



Australian Government

Department of Health

Therapeutic Goods Administration



Guidance
for the use of
medicinal cannabis
in the treatment of
epilepsy
in paediatric and
young adult patients
in Australia

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Introduction

A set of guidance documents has been made available to assist doctors and their patients who choose to prescribe medicinal cannabis in Australia under current access schemes. These have been developed based on reviews of available evidence for the use of medicinal cannabis in five different settings. Included is an overview addressing the evidence base for medicinal cannabis therapy generally as well as specific documents relating to medicinal cannabis in the treatment of palliative care, epilepsy, chemotherapy-induced nausea and vomiting (CINV), multiple sclerosis (MS) and chronic pain.

This document reflects the evidence supporting the use of medicinal cannabis in treating epilepsy in particular patient groups and the recommendations of the Epilepsy Working Group.

Note: These guidance documents are based on evidence available at the time of publication and will be updated as new evidence emerges. Each document should be read in conjunction with the '*Guidance to the use of medicinal cannabis in Australia—Overview*'.

Review method

The Australian Government Department of Health commissioned a team from the University of New South Wales, University of Sydney and University of Queensland under the coordination of the National Drug and Alcohol Council (NDARC) to review the available evidence for the use of medicinal cannabis in the above five settings.

The researchers conducted a review of previously published reviews from multiple databases such as Medline, Embase, PsychINFO and EBM Reviews based on PRISMA⁶⁸. [PRISMA](#) is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and is an evidence-based minimum set of items for reporting on randomised controlled trials (RCTs). These guidelines have been developed because of concern for low quality trials and aim to improve the quality of medical research, remove bias and improve transparency and accurate reporting of findings. Searches were guided by a specialist Librarian using specific search terms and were limited to studies published between 1980 and early 2017. Two reviewers independently examined titles and abstracts for relevance using Covidence Software and the Cochrane Risk of Bias Tool was used to assess studies, aiming to increase accuracy. The GRADE (grading of recommendations, assessment, development and evaluation) approach, an internationally recognised standard applying to weighting of evidence in scientific and medical literature was used to evaluate the quality of evidence.

In July 2017, the department also convened five separate Working Groups to consider the available evidence for the use of medicinal cannabis in the treatment of each of the settings. The five groups consist of individuals from a wide range of backgrounds and organisations, including senior staff from each state and territory Department of Health, fifteen healthcare professional organisations, clinical staff from twenty-nine hospitals and healthcare systems, fourteen outpatient or Primary Health Networks and eighteen consumer representative groups.



Definition of epilepsy

Epilepsy is a disorder of the brain defined by at least two unprovoked seizures occurring at least 24 hours apart, or the diagnosis of an epilepsy syndrome, or one unprovoked seizure with a high probability of further seizures.

Caveats

This document provides a guidance for health professionals in the use of medicinal cannabis products which are unapproved medicines, in the context of limited evidence of efficacy in epilepsy.

The treatment of epilepsy, especially in children with drug resistant seizures, presents particularly emotive circumstances. There are reasonably held beliefs by patients and families that exceptions to standard quality and safety data for medicines are acceptable in this context. However, this vulnerable group of patients should not be put at higher risk by treatment with medicinal cannabis products. This Guidance addresses the tension between patient autonomy and the underlying therapeutic principle to 'do no harm' and intends to facilitate the patient's or parents' wish to have a trial of treatment to better manage the patient's epilepsy.

The scope of the document is broad, and is not specific to diagnosis or symptom cluster, but includes possible dosing suggestions for particular symptoms.

In addition to the limited evidence for benefit and safety of medicinal cannabis products in epilepsy, there are further caveats in this setting.

1. Guidance can only relate recommendations to the conditions, drugs and doses which have been studied. For example, evidence of efficacy in another condition from one product and dose should not be extrapolated to another condition with the same product and dose.
2. There are disparities and limitations in how the evidence was obtained and reviewed.
3. Dose-response information for efficacy is minimal, in particular for starting doses. This is particularly relevant when applying data from young people to older people or people with chronic kidney and liver disease.
4. Dose-response information for toxicity is also lacking, particularly for side effects which may occur at variable doses and before efficacy is evident.
5. There is no dose equivalence safety or efficacy data between products or between specific medicinal cannabis products and current best practice.

As with all therapies, medical practitioners must exercise their professional judgment in determining if this is an appropriate treatment for an individual patient.

At this time, the use of medicinal cannabis products should only be considered where conventional treatments have been tried and proven unsuccessful in managing the patient's symptoms.



