# Safety of cannabidiol prescribed for children with refractory epilepsy

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Cannabidiol as add-on therapy is reported to reduce convulsive seizures in patients with Dravet syndrome and to reduce drop seizures in patients with Lennox–Gastaut syndrome.[1,2] In Australia, experience with prescription cannabis for treating epilepsy is limited and the safety of the available products has not been established. Open-label prescribing of one cannabidiol formulation tested in controlled trials (Epidiolex [GW Pharmaceuticals]) is restricted to compassionate schemes in New South Wales and Queensland.

The Department of Health and Human Services (Victoria) invited paediatric neurologists to submit applications on behalf of children with severe refractory epilepsy for state-sponsored access to cannabidiol (CBD Max [Tilray]: 98% cannabidiol in grapeseed oil, 100 mg/mL). Approved patients of the Royal Children's Hospital (RCH) were referred to the author for treatment under the Therapeutic Goods Administration Special Access Scheme, Category B. Baseline biochemistry, haematology, and therapeutic drug level monitoring (when clinically available) was performed. Cannabidiol was added to the child's usual medication as a twice-daily dose, titrated in weekly steps from 5 to 20 mg/kg/day. Clinical review and blood tests were repeated monthly for 3 months and then every 3 months. Adverse events and reasons for discontinuation of treatment were recorded. Data collation was approved by the RCH Human Research Ethics Committee (study, 36328A).

Twenty children aged 2–17 years (median, 10 years) were treated for 9–40 weeks (median, 23 weeks) between February and November 2017; 15 were girls (Box). Thirteen achieved the target dose; seven achieved doses of 10–17.5 mg/kg/day. Sixteen children experienced treatment-emergent adverse events, including somnolence, nausea or vomiting, anorexia, and appetite increase. Eight of ten children taking clobazam and three of ten children not taking clobazam experienced somnolence; this was managed by reducing the clobazam dose if applicable. There were 11 serious adverse events in five children leading to hospitalisation, of which two (somnolence with dehydration; status epilepticus) were attributed to cannabidiol treatment. New abnormal liver function was measured in five children; three with transient alanine aminotransferase level elevation were taking valproate. Measured anti-epileptic medication levels were unchanged; one child had markedly elevated sirolimus levels. One child discontinued treatment after a serious adverse event (somnolence and anorexia); eight children discontinued (after 9–23 weeks) because of lack of effectiveness. Eleven continued treatment beyond 17–40 weeks, with the parents of nine reporting clinically significant seizure reduction (greater than 50%).

The adverse events profile of CBD Max was very similar to that reported for Epidiolex;[3] despite a high adverse event rate, discontinuation of treatment because of these events was similarly infrequent in open-label use. Adverse events were generally mild, transient and not dissimilar to those associated with other add-on therapies. Cannabidiol has a potent inhibitory effect on several cytochrome P450 isozymes, and pharmacokinetic interaction with concurrent anti-epileptic medication probably explains many

**Adverse events experienced by 20 children prescribed cannabidiol as add-on therapy for epilepsy**

| Characteristic | Number of children |
|---|---|
| Epileptic syndrome diagnosis | |
| Lennox–Gastaut syndrome | 12 |
| Epilepsy with myoclonic-astatic seizures | 3 |
| Myoclonic encephalopathy | 2 |
| Epilepsy of infancy with migrating focal seizures | 1 |
| Early infantile epileptic encephalopathy | 1 |
| Focal epilepsy | 1 |
| Aetiology | |
| Early acquired brain injury | 3 |
| Single gene defects | 3 |
| Brain malformation | 2 |
| Tuberous sclerosis complex | 1 |
| Chromosome micro-duplication | 1 |
| Unknown | 10 |
| Comorbid conditions | |
| Intellectual disability | 19 |
| Autism | 8 |
| Physical disability (mobility-dependent) | 8 |
| Concurrent medications (selected) | |
| Clobazam | 10 |
| Sodium valproate | 9 |
| Phenytoin | 2 |
| Phenobarbitone | 1 |
| Sirolimus | 1 |
| Non-serious adverse events | |
| Somnolence | 11 |
| Nausea or vomiting | 5 |
| Anorexia | 5 |
| New liver function abnormality | 5 |
| Appetite increase | 2 |
| Diarrhoea | 1 |
| Elevated sirolimus levels | 1 |
| *Any non-serious event* | *16* |
| Serious adverse events | |
| Somnolence and anorexia (2 events) | 1 |
| Status epilepticus (1 event) | 1 |
| Pneumonia (4 events) | 2* |
| Increased seizure frequency (1 event) | 1* |
| Increased non-epileptic clonus (1 event) | 1* |
| Constipation (1 event) | 1* |
| Low cardiac output state (1 event) | 1* |
| *Any serious event* | *5* |

* Not regarded as cannabidiol-related. ◆





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adverse events in patients with epilepsy.[4] In particular, inhibition of CYP2C19 metabolism of *N*-desmethylclobazam, the major active metabolite of clobazam, may cause sedation, affect blinding in controlled studies,[2] and contribute to the efficacy of cannabidiol in patients taking clobazam.[5]

While medicinal cannabis products are portrayed in the media and perceived by the public to be effective, natural therapies, cannabidiol is still a pharmaceutical in development, with potential benefits that require further delineation, and with short term adverse effects that must be understood and mitigated.

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1 Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017; 376: 2011-2020.

2 Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox–Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018; 391: 1085-1096.

3 Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol* 2016; 15: 270-278.

4 Gaston TE, Bebin EM, Cutter GR, et al. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia* 2017; 58: 1586-1592.

5 Tang R, Fang F. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome [letter]. *N Engl J Med* 2017; 377: 699-700. ■