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Review article

Cannabis for refractory epilepsy in children: A review focusing on CDKL5 Deficiency Disorder

Tristan Dale[a,b], Jenny Downs[b,c], Heather Olson[d], Ann Marie Bergin[d], Stephanie Smith[b], Helen Leonard[b,*]

[a] UWA Medical School, Faculty of Health and Medical Sciences, University of Western Australia, Perth, WA, Australia[1]
[b] Telethon Kids Institute, University of Western Australia, Perth, WA, Australia[2]
[c] School of Physiotherapy and Exercise Science, Curtin University, Perth, WA, Australia[3]
[d] Department of Neurology, Division of Epilepsy and Clinical Neurophysiology, Boston Children's Hospital, Boston, MA, USA[4]

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ABSTRACT

Severe paediatric epilepsies such as CDKL5 Deficiency Disorder (CDD) are extremely debilitating, largely due to the early-onset and refractory nature of the seizures. Existing treatment options are often ineffective and associated with a host of adverse effects, causing those that are affected to seek alternative treatments. Cannabis based products have attracted significant attention over recent years, primarily driven by reports of miraculous cures and a renewed public preference for 'natural' therapies, thus placing intense pressure on health professionals and the government for regulatory change. This study provides a comprehensive overview of the potential role for cannabis in the treatment of CDD. Key areas discussed include the history, mechanism of action, efficacy and safety of cannabis based preparations as well as the burden related to CDD. The evidence supports the use of cannabinoids, especially cannabidiol, in similar forms of refractory epilepsy including Dravet and Lennox–Gastaut syndromes. Evidence for cannabinoids specifically in CDD is limited but growing, with multiple anecdotal reports and an open-label trial showing cannabidiol to be associated with a significant reduction in seizure activity. This review provides the first comprehensive overview of the potential role for cannabis based preparations in the treatment of CDD and provides justification for further clinical and observational research.

1. Background

Epilepsy is the most frequent chronic neurological condition in childhood, with approximately 1 in 150 children being diagnosed with a form of epilepsy during the first 10 years of life (Aaberg et al., 2017). The quality of life for many of these patients is becoming increasingly favourable with around 4 in 5 reaching a state of remission at 5 years (Berg and Rychlik, 2015). However, the remaining 1 in 5 may experience repeated cycles of relapse and remission, or otherwise be affected by non-remitting, refractory epilepsy. These non-remitting forms are typically characterised by seizures that are poorly responsive to available treatment options including antiepileptic drugs, the ketogenic diet, high doses of steroids, and neurostimulation therapies (Granata et al., 2009).

Patients with these forms of severe, refractory epilepsy are at increased risk of mortality due to accidents, sudden unexpected death in epilepsy as well as respiratory infections (French, 2007; Laxer et al., 2014). These seizure related accidents occur at high frequency, particularly in those who are mobile, and include lacerations, head injury, burns and dental injuries (Wirrell, 2006). Adding to this burden is the extensive impairment of neurodevelopment caused by the underlying epileptogenic processes, which appears to be independent of the seizures themselves (Laxer et al., 2014).

One of the most debilitating forms of treatment-resistant epilepsy is CDKL5 Deficiency Disorder (CDD) – a genetic epilepsy characterised by early-onset intractable seizures, global developmental delay, profound

* Corresponding author at: Telethon Kids Institute, Northern Entrance, Perth Children's Hospital, 15 Hospital Avenue, Nedlands, WA 6009, Australia.
E-mail addresses: Tristan.Dale@telethonkids.org.au (T. Dale), Jenny.Downs@telethonkids.org.au (J. Downs), Heather.Olson@childrens.harvard.edu (H. Olson), AnnMarie.Bergin@childrens.harvard.edu (A.M. Bergin), Stephanie.Smith@telethonkids.org.au (S. Smith), Helen.Leonard@telethonkids.org.au (H. Leonard).
[1] 35 Stirling Highway, Crawley, WA 6009, Australia.
[2] Northern Entrance, Perth Children's Hospital, 15 Hospital Avenue, Nedlands, WA 6009, Australia.
[3] GPO Box U1987, Perth, WA 6845, Australia.
[4] 300 Longwood Avenue, Boston, MA 02115, USA.

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hypotonia and severe impairment in gross motor skills (Mangatt et al., 2016). This early onset encephalopathy is also associated with poorer child health including sleep disturbances, respiratory and gastrointestinal issues, which in turn contribute to the severe impact of this disorder that extends beyond individuals affected, causing reduced parental wellbeing and poorer quality of life for affected families (Fehr et al., 2013; Mori et al., 2017).

Since seizures in CDD are often resistant to available medication, dietary, and neurostimulation therapies in isolation, a combination of treatments is regularly trialled, often with little effect. Indeed, the polytherapy of these treatments may even exacerbate the cognitive, psychiatric, and motor deficiencies that are associated with the underlying condition (Cramer et al., 2010; Perucca and Gilliam, 2012). Additionally, they may introduce a host of adverse systemic effects including sedation, somnolence, distractibility, hyperactivity, insomnia, and dizziness (Aldenkamp et al., 2016; Perucca and Gilliam, 2012). Even in the absence of adverse effects on neurological examination, the use of multiple treatment options may cause a worsening of perceived quality of life, cognitive deficits and behavioural problems (Lagae, 2006).

