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Review Article

Adjunctive Use of Cannabidiol in Pediatric Drug-Resistant Epilepsy: A Comprehensive Review of Efficacy, Safety, Pharmacology, Clinical Evidence and Future Directions of Cannabidiol as Adjunctive Treatment in DRE

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ABSTRACT

Epilepsy in children is a significant therapeutic problem, with drug-resistant epilepsy (DRE) being a problem in about 20-30% of children with epilepsy. The morbidity, cognitive, behavioural, psychosocial, quality of life and mortality risks are significant if the seizures are not controlled by at least 2 well-tolerated and effective seizure medications. The non-psychoactive Phyto cannabinoid found in Cannabis sativa has transformed the lives of people with a variety of paediatric epilepsy conditions such as Dravet syndrome (DS), Lennox–Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC) associated epilepsy. Over the past decade, numerous RCTs, open-label extension studies, expanded access programs, retrospective studies and real-world observational studies demonstrate that there is a significant number of frequency reductions and in general, high tolerability for adjunctive CBD treatment. Authors found this purified CBD pharmaceutical product to be a means to provide clinicians a therapeutic tool with good evidence for children with epilepsy, as that is a disease that is refractory to conventional ASMs. This review extensively reviews studies on the epidemiology and burden of pediatric DRE, pharmacologic properties of CBD, mechanism of antiseizure activity, pharmacokinetics and pharmacodynamics of CBD, safety and tolerability, drug–drug interactions, dosing strategies, regulatory status and future research directions. CBD has clinical meaning to reduce seizures; randomised controlled trials and real-world evidence.CBD is clinically significant and has clinically meaningful seizure reduction and is found to be safe and well tolerated with an acceptable side effect profile. But long-term safety, optimal dose, economic availability and use for the epilepsy syndromes yet to be approved are problematic.

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INTRODUCTION

Epilepsy is a common chronic neurological condition in children, around the world and is a public health concern. It's a condition of the brain that involves frequent, random seizures developed by irregular activity within the brain's electrical signals. WHO estimates that globally, nearly 50 million people, children included, are someone who suffers from epilepsy. The developing brain leads to the possibility of significant long-term cognitive, behavioral, learning or socio-emotional deficits in kids with recurrent seizures.

Although much progress has been achieved in the diagnosis and treatment of epilepsy, there are still many children that are not fully controlled. 20-30% of children who are taking an appropriate and effective medication to control childhood seizures still continue to have convulsions. The ILAE is unable to have seizures controlled by at least two appropriately selected, tolerated and safely taken antiseizure medications, or two or more of them, without success.

Drug-resistant epilepsy is so much more than a neurological disorder with a seizure disorder. It can have a tremendous impact on the life of most children and on the family. Seizure activity precludes learning of language and memory, attention and concentration, academic attainment, emotional development and sociability. Children may have developmental delay, intellectual disability, behavioural disorders and psychiatric comorbidities; however, parents/caregivers experience emotional stress and financial cost and lower quality of life. This has spurred a change to focus on managing epilepsy without side effects of the medications and with good control.

Classic childhood seizures that are more difficult to treat such as those that occur in the Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) and tuberous sclerosis complex (TSC)-associated epilepsy (TAS) are very early onset, very early developmental impairment, and very severe and not well controlled by standard epilepsy therapy. Numerous antiseizure drugs are available that are effective in the majority of children, however, despite the use of some of them, many children remain disabled by seizures. While a few anti-seizure drugs (valproate, clobazam, topiramate, lamotrigine, rufinamide, stiripentol and fenfluramine) are available, many children continue to have disabling seizures despite using these drugs. Alternative therapies such as ketogenic diet therapy, vagus nerve stimulation and epilepsy surgery work for some patients only, and aren't used by everyone.

