Cannabis for paediatric epilepsy: challenges and conundrums

Kerrie-Anne Chen[1], Michelle A Farrar[1,2], Michael Cardamone[1,2], John A Lawson[1,2]

Cannabinoids have been used as therapeutic agents for thousands of years.[1] Uses have ranged from cure-all elixirs to specific treatment of malaria, pain and fatigue.[2,3] Cannabis was listed in the United States Pharmacopeia from 1851 to 1942; however, in 1961, the United Nations Single Convention on Narcotic Drugs labelled cannabis a "severely dangerous drug with no significant medical usefulness".[3] Personal use of cannabis and access for medical research was made illegal in many countries, such that there is limited evidence of safety or efficacy to guide clinicians.[4]

The role of medicinal cannabis products is relevant to children with drug-resistant epilepsy, for whom treatment is challenging and associated with significant comorbidity. Anecdotal media reports of miracle cures, the appeal of using a natural product and attitudes regarding its recreational use have strongly influenced the community perception and promoted political support for access to, and research into, medicinal cannabis products, creating a complex environment (Box 1).[5-7] Public opinion can significantly affect government policy;[8,9] however, high quality scientific evidence is essential to guide medical decision making and the political and legal framework. In Australia, medicinal cannabis products are now regulated under a therapeutic goods framework following recent legislative and regulatory changes. The recreational use, cultivation, sale or supply of cannabis remains illegal in Australia.

To consider the clinical aspects of medicinal cannabis products in paediatric drug-resistant epilepsy and practical issues regarding prescription, we have reviewed relevant articles identified following searches of MEDLINE, PubMed and the Cochrane Library, published from 1950 to November 2017, government websites and influential media reports using the search terms "cannabis", "medicinal marijuana" and "epilepsy".

Summary

- Research is expanding for the use of cannabidiol as an anticonvulsant drug. The mechanism of cannabidiol in paediatric epilepsy is unclear but is thought to play a role in modulation of synaptic transmission.
- Evidence for its efficacy in treating epilepsy is limited but growing, with a single pharmaceutical company-funded randomised double-blind controlled trial in children with Dravet syndrome.
- Progress towards the use of medicinal cannabinoids incorporates a complex interplay of social influences and political and legal reform.
- Access to unregistered but available cannabidiol in Australia outside of clinical trials and compassionate access schemes is state dependent and will require Therapeutic Goods Administration approval, although the cost may be prohibitive.
- Further clinical trials are needed to clearly define efficacy and safety, particularly long term.

The impact of refractory epilepsy

Drug-resistant epilepsy is defined by the International League Against Epilepsy as the failure of adequate and well tolerated trials of two appropriately chosen antiepileptic drugs.[10] Although definitions differ between studies, in children with epilepsy, about 10% are intractable, despite the increasing repertoire of antiepileptic medications over the past 20 years.[11,12] Drug-resistant epileptic patients have significant comorbidity, with high rates of cognitive impairment, physical and psychiatric disease, educational and occupational underachievement. Further, the mortality rate for people with epilepsy is 1.6–11.4 times greater than that of the general population at all ages.[13] Seizure control within the past 5 years was the only multivariate predictor of survival.[13] As such, drug-resistant epilepsy represents an area in which improved efficacy of therapy could contribute to significant improvement in multiple aspects of health care and quality of life.

Cannabidiol

Cannabis plants contain more than 545 chemical constituents. Δ^9-tetrahydrocannabinol (THC) is the most abundant cannabinoid, responsible for the psychoactive effects of cannabis.[4] Cannabidiol is the second most abundant and, although it resembles THC in its structure, pharmacology and function differ.[14] Formulations of cannabis-based drugs have been developed, with varied ratios of THC to cannabidiol. There are few pharmaceutical grade products available; however, there is an abundance of artisanal oral cannabis extracts available locally or purchased via the internet. The requirement for regulated production, analysis and oversight of medicinal cannabis products was highlighted in a recent US study demonstrating differences in labelling ingredients of cannabidiol products sold online to actual product constituents determined by laboratory analysis.[15]

How cannabidiol works

The physiology and pharmacology of cannabidiol and the endocannabinoid system remain to be fully elucidated. Among multiple targets, cannabinoid receptors types 1 and 2 have poorly understood functions in the brain.[1] While THC binds strongly to these receptors, cannabidiol has very low affinity for these receptors and may be antagonistic at nanomolar concentrations in vitro and counteract the psychotropic effects of THC.[16,17]

G protein-coupled receptor 55 is a likely target of cannabidiol, sharing some structural similarities with cannabinoid receptors.[18] It is widely distributed in the body; in the brain, it is found in the hippocampus, frontal cortex, cerebellum and deep grey matter.[19] Cannabidiol functions as a partial antagonist of these receptors, with reduced pyramidal cell excitatory signals as an anticonvulsant mechanism.[18]