Therefore, there is urgent need for safer and more effective antiseizure therapies for CDD and other refractory epilepsies in children. In recent years, this has led patients and families to seek alternatives for seizure control, such as medicinal cannabis. Cannabis treatments for epilepsy have been the subject of prominent attention in the community, primarily driven by the appeal of a 'natural' product and anecdotal reports of miracle cures (Maa and Figi, 2014; McLaren et al., 2008). This public pressure has encouraged rapid legislative and regulatory changes. However, scientific evidence on the safety and efficacy of cannabinoids in refractory epilepsy is essential before this can be considered a potential mainstream treatment.

Despite the growing interest in cannabis for the treatment of refractory epilepsy, there has been no comprehensive review of the evidence for cannabis based preparations in the treatment of CDD. Therefore, this article aims to provide a thorough narrative review of the history, mechanism of action, efficacy and safety of medicinal cannabis preparations for childhood onset refractory epilepsy, with a focus on CDD.

2. The burden of refractory epilepsy in CDKL5 Deficiency Disorder

As defined by the International League Against Epilepsy (ILAE), epileptic encephalopathies are conditions where "the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone, and that these can worsen over time" (Berg et al., 2010). The key concept in this definition is that a genetic mutation may be the underlying cause of the epilepsy, however, the excessive seizure activity may worsen the clinical course of the disease (Berg et al., 2010). Epileptic encephalopies are characterised by three main features: refractory seizures, severe abnormalities on electroencephalography, and developmental delay or intellectual disability (Esmaeeli Nieh and Sherr, 2014; Hwang and Kwon, 2015). The refractory nature of the seizures creates a devastating impact on the lives of those affected, and leads to an acceleration of cognitive and behavioural impairments. Of these epileptic encephalopathies, one of the most debilitating is CDD, largely due to the seizures which can present as early as the neonatal period, but most commonly in early infancy (Fehr et al., 2013).

CDD, which was originally thought to be an atypical variant of Rett syndrome, is a rare X-linked condition caused by mutations in the cyclin-dependent kinase-like-5 (*CDKL5*) gene (Fehr et al., 2013). The *CDKL5* gene encodes for a serine/threonine kinase that is involved in cell signaling and neuron morphogenesis, and so mutations lead to profound abnormalities of neurological development which manifest as complex neonatal seizures, hypotonia, poor visual tracking, and rarely, microcephaly (Axeen and Olson, 2018). Although many of these features are shared by other epileptic encephalopathies, CDD presents with a distinct clinical profile and may include subtle facial, limb and hand phenotypes that help to distinguish it as its own clinical entity (Fehr et al., 2013).

An important source of much of the epidemiological data in CDD is the International CDKL5 Database, a collaborative and growing dataset established in 2012, which collects information from families affected by CDD. Caregivers are asked to complete an online questionnaire or paper-based equivalent and refer to available medical records where appropriate. This database gathers important information about key features of the disease including clinical presentation, past and current treatments as well as characteristics of any seizure activity. The data from this database found seizures to be the most consistent feature of CDD, with only three cases in the literature never reporting seizures (Fehr et al., 2016; Martínez et al., 2012; Weaving et al., 2004). The seizures typically develop within the first few months of life, even as early as at birth, and often continue on an intractable course (Fehr et al., 2013). Of 172 patients analysed in 2016, the median age of seizure onset was 6 weeks, with a median seizure rate of 2 per day (Fehr et al., 2016). Those who were able to walk and use spoken language had lower rates of seizures than those who did not have these abilities. Interestingly, the seizure rate was lower in those with truncating mutations between aa172 and aa781 compared to those with no functional protein (Fehr et al., 2016).

The early-onset seizures that define this group vary from spasms and eyelid myoclonia to generalised tonic-clonic seizures (Bahi-Buisson et al., 2008). In addition, those affected by CDD generally experience global developmental delay with persistent and major deficits in motor, communication and cognitive skills (Fehr et al., 2015; Mangatt et al., 2016). There is some evidence to suggest that the course of epilepsy progresses through three stages – (1) early epilepsy without severe encephalopathy patterns on EEG, (2) epileptic encephalopathy with infantile spasms and (3) multifocal and myoclonic epilepsy (Bahi-Buisson et al., 2008).

The seizures in CDD are particularly resistant to existing treatments, with over two-thirds of patients having daily seizures despite multiple antiepileptic drugs (AEDs) (Fehr et al., 2016). Furthermore, around 1 in 3 patients may experience an aggravation in seizures to at least one AED (Müller et al., 2016). The severe, refractory nature of this epilepsy prompts caregivers to seek alternative treatments, with about half of the children having tried the ketogenic diet and one in six having had a vagal nerve stimulator inserted (Lim et al., 2018, 2017). Both of these treatment options are thought to have a measurable antiseizure effect, with 59% of patients on the ketogenic diet experiencing improvement in seizure frequency, duration or intensity, and a similar improvement for 69% of patients using vagal nerve stimulation (VNS) (Lim et al., 2018, 2017). However, neither treatment caused any patient to become seizure-free, and side effects were cited in both of these treatments, leading to poor long-term adherence with the ketogenic diet (median duration of 17 months) and termination of VNS in around one in ten cases (Lim et al., 2018, 2017).