This has led to the search for new therapies, based on different modes of action. One of the most promising developments over the past decade is the emergence of purified and non-psychoactive phytocannabinoid, cannabidiol (CBD), from Cannabis sativa. Unlike Δ9-tetrahydrocannabinol (THC), the more well-known "high that marijuana causes in its users, CBD is not intoxicating or euphoric and thus can be administered to children for therapeutic purposes. From laboratory studies and randomized controlled trials, open-label extension trials, expanded access trials and real-world clinical studies, there has been growing evidence of a reduction in the frequency of seizures in certain types of drug-resistant epilepsy for adjunctive cannabidiol treatment in children and adolescents with epilepsy, with little to no significant adverse events reported.

CBD's anti convulsant properties seem to be multi-targeting and do not have a direct effect on a single target. It is a TRPV channel modulator, a G protein coupled receptor 55 (GPR55) antagonist, an adenosine signaling regulator, a calcium homeostat and an anti-inflammatory, anti-oxidant

and a neuro-protective agent. Unlike conventional antiseizure medications, these mechanisms can lead to cannabidiol being effective even when patients have tried several conventional antiseizure medications.

Prescription use of CBD for the treatment of pediatric epilepsy has drastically altered with approval from the FDA and others. There is now a clinical consensus on the usefulness of using CBD as an adjunctive therapy in the treatment of Dravet syndrome, Lennox–Gastaut syndrome and tuberous sclerosis complex (TSC) (known as beneficial treatment); its use in other developmental and epileptic encephalopathies (DEEs) is currently being investigated.

The amount of evidence will only be growing faster, so a damning must be done on the existing information. This paper will attempt at a critical analysis of the burden and epidemiology of drug-resistant childhood epilepsy, CBD pharmacology and pharmacokinetics, supporting clinical data for the use of CBD, safety aspects and drug interactions of CBD, CBD dosing considerations, regulatory approval for CBD, and future research avenues. This review unites the data from RCTs with the data from observational studies and clinical experience in the current use of CDB in pediatric epilepsy therapy, providing an up-to-date overview of the role of CDB in epilepsy management in children.

METHODOLOGY

This review was done in line with the principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The goal of this review was to summarize the most recent data on the efficacy, safety, pharmacology, pharmacokinetics, drug-drug interactions, dosing and potential future applications of CBD in pediatric DRE. A systematic search in international biomedical databases (PubMed/MEDLINE, Embase, Scopus, Web of Science and Cochrane Library) was carried out to find relevant studies.

To maximise retrieval of eligible studies, various Boolean combinations of Medical Subject Headings (MeSH) and free-text keywords were used. The search used the following key words: cannabis sativ (cannabidiol), CBD, drug-resistant epilepsy, refractory epilepsy, paediatric epilepsy, Dravet syndrome, Lennox–Gastaut syndrome, tuberous sclerosis complex, and developmental and epileptic encephalopathy. Inclusion criteria for studies included a pediatric drug-resistant epilepsy population that received cannabidiol as an adjunctive therapy or as monotherapy (the latter of which is more commonly reported).

Experimental studies were included as randomized controlled trials (RCTs), prospective and retrospective observational studies, cohort studies, expanded access programs, open label extension studies, systematic review and meta-analyses. Outcomes measured included seizure frequency reduction, responder rate, seizure freedom, quality of life, adverse events, pharmacokinetic and clinically relevant drug interactions. The major efficacy analysis simply included studies in adults, where the dose and concentration of CBD were not known, editorials, conference abstracts without primary data available, duplicate publications and scientific studies performed on animals.

However, where relevant, the pre-clinical data were considered and given an explanation as to the pharmacological mechanisms. Studies were selected employing research guidelines of PRISMA. Duplicate articles were followed by filtering of titles and abstracts for relevance then articles were assessed for full text. The following study characteristics, patient demographics, epilepsy syndrome, amount of cannabidiol,

duration of treatment, and outcomes of the seizures and adverse events were extracted, as well as the patients who dropped out during treatment and key conclusions drawn.

Considering the diversity of the studies included in the review in terms of design, dosages, patient populations and reported outcomes, upon qualitative meta-analysis was opted for and the narrative synthesis approach was applied. Although the evidence was poor quality based on the randomized controlled trials, the real world studies and long-term extension studies were also covered as these would have provided data of long-term effectiveness, retention rates and clinical practice. Overall, this approach made a comprehensive and comprehensive examination of the existing evidence on the use of CBD treatment in the drug-resistant epilepsy in children.

