ACRE
Australian Centre for Cannabinoid Clinical and Research Excellence

PRESCRIBING GUIDANCE

PRESCRIBING CANNABIS MEDICINES FOR MANAGEMENT OF ANXIETY DISORDERS IN CLINICAL TRIALS

About this document

This Prescribing Guidance has been developed to provide practical information to assist NSW medical practitioners in their decision-making regarding prescription of cannabis medicines in a clinical trial setting for the pharmaceutical management of anxiety disorders in clinical trial settings. This Guidance:

- Focuses on cannabidiol as cannabis medicines containing tetrahydrocannabinol (THC) are not recommended in active mood or anxiety disorders.
- Acknowledges the limitations of current published evidence pertaining to the use of cannabis medicines. Management of anxiety is multifaceted although there are medicines that are Australian Register of Therapeutic Goods (ARTG) registered for this setting. Cannabis medicines should only be considered when registered medicines and other accepted treatments have been unsuccessful in managing symptoms or medical condition. Due to limited evidence, clinical trials provide the best framework for use in anxiety.
- Provides links to resources that outline standard, registered therapeutic options in the management of anxiety which could be used prior to considering the use of cannabis medicines.
- Details relevant considerations for prescribing cannabis medicines, including precautions and adverse events, drug interactions, dosing and monitoring outcomes.
- There is a need for high quality randomised controlled trials (RCTs) with larger cohorts to examine the safety and efficacy of cannabis medicines in anxiety disorders, when current therapies including non-pharmacological have failed.

Current clinical trials

Clinical trials related to treatment of anxiety disorders that are currently recruiting can be located via searching the Australian New Zealand Clinical Trials Registry.

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 patients with anxiety disorders prior to considering the therapeutic use of cannabidiol. Important considerations include:

Useful resources for clinicians managing anxiety

eTG complete – Generalised anxiety disorder; Social anxiety disorder; Separation anxiety disorder (available through http://www.ciap.health.nsw.gov.au for NSW Health employees)[1]

The Royal Australian & New Zealand College of Psychiatrists:

- Anxiety disorders: clinical practice guidelines and associated resources[2]
- Clinical Memorandum on Therapeutic use of medicinal cannabis products[3]

International resources include:

- American Psychiatric Association (APA) practice guidelines: Practice guideline for the treatment of patients with panic disorder (2009)[4]

- Royal College of Psychiatrists (UK) position statement: Cannabis-based medicinal products (2019)[5]
- National Institute for Health and Care Excellence (NICE) resources:
  - Generalised anxiety disorder and panic disorder in adults: management (2019)[6]
  - Social anxiety disorder: recognition, assessment, and treatment (2013)[7]

Summary of best practice in the treatment of anxiety

Multidisciplinary care, including a GP with additional psychiatrist/psychologist is a core component of best practice management. See links above for best practice management of anxiety.

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 prescriber should have key involvement in provision of care, including the patient's general practitioner in liaison with a specialist practitioner (i.e., a psychiatrist), and ongoing involvement in the patient's care. All members of the treating team should be aware of the decision to prescribe cannabis medicines and documented in the patient's record to allow early identification of adverse events and potential drug interactions. Follow up and assessment of efficacy and tolerability is essential.
Given the current status of most cannabis medicines as unregistered medicines, prescribers should consider seeking advice from their medical indemnity insurers prior to prescribing.

Patients should be advised that they are not able to drive while treated with medicines containing THC
Information about driving and cannabidiol can be found in the NSW Health's Prescribed Cannabis Medicines and Fitness to Drive Factsheet.[8]

The patient

The patient or patient's Person Responsible (i.e. parent/s, carer) must give informed consent to treatment, therapeutic goals, stopping criteria, and be aware that most available cannabis medicines are unregistered and non-reimbursed (see products available for exceptions). Lastly, that individual efficacy and side effects of cannabidiol are still being researched, but possible effects and side effects of treatment should be discussed.

Prescribing a cannabis medicine: important considerations

The following has been adapted from the Therapeutic Goods Administration's (TGA) Guidance for the use of medicinal cannabis in Australia: Patient information.[9]

Cannabis products

A variety of cannabis products are available.