Efficacy indicators

The role of therapeutic substances in treating epilepsy is primarily focused on reducing seizure frequency, with the ultimate goal of achieving complete seizure freedom. It is also important to optimise the quality of life for the epilepsy patient, and to consider adverse events and likelihood of treatment withdrawal. Various studies on the use of medicinal cannabis products in the treatment of epilepsy have assessed:

- as the primary endpoint, achieving a 50 percent or greater reduction in seizures
- as secondary endpoints:
 - achieving complete seizure freedom
 - improvements in quality of life
 - adverse events (including all-cause, serious, and treatment-related adverse events)
 - study withdrawals (all cause, and due to adverse events).

Numbers needed to treat or harm

The number needed to treat (NNT) and the number needed to harm (NNH) have been used to provide a clinically interpretable summary of the magnitude and uncertainty of the evidence in this document. NNT is the number of people needed to treat for one person to improve on the outcome of interest. The lower the NNT, the more effective the intervention or exposure. A NNT of one means that, on average, every person exposed to an intervention will improve on that outcome of interest. Similarly, the NNH is the number of people needed to treat for one person to experience the negative outcome of interest (such as adverse events or study withdrawal). The lower the NNH, the more harmful the intervention or exposure. A NNH of one means that, on average, every person exposed to an intervention will experience a negative outcome of interest. NNT and NNH are presented with 95 percent confidence intervals (CI) to convey the potential variation in these outcomes.

Adverse events

Details of adverse events with most medicinal cannabis products are lacking. However, sedation, nausea and dizziness *vide infra* have been commonly reported. Serious adverse events have been described clinically, such as psychosis and cognitive distortion requiring external assistance, but the severity, time course and dose details are not well described in the literature.

The recent randomised control trial (RCT) of cannabidiol (CBD) for Drug-Resistant Seizures in the Dravet Syndrome¹ found that the common adverse events (>10 percent frequency) in the CBD group were vomiting, fatigue, pyrexia, upper respiratory tract infection, decreased appetite, convulsion, lethargy, somnolence, and diarrhea. Elevated levels of liver aminotransferase enzymes (alanine aminotransferase or aspartate aminotransferase level greater than three times the upper limit of the normal range) were also observed.



Role in treatment

There is as yet limited high quality evidence for the use of medicinal cannabis products in epilepsy. CBD has some evidence of efficacy when used as an adjuvant to other AED therapy, however comparative data with current best therapies are unavailable. Most published clinical and pre-clinical data on efficacy in epilepsy is with CBD. Its role in treatment is as an add-on treatment to current treatment in drug resistant epilepsy where four or five other anti-epileptic drugs (AEDS) have not controlled the epilepsy. There does not appear to be any information on the use of medicinal cannabis products being administered as 'rescue' therapy for status epilepticus.

Commencement and stopping rules

Commencing CBD in the treatment of paediatric epilepsy needs the involvement of paediatric neurologists due to the complexity of patients likely seeking this treatment.

Current advice is that CBD should be commenced orally at 5mg/kg/day in two divided doses. This can then be titrated up on a weekly basis by 5mg/kg/day to 20mg/kg/day with a maximum dose of 1gm/day. The more recent studies that describe data based on participant weight^{2,3,4} reported CBD dose ranges of 2.5-20mg/kg/day across a mean treatment length of 14 weeks. Earlier RCTs^{5,6,7} reported using 100mg of CBD administered two to three times per day for a treatment period between eight to twenty six weeks.