PEDIATRIC DRUG-RESISTANT EPILEPSY

Epilepsy is one of the most difficult problems in paediatric neurology with drug resistant epilepsy (DR) being the most challenging. Nearly, one-third of children continue to have recurrent seizures despite many drugs being available which help to treat seizures. Rather than on who suffers from the most frequent or longest lasting seizures, the ILAE definition highlights the importance of failing to benefit from two types of anti-convulsant drugs for which there have been careful choices and appropriate dosing.

The success of achieving full seizure control with additional medications further declines at this point, with the possibility of epilepsy surgery, newer medications (e.g. cannabidiol) or neuromodulation therapy being discussed. Epilepsy is a disease that affects 0.5-1% of the children in the world and in 20-30% of these children medication does not control the disease. Actions of impact transcend the number of seizures. Children may have recurrent admissions, emergency needs, need multidisciplinary rehabilitation, special educational provision and require long term ongoing follow up of their neurology.

Often families struggle with limited resources, stress, job instability and the uncertainty of how things will affect them in the future. Some clinical parameters predispose it to resistance to the drugs. Early onset of seizures and developmental delay, structural brain abnormalities, symptomatic epilepsy, abnormal neurological examination and genetic epileptic encephalopathies are all universally associated with poor seizure control. Therefore, early recognition of these risk factors could result in appropriate and timely referral service to specialized epilepsy centres and advance therapeutic options. Drug resistance is a complicated and complex phenomenon.

To explain the lack of effectiveness of antiseizure medications in the CNS, the transporter hypothesis has been proposed, suggesting that they are over-expressed at the blood–brain barrier, along with the expression of a drug-efflux protein called P-glycoprotein. The target hypothesis is another important reason, suggesting that adaptations in the sites where neurons bind the neurotransmitter, ionic channels or synaptic protein resulting in a decreased response to a drug following the prolonged exposure of the drug. Molecular genetics research has also yielded insights into genes that are related to serious developmental epileptic encephalopathies that have proven difficult to treat with medications (such as SCN1A, SCN2A, SCN8A, STXBP1, CDKL5 and PCDH19).

The last couple of years, there is been more emphasis on the neuroinflammatory aspects of epilepsy. Microglia activation, elevation of inflammatory cytokines, breakdown of the blood–

brain barrier and chronic immune activation seem to play a role in epileptogenesis and also in the decreased sensitivity to conventional antiseizure drugs. The results are able to be very important to both anti-inflammatory and anticonvulsant effects of cannabidiol. Severe cases of paediatric epilepsy syndromes include cases of Dravet syndrome, Lennox–Gastaut syndrome and those with epilepsy due to tuberous sclerosis complex (TSC). SCN1A pathogenic variants are responsible for the development of the dravet syndrome, which usually strikes in infancy, characterized by prolonged febrile seizures followed by the emergence of different types of seizures, developmental delay and cognitive impairment.

Lennox–Gastaut syndrome is a syndrome characterized by epilepsy, their spectral profile, EEG abnormalities, cognitive dysfunction and permanent neurological disability. Epilepsy in tuberous sclerosis often starts early in life, and is often accompanied by intellectual disability, developmental delay and autism spectrum disorder. When seizures are not controlled in a child for prolonged periods of time they have long-term detrimental brain development effects. Seizures are extremely frequent and cause impairment of language acquisition, executive functioning, memory, attention, learning and academic functioning. There is also the possibility that children may become disabled due to their development and onset of behavioural disorders, anxiety, depression, autism spectrum disorder and attention-deficit/hyperactivity disorder. As importantly, developmental outcome is always poorer when seizures start in the early childhood period (studies show) and when there is a high seizure burden (studies show).