A common feature of many epilepsy treatments is a temporary decrease in seizure frequency with a subsequent return to baseline, known as the honeymoon phase (Avanzini, 2006). While this phenomenon is found within many aetiologies of epilepsy, it has been more consistently described in patients with CDD (Archer et al., 2006; Moseley et al., 2012). During the honeymoon phase in CDD the transient decrease in seizures with antiepileptic medication is still accompanied by developmental arrest and a loss of physiological features on the interictal EEG (Bahi-Buisson et al., 2008). As reported by just over a third of families, the honeymoon phase occurs with a median duration of 6 months and may last up to 72 months (Fehr et al., 2016). Interestingly, the attainment of a seizure-free period is thought to be predictive of reduced seizure frequency in the longer term (Fehr et al., 2016). The rapid return of seizures was highlighted by one retrospective study of 39 CDD patients which found the responder rate (> 50% reduction in

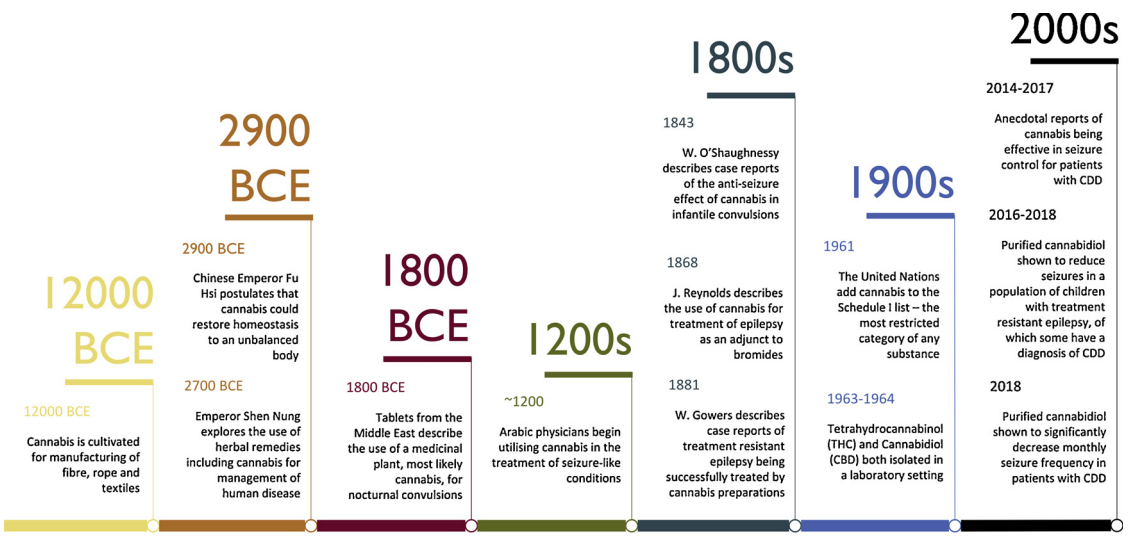

Fig. 1. A timeline illustrating the major developments in the history of cannabis for the treatment of epilepsy, focusing on CDKL5 Deficiency Disorder.

seizure frequency) to at least one AED or the ketogenic diet to decline from 69% at 3 months, to 45% at 6 months, and 24% at 12 months (Müller et al., 2016).

The debilitating nature of the intractable seizures is thus compounded by the lack of long-term efficacy and the adverse effect profile of existing treatment options, and so alternative treatments are urgently needed.

3. The history of cannabis in epilepsy

Cannabis is thought to be one of the oldest plants cultivated for human use, with uses in the manufacturing of fibre, rope and textiles dating back as early as 12,000 BCE (Friedman and Sirven, 2017). Since then, cannabis has been used for a variety of industrial applications as well as for both recreational and medical use, as illustrated in Fig. 1 (Zuardi, 2006).

The first historical mention of cannabis for medical use arises from Chinese literature around 2900 BCE, when Chinese Emperor Fu Hsi postulated that cannabis could restore homeostasis to an unbalanced body (Deitch, 2003). Around 2700 BCE, Emperor Shen Nung explored a variety of herbal remedies for human disease, including cannabis (Friedman and Sirven, 2017). Medical texts originating from the Middle East and Europe then described cannabis being used for medicinal purposes including malaria, vitamin deficiencies, rheumatic diseases, appetite stimulation and constipation (Abel, 2013; Kalant, 2001). Around 1800 BCE, ancient tablets from the Middle East describe the use of a medicinal plant, most likely cannabis, for nocturnal convulsions (Lozano, 2001; Russo, 2005). By the turn of the 11th century, Arabic physicians had begun using cannabis in the treatment of seizure-like conditions (Friedman and Sirven, 2017).

During the 18th century, British surgeon W. O'Shaughnessy described the use of cannabis in the treatment of epilepsy which followed into the 19th century where neurologists, J. Reynolds and W. Gowers, described case reports of treatment resistant epilepsy being successfully treated by cannabis preparations (Friedman and Sirven, 2017). By the 20th century, cannabis preparations appeared in pharmacopoeias across the world, including Europe and North America (Kalant, 2001).

