70 kg, this is equivalent to 14 mL of beer, or 6 mL of wine per dose, but relatively more in children. The alcohol content should be taken into account in pregnancy and high-risk groups such as patients with liver disease.

2.9 | Drug interactions

The current available information on drug interactions with cannabinoids is mainly sourced from the product information on the registered Marinol (THC),¹⁶ Sativex (THC and CBD combination)¹⁷ and recently Epidyolex (CBD)¹⁸ products. Drug interactions with CBD have been well summarised in the literature.¹⁹ Ongoing reporting of potential interactions and adverse events to the TGA is vital to improve data in this area and clinicians and pharmacists are encouraged to report all possible, potential and likely adverse risk.

2.10 | Pharmacokinetic interactions

- THC and CBD are metabolised by the cytochrome P450 enzyme system. CBD has significant inhibitory effects on CYP3A4 and CYP2C19, which are also involved in the metabolism of clobazam. In previous studies, CBD doses of 20 mg/kg/d were shown to

increase the exposure of the active metabolite of this commonly co-administered benzodiazepine (N-desmethyloclobazam) with an average 5-fold increase in children with refractory epilepsy²⁰ and with 3-fold increase in adults with epilepsy.²¹

- If concomitant drug treatment with CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, fluoxetine) or inducers (e.g., rifampicin, carbamazepine, St John's wort) is started or stopped, a change in dose may be required.
- In the TSC CBD study,⁸ participants were excluded if they were also taking an mechanistic target of rapamycin inhibitor. In one single-centre series,²² CBD resulted in increased serum levels of everolimus and/or sirolimus with doubling or tripling the trough concentration. In some cases, this resulted in clinical toxicity and laboratory abnormalities.
- Based on in vitro data, inhibition of p-glycoprotein at the intestinal level by CBD is possible. Therefore, caution is recommended upon concomitant treatment with digoxin and other substrates for p-glycoprotein.²³

2.11 | Pharmacodynamic interactions

2.11.1 | Sedation

Care should be taken with hypnotics and drugs with potential sedating effects as there may be an additive effect on sedation and muscle relaxing effects. This may include other ASMs, opioids, benzodiazepines, anticholinergics and antihistamines.

Cannabis medications may interact with alcohol, affecting coordination, concentration and ability to respond quickly.

2.11.2 | Dosing

In general:

- Patient response (efficacy and toxicity) to these medications varies widely.
- Start at low dose (2–5 mg/kg/d CBD in 2 divided doses)
- Slow titrate to effect whilst monitoring for side effects (e.g. increase CBD by max 5 mg/kg/d per wk). Care with chronic dosing due to fat retention of active metabolite; dose may need to be altered.
- Note some cannabinoids auto-inhibit their own metabolism and some have active metabolites with longer half-lives; therefore, dose or frequency may need to be reduced over time, unless tolerance occurs.
- Current therapeutic dosing range of CBD is 5–20 mg/kg/d given in 2 divided doses. Higher doses up to 50 mg/kg/d have been trialled but were associated with higher rates of adverse events. Recommended initial target dose is 10 mg/kg/d in 2 divided doses.
- Obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment.

- Dosage adjustment is recommended for patients with moderate or severe hepatic impairment.
- Note that these doses are for the Epidyolex product and cannot necessarily be applied to other oral CBD formulations, or other types of epilepsy.
- This information does not apply to dosing via inhaled, or transdermal methods.
- Measurement of concentrations of concomitant drugs where there is a potential or actual drug–drug interaction is recommended.

2.11.3 | Adverse effects

The most common side effects of CBD reported from the clinical trials are sleepiness, diarrhoea, decreases in appetite and weight, and drug interactions. Somnolence is reported to occur in up to 60% of trial patients,²⁴ though many patients respond to dosage adjustment. Regular monitoring of liver function tests is required as CBD can cause hepatotoxicity. Some trials have also noted an increase in seizures and occasional status epilepticus with CBD.

Other short-term side effects reported only with THC-containing cannabinoid compounds include increased risk of cardiac and cerebrovascular events, anxiety and psychosis risk, dependency, and withdrawal.²⁵

2.11.4 | Cessation and withdrawal

There is no recognised withdrawal syndrome associated with cessation of CBD. In general, if cessation is nonurgent the schedule for Epidyolex of decreasing the dose by 10% every 2 days until ceased can be followed. If urgent, one should cease the drug immediately and take usual safety measures when rapidly withdrawing an anticonvulsant drug. This includes the potential for drug interactions in the opposite direction to those described above.

