Cannabidiol

First published 17 December 2020
https://doi.org/10.18773/austprescr.2020.080

Approved indication: epilepsy (Lennox-Gastaut syndrome, Dravet syndrome)

Epidyolex (Emerge Health)
oral solution containing 100 mg/mL

Cannabidiol is indicated for adjunctive therapy for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients aged two years and older. It is a constituent of the marijuana plant *Cannabis sativa* but unlike tetrahydrocannabinol (THC) cannabidiol does not have psychoactive effects like euphoria.

It is not clear how exactly cannabidiol works to reduce seizures, but it is thought to affect the transmission of electrical signals by modulating the movement of calcium in neurones. Cannabidiol also affects signalling mediated by adenosine which has an important role in seizure suppression.

Adding cannabidiol to other epilepsy medicines has been investigated in four randomised, placebo-controlled trials – two in patients with Lennox-Gastaut syndrome[1,2] and two in patients with Dravet syndrome[3,4] (see Table). The majority of participants in the trials were children with uncontrolled seizures who were already taking at least two antiepileptics. The most commonly used were clobazam and valproate.

Following a four-week baseline period, an oral solution of cannabidiol (titrated to a dose of 10 mg/kg or 20 mg/kg) or placebo was added twice a day to the patient's usual antiepileptic therapy for 14 weeks. In the Lennox-Gastaut syndrome trials, patients were having at least eight drop seizures a month at baseline. These were defined as atonic, tonic or tonic-clonic seizures that could cause a sudden fall. By the end of the treatment, cannabidiol had lowered the frequency of drop seizures per month more than placebo (by 37–44% vs 17–22%).[1,2] In the Dravet syndrome trials, patients were having at least four convulsive seizures a month at baseline. By the end of the treatment, cannabidiol had lowered the seizure frequency per month more than placebo (by 39–49% vs 13–27%) (see Table).[3,4] This effect seemed to be maintained in a 48-week open-label extension study of all four trials.[5,6]

The proportion of patients (or their caregivers) who reported improvement on a global impression of change (GIC) scale at last visit was higher in the cannabidiol groups than in the placebo groups (see Table). However, trials that assessed quality of life[1,3,4] did not find a statistically significant difference between cannabidiol and placebo.

Table **Efficacy of cannabidiol in severe epilepsy**

Study	Treatment group (participants)	Reduction in the frequency of seizures per month from baseline	Improvement in overall condition from baseline on the patient's or caregiver's GIC scale*
Lennox-Gastaut syndrome trials (mean age 15 years)†			
Devinsky 2018[1]	Cannabidiol 10 mg/kg/day	37.2%	66% (48 of 73 patients)
	Cannabidiol 20 mg/kg/day	41.9%	57% (43 of 75 patients)
	Placebo	17.2%	44% (33 of 75 patients)
Thiele 2018[2]	Cannabidiol 20 mg/kg/day	43.9% (from a median of 71.4 to 31.4)	58% (49 of 84 patients)
	Placebo	21.8% (from a median of 74.7 to 56.3)	34% (29 of 85 patients)
Dravet syndrome trials (mean age 9 years)‡			
Devinsky 2017[3]	Cannabidiol 20 mg/kg/day	38.9% (from a median of 12.4 to 5.9)	61.6% (37 of 60 patients)
	Placebo	13.3% (from a median of 14.9 to 14.1)	34.4% (20 of 58 patients)
Miller 2020[4]	Cannabidiol 10 mg/kg/day	48.7%	68.1% (45 of 66 patients)
	Cannabidiol 20 mg/kg/day	45.7%	60.6% (40 of 66 patients)
	Placebo	26.9%	41.5% (27 of 65 patients)

* GIC global impression of change at last visit
† efficacy was defined as median percent reduction in the frequency of drop seizures per month from baseline
‡ efficacy was defined as median percent reduction in frequency of convulsive seizures per month from baseline

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

The most common adverse events with cannabidiol (affecting at least 10% of patients) were somnolence and sedation, decreased appetite, diarrhoea, fever, fatigue, vomiting and weight loss. These effects appeared to be dose related.[2,3]