However, in the early 20th century, the use of cannabis for medicinal purposes began to significantly decline. During this period, the considerable variations in the different plant preparations created poor replicability and other medications with known efficacy for cannabis' indications entered mass-production (Arzimanoglou et al., 2010; Haas, 1983). This was compounded by hefty tax impositions in many countries (Musto, 1972). Finally, legal restrictions hastened further decline in medical use, with international prohibitions against cannabis possession and trafficking (Nadelmann, 1990). In 1961, the United Nations added cannabis to the Schedule I list – the most restricted category of any substance (United Nations, 1961). This era of rapid change occurred before the completion of the first clinical trials, leaving the evidence for the antiepileptic properties of cannabis limited to anecdotes and case reports alone.

Despite the legal restrictions, scientific development has continued over recent decades, with the main chemical constituents of cannabis, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) both being isolated by 1964 (Gaoni and Mechoulam, 1971; Mechoulam and Shvo, 1963). In the 1990s, both the cannabinoid type 1 (CB1R) and type 2 (CB2R) receptors, were reproduced in a laboratory setting (Matsuda et al., 1990).

There has since been a modern resurgence, initially driven by AIDS activists who pushed for the creation of California's Compassionate Use Care Act of 1996 as a way to access the medication for its anti-nausea, appetite stimulating and analgesic properties (Bergstrom, 1997). Since then, there has been a rapid worldwide movement to re-legalise cannabis for medicinal purposes extending to countries including Belgium, the Netherlands, Canada, Australia, Uruguay and certain regions throughout the United States. In 2018, the US Food and Drug Administration passed their first approval of a drug containing cannabis-derived substances – a purified form of CBD produced by GW Research for the treatment of Dravet syndrome and Lennox–Gastaut syndrome (LGS) (Mullard, 2018; U.S. Food and Drug Administration, 2018). At the time of writing, the European Medicines Agency is also reviewing this product for treating seizures associated with Dravet syndrome and LGS, with a decision expected in early 2019 (Wise, 2018). Additionally, following reports prepared by the WHO for the Fortieth meeting of the Expert Committee on Drug Dependence in June 2018, the United Nations will also conduct a review of cannabis' classification under international drug treaties (World Health Organization, 2018).

There has been a recent movement around the globe to increase the access to medicinal cannabis products, especially CBD, with many countries now making these products accessible on prescription from a specialist practitioner (Destrée et al., 2018). However, due to the rapid legislative and regulatory changes there are often conflicting laws at state and federal levels, as well as confusion regarding the legality of production and supply. Despite the complex and convoluted legal environment, the use and acceptance for marijuana is at an all-time high with approximately 6 in 10 Americans (61%) supporting its legalisation – almost double the support compared to the year 2000 (31%) (Hartig and Geiger, 2018). The Medical Marijuana Registry Program statistics

for July 2018 showed 88,143 patients in Colorado have an active medical marijuana registration (Colorado Department of Public Health and Environment, 2018). The majority of patients within this state were using cannabis for its effects in severe pain, nausea, muscle spasms, cancer, psychiatric conditions, however, there are 2,785 patients who reported using it for control of seizure activity. In Australia, nearly two thirds of general practitioners reported patients enquiring about medicinal cannabis in the past 3 months, and more than half advocate for provision of this substance on prescription (Karanges et al., 2018).

The strong support for medicinal cannabis from both the public and medical communities has driven the rapid legislative and regulatory changes seen around the globe. This pressure is likely to intensify into the future and so it is expected that additional countries will consider legalisation of cannabis-based medications – however, the key to this progression lies in further scientific evidence to support its use.

4. Chemistry and mechanism of action of cannabis

Cannabis encompasses a genus of flowering plants, comprising mainly of two species: *Cannabis sativa* and *Cannabis indica* (McPartland and Guy, 2017). These complex plants contain over 100 biologically active cannabinoids, with the 2 major compounds best characterised being tetrahydrocannabinol (THC) and cannabidiol (CBD). In the plant, the cannabinoids are synthesised and collected as cannabinoid acids, but when the leaves, stems and flower pods are heated and dried to form 'marijuana', the acids gradually transform into their respective forms, such as CBD or THC (Atakan, 2012). Other forms of processed cannabis include resins, known as 'hashish' and other oil-based extracts known as 'hashish oil', all of which have been sought throughout history, primarily for their psychoactive properties (Perucca, 2017). For medical indications, oral preparations including oils are preferred as this route is more easily controlled compared to forms such as inhalation. Despite greater product consistency of oral cannabis preparations, patients still seek to obtain cannabis from local growers, online purchases or personal cultivation which leads to a lack of quality validation and standardisation (Chen et al., 2018a). These artisanal forms are unregulated in their production and so the content of CBD and other cannabinoids is highly variable. Over the last few decades, sample cannabis strains from the United Kingdom, Europe, and the United States have shown a consistent increase in potency as measured by concentration of THC (Mehmedic et al., 2010). Over the two decades between 1995 and 2014, one study found the THC content of illicit cannabis plant material rose from 4% in 1995 to approximately 12% in 2014, while in the same period, the CBD content fell from 0.28% to approximately 0.15% (ElSohly et al., 2016). Therefore, the ratio of THC to CBD has increased from 14:1 in 1995 to approximately 80:1 in 2014. This progressive and unregulated increase in potency may accentuate many of the adverse effects of cannabis based preparations including heightened psychoactivity. Although the illicit and artisanal forms of cannabis are not representative of the strains produced by licensed producers, they are still highly sought after, and so the lack of product consistency has the potential to be hazardous.