3 | SUMMARY AND RECOMMENDATIONS

This guidance is based on expert clinical practice from a spectrum of clinicians treating epilepsy in Australia. As there are few clinical data on comparative efficacy of cannabinoids with registered epilepsy therapies, cannabinoids are only recommended for use currently in drug resistant epilepsy, in carefully selected compliant patients with specific epilepsy phenotypes. Rather than re-review the paucity of data on specific cannabinoids, this guidance was developed based on clinical practice and experience, and the RCT data that are available. There are several narrative reviews on this topic already published, and although helpful for guidance, they are not always appropriate for clinicians prescribing in practice who request instead experience informed clinical guidance. Further, clinical practice guidance is directly translatable to practice, particularly in those health systems and populations similar to that in Australia. As such this group has

provided general and population-/disease-specific guidance in terms of inclusion, exclusion and product information based on clinical practice, supplemented by the quality clinical trial data. It is expected that this guidance will be updated as more clinical practice evidence and clinical trial data are published.

4 | FURTHER INFORMATION

ACRE's NSW Cannabis Medicines Prescribing Guidance are intended to give interim practical information to assist medical practitioners in their decision-making around prescribing and managing the use of cannabis medicines. They may be a useful resource for prescribers in other jurisdictions.

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

CONTRIBUTORS

J.L. is the paediatric epilepsy lead physician in ACRE. He conceived of the idea and brought the clinicians together (T.O.B., D.J., J.F., N.L., J.M., J.L.). J.M. is the Director of ACRE and provided the clinical pharmacology expertise. M.G. and E.R. undertook the literature review, which was checked by all authors.

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APPENDIX 1

Citation	GWPCARE1 part A (NCT02091206)	Abstract results (not paraphrased)
<p>Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, Greenwood S, Morrison G, Sommerville K; GWPCARE1 Part A Study Group. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. <i>Neurology</i>. 2018 Apr 3;90(14):e1204-e1211. doi: 10.1212/WNL.0000000000005254. Epub 2018 Mar 14. PMID: 29540584; PMCID: PMC5890607.</p>	GWPCARE1 part A (NCT02091206)	<p>34 patients were randomized (10, 8 and 9 to the 5, 10 and 20 mg/kg/d CBD groups, and 7 to placebo); 32 (94%) completed treatment. Exposure to CBD and its metabolites was dose proportional (AUC_{0-t}). CBD did not affect concomitant AED levels, apart from an increase in N-CLB (except in patients taking stiripentol). The most common AEs on CBD were pyrexia, somnolence, decreased appetite, sedation, vomiting, ataxia and abnormal behaviour. Six patients taking CBD and valproate developed elevated transaminases; none met criteria for drug-induced liver injury and all recovered. No other clinically relevant safety signals were observed.</p>
<p>Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al.; Cannabidiol in Dravet syndrome study group. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. <i>N Engl J med</i>. 2017;376:2011–2020.</p>	GWPCARE1 part B	<p>The median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with cannabidiol, as compared with a decrease from 14.9 to 14.1 with placebo (adjusted median difference between the cannabidiol group and the placebo group in change in seizure frequency, –22.8 percentage points; 95% confidence interval [CI], –41.1 to –5.4; $P = .01$). The percentage of patients who had at least a 50% reduction in convulsive-seizure frequency was 43% with cannabidiol and 27% with placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; $P = .08$). The patient's overall condition improved by at least 1 category on the 7-category caregiver global impression of change scale in 62% of the cannabidiol group as compared with 34% of the placebo group ($P = .02$). The frequency of total seizures of all types was significantly reduced with cannabidiol ($P = .03$), but there was no significant reduction in nonconvulsive seizures. The percentage of patients who became seizure-free was 5% with cannabidiol and 0% with placebo ($P = .08$).</p>
<p>Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, Saneto RP, Checketts D, Dunayevich E, Knappertz V; GWPCARE2 study group. Dose-ranging effect of adjunctive Oral Cannabidiol vs. placebo on convulsive seizure frequency in Dravet syndrome: A randomized clinical trial. <i>JAMA Neurol</i>. 2020 May 1;77(5):613–621. Doi: 10.1001/jamaneuro.2020.0073. Erratum in: <i>JAMA Neurol</i>. 2020 May 1;77(5):655. PMID: 32119035; PMCID: PMC7052786.</p>	GWPCARE2 (NCT02224703)	<p>The percentage reduction from baseline in convulsive seizure frequency was 48.7% for CBD10 group and 45.7% for the CBD20 group vs. 26.9% for the placebo group; the percentage reduction from placebo was 29.8% (95% CI, 8.4–46.2%; $P = .01$) for CBD10 group and 25.7% (95% CI, 2.9–43.2%; $P = .03$) for the CBD20 group. The most common adverse events were decreased appetite, diarrhoea, somnolence, pyrexia and fatigue. Five patients in the CBD20 group discontinued owing to adverse events. Elevated liver transaminase levels occurred more frequently in the CBD20 ($n = 13$) than the CBD10 ($n = 3$) group, with all affected patients given concomitant valproate sodium.</p>
<p>Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, Roberts C, Checketts D, VanLandingham KE, Zuberi SM; GWPCARE3 study group. Effect of Cannabidiol on drop seizures in the</p>	GWPCARE3	<p>The median percent reduction from baseline in drop-seizure frequency during the treatment period was 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group and 17.2% in the placebo group ($P = .005$ for the 20-mg cannabidiol group vs. placebo group and $P = .002$ for the 10-mg cannabidiol group vs. placebo group). The most common adverse events among the patients in the cannabidiol groups were somnolence, decreased appetite and diarrhoea; these events occurred more frequently in the higher-dose group. Six patients in the 20-mg cannabidiol group and 1 patient in the 10-mg cannabidiol group</p>