- There are up to 100 cannabinoids (chemical compounds) in the cannabis plant, many are active.
- THC is responsible for the psychosis seen with cannabis use.
- Cannabidiol has neurologic effects including seizure activity, sedation, and dizziness, however psychosis has not been reported. It may be useful in the management of seizures and may have anxiolytic and antipsychotic effects for some people. Adding cannabidiol to a THC product in a patient with toxicity to reduce toxicity is unproven and may increase the THC exposure. It is more appropriate to reduce the dose and/or frequency of THC.
- Different cannabis products can contain different ratios of cannabinoids and excipients which can significantly alter the pharmacokinetics.
- There is ongoing research in the area, and it is anticipated that information 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%),[10] and variable. When administered with a high fat/calorie meal, systemic exposure to CBD was observed to increase over fourfold.[11,12]
- Following oral administration, CBD appears rapidly in the plasma with reported median or mean Tmax (time to maximum concentration) values ranging from 3 to 5 hours (or longer).[13]
- Steady-state plasma concentrations are achieved after ~2-4 days of twice daily dosing.[13]
- Cannabidiol exhibits a multiphasic elimination profile and the reported estimates of terminal elimination half-life vary from 10 to 17 hours.
- While plasma exposure, measured by Cmax and AUC tends to increase with increasing dose, when dosing is in the range from 1500 mg to 6000 mg, a less than dose-proportional increase has been observed.[12] Of note, doses that have been trialled for anxiety are between 300 mg and 600 mg daily. In most studies pertaining to anxiety, acute single doses have been used.
- Dose and frequency adjustments may be required over time due to auto-inhibition of metabolism, active

metabolite accumulation in fat with chronic dosing and active metabolites with longer half-lives.

- Although cannabidiol is highly lipophilic and can cross the blood brain barrier, rate and extent is influenced by route of administration and formulation.[14] Further research is needed to better understand the relationship between plasma concentration and therapeutic effect.

Products available

Epidyolex® (CBD 100 mg/mL) oral liquid[13] is registered for the indication of epilepsy, as an adjunctive therapy for Lennox Gastaut Syndrome, or Dravet Syndrome[15] associated seizures in patients ≥ 2 years of age in Australia. It is noted that some cannabinoids have different Scheduling than others, with CBD available as Schedule 3 as soon as a registered product is available for a specified indication. Not all cannabinoids have safety or efficacy evidence in epilepsy, for example and may cause harms. The Medicinal cannabis: Role of the TGA[16] and Over-the-counter access to low dose cannabidiol[17] webpages detail information on the Scheduling of cannabis medicines and the NSW Health cannabis medicines webpage[18] 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[19] and the Therapeutic Goods (Microbiological Standards for Medicines) (TGO 100) Order[20] are available. The TGA has published a list of Medicinal cannabis products by active ingredients[21], 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. Self-prescription of unregulated local artisanal, homegrown or self-imported online cannabis products has potential risks and is strongly discouraged.[22-23]

The TGA's Guidance for the use of medicinal cannabis in Australia: Overview[24] notes that cannabis medicine products containing THC are generally not appropriate for patients who have a previous psychotic or concurrent active mood or anxiety disorder.

This guidance focuses on 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 is based on a literature review in MEDLINE and Embase from inception to March 2022. Reference lists of review articles were also searched and articles published during development were added. Exclusions included observational studies, studies looking at reduction of anxiety in comorbid conditions, case-series and case reports. Several small RCTs were located (see Table 1 and Table 2).

A systematic review by Skelley et al.[25], concluded that research is needed to determine cannabidiol dosing and whether it has a place in treatment of anxiety disorders.

Single dose studies

In two studies involving healthy subjects who participated in a simulated public speaking test or test of public speaking in a real situation, an inverted U-shaped dose-response curve was observed.[26-27] Further confirmatory studies exploring the dose-response relationship involving plasma concentrations are needed.

A neuroimaging study was conducted in healthy volunteers to assess the effects of 400 mg of cannabidiol on regional cerebral blood flow (rCBF). The authors of the study suggest that the potential anxiolytic properties of cannabidiol may be mediated by action on limbic and paralimbic areas of the brain.[28]

Guidance for adult and young adult patients

Cannabis medicines, including cannabidiol should be avoided by patients who are pregnant, planning on becoming pregnant or breastfeeding.[13, 36]

Patients should be advised that there are considerations in relation to driving and workplace drug screening while treated with cannabidiol.

Information about driving and cannabidiol can be found in the NSW Health's Prescribed Cannabis Medicines and Fitness to Drive Factsheet.[8]

See additional precautions and contraindications below.