All cannabis preparations, both illicit and licensed, may contain over 60 different compounds including cannabinoids, terpenoids, flavonoids and other active metabolites which may have effects within the central nervous system (McPartland and Russo, 2001). This is especially relevant considering the potential role of cannabinoid signalling processes during neural development (Fernández-ruiz et al., 2004). The complex chemical make-up of cannabis, coupled with the lack of long-term safety data, mean that the consumption of cannabis has inherent risks, especially within paediatric populations.

The psychoactive properties of cannabis are derived mostly from the presence of THC, whereas CBD is thought to be relatively non-psychoactive, and so different strains have been bred with differing THC/CBD ratios to target specific effects (Chandra et al., 2017). The pharmacological actions of these cannabinoids is thought to be mediated through a variety of receptor targets both directly and indirectly, primarily though cannabinoid G-coupled receptor type 1 (CB1R) and 2 (CB2R).

The distribution of CB1 receptors throughout the central nervous system reflects the main roles of the endocannabinoid system in emotion, memory, reward, dependence, appetite, sociability, motivation, cognition and pain (Piomelli, 2003). CB2 receptors are thought to play a principal role in immune signalling through their expression in microglia, with strong evidence also supporting their presence in other distinct regions including the brainstem (Basu and Dittel, 2011; Van Sickle et al., 2005). While this provides a key target for exogenous cannabinoids CBD and THC, endogenous agonists of the cannabinoid receptors have also been discovered, of which the most researched are arachidonic acid derivatives, N-arachidonoyl-ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) (Bisogno, 2008).

Recently, there has been strong evidence for cannabinoids playing a role in the inhibition of synaptic transmission and modulation of neuronal firing rate, primarily through suppression of glutamate release (Zou and Kumar, 2018). In epilepsy, it is believed that glutamate contributes to a state of chronic, dyssynchronous network activity which results in excessive neuronal firing and pathological alterations in signal transmission (Barker-Haliski and White, 2015). This simple model underpins the potential for modulation of seizure activity through the use of cannabinoids.

Despite the apparent simplicity of this model, cannabinoids have other complex pharmacological mechanisms of action. THC has been demonstrated to induce variable anticonvulsant effects, muscle relaxation, analgesia, appetite stimulation, anti-inflammatory effects, as well as psychoactivity (Reddy and Golub, 2016). Contrastingly, CBD is mostly devoid of the adverse psychoactive effects and possesses anticonvulsant, analgesic, anti-anxiety, anti-emetic, immune-modulating, anti-inflammatory, neuroprotectant, and anti-tumorigenic properties (Reddy and Golub, 2016).

Experimental results have suggested that the anti-seizure activity of THC may be underpinned by partial agonism of CB1 receptors, which also explains the psychoactivity (Blair et al., 2015). CBD has a very weak affinity for the CB1 and CB2 receptors and so its anti-seizure activity is thought to be mediated through the blocking of anandamide breakdown (Gaston and Szaflarski, 2018). Other mechanisms have also been postulated including antagonism of G protein-coupled receptor 55 (GPR55), suppression of adenosine reuptake, activation of transient receptor potential of vanilloid type-1 (TRPV1), modulation of voltage-dependent anion selective channel protein (VDAC1), targeting of abnormal sodium channels, blocking of T-type calcium channels, and limiting of inflammation and oxidative stress (Ibeas Bih et al., 2015). In fact, studies suggest that CBD may be antagonistic, even at very low concentrations and thus protect against the adverse psychotropic effects of THC, while providing its own beneficial effects (Niesink and van Laar, 2013).

5. Preclinical evidence for cannabinoid products in epilepsy

There is growing preclinical evidence that supports the involvement of endocannabinoid signalling in early brain development, as well as the role of this system in paediatric epilepsy. Studies have described the anticonvulsant effects of cannabinoids including CBD and cannabidivarin in a variety of preclinical animal models (Hill et al., 2012; Jones et al., 2016). In addition to CBD, the anticonvulsant effects of THC have also been demonstrated in mice (Wallace et al., 2001). This protective effect of cannabinoids on seizure activity has been replicated using endogenous cannabinoids such as anandamide in rodent models (Wallace et al., 2002). Cannabinoids are also thought to act synergistically with regular anticonvulsants in mice including valproate, carbamazepine and ethosuximide to produce a heightened anticonvulsant effect (Luszczki et al., 2011a, 2011b). Indeed, cannabinoids for early-onset epilepsy syndromes such as CDD may be beneficial for more than

just seizures, with CBD also reducing autistic-like social deficits in a mouse model of Dravet syndrome (Kaplan et al., 2017b).