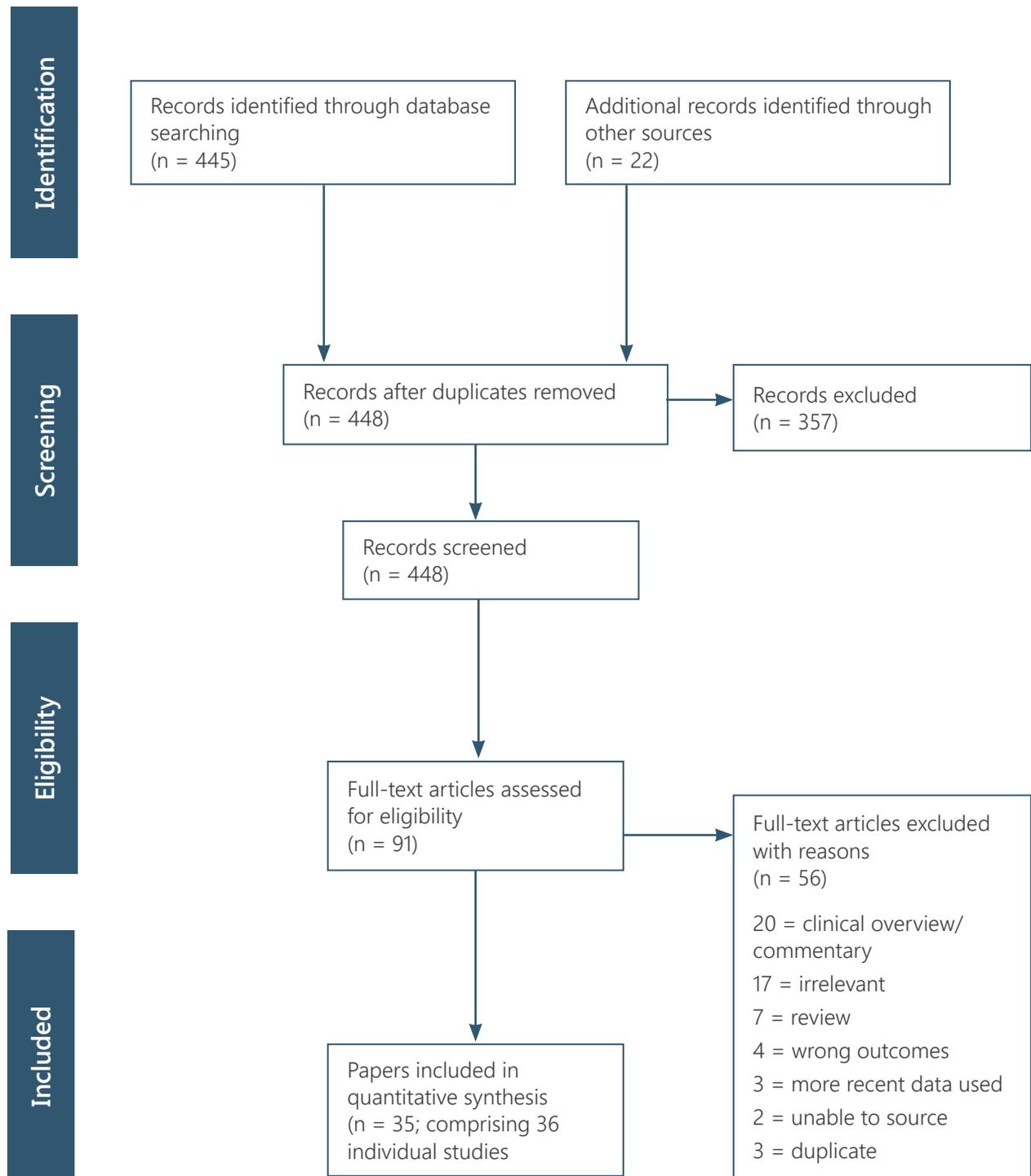
There is little information on dose–response so starting doses should be low, and the dose increased in response to lack of efficacy until maximum dose is reached or toxicity outweighs any benefit. If efficacy is limited or the adverse events outweigh the efficacy then consideration of stopping the treatment should be discussed.

Regular surveillance of drug–drug interactions and liver functions need to be taken into account when considering continuation or stopping of CBD. The prescribing doctor and pharmacist should collect information on pharmacovigilance. This will help refine guidance documents and provide additional data.



NDARC Review

Figure 1. PRISMA flowchart of study selection



Overview

Table 1. Key to grading of quality of evidence – based on GRADE Quality of Evidence ⁸

High	We are very confident the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Place in therapeutic hierarchy

The use of medicinal cannabis in the controlled trials was as an adjunctive treatment – that is, they were used in addition to other AEDs. Some trials suggested that CBD was more effective when used in conjunction with clobazam^{9,10}. Some parents report that they have taken their child off other AEDs once they started using medicinal cannabis because it was effective in controlling seizures and produced fewer side effects^{11,12}. It is unclear whether this decision was discussed or made in consultation with prescribing doctors.

Evidence is unavailable for first line or sole use of medicinal cannabis or cannabinoids in epilepsy. Should the treating physician elect to initiate cannabinoid therapy in epilepsy patients, it is recommended that it be used as an adjunctive treatment. Epilepsy management may be re-assessed once starting medicinal cannabis therapy. The pharmacokinetic (PK) and pharmacodynamic (PD) interactions of cannabinoids with other AEDs are predicted but as yet not fully elicited. A recent paper¹³ noted significantly changed serum levels of clobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine with medicinal cannabis. Oversight by the Therapeutic Goods Administration (TGA) of the quality standard of medicinal cannabis preparations supplied is important to protect the health of the Australian public.

Recommendation

Epilepsy treatment with medicinal cannabis or cannabinoids is only recommended as an adjunctive treatment – that is, in addition to existing anti-epileptic drugs.