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Citation	Abstract results (not paraphrased)
<p>Lennox-Gastaut syndrome. <i>N Engl J Med.</i> 2018 May 17;378(20):1888–1897. Doi: 10.1056/NEJMoa1714631. PMID: 29768152.</p>	<p>discontinued the trial medication because of adverse events and were withdrawn from the trial. 14 patients who received cannabidiol (9%) had elevated liver aminotransferase concentrations.</p>
<p>Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. <i>Lancet.</i> 2018 Mar 17;391(10125):1085–1096. doi: 10.1016/S0140-6736(18)30136-3. Epub 2018 Jan 26. PMID: 29395273.</p>	<p>The median percentage reduction in monthly drop seizure frequency from baseline was 43.9% (IQR –69.6 to –1.9) in the cannabidiol group and 21.8% (IQR –45.7 to 1.7) in the placebo group. The estimated median difference between the treatment groups was –17.21 (95% CI –30.32 to –4.09; $P = 0.0135$) during the 14-week treatment period. Adverse events occurred in 74 (86%) of 86 patients in the cannabidiol group and 59 (69%) of 85 patients in the placebo group; most were mild or moderate. The most common adverse events were diarrhoea, somnolence, pyrexia, decreased appetite and vomiting. 12 (14%) patients in the cannabidiol group and 1 (1%) patient in the placebo group withdrew from the study because of adverse events. One patient (1%) died in the cannabidiol group, but this was considered unrelated to treatment.</p>
<p>Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, O'Callaghan FJ, Wong M, Sahebkar F, Checketts D, Knappertz V; GWPCARE6 study group. Add-on Cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: A placebo-controlled randomized clinical trial. <i>JAMA Neurol.</i> 2021 Mar 1;78(3):285–292. Doi: 10.1001/jamaneurol.2020.4607. PMID: 33346789; PMIDID: PMC7754080.</p>	<p>Interim analysis—the percentage reduction from baseline in the type of seizures considered the primary end point was 48.6% (95% CI, 40.4–55.8%) for the CBD25 group, 47.5% (95% CI, 39.0–54.8%) for the CBD50 group and 26.5% (95% CI, 14.9–36.5%) for the placebo group; the percentage reduction from placebo was 30.1% (95% CI, 13.9–43.3%; $P < .001$) for the CBD25 group and 28.5% (95% CI, 11.9–42.0%; nominal $P = .002$) for the CBD50 group. The most common adverse events were diarrhoea (placebo group, 19 [25%]; CBD25 group, 23 [31%]; CBD50 group, 41 [56%]) and somnolence (placebo group, 7 [9%]; CBD25 group, 10 [13%]; CBD50 group, 19 [26%]), which occurred more frequently with cannabidiol than placebo. 8 patients in CBD25 group, 10 in CBD50 group and 2 in the placebo group discontinued treatment because of adverse events. 28 patients taking cannabidiol (18.9%) had elevated liver transaminase levels vs. none taking placebo.</p>
<p>Brodie MJ, Czapinski P, Pazdera L, Sander JW, Toledo M, Naples M, Sahebkar F, Schreiber A; GWEP1330 Study Group. A Phase 2 Randomized Controlled Trial of the Efficacy and Safety of Cannabidiol as Add-on Therapy in Participants with Inadequately Controlled Focal Seizures. <i>Cannabis Cannabinoid Res.</i> 2021 Dec;6(6):528–536. doi: 10.1089/can.2020.0075. Epub 2021 Feb 15. PMID: 33998885; PMIDID: PMC8713263.</p>	<p>Median baseline focal seizure frequencies were 17–18 per 28 days in both groups, and similar reductions in frequency were observed in the CBDV (40.5%) and placebo (37.7%) groups during the treatment period (treatment ratio [% reduction] CBDV/placebo: 0.95 [4.6]; CI: 0.78–1.17 [–16.7 to 21.9]; $P = .648$). There were no differences between the CBDV and placebo groups for any seizure subtype. There were no significant treatment differences between CBDV and placebo groups for any of the secondary efficacy outcome measures. Overall, 59 (72.8%) of participants in the CBDV group and 39 (48.1%) in the placebo group had ≥ 1 treatment-emergent adverse event (AE); the 3 most common were diarrhoea, nausea and somnolence. The incidence of serious AEs was low (3.7% in the CBDV group vs. 1.2% in the placebo group). There was little or no effect of CBDV on vital signs, physical examination or electrocardiogram findings. Elevations in serum transaminases (alanine aminotransferase or aspartate aminotransferase) to levels $>3 \times$ upper limit of normal occurred in 3 participants taking CBDV (2 discontinued as a result) and 1 taking placebo; however, none met the criteria for potential HY's law cases.</p>
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