Safety studies have found CBD to be well tolerated by both rats and mice, with minimal observable side effects (Jones et al., 2016). However, the early expression of cannabinoid receptors in the developing human brain indicates that the activation of these receptors may be critical in corticogenesis and neurodevelopment (Zurolo et al., 2010). Indeed, CB1 receptors are expressed throughout the developing rat hippocampus, and CB1 receptor-knockout mice show profound suppression of hippocampal neurogenesis, supporting a role for cannabinoid signalling in neurodevelopment (Jiang et al., 2005; Jin et al., 2004). CB1 receptor activation is thought to have a role in synaptogenesis and/or pruning which may regulate neuronal differentiation and migration (Gómez et al., 2008). Therefore, early exposure to cannabinoids has the potential to lead to adverse long term changes in neurodevelopment such as cognitive deficits in visuospatial function, inattention, hyperactivity and higher prevalence of psychiatric disorders, thus affirming the need for long-term studies (Sundram, 2006). Although the neurodevelopmental effects of cannabis remain unclear, this must be balanced against the neurodevelopmental consequences of uncontrolled seizures in children (Bergen, 2006).

6. Clinical evidence for cannabinoid products in paediatric epilepsy

In recent years there have been a number of studies investigating the clinical utility of cannabis-derived products in paediatric epilepsy. One open-label prospective cohort study in 2016 of CBD in paediatric drug-resistant epilepsy found a median reduction of monthly motor seizures of 36.5% over 3 months, from a baseline median of 30 seizures to 16 seizures per month (Devinsky et al., 2016). In May 2017, this was expanded with a randomised double-blind placebo-controlled trial investigating the anti-seizure activity of CBD on 120 children with Dravet syndrome – a severe paediatric epilepsy associated with treatment-resistant seizures and a high mortality rate (Devinsky et al., 2017). Those given an oral CBD solution (in addition to standard antiepileptic treatment) had a decrease in median convulsive seizure frequency from 12.4 to 5.9 per month compared with from 14.9 to 14.1 per month with placebo. However, the CBD group experienced more frequent adverse events including diarrhoea, vomiting, fatigue, fever, somnolence, and abnormal results on liver-function testing (Devinsky et al., 2017). Although promising, the decrease in seizure activity could be explained, at least in part, by drug-drug interactions between AEDs and cannabinoids. A 2015 study found that treating paediatric refractory epilepsy with both clobazam and CBD caused a significant increase in the level of the active metabolite of clobazam, N-desmethylclobazam (Geffrey et al., 2015). This is especially important because this potentiation of a drug with proven antiepileptic activity such as clobazam may underpin the anti-seizure effects of CBD and thus lead to an overestimation of CBD's efficacy (Devinsky et al., 2016). Interaction with common AEDs including, rufinamide, zonisamide, topiramate, eslicarbazepine as well as abnormal liver function tests in patients taking concomitant valproate have also been noted (Geffrey et al., 2015).

In two recent randomised controlled trials of children and adults with the Lennox–Gastaut syndrome, the addition of CBD to conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures than placebo (Devinsky et al., 2018a; Thiele et al., 2018). Additionally, a 2017 small open-label case series of CBD in patients with treatment-refractory epilepsy in Sturge-Weber syndrome, reported seizure reduction in three of the five patients (Kaplan et al., 2017a). In another open-label case series of CBD for patients diagnosed with febrile infection-related epilepsy syndrome, a seizure reduction was reported in six of the seven patients (Gofshteyn et al., 2017). Similarly, patients with refractory seizures in the setting of tuberous sclerosis complex had a median decrease in weekly seizures of 48.8% after three months of CBD intervention (Hess et al., 2016).

Several retrospective, observational cohort studies reported similar findings that include other types of severe childhood epilepsy. In a recent internet-based survey, 84% of parents who had administered a cannabinoid product to 19 children with epilepsy reported substantial reductions in seizure frequency, with two (11%) reporting complete seizure freedom (Porter and Jacobson, 2013). This finding was reiterated by a study in 2015 which focused on two particularly severe syndromes, Infantile Spasms (IS) and Lennox–Gastaut syndrome (LGS) (Crumrine, 2002; Hussain et al., 2015). Of the 117 parents of children with epilepsy (including 53 with IS or LGS) who had administered a CBD product to their children, 85% of all parents reported a reduction in seizure frequency, and 14% reported complete seizure freedom. However, the opt-in, self-selection design of each of these surveys may lead to selection bias as the study cohort was likely to be enriched with patients who had favourable experiences with cannabis. Additionally, the lack of placebo controls and unblinded self-assessment of efficacy may lead to overestimation of the effect size, and the unregulated dose and product in each survey impairs the reproducibility.

In a retrospective chart review of 119 paediatric patients with epilepsy, oral cannabis extracts were found to have improved seizures in 49% of the cohort (Treat et al., 2017). In a second retrospective cohort study, an improvement in seizure control was reported for 57% of a total of 75 patients with paediatric refractory epilepsy and a 50% reduction in seizure activity for 33% (Press et al., 2015). However, as both studies were undertaken by the same research group, we cannot rule out the fact that some patients were included in both studies. Additional benefits reported included improvements in behaviour, alertness, communication and motor skills. However, adverse events occurred in 44% of patients including increased seizures (13%) and somnolence/fatigue (12%) as well as further adverse events including abnormal motor activity, developmental regression, status epilepticus, and even death. Interestingly, in this same study, families who moved to the study location to obtain medicinal cannabis products were indeed more likely to report a benefit (47%) than families who already lived in Colorado (22%), which in part may be an inflation in the placebo effect linked to efforts undertaken by parents to obtain the product. A further retrospective chart review undertaken in Israel in 2015 found that 89% of 74 paediatric patients treated with CBD-enriched medical cannabis reported a reduction in seizure activity (Tzadok et al., 2016).