Treatment efficacy

1. Proportion of patients experiencing 50 percent or greater reduction in seizure frequency

In two RCTs comprising 291 patients (mean age: 25.9 years, range: 10–45 years), CBD was more likely to produce a greater than 50 percent reduction in seizures than placebo (Relative Risk [RR] 1.74, 95 percent CI: 1.24–2.43). The NNT for one person to achieve a 50 percent reduction



in seizures was eight (95 percent CI: 6–17). Estimates did not differ by epilepsy type, sample age or study risk of bias.

An estimated 48.5 percent of the 970 patients in 17 observational studies achieved a 50 percent or greater reduction in seizures (95 percent CI: 39.0–58.1). This estimate is marginally larger than the proportion of responders in the two larger, high-quality RCTs (42.6 percent¹⁴ and 44.2 percent¹⁵). Estimates did not differ by epilepsy type, sample age or study risk of bias.

Table 2. Summary of evidence for cannabinoids in achieving 50 percent or greater reduction in seizure frequency

Cannabinoid used	Outcome summary	NNT (95%CI)	GRADE rating*
CBD	Favours CBD	8	++OO LOW
	Two double-blind RCTs suggest that CBD increases the likelihood of achieving 50 percent or greater reductions in seizures relative to placebo	(6–17)	
	Open label trials and observational studies reported that just under half (48.5 percent) of participants achieved a 50 percent or greater reduction in seizures.	n/a	++OO LOW
Oral cannabis extracts (OCEs) Insufficient evidence	A retrospective chart review study suggest OCEs may help achieve 50 percent or greater reductions in seizures, however the lack of controlled evidence restricts the conclusiveness of this finding	n/a	+OOO VERY LOW
CBD:THC Insufficient evidence	A retrospective chart review study and a case study suggests CBD:THC or CBD:THCA may help achieve 50 percent or greater reductions in seizures, however the lack of controlled evidence restricts the conclusiveness of this finding.	n/a	+OOO VERY LOW
Cannabis sativa Insufficient evidence	A case study suggests that smoking herbal cannabis cigarettes may help reduce seizures in partial epilepsy, however the lack of controlled studies weakens the conclusiveness of this finding	n/a	+OOO VERY LOW

* +++++ HIGH: We are very confident that the true effect lies close to that of the estimate of the effect.
 ++++O MODERATE We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
 ++OO LOW: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
 +OOO VERY LOW: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.



2. Complete seizure freedom

The pooled RR from three RCTs examining CBD in achieving complete seizure freedom compared to placebo was 6.17 (95 percent CI: 1.50–25.32). The NNT for one person to achieve complete seizure freedom was 171 (95 percent CI: 155–339). There were no differences identified in the RR of complete seizure freedom based on epilepsy type, age group, or study risk of bias.

The pooled prevalence of participants achieving complete seizure freedom in the 14 observational studies with no comparison group was 8.5 percent (95 percent CI: 3.8–14.5). The proportion of participants achieving complete seizure freedom did not differ significantly by epilepsy type, participant age or risk of bias.

Table 3. Summary of evidence for cannabinoids in achieving complete seizure freedom

Cannabinoid used	Outcome summary	NNT (95%CI)	GRADE rating*
CBD	Favours CBD Three RCTs suggest that CBD increases the likelihood of achieving complete seizure freedom relative to placebo.	171 (155–339)	++OO LOW
	Open label trials and observational studies reported that 8.5 percent of participants reported achieving complete seizure freedom	n/a	++OO LOW
Oral cannabis extracts (OCEs)	Insufficient evidence A retrospective chart review study suggest OCEs may help achieve complete seizure freedom, however this only occurred in two of the 75 patients surveyed.	n/a	+OOO VERY LOW
CBD:THC/THCA	Insufficient evidence A retrospective chart review study suggests that CBD:THC or CBD:THCA may achieve complete seizure freedom but the lack of controlled studies weakens the conclusiveness of this finding.	n/a	+OOO VERY LOW

Note: OCE – Oral Cannabis extracts of varied composition; THCA – Tetrahydrocannabinolic acid.

- * +++++ HIGH: We are very confident that the true effect lies close to that of the estimate of the effect.
 ++++O MODERATE We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
 ++OO LOW: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
 +OOO VERY LOW: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.



3. Quality of life outcomes

Quality of life in the two RCTs^{16,17} was measured by parents'/caregivers' global impression of change. The pooled RR of parents/caregivers reporting that patients' overall condition had improved (using the patient global impression of change measure) in those receiving CBD versus placebo of was 1.73 (95 percent CI: 1.33–2.26), and this did not differ on the basis of epilepsy type, sample age or study risk of bias. The NNT for one person receiving CBD to experience an improvement in parental-reported quality of life was five (95 percent CI: 4–9).