Now, paediatric drug resistant epilepsy is manageable, but it is now required a multi-disciplinary approach along with a personalized approach. The main treatment for the condition are anti-seizure drugs which, in selected patients may necessitate non-drug therapies like ketogenic dietary therapy, vagus nerve stimulation, responsive neurostimulation (RNS) and epilepsy surgery. In either case, numerous children continue to be uncontrolled with these therapies indicating there is a need for more innovative therapies that would have a different mechanism of action. A potentially great development has been the discovery of Cannabidiol. Has several mechanisms of action in multiple biological pathways associated with neuronal excitability, inflammation, oxidative stress and synaptic transmission, distinct of its traditional antiseizure drug properties. It is now known to be clinically significant for seizure reduction for various paediatric epilepsy syndromes, and therefore is a component of present-day epilepsy therapy. In summary, Pediatric DR epilepsy is a significant medical, developmental, psychological and socio-economic issue that continues to be a significant challenge in neurology. Although good treatment has been obtained for many children, a large proportion suffer from refractory seizures. The arrival of cannabidiol, which is a scientifically proven therapy, provides an important unmet clinical need, and is a huge leap in therapy for severe childhood epilepsies.

CANNABIDIOL PHARMACOLOGY AND MECHANISM OF ACTION

The past decade has seen a major advancement in the treatment of drug-resistant epilepsy in the form of cannabidiol (CBD), a new drug for the condition and a substance that comes naturally from cannabis. Unlike typical antiseizure drugs (ASDs) that target one or only a handful of molecular targets, CBD has a broad and complex pharmacological profile with numerous pharmacological activities. This unique property is

at the heart of its effectiveness in a number of highly-refractory childhood epilepsy syndromes, and has generated much interest among researchers and clinicians alike for greater efficacy and effective treatment of refractory childhood epilepsy.

Cannabidiol (CBD) is a phytocannabinoid, or chemical compound naturally present in the Cannabis sativa plants. There are over 100 cannabinoids found in the cannabis plant, of which the two most studied are, cannabidiol and THC or Δ9-tetrahydrocannabinol. Although they are botanically related these compounds are chemically, and pharmacologically, very different. The psychoactive agents in THC stimulate CB1 receptors which activate the central nervous system, while CBD seems to have little affinity for CB1 receptors and thus does not cause intoxication or euphoria. Due to the lack of any psychotropic effects, cannabidiol is well suited for children and maintaining cognitive development and behavioural function are also paramount in this population.

CBD interacts with the endocannabinoid system, but does not only act on cannabinoid receptors to produce its anticonvulsant effects. Instead, CBD exercises several molecular mechanisms that, when combined, have an effect on the modulatory functions of neuronal excitability, synaptic transmission, intracellular calcium regulation, inflammation, oxidative stress and neuroprotection. This multimodal action is different to those of classic anti-seizure medications, and may account for the fact that it has proven to be effective in children who have not been responsive to two or more classic anti-seizure medications.

The normal function of neurons is essential for the proper actions of the endocannabinoid system. Its main components are endogenous cannabinoids such as anandamide or 2-Arachidonoylglycerol (2-AG), cannabinoid receptors (CB1 and CB2) and enzymes that facilitate the creation and destruction of endocannabinoids. The CB1 receptors are found in many areas of the brain that promote seizures including the basal ganglia, cerebral cortex, cerebellum and hippocampus. Excessive release of neurotransmitters and/or hyperexcitability of neurons is inhibited by activation of CB1. Whereas, unlike THC, cannabidiol has exhibited very weak direct binding with the CB1 and CB2 receptors. Instead, it is a negative allosteric modulator of the CB1 receptor which works to reduce the activity of the receptor and help to reduce the effect of THC on the receptor. Additionally, CBD helps to boost endogenous cannabinoid signaling by another mechanism, by inhibition of reuptake and degradation of anandamide in the central nervous system.

The effects are part of its pharmacological profile, and although there are indications that the non-cannabinoid action is responsible for most of its anticonvulsant activity. One of the well studied mechanisms is the antagonism of G protein-coupled receptor (GPR55). Several regions of the brain have been involved in epilepsy have been shown to contain this receptor, and it has been associated with neuronal excitability. GPR55 activation results in calcium release to the cytosol and is involved in facilitating excitatory neurotransmission, directly working towards the production of seizures.