Beyond seizure control, cannabinoids have been associated with a number of other benefits including sleep, mood, behaviour, alertness, language and communication – however, these variables are often measured through self-reporting without control data (Hussain et al., 2015; Press et al., 2015; Tzadok et al., 2016). These uncontrolled measures are highly subjective to the placebo effect and so the benefits may be overstated. Indeed, one study of Dravet syndrome found that those treated with CBD experienced no significant difference in sleep, behavioural adaptation scores or quality of life compared to the placebo group, despite a significant reduction in convulsive seizures (Devinsky et al., 2017). While there is mixed evidence for cannabis' effects beyond seizure control, there is a lack of data that is specific to CDD. Considering the potential benefits to overall neurologic function, long-term follow-up including the collection of control data is urgently needed to better characterise these responses.

7. Clinical evidence for cannabis in CDKL5 Deficiency Disorder

There is growing evidence to suggest that cannabis-derived products including CBD likely reduce seizures among populations of children with mixed aetiologies of drug-resistant epilepsy (Elliott et al., 2018; Perucca, 2017). However, it is unclear how applicable this is to aetiologies of refractory epilepsy such as CDD. To date, most of the evidence for medicinal cannabis in CDD is derived from research in similar early-onset epileptic encephalopathies including Dravet syndrome and Lennox–Gastaut syndrome (LGS). Since LGS may be the result of a broad range of aetiologies, the reports of effective treatments are

considered likely to be generalisable to conditions including CDD. However, many unique characteristics still differentiate the different aetiologies of refractory epilepsy and so the true effect of cannabis in CDD requires further investigation (Bourgeois et al., 2014).

Whilst the research into severe refractory epilepsy syndromes supports a role for medicinal cannabis, as outlined above, the specific research in patients with CDD is limited and primarily involves unverified anecdotal reports (Cowles, 2014; Dell, 2015; ECHO, 2017). Beyond this, whilst a few studies of cannabinoids in paediatric epilepsies feature patients with a diagnosis of CDD, they do not analyse CDD patients as their own entity (Devinsky et al., 2016; Geffrey et al., 2015; Rosenberg et al., 2017; J.P. Szaflarski et al., 2018; M. Szaflarski et al., 2017). In one such study, of 580 patients accessing purified CBD through extended access programs in the United States, 18 had a confirmed diagnosis of CDD (J.P. Szaflarski et al., 2018). This study found that for the 580 patient cohort, adjunct CBD reduced median monthly convulsive seizures by 51% and total seizures by 48% at 12 weeks. However, the effect on the subset of CDD patients is not reported. In a similar trial of purified CBD through expanded access programmes, of 162 patients with treatment-resistant epilepsy, 8 had a diagnosis of CDD (Devinsky et al., 2016). The total study population reported a 36.5% reduction in median monthly motor seizures – however, the effect on the CDD population is again unclear.

A recent meta-analysis described significant improvement in seizure control in paediatric populations with treatment-resistant epilepsy including some patients with CDD (Pamplona et al., 2018). The study found that a 50% or more reduction in the frequency of seizures was observed in 39% of 622 patients in response to CBD based products. Although this study does not outline the exact number of patients with CDD, the keyword search specifies only 3 treatment resistant epilepsies – CDD, LGS and Dravet syndrome. Therefore, while it is likely that these patients constitute a significant portion of the study population, this requires confirmation before the findings can be generalised to CDD populations.

At the time of writing, only one study has performed a quantitative analysis which reports the anti-seizure effect of cannabis in patients with a specific diagnosis of CDD (Devinsky et al., 2018b). In 2018, this open-label study explored the use of pharmacologic grade purified CBD in patients with severe, treatment resistant, childhood-onset epilepsies including CDD as well as Aicardi, Dup15q, and Doose syndromes (Devinsky et al., 2018b). In patients with CDD, the median monthly convulsion frequency decreased from 66 at baseline ($n = 17$) by 41% to 36 at week 12 ($n = 11$), and by 60% to 36 at week 48 ($n = 10$). This is the most promising study for cannabinoids in CDD and suggests the need for further placebo-controlled randomised trials in a larger population sample to formally assess the safety and efficacy of cannabis based products in this particular disease.

Although there is increasing evidence towards the efficacy of cannabinoids, especially cannabidiol for CDD, there is a paucity of long-term follow-up data that is specific to CDD patients. While CBD in mixed aetiologies of refractory epilepsy has been followed over periods up to 4 years, the length of follow-up specific to CDD is limited to 48 weeks (Devinsky et al., 2018b; Sands et al., 2018). Considering the prominence of the honeymoon phase observed in CDD patients in response to other antiepileptic treatments (Bahi-Buisson et al., 2008; Fehr et al., 2016; Müller et al., 2016), follow-up studies are urgently needed to determine whether the same phenomenon is applicable to cannabis based therapy. In addition, follow-up studies are essential to detect other adverse events which may not arise in the initial period following cannabinoid treatment.