A pooled estimate from observational studies of the proportion of patients with improved quality of life when using medicinal cannabis was 55.8 percent (95 percent CI: 40.5–70.6). This included improvements in mood (95.9 percent, 95 percent CI: 74.1–100), cognitive skills (76.1 percent, 95 percent CI: 53.8–93.6), alertness (54.0 percent, 95 percent CI: 28.3–78.9) and sleep (50.9 percent, 95 percent CI: 9.8–91.4). Samples comprising adults only reported higher proportions of participants experiencing improved appetite, mood and sleep (89.3 percent, 95 percent CI: 75.5–98.3) compared to paediatric samples (30.1 percent, 95 percent CI: 16.7–44.9).

Table 4. Summary of evidence for cannabinoids in improving quality of life outcomes

Cannabinoid used	Outcome summary	NNT (95%CI)	Evidence GRADE rating*
CBD	Favours CBD Data from two RCTs suggest that CBD increased the likelihood of parents self-reporting that their child was 'much or very much improved' on the Patient Global Impression of Change scale, relative to placebo.	5 (4–9)	++OO LOW
	Open label trials and observational studies reported that over half (55.8 percent) of samples using CBD reported improvements in quality of life indicators, including mood, cognitive skills, alertness and sleep.	n/a	++OO VERY LOW
Oral cannabis extracts (OCEs)	Insufficient evidence A retrospective chart review study suggests OCEs may improve overall quality of life and personal functioning. But the lack of controlled studies restricts the conclusiveness of this finding	n/a	+OOO VERY LOW
CBD:THC	Insufficient evidence A case study suggests CBD:THC contributed to better functioning and quality of life, however the lack of controlled studies restricts the conclusiveness of this finding.	n/a	+OOO VERY LOW
Cannabis sativa	Insufficient evidence Case series report improvements of overall quality of life and wellbeing but the lack of controlled studies restricts the conclusiveness of this finding.	n/a	+OOO VERY LOW



Cannabinoid used	Outcome summary	NNT (95%CI)	Evidence GRADE rating*
THC	Insufficient evidence Case reports suggest that the use of THC contributed to overall improvements in patient ability and quality of life, however the lack of controlled studies restricts the conclusiveness of this finding	n/a	+OOO VERY LOW

* +++++ HIGH: We are very confident that the true effect lies close to that of the estimate of the effect.
 +++O MODERATE We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
 ++OO LOW: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
 +OOO VERY LOW: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Recommendation:

Should the treating physician elect to initiate medicinal cannabis therapy in epilepsy patients, it is recommended that CBD be used as adjunctive therapy to existing AEDs in children or young people aged up to 25 years, with the primary aim of decreasing seizure frequency and improving overall quality of life. Achieving full seizure remission is likely to be rare. There is insufficient evidence to provide recommendations for adults aged over 25 years.

4. Tolerability and persistence in treatment

4a. Adverse events

A meta-analysis of 516 patients in three RCTs^{18,19,20} found that patients who received CBD had a small but significant increase in the risk of experiencing any adverse event compared to those who received placebo (pooled RR 1.24, 95 percent CI: 1.13–1.36). The NNH for one person receiving CBD to experience any adverse event was 3 (95 percent CI: 3–6). There was no difference in the likelihood of experiencing any adverse event based on epilepsy type, sample age or study risk of bias.

Pooled estimates of 651 patients in 12 non-RCTs were that 50.6 percent of patients experienced any adverse event (95 percent CI: 31.7–69.4). This did not differ based on epilepsy type. Mixed paediatric and adult samples had significantly higher proportions of participants reporting any adverse event (82.8 percent, 95 percent CI: 75.6–89.1) compared to adult-only and paediatric-only studies. The most common specific adverse events included drowsiness (22.6 percent, 95 percent CI: 15.3–30.7), ataxia (17.1 percent, 95 percent CI: 1.1–41.7) and diarrhoea (11.3 percent, 95 percent CI: 2.8–23.0).

Adverse events that were reported by more than 5 percent of the samples with at least 75 participants were:

- Diarrhoea (20 percent)
- Somnolence (18 percent)
- Decreased appetite (17 percent)
- Increased appetite (17 percent)



- Worsening of seizures (15 percent)
- Pyrexia (13 percent)
- Convulsion (12 percent)
- Fatigue (, 11 percent)
- Status epilepticus (10 percent)
- Gastrointestinal problems (9 percent)
- Irritability (8 percent)
- Weight gain (7 percent)
- Weight loss (7 percent)
- Nausea (7 percent)
- Behavioural difficulties (7 percent)
- Vomiting (6 percent).