The transient receptor potential vanilloid 1 channels are likely targets of cannabidiol. These are ligand-activated non-selective cation channels, permeable to sodium, calcium, and magnesium.[18] Activation of the receptor by cannabidiol produces neuronal

[1] Sydney Children's Hospital, Randwick, Sydney, NSW. [2] UNSW Sydney, Sydney, NSW. john.lawson@health.nsw.gov.au ▪ doi: 10.5694/mja17.00699
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1 Current issues in medicinal cannabis and epilepsy

Medical	Limited published evidence of efficacy and safety, dosing or indication About 10% of children with epilepsy are drug resistant and treatment is challenging, with a need for novel therapies
Ethical	Patients sourcing artisanal products in the absence of a pharmaceutical grade product, and risk of harm Use of unapproved products in children and parental responsibility
Social	Public misconception of the safety and efficacy of medicinal cannabis, anecdotal reports of remarkable results in the media Appeal of using a natural compound; the "naturalistic fallacy" Advocacy for children with serious disability Blurring of boundaries of legalisation for medicinal and recreational cannabis use Significant public impetus to supply and allow use of medicinal cannabis The financial responsibility of unregistered products
Political	Political statements encourage public misconception regarding availability and access to medicinal cannabis Political decisions influenced by community demand and case reports
Legal and regulatory	Medicinal cannabis products are now regulated under the standard therapeutic goods framework following legislative and regulatory changes ◆

hyperexcitability, potentially causing a paradoxical desensitisation through fast inactivation.[18,20,21]

Current clinical evidence for using cannabidiol for epilepsy

Until recently, the clinical evidence of efficacy and safety of cannabidiol and other medicinal cannabis products in epilepsy was summarised by a Cochrane review of four small randomised controlled trials and several cohort studies, case reports and surveys.[4,22-32] Taken together, no reliable conclusions regarding the efficacy of cannabinoids as a treatment for epilepsy could be drawn with methodological flaws and biases presenting significant limitations. These included small sample sizes, open-label design, lack of a robust outcome measure, self-selection and participant bias, inconsistent formulations of cannabidiol and a heterogeneous population.

In May 2017, a single pharmaceutical company-funded randomised double-blind placebo-controlled trial of cannabidiol for drug-resistant epilepsy in children with Dravet syndrome was published.[33] Dravet syndrome is a severe form of genetic epilepsy and in almost all patients is due to loss of function mutations in the *SCN1A* gene that encodes the voltage-gated sodium channel alpha-1 subunit. In this multicentre study, which included 120 children and young adults with Dravet syndrome, the median decrease in convulsive seizure frequency per month was from 12.4 to 5.9 with cannabidiol compared with from 14.9 to 14.1 with placebo (adjusted median difference in change in seizure frequency between cannabidiol and placebo groups, − 22.8%; 95% CI, − 41.1 to − 5.4; $P = 0.01$).[33] Several critics have suggested that drug−drug interactions, with increases in clobazam concentrations, may be a mechanism for the reduction in seizure frequency leading to an overestimation of cannabidiol efficacy.[34] Secondary endpoint outcomes varied between the cannabidiol and placebo groups. The cannabidiol group showed at least one point improvement on the Caregiver Global Impression of Change scale ($P = 0.02$), and a greater proportion of patients with at least a 50% reduction in convulsive seizure frequency (odds ratio, 2.00; 95% CI, 0.93−4.30; $P = 0.08$) or seizure freedom ($P = 0.08$).[33] The cannabidiol group experienced more frequent adverse events including vomiting, fever, illness, anorexia, seizures, sedation, diarrhoea and abnormal liver function test results; 14.8% of the group withdrew during the study period.[33] There is a need for more scientific studies to understand the risk, benefits and reproducibility of cannabidiol in children with intractable epilepsy. Further randomised controlled trials with cannabidiol in Dravet syndrome are being undertaken; however, the generalisability of findings to non-sodium channel-mediated epilepsies also remains uncertain.

Several observational cohort studies report similar findings that include other types of severe childhood epilepsy. Two retrospective cohort studies of patients receiving oral cannabis extracts found that 57−89% had any improvement in seizure frequency, with 33−51% having > 50% decrease in baseline seizure frequency.[27,30] An open-label prospective cohort study of cannabidiol in an expanded-access program in paediatric drug-resistant epilepsy demonstrated a median reduction of monthly motor seizures of 35% over 3 months, with 39% of patients experiencing a > 50% decrease in convulsive seizures.[35]