In another study, 300 mg of cannabidiol reduced subjective post-stress anxiety following a simulated public speaking test in healthy volunteers.[29] Whereas, in a study examining single dose CBD (150 mg, 300 mg or 600 mg) in college students with moderate to severe test anxiety, no effect was observed.[30]

Three published studies included participants with social anxiety disorder. In a study using 400 mg of cannabidiol, a reduction in subjective anxiety was noted. Neuroimaging revealed changes in brain activity in limbic and paralimbic areas.[31] Another trial involved pre-treatment with 600 mg of cannabidiol prior to a simulated public speaking test. Reductions in anxiety, cognitive impairment and speech performance discomfort were observed.[32] More recently, treatment outcomes were not improved with the augmentation of therapist assisted exposure therapy sessions with 300 mg cannabidiol in participants with treatment refractory social anxiety disorder or panic disorder with agoraphobia.[33]

Short term daily dose study

Cannabidiol 300 mg daily for 4 weeks has been trialled in teenagers with social anxiety disorder. A significant reduction in anxiety was reported.[34]

Methodological considerations

A randomised crossover study in healthy volunteers evaluated cannabidiol expectancy effects of cannabidiol on acute stress and anxiety.[35] The authors reported that cannabidiol expectancy had an impact on several subjective and physiological responses and anxiolytic effects, highlighting the need to control for this in future research.

It is worth noting limitations of RCTs published to date include a predominance of single acute dosing studies and small cohorts. Additional methodological limitations include non-representative cohorts of healthy volunteers, models of anxiety using simulated public speaking tests, and subjective anxiety scores.

Table 1. Trials pertaining to cannabidiol and anxiety in healthy volunteers.

Population	Intervention	Participants (n =)	Outcomes
Healthy volunteers aged 20 to 30 years[29]	Single dose CBD 300 mg capsule; diazepam 10 mg; ipsapirone 5 mg; placebo	10 (CBD300); 10 (diazepam 10 mg); 10 (ipsapirone 5 mg); 10 (placebo)	CBD significantly reduced subjective post stress anxiety (VAMS) following a simulated public speaking test.
Healthy males aged 25 to 42 years[28]	Single dose CBD 400 mg capsule; placebo	10 (CBD400, then placebo using crossover design)	A significant reduction in subjective anxiety (VAMS) and increased sedation was reported with CBD. ^{99m}Tc-ECD SPECT was used to measure rCBF. Outcomes included a significant reduction in ECD uptake in the medial temporal cluster (left amygdala-hippocampal complex, extending into the hypothalamus) and left posterior cingulate gyrus. A cluster of greater activity was observed in the left parahippocampal gyrus.
Healthy subjects aged 18 to 35 years[27]	Single dose CBD 100 mg; CBD 300 mg; CBD 900 mg capsule; clonazepam 1 mg; placebo	12 (CBD100); 11 (CBD300); 12 (CBD900); 12 (Clonazepam); 12 (placebo)	In the post speech phase of a test of public speaking in a real situation, a significant reduction in subjective anxiety measures was observed with CBD300, but not with CBD100 or CBD900.
Healthy males[26]	Single dose CBD 150 mg; 300 mg; 600 mg; placebo	15 (CBD150); 15 (CBD300); 12 (CBD600); 15 (placebo)	A significant reduction in anxiety during the speech phase of a simulated public speaking test was observed after pretreatment with CBD300, but no significant differences (VAMS) were observed with CBD150 and CBD600.
Healthy college students with moderate to severe test anxiety mean age 20.48 years[30]	Single dose hemp-derived CBD 150 mg; 300 mg; 600 mg; placebo	12 (CBD150);7 (CBD300); 7 (CBD600); 6 (placebo)	No effect based on self-reported measures. With the 600 mg CBD dose, bodily symptoms of anxiety increased across study time points compared to lower doses.

CBD = cannabidiol;; rCBF = Regional cerebral blood flow; 99mTc-ECD SPECT = Technetium 99m ethyl-cisteinate dimer brain perfusion single-photon emission computed tomography; VAMS = Visual Analogue Mood Scale.

Table 2. Trials pertaining to cannabidiol and anxiety disorders

Population	Intervention	Participants (n =)	Outcomes
Subjects with SAD (n = 24) and healthy controls[32]	Single dose CBD 600 mg capsule; placebo; no treatment	12 (CBD600); 12 (placebo); 12 (healthy controls, no treatment)	CBD was administered prior to a simulated public speaking test. Reductions in anxiety, cognitive impairment and discomfort in speech performance and decreased alert in anticipatory speech were observed.
Subjects with SAD aged 20 and 33 years[31]	Single dose CBD 400 mg; placebo	10 (CBD400, then placebo using crossover design)	Reductions in subjective anxiety were noted following CBD administration based on VAMS scores. ^{99m}Tc-ECD SPECT was used to measure rCBF. Attenuated ECD uptake was observed in the left parahippocampal gyrus, hippocampus and inferior temporal gyrus. An increase in ECD uptake in the right posterior cingulate gyrus was reported.
Subjects with SAD and avoidant personality disorder aged 18 to 19 years[34]	CBD 300 mg; placebo daily for 4 weeks	17 (CBD300); 20 (placebo)	A significant reduction in anxiety was reported based on the Fear of negative Evaluation Questionnaire and Liebowitz Social Anxiety Scale.
Subjects with treatment refractory SAD or panic disorder with agoraphobia mean age 36.7 years[33]	CBD (synthetic encapsulated powder) 300 mg administered prior to therapist-assisted exposure therapy (8 weekly sessions); placebo	39 (CBD300); 41 (placebo)	No difference in treatment outcome based on Fear Questionnaire scores.