4b. Serious adverse events

Three RCTs^{21,22,23} found that patients in the CBD treatment groups were more likely to experience any serious adverse event than patients in placebo conditions (pooled RR 2.55, 95 percent CI 1.48 to 4.38). Specific serious adverse events recorded included status epilepticus and elevated aminotransferase levels. The NNH for one person using CBD to experience any serious adverse event was calculated to be 23 (95 percent CI: 18–40).

Patients receiving CBD also had increased odds of experiencing treatment-related serious adverse events (RR 5.93, 95 percent CI: 1.38–25.46). The NNH for one person to experience a treatment-related serious adverse event was 191 (95 percent CI: 167–529).

In the five non-RCT studies^{24,25,26,27,28,29} with 201 patients, the pooled estimate of patients experiencing any SAE were 2.2 percent (95 percent CI: 0–7.9). Only one observational study reported treatment-related serious adverse events³⁰, with 1.1 percent (95 percent CI: 0.6–1.8) of participants reporting this outcome.

4c. Withdrawal from treatment

Study withdrawals are used as an indicator of tolerability and effectiveness of a treatment. In RCTs, there was no difference in the likelihood of study withdrawal for any reason between patients given CBD and who received placebo (pooled RR 2.96, 95 percent CI: 0.64–13.78). This did not differ on the basis of epilepsy type, sample age or study risk of bias.

A pooled estimate of the proportion of participants withdrawing from the study for any reason in four non-RCTs^{31,32,33,34} was 28.0 percent (95 percent CI: 5.2–59.5). Pooled estimates of withdrawal were higher for paediatric-only samples (47.9 percent; 95 percent CI: 40.9–55.0), compared to mixed paediatric and adult samples (15.2 percent; 95 percent CI: 11.3–19.6).

Based on two RCTs^{35,36}, patients receiving CBD were more likely to withdraw from the study due to experiencing adverse events (pooled RR 4.87, 95 percent CI: 1.10–21.68), with no difference based on epilepsy type, sample age or study risk of bias. The NNH for one person to withdraw from CBD treatment due to adverse events was 164 (95 percent CI: 140–267).

The pooled estimate for withdrawals from the study due to adverse events in six studies (10, 11, 18–21) was 4.1 percent (95 percent CI: 0.9–8.8), and did not differ based on epilepsy type, sample age or study risk of bias.



Table 5. Summary of evidence for CBD in increasing adverse events and study withdrawals

Outcomes	Outcome summary	NNH (95%CI)	Evidence GRADE rating*
All-cause adverse events	Favours placebo Data from three RCTs suggest that CBD increased the likelihood of experiencing any adverse event relative to placebo.	3 (3–6)	++OO LOW
	Open label trials and observational studies reported that over half (50.6 percent) of samples using CBD reported experiencing any adverse event.	n/a	+OOO VERY LOW
Serious adverse events	Favours placebo Data from three RCTs suggest that CBD increased the likelihood of experiencing any serious adverse event relative to placebo.	23 (18–40)	++OO LOW
	Open label trials and observational studies reported that 2.2 percent of samples using CBD reported experiencing a serious adverse event.	n/a	++OO LOW
Treatment-related serious adverse events	Favours placebo Data from three RCTs suggest that CBD increased the likelihood of experiencing a serious treatment-related serious adverse event relative to placebo.	191 (167–529)	++OO LOW
	One observational study reported that 1.1 percent of participants experienced a serious treatment-related adverse event.	n/a	+OOO VERY LOW
Withdrawals (all-cause)	Favours neither Data from four RCTs suggest that there was no difference in withdrawal from treatment between patients receiving CBD and placebo.	n/a	++OO LOW
	Open label trials and observational studies reported that 28 percent of samples using CBD reported withdrawing from treatment for any reason.	n/a	+OOO VERY LOW
Withdrawals (due to adverse events)	Favours placebo Data from two RCTs suggest that CBD increased the likelihood of withdrawing from treatment due to experiencing adverse events.	n/a	++OO LOW
	Open label trials and observational studies reported that 4.1 percent of samples using CBD reported withdrawing from treatment due to adverse events.	n/a	+OOO VERY LOW

* +++++ HIGH: We are very confident that the true effect lies close to that of the estimate of the effect.
 ++++O MODERATE We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
 ++OO LOW: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
 +OOO VERY LOW: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.