Cannabidiol acts as an antagonist of GPR55, decreases calcium influx and limits the hyper-excitability of neurons. In preclinical studies, this modulation is a prominent mechanism that explains the antiseizure effects of CBD, because it has been consistently demonstrated that modulation leads to a reduction in the susceptibility to seizures. The other target of

interest is the transient receptor potential vanilloid type 1 (TRPV1) channel. TRPV1 channels control calcium influx into neurons, are involved in pain perception, inflammation and neuronal signaling. Cannabidiol does a couple of things: it activates these receptors but over time reduces response by the receptors on the neurons. In the brain, this process can function as a stabilising factor in hyper-excitable neuronal network and reduce seizures. Still another mechanism is the control of the calcium homeostatis inside of the cell.

Among the many processes in which calcium ions participate, are neurotransmitter release, plasticity of synapses, expression of genes and survival of neurons. Muscle cells may become over-calcified in the cell, causing hyperexcitability of the neurons and epileptogenesis. The impact of CBD on multiple pathways that regulate calcium levels (GPR55, TRPV channels, mitochondrial calcium stores) ensure that calcium levels are kept at a steady level within the cells and prevent excessive amounts of calcium from causing damage to the cell. Cannabidiol is also demonstrated to modulate the endogenous systems of inhibition that are in use for a long time with anticonvulsant properties, such as adenosine signalling.

CBD has been shown to be an inhibitor of equilibrative nucleoside transporter-1 (ENT1), which acts to reduce adenosine reuptake and raise extracellular adenosine. Activating Adenosine receptors brings an increase in inhibitory transmission, a decrease in inflammation and strengthens the neurons. The therapeutic effect of cannabidiol can also be attributed to the absence of drug interaction with the adenosine pathway as many traditional antiseizure drugs lack such interaction. The modulation of excitatory and inhibitory neurotransmission is not the only effect of CBD. A seizure is caused by an imbalance between excitation producing by glutamate, and inhibition by gamma AminoButyric Acid (GABA).

CBD has an anti-inflammatory effect and also appears to have a double effect by blocking overactive glutamatergic activity and boosts inhibitory GABAergic neurotransmission. The exact mechanisms remain under investigation but reestablishment of this excitatory/inhibitory balance is a critical component to seizure control. Neuroinflammation has proven to be an important mechanism of epilepsy and has been correlated with drug-resistance and epileptogenesis. The involvement of microglia and astrocyte activation, elevation of blood-brain barrier permeability, elevation of inflammatory cytokines (tumour necrosis factor-alph, interleukins 1 beta, 6) and that of refractory epilepsy have been linked. CBD's anti-inflammatory benefits are impressive, as it has been demonstrated to block the production of cytokines, to modulate the activation of immune cells and to impair inflammatory pathways.

Such effects may not only reduce the incidence of seizures, but help prevent the disease process to progress. Anti-inflammatory properties are not the only wound-healing benefits of cannabidiol, as it also works as a powerful antioxidant and a neuroprotective agent. Recurrent seizures trigger additional ROS generation, which results in damage to neuronal membranes, proteins and DNA and hence cause cognitive impairment and neurodegeneration. CBD acts as a free radical scavenger, inhibits lipid peroxidation and is protective in regards to neurons from oxidative stress. Studies in animals have linked reduced neuronal injuries to seizures in animals treated with cannabidiol, suggesting that the effect of treating with cannabidiol might be more than what the symptoms of seizures are.

In humans, although evidence of disease modifying effects is lacking, the neuroprotective

effects are an area of research interest. There also are emerging indications that cannabidiol interacts with a variety of serotonin receptors, receptors of the peroxisome proliferator-activated receptor (PPAR) family, mitochondrial signaling pathways and epigenetic regulatory pathways. These results reinforce the hypothesis of the multimodal and neuromodulatory activity of CBD rather than a drug specific to a receptor. Additional molecular and pharmacogenomic analysis of treatment response should be done in the future to better understand the heterogeneity of response and help target these treatments.