8. Safety of medicinal cannabis products

The acute adverse effects of cannabinoids in patients with treatment-resistant epilepsy are well-documented in randomised controlled and open-label trials and most commonly include somnolence, sedation, diarrhoea, nausea, vomiting and appetite changes (Chen et al., 2018b; Devinsky et al., 2016). Additionally, due to their actions on inflammatory signalling, cannabinoids have been shown to induce apoptosis of certain immune cell populations in vitro, and thus constitute a theoretical risk of immunosuppression (Rieder et al., 2010).

Due to a lack of specific research in CDD populations, safety data is restricted to study populations that contain at least some patients with a diagnosis of CDD. Of 162 patients with treatment resistant epilepsy, serious adverse events including status epilepticus, diarrhoea and weight loss were observed in 30% ($n = 48$) of patients, however only 5% ($n = 8$) had a diagnosis of CDD, making interpretation difficult (Devinsky et al., 2016). However, the overall safety and tolerability of cannabidiol was still considered 'acceptable', for the entire population since only five (3%) of the 162 patients discontinued treatment due to one of these adverse events (Devinsky et al., 2016). Another study found that of 607 refractory epilepsy patients treated with add-on CBD, 76% remained on CBD at a median follow-up of 48 weeks (J.P. Szaflarski et al., 2018). However, this study population featured only 19 (3%) of patients with CDD.

One study which focused on refractory epilepsy of multiple aetiologies in 26 patients found that over a 4-year period, CBD was well tolerated in around 20% ($n = 5$) of patients, but 81% ($n = 21$) suffered adverse events (Sands et al., 2018). These adverse events included decreased appetite, diarrhoea, weight loss as well as more serious events including status epilepticus, catatonia and hypoalbuminemia. Beyond this, the long-term adverse effect profile of cannabinoids have not been comprehensively studied in the context of epilepsy treatment, and so many of the long-term consequences have been extrapolated from studies of recreational cannabis use. These long term sequelae include cognitive deficits, decreased motivation and increased likelihood of psychotic disorders (Wilkinson et al., 2014). It remains unclear whether the adverse neurological effects are mediated by the psychoactive cannabinoid compounds such as THC, or whether long-term exposure to CBD may have a similar deleterious effect (Friedman and Devinsky, 2015). Until more research is performed, the neurodevelopmental risks of cannabinoid-based therapies should be contrasted against the potential benefits for seizure control, since seizure activity may also impair normal neurodevelopment (Ben-Ari and Holmes, 2006). Dependence and addiction are also reported with long-term recreational cannabis use. However, it is unclear whether the same risks are pertinent in isolated cannabinoid based treatments, especially when administered in a clinical setting. There is very limited data available on the effects of specific cannabinoids other than THC, although the relative absence of psychoactive effects reported for CBD suggests that this compound has a relatively low likelihood of abuse (Friedman and Devinsky, 2015).

It should be noted that despite the large majority of efficacy studies focusing on cannabis in paediatric populations, most of the safety data is derived from adult populations, and so the adverse effect profile in children requires further investigation.

9. Conclusion and future directions

Refractory epilepsy in children encompasses a vast group of conditions associated with intractable seizures. One of the most debilitating of these refractory epilepsies is CDD – a genetic epilepsy characterised by early-onset seizures activity, profound hypotonia, global developmental delay, and severely impaired gross motor skills (Mangatt et al., 2016). Due to the host of adverse effects and low efficacy of existing treatments, cannabis based interventions are being increasingly sought by those affected with CDD and other similar early onset epilepsies.

To date, the heightened interest in cannabinoid therapies has been accelerated by public perception and media hype, however, any true advancements must be grounded by robust scientific evidence. Clinical evidence for medicinal cannabis in refractory paediatric epilepsies such as Lennox–Gastaut syndrome and Dravet syndrome has hastened the

approval of a cannabis-derived products in the USA, yet it is unclear how generalisable these findings are to similar aetiologies including CDD. Recent data from an open-label trial shows a reduction in seizure activity in CDD, however, this requires replication in a larger population (Devinsky et al., 2018b). This is of utmost importance since the community pressure on health professionals and governments is likely to continue intensifying into the future.

Before cannabis based treatments will be routinely considered, there are multiple issues that must first be addressed. Primarily, there is the urgent need for further evidence into the safety and efficacy of this product, both in the short and long-term. Additionally, health professionals and researchers must address the public's perception and inherent concerns about the prescription of a drug that has been outlawed for many decades. Regardless of the legal status of medicinal cannabis, caregivers of those affected with severe paediatric epilepsy will continue to seek alternatives to existing therapies, and so further high quality research is essential to direct medical decision making as well as provide a basis for the growing calls for political, legal and regulatory changes.

10. Literature search

The literature search was performed using medical databases EMBASE, the Cochrane Library and Medline. The following key terms were searched in various combinations: ‘cannabinoid’, ‘cannabidiol’, ‘marijuana’, ‘cannabis’, ‘medical marijuana’, ‘tetrahydrocannabinol’, ‘children’, ‘paediatric’, ‘seizure’, ‘epilepsy’, ‘CDKL5’, ‘CDD’. The reference lists of relevant results were manually assessed for potential inclusions. Articles included for review of clinical evidence primarily examined the use of cannabis or cannabis-derived products for treatment of seizures in patients with refractory epilepsy. Non-English articles were also excluded.

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12. Statement of compliance

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

13. Declarations of interest

None.

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