Clinical cannabis research may be particularly prone to the placebo effect, prompting caution. In part, this may be linked to efforts undertaken to obtain products by parents. This was shown in a study of 75 children in Colorado.[30] Families who moved to Colorado to obtain medicinal cannabis products were more likely to report a benefit (47%) than families who lived in Colorado (22%).[30] Three online surveys inviting responses from social media groups of patients or caregivers with epilepsy found that 81−85% showed any improvement in seizure frequency.[28,31,36] However, in a retrospective cohort study of 119 children receiving medicinal cannabis products for epilepsy, there was a 71% cessation rate after 2 years, related to lack of perceived benefit or adverse events.[23]

Pharmacokinetics and drug interactions

Understanding the pharmacokinetics of cannabidiol is important for safe prescribing, monitoring and limiting toxicity. Challenges include low oral bioavailability, inconsistent absorption with oral preparations, accumulation in adipose tissues and interactions with drugs metabolised in the liver cytochrome P450 enzymes.[2,14,18,37] Consequently, differences in route of administration, formulation and physiological factors will affect pharmacokinetics. For example, storage in adipose tissue means steady state may not be reached for several weeks after starting treatment, and that cannabidiol may remain detectable and active for many weeks after cessation.[2,16,20,38] Of relevance in children with drug-resistant epilepsy are interactions between cannabidiol and other commonly used antiepileptic medications. A recent study which included 42 children demonstrated two- to eightfold increases in levels of topiramate, rufinamide and clobazam metabolites;[39] the latter of these was associated with sedation.[40] Further, in patients taking concomitant valproate with

2 Key clinical points and recommendations in prescribing cannabis for children with drug-resistant epilepsy

Context and population	Prescription of cannabidiol is frequently raised in medical consultations for children with drug-resistant epilepsy as treatment is challenging and seizures continue with significant comorbidities
Scientific data	Recent studies indicate that cannabidiol may be effective (median reduction in seizure frequency, 22%) as an adjunctive therapy for Dravet syndrome[37] Further studies are required to understand the risk, benefits and reproducibility of cannabidiol use for children with intractable epilepsy
Prescribing	Options for prescribing cannabidiol in this population currently include state-based compassionate access schemes, and the Therapeutic Goods Administration Special Access Scheme Category B pathway
Dose	The dosage of oral cannabidiol will vary depending on formulation and may be gradually increased; however, it will take several weeks to reach a steady state due to accumulation in adipose tissue
Safety	There are limited safety data, particularly long term, for cannabidiol; the long term effects of recreational cannabis use are concerning
Side effects	Side effects are common and may be the reason for cessation in some patients These include diarrhoea, vomiting, fatigue, pyrexia, somnolence, and abnormal liver function test results
Interactions	Cannabidiol is largely metabolised by the liver via cytochrome P450 enzymes Concomitant cannabidiol may increase levels of commonly used antiepileptic medications; eg, topiramate, rufinamide and clobazam metabolites (leading to sedation)
Monitoring	Clinically monitor weight Check full blood count, electrolytes, urea and creatinine levels, and liver function at baseline, monthly for first 3 months and then every 3 months ◆

cannabidiol, aspartate aminotransferase and alanine aminotransferase levels were higher, with abnormal liver function test results observed in 29% patients in this small series.[39] In view of this, we suggest that cannabidiol be titrated from a starting dose of 5 mg/kg/day in two divided doses, increasing to a maximum of 25 mg/kg/day if needed and tolerated, and that monitoring of serum antiepileptic drug levels and liver function tests be conducted monthly for the first 3 months, and then every 3 months thereafter (Box 2).

Clinical studies are now focused on developing a comprehensive understanding of the pharmacological aspects of cannabidiol.[14,18,38,41] Caution regarding the limited safety and long term data are warranted.

Safety of medicinal cannabis products

Most of the clinical safety data for medicinal cannabis products are derived from the above-mentioned literature. Commonly reported short term adverse events include sedation, nausea, vomiting, appetite decrease and increased seizure frequency.[17,23,27,30,35] In addition, in vitro studies also suggest possible immunosuppression, with lymphocyte apoptosis and reductions of interleukins 8 and 10.[14] There are no long term data regarding the use of cannabidiol; however, there are well documented adverse health effects of long term recreational cannabis use, including lower birth weight and detrimental impacts on cognitive function and attention for children exposed to cannabis in utero.[4,42] Chronic use of cannabis in adolescence was associated with poor academic performance, reduced high school graduation, increased incidence of other drug addiction and mental health disorders.[4,42] In US states where cannabis has been legalised, medical consultations for accidental paediatric cannabis exposure have increased by 30% in regional poison centre calls from 2005 and 2011, compared with a non-significant increase of 1.5% per year in states where it has not been legalised.[42]

Safety is a concern in patients using artisanal cannabis products, including smoked cannabis and cannabidiol-enriched mixed preparations from crude plant extracts. Effects from mixed preparations should be interpreted with caution as cannabis is a complex mix of compounds, such that individual effects are unknown.[3,43] Most non-pharmaceutical grade backyard cannabis formulations are inconsistent between batches and may contain other toxic compounds such as pesticides, bacteria and fungi.[44] These compounds interact with other antiepileptic drugs.[39] Patients typically experiment with different formulations of cannabis with varying and inaccurate dosages to achieve the desired effect without medical supervision.