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Such effects may not only reduce the incidence of seizures, but help prevent the disease process to progress. Besides being anti-inflammatory, Cannabidiol is also highly antioxidant and neuro-protective. Recurrent seizures trigger additional ROS generation, which results in damage to neuronal membranes, proteins and DNA and hence cause cognitive impairment and neurodegeneration. CBD acts as a free radical scavenger, inhibits lipid peroxidation and is protective in regards to neurons from oxidative stress. In animal research, a reduction in neuronal injuries was seen after seizures in animals treated with cannabidiol, indicating that the benefits of treatment with cannabidiol may be more than just symptoms of seizures.

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PHARMACOKINETICS AND PHARMACODYNAMICS OF CANNABIDIOL

Cannabidiol pharmacokinetics and pharmacodynamics have to be understood, for maximizing its potential clinical application in the treatment of drug resistant epilepsy in pediatrics. Pharmacology focuses on the mechanism by which the body's processes cause CBD to be an anticonvulsant while pharmacokinetics are related to the absorption, distribution, metabolism and elimination of the drug by the body. These processes in turn can have a significant impact on therapeutic response; in children treated with more than one concurrent antiseizure medication.

Cannabidiol taken by mouth is in the form of a highly refined medication. After being ingested, the absorption takes place in the gastrointestinal tract. The bioavailability of CBD is relatively low, and variable due to its poor aqueous solubility, high lipophilicity and high first-pass hepatic metabolism. As a result, the dose of a specific drug in the blood is quite different between individuals who get the same amount of the drug per kg of body weight.

Eating is one of the most clinically relevant where it can influence the process of absorption of the cannabidiol. Giving the drug with a meal, especially a meal that is high in fat, significantly raises peak plasma concentration and the amount of drug that gets into the body and stays there to work by better solubilizing the drug in the intestines and facilitating intestinal lymphatic absorption. Patients will be urged to take cannabidiol in a fixed dose, either with or without food, because of this to reduce the pharmacokinetic variability.

After getting absorbed, CBD becomes widely spread all over the body as it's highly fat soluble. It is easily absorbed across the blood brain barrier and targets lipid laden tissues such as the CNS where it produces its therapeutic benefits as well. CBD also has a high degree of plasma protein binding (mainly to lipoproteins and albumin) that may affect the interactions with other highly protein bound drugs.

Pediatric patients could be different with regard to distribution, as it varies with developmental changes in body composition which affects drug disposition. Age differences in tissue distribution may be associated with body fat and total body water content of different ages, with younger children having lower levels of body fat and higher levels of TBBW.

The liver has become the main site of metabolism of cannabidiol. CBD is metabolized into numerous metabolites by the cytochrome P450 enzyme system (mainly CYP2C19 and CYP3A4). The two most active metabolites of CBD, via both serum and urine, are 7-hydroxy-cannabidiol (7-OH-CBD), which has anticonvulsant activity and contributes to therapeutic efficacy, and 7-carboxy-cannabidiol (7-COOH-CBD) that is pharmacologically inactive, with levels being the highest in blood circulation.

Medications that interact with CBD are not uncommon because of its use of and inhibition of CYP450 enzymes. Variability in drug exposure could also be due to genetic polymorphisms of CYP2C19 activity. Pharmacogenomic testing is not routinely used in an epilepsy practice, however in the future, individualized doses could become more and more important as precision medicine develops.

Eliminated mainly in the feces in the bile and to a lesser extent in the urine. In terms of its elimination half-life, Cannabidiol has a comparatively long half-life which allows for a standard dosage twice a day in clinical practice. Steady state concentrations can take several days to develop, dose changes should be made slowly, ensuring they are the most effective doses for maximum effect, but to prevent the higher doses causing worsened side effects.

Early on the pharmacodynamic differences between cannabidiol and conventional antiseizure drugs are remarkably different. CBD doesn't act against a specific receptor or ion channel, but is able to generate a number of modulation results on a variety of biological pathways that play a role in the generation of seizures. It is important to note that, there is no universally accepted therapeutic plasma concentration. As there is great variability