Recommendation:

Patients and prescribing clinicians should be aware of likely adverse events such as diarrhoea, drowsiness, and changes to appetite. Adverse events such as a worsening of seizures, convulsions, severe diarrhoea or behavioural difficulties may affect the aims of the epilepsy treatment and increase the likelihood of treatment withdrawal, and should be evaluated on a case by case basis. If treatment is likely to be long-term, it is important that any side-effects from medicinal cannabis are not greater than side effects experienced with other AEDs, and that their response to treatment is regularly assessed.

Evidence on time to response

Treatment duration in RCT and open label clinical trials was a median of 16 weeks (range two to 52 weeks). Two RCT administered Epidiolex for a two-week test period that was followed by a twelve-week maintenance period. One study reported that treatment effects were evident within two weeks of starting treatment³⁷ but no such claims were made in the other RCTs.

Recommendation:

In the absence of strong evidence for dosing and specific preparations of cannabis or cannabinoids in epilepsy treatment, it is recommended that should the treating physician elect to initiate medicinal cannabis therapy in epilepsy patients, patients should be re-evaluated after 12 weeks for evidence of response to treatment.

Recommended review process for auditing patient outcomes, including suggested outcomes to evaluate

From the available evidence, outcomes that have been assessed in the effectiveness of medicinal cannabis in epilepsy treatment include:

- fifty percent or greater reduction in seizures (also referred to as a 'treatment responder')
- complete freedom from seizures
- improved quality of life.

While a decrease in seizures can be more easily measured objectively, many of the studies included in the review also reported improvements in various aspects of daily functioning (such as eating and drinking independently, and improved social behaviour) that may improve patients and their parents' quality of life. These improvements in patients' quality of life may be assessed on a case-by-case basis with their doctor.



When to stop

There is little evidence in the studies in the review to guide decisions about when treatment should be discontinued. Since most of the recent RCTs and open label trials of Epidiolex were run over a twelve week period, it may be reasonable to decide if treatment has produced benefits within this period and to discontinue treatment if there are no signs of improvement.

Recommendation:

In the absence of strong evidence for dosing and specific preparations of medicinal cannabis in epilepsy treatment, it is recommended that CBD be used and re-evaluated after twelve weeks of therapy, to ascertain whether there has been any benefit from its introduction.

Summary of cannabinoids

Table 6. Summary of cannabinoids tested for treatment-resistant epilepsies

Cannabinoid product	Condition	Preparation	Administration	Standardised
CBD	Treatment-resistant epilepsy	Oral solution, in one study as CBD product	Oral	Yes
	Dravet syndrome	Oral solution, in one study as CBD product	Oral	Yes
	Lennox-Gastaut syndrome	Oral solution, in one study as CBD product	Oral	Yes
	Secondary generalised epilepsy	Capsule	Oral	Yes
CBD:THC	Dravet syndrome	Oil	Oral	Not specified
THC	Generalised seizures	Capsule (as dronabinol)	Oral	Yes
	Treatment-resistant epilepsy	Oil; cigarette; tea	Oil: Oral Cigarette: Inhalation Tea: Oral	Not specified
Herbal cannabis and other products	Dravet syndrome	Oil	Oil: Oral	Not specified
	Lennox-Gastaut syndrome	Oil; tincture	Oil: Oral	Not specified
	Secondary generalised epilepsy	Oil	Oil: Oral	Not specified

Cannabidiol (CBD)

CBD was administered in oral solution form in the clinical trials or case studies of patients who qualified for compassionate access schemes^{38,39,40,41,42,43}. In the studies using Epidiolex, the product is standardised and manufactured by GW Pharmaceuticals. It is not clear whether pharmaceutical grade standardised products were used in the 1980 study with 15 epileptic patients⁴⁴.



Other CBD products, such as 'purified CBD' or high-concentration CBD, are also taken orally, possibly in an oil or tincture form. They are most likely not to be standardised^{45,46,47,48}.

Cannabidiol: Tetrahydrocannabinol(CBD:THC)

CBD:THC products were administered orally as an oil. The product was standardised but not of pharmaceutical grade⁴⁹.

Tetrahydrocannabinol (THC)

THC products were in oral capsules and of pharmaceutical standard (i.e. Marinol, dronabinol)⁵⁰.

Cannabis sativa and other products

Cannabis sativa, in its herbal form, was smoked, drunk or vaporized. The products were not standardised, and information about dosage range was not given^{51,52}.

CBD-enriched cannabis products were taken orally, in either an oil or tincture, and probably not standardised (20). Similarly, oral cannabis extracts were taken orally as either an oil or tincture, and probably not standardised product⁵³.

Summary of dosing information

Cannabidiol (CBD)

The trial evidence suggests that doses of 20mg/kg/day of CBD (Epidiolex) are effective at reducing seizures in Dravet and Lennox-Gastaut syndromes^{54,55}. Older evidence suggests that doses of 100mg of CBD two to three times per day substantially reduced seizures compared to placebo⁵⁶.

In other open label trials, CBD doses have ranged between 2–50mg/kg/day. Dosage typically starts between 2–5mg/kg/day and is increased either until seizures are reduced or the patient experiences adverse effects that lead to discontinuation.

Purified CBD extracts were dosed at between 200–280mg/day⁵⁷, or 2.9–12mg/kg day^{58,59}. There is no clinical trial evidence to support the effectiveness of this dose range.

The Mayo Clinic reports that, to treat epilepsy, 200 to 300mg of CBD can be taken by mouth for up to four and a half months⁶⁰.

Cannabidiol: Tetrahydrocannabinol (CBD:THC)

There is one case report of the use of doses of a sublingual preparation of the plant extract of a CBD:THC strain of cannabis of 4mg/lb (approximately 2mg/kg) a day but there is no clinical trial evidence to support the effectiveness of this product at this dose⁶¹. Another parent self-report survey reported CBD dosages ranging between 1–28mg/kg/day and THC dosages ranging between 0.01–0.7mg/kg/day. There was no consistent dosing pattern and not all children were given CBD-enriched extracts that also included THC (200). There is no controlled clinical evidence to support the effectiveness of this product or dose.

The Israeli medical cannabis clinical guide recommends that both adults and children receive CBD-rich flos, oil or cookies (for children only). It is recommended that adults begin using



products that contain 1 percent THC:20 percent CBD; treatment may be altered to 0 percent THC:24 percent CBD, or slightly higher THC products may be used if necessary, such as 3 percent THC:15 percent CBD or 5 percent THC:10 percent CBD. For children, it is recommended that they begin with 0 percent THC:24 percent CBD products; a slightly higher THC concentration of 3 percent THC:15 percent CBD may be used if necessary⁶².

Tetrahydrocannabinol (THC)

A series of case studies reported the use of THC in treating epilepsy or generalised seizures⁶³. THC was dosed between 0.7–0.14mg/kg one to two times per day but there is no controlled clinical evidence to support the effectiveness of this product or dose. Israeli medical cannabis supplier, Tikun Olam Ltd, a supplier of medicinal cannabis in Israel, suggests that in the absence of other instructions, the general guidelines for smoking or vaporizing cannabis are to take two or three inhalations and wait for several minutes for the cannabis to take effect. Inhalations are repeated until the desired dose is reached ('based on the feeling'). Oral products should be taken in small quantities, and patients should wait two hours to feel the effects of the active ingredients. This small ingestion and waiting for two hours is repeated until reaching the desired dose. Once the optimal dose is achieved, patients should wait six hours before taking another dose. Doses may increase slowly over a number of weeks⁶⁴.

Cannabis sativa

Cannabis sativa was reportedly dosed in a range between 0.5–8g of marijuana per day. These reports were not able to estimate the dosage of CBD, THC or other cannabinoids that the patient received^{65,66}. There is currently no controlled clinical evidence to support the effectiveness of this product or dose range in epilepsy.

Drug-drug interactions

There has been a recent study published on the interactions between cannabidiol and commonly used AEDs⁶⁷. Its aim was to identify potential pharmacokinetic interactions between the pharmaceutical formulation of cannabidiol (CBD; Epidiolex) and the commonly used AEDs through an open-label safety study. In the study, serum levels were monitored to identify interactions between CBD and AEDs. It found increases in topiramate, rufinamide, and N-desmethyloclobazam and a decrease in clobazam (all $p < 0.01$) serum levels were seen with increasing CBD dose. Increases in serum levels of zonisamide ($p = 0.02$) and eslicarbazepine ($p = 0.04$) with increasing CBD dose were seen in adults. Except for clobazam and desmethyloclobazam, all noted mean level changes were within the accepted therapeutic range. Sedation was more frequent with higher N-desmethyloclobazam levels in adults ($p = 0.02$), and AST/ALT levels were significantly higher in participants taking concomitant valproate ($p < 0.01$).

It concluded that significantly changed serum levels of clobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine were seen. Abnormal liver function test results were noted in participants taking concomitant valproate. This study emphasized the importance of monitoring serum AED levels and LFTs during treatment with CBD.

Recommendation

Prescribing clinicians should also be aware of the potential drug–drug interactions with CBD and anti-epileptic drugs.



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