Prescribing medicinal cannabis in Australia: regulatory process

In Australia, law reforms have facilitated access to medicinal cannabis products, which are now regulated by the Therapeutic Goods Administration (TGA; https://www.tga.gov.au/access-medicinal-cannabis-products) and the Office of Drug Control. Cannabidiol is the only medicinal cannabis product relevant to paediatric epilepsy and is schedule 4 in most states, available by prescription without other authority required.[45] However there is no cannabidiol product on the Australian Register of Therapeutic Goods. Currently health professionals may provide access to cannabidiol for appropriate patients as an unapproved drug through the Special Access Scheme (SAS), Authorised Prescriber Scheme (APS), a clinical trial, or a state-based compassionate access scheme. The TGA pathways for prescription of medicinal cannabis products are the same as those for any other unregistered medicine.

The SAS allows individual patients with a clinical need to access unregistered medicines. It requires a case-by-case application to the TGA for approval, including clinical patient information, the proposed product and supplier. To become an Authorised Prescriber, after local ethics committee approval, a medical practitioner must apply to the TGA to allow them to prescribe a specific medicine for patients with a specific indication, without subsequent approval required for individual patients. The TGA bases its SAS or APS approval on three criteria: patients' clinical need, product efficacy and safety, and prescribers' experience. The

prescribing medical practitioner has several responsibilities, including providing informed consent and a treatment plan and monitoring, and complying with reporting requirements including reporting any adverse event to the TGA.[46] Once SAS or APS approval has been granted, the prescriber must arrange for the provision of the product with the supplier and local pharmacy and provides the patient with a prescription.

In a practical sense for paediatric epilepsy, this means that general practitioners or paediatricians can only apply via the SAS scheme with supporting documentation from a paediatric neurologist. Authorised prescribers are usually paediatric neurologists prescribing within a compassionate access scheme. The Royal Australian College of General Practitioners, Royal Australasian College of Physicians, Australian and New Zealand College of Anaesthetists Faculty of Pain Medicine, and Epilepsy Society of Australia have all issued position statements calling for more evidence before allowing access to the general public.[37,47]

Available medicinal cannabis products

There are three main forms of cannabis used for medicinal purposes: a pharmaceutical grade medication, produced under strict manufacturing guidelines with standardised amounts of active compounds and dosing; medicinal grade herbal cannabis from a medicinal cannabis producer, produced in a standardised and controlled environment, free from additives; and products in varying final forms (herbal preparations, extracts, sprays, capsules) and recreational cannabis.[48] The government has approved legislation for the importation of medicinal cannabis products, and there are currently several companies licensed under the Customs (Prohibited Imports) Regulations 1956 to import unregistered medicinal cannabis products (a full list is available at https://www.odc.gov.au/importers-and-manufacturers-medicinal-cannabis-products).[49] Before a product can be prescribed, the manufacturer must complete a declaration of compliance with Therapeutic Goods Order No. 93 (Standard for Medicinal Cannabis).[50]

The issue of cost has received scant attention. Access to medicinal cannabis products outside a clinical trial or compassionate access scheme means the onus of financial responsibility falls on the patient and the cost of these imported products may be prohibitive. Hospital drug committees would be challenged to approve a product with limited safety and efficacy data. For a child weighing 20 kg, the cost of the imported medicinal cannabis product may be in the range of $1000–2000 per month.

Future directions

Cannabinoids in epilepsy represent an important area of research for our patients with the most intractable forms of epilepsy, and there is a need for better treatment and more high quality trials assessing effectiveness. The public perception and media hype must be tempered by clinical evidence. Clinical trial data so far indicate cannabidiol may have an effect in the treatment of epilepsy in Dravet syndrome; however, this requires replication. In parallel, there have been substantive legislative changes to facilitate provision of and access to cannabidiol. Community pressure on governments, health professionals and regulatory bodies will continue to intensify.

Several issues require resolution before increasing access to medical cannabis. These include the need for further evidence for long term safety; efficacy, dosing and indications; assuring a high quality and consistent product; and allaying concerns about the medical supply of a potential drug of addiction. Increased public interest, government funding and individual large philanthropic bequests are helping to bridge the critical translation gaps from drug development, manufacturing, and clinical trials. Cannabidiol may offer a further option of treatment in drug-resistant epilepsy; however, further high quality, scientifically rigorous trials are awaited to guide medical decision making and the political and legal framework.

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