CBD = cannabidiol; SAD = social anxiety disorder; rCBF = Regional cerebral blood flow; ^{99m}Tc-ECD SPECT = Technetium 99m ethyl-cisteinate dimer brain perfusion single-photon emission computed tomography; VAMS = Visual Analogue Mood Scale.

Precautions

- Some products, such as Epidyolex® contain alcohol (79 mg/1 mL).[13] Alcohol content 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 (see below).

Contraindications

- Any allergies to carrier oil (e.g. sesame) or other excipients.
- Elevated transaminases >3x upper limit normal (ULN) and bilirubin >2x ULN.[13]

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.[13]

Cannabidiol can cause hepatotoxicity and elevated liver transaminases.[13]

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®[13], 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.

A brief reference summary table has been included below, however potential drug interactions with cannabidiol are not limited to this (see Table 3).

Table 3. Cannabidiol drug interaction brief reference summary

Drug	Publication type examples	Reported outcomes
Brivaracetam	Case series[37]	Increased plasma brivaracetam concentrations.
Citalopram and escitalopram	Open label trial[38]	Elevated citalopram concentration.
Clobazam	Open-label trials, phase II randomized trial[39-42]	Increased active metabolite N-desmethylclobazam (nCLB) concentrations. Sedation.
Everolimus and sirolimus	Paediatric case report and retrospective review[43-44]	Increased everolimus and sirolimus concentrations.
Fluoxetine	Case report[45]	Insomnia, hyperactivity, increased agitation, exacerbation of obsessive-compulsive disorder.
Lithium	Case report[46]	Elevated lithium concentration.
Methadone	Case report[47]	Raised methadone concentration. Sleepiness and fatigue.
Rufinamide, topiramate, zonisamide	Open-label trial[39]	Increased concentrations within normal therapeutic ranges.
Stiripentol	Open-label trial, phase II randomized trial[42,48]	A small increase in stiripentol concentrations.
Tacrolimus	Case reports and/or series[49-50]	Altered tacrolimus concentrations.
Tamoxifen	Case report[51]	Reduction in tamoxifen active metabolite concentration.
Valproate	Open-label trial, phase II randomized trial, systematic chart review[39,42,48,52]	Elevated liver function tests. Thrombocytopenia.
Warfarin	Case reports[53-55]	Elevated INR Recent published case report indicated no interaction – Potential dose threshold.

Dosing in general (2 years of age and older)

- Start at low dose and frequency.
- Titrate to effect whilst monitoring for side effects.
- Patient response to these medications varies widely.
- Favour lower doses in older patients (>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.
- There is limited high quality data on which to base cannabidiol dosing recommendations in anxiety disorders.
- 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.[13]
- 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 reviewing the patient weekly 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. **Symptom control**
   Pre-defined subjective and objective measures of success should be negotiated with the patient prior to commencement of therapy. This can be measured by using a validated tool, for example GAD-7.
2. **Drug adverse events**
   Careful monitoring of patients for adverse events and the need for a change in dosage is important. Adverse events may become apparent after commencement or after change in dose. Adverse events may be related to other concurrent medications. Doses of these medicines should be adjusted as appropriate. Significant adverse events observed with unregistered medicines must be reported to the TGA. Although some of the adverse events are well known (e.g. diarrhoea, somnolence) it is still important to notify the TGA[56] when these events occur to enable patterns of toxicity and contributing factors to be elucidated, to support future prescribing information.
3. **Pathology monitoring**
   Monitoring including drug concentrations is generally only indicated when medications have specific characteristics (e.g. a narrow therapeutic index), where patients have a 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, for example with some concurrent HIV medicines. Cannabidiol may cause hepatocellular injury. Liver function biochemistry should be monitored prior to initiation and periodically as clinically indicated.

Cessation and withdrawal

There is no recognised withdrawal syndrome associated with cessation of short-term CBD in healthy volunteers.[57]

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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