Cannabidiol also causes dose-related increases in liver transaminases and is contraindicated when transaminase concentrations are greater than three times the upper limit of normal and bilirubin concentrations are greater than two times the upper limit of normal. Overall, 13% of patients receiving cannabidiol had elevated alanine aminotransferase (>3 times the upper limit of normal) compared to 1% of those who received placebo. The incidence was higher in those taking concomitant valproate (17%) or concomitant valproate and clobazam (23%). Serum transaminases should be tested before cannabidiol is started and regularly during treatment. The cannabidiol dose (or other antiepileptic) may need to be reduced, interrupted or discontinued if signs of hepatic dysfunction develop.

Cannabidiol increases concentrations of co-administered clobazam by 3–4-fold, probably through inhibition of cytochrome P450 (CYP) 2C19. Increases in the active cannabidiol metabolite (7-hydroxy-cannabidiol) are also observed. As a consequence, somnolence and sedation are increased with this combination and the clobazam (or cannabidiol) dose may need to be reduced. Cannabidiol may also increase co-administered stiripentol, phenytoin and lamotrigine so patients should be carefully monitored for adverse reactions.

Cannabidiol is extensively metabolised in the liver by CYP2C19 and 3A4 and uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A7, 1A9 and 2B7 so there is a potential for many drug interactions. Concurrent use of moderate and strong inducers of CYP2C19 (e.g. rifampicin) and CYP3A4 (e.g. carbamazepine, enzalutamide, St John's wort) may decrease cannabidiol concentrations and reduce its effectiveness. Conversely inhibitors of CYP2C19, CYP3A4, UGT1A7, UGT1A9 and UGT2B7 enzymes may increase cannabidiol exposure and increase the risk of adverse effects. If these combinations are used, the dose of cannabidiol or the interacting drug may need to be reduced.

Following oral administration of cannabidiol, maximum plasma concentrations are reached within 2.5–5 hours. Its half-life is 56–61 hours and, following metabolism in the liver, most of the dose is excreted in the faeces. The recommended starting dose is 2.5 mg/kg taken twice a day for a week. After that, the dose should be titrated to a maintenance dose of 5 mg/kg twice daily based on therapeutic effect and patient tolerance. The maximum recommended dose is 10 mg/kg taken twice a day.

As food can increase the absorption of cannabidiol, the dose should be taken consistently with or without food each day. Dose adjustments are not needed in renal impairment, but lower doses are recommended in patients with moderate–severe hepatic impairment.

Cannabidiol reduces the frequency of treatment-resistant drop seizures in patients with Lennox-Gastaut and convulsive seizures in Dravet syndrome when added to usual antiepileptic therapy. However, cannabidiol has many potential drug interactions, particularly with other antiepileptic medicines. Somnolence and elevations in liver transaminases are common and patients need to be closely monitored.

T manufacturer provided the product information

REFERENCES

1. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al.; GWPCARE3 Study Group. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med 2018;378:1888-97. https://doi.org/10.1056/NEJMoa1714631
2. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al.; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:1085-96. https://doi.org/10.1016/S0140-6736(18)30136-3
3. 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. N Engl J Med 2017;376:2011-20. https://doi.org/10.1056/NEJMoa1611618
4. Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry S, et al.; GWPCARE2 Study Group. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome: a randomized clinical trial. JAMA Neurol 2020;77:613-21. https://doi.org/10.1001/jamaneurol.2020.0073
5. Thiele E, Marsh E, Mazurkiewicz-Beldzinska M, Halford JJ, Gunning B, Devinsky O, et al. Cannabidiol in patients with Lennox-Gastaut syndrome: interim analysis of an open-label extension study. Epilepsia 2019;60:419-28. https://doi.org/10.1111/epi.14670
6. Devinsky O, Nabbout R, Miller I, Laux L, Zolnowska M, Wright S, et al. Long-term cannabidiol treatment in patients with Dravet syndrome: an open-label extension trial. Epilepsia 2019;60:294-302. https://doi.org/10.1111/epi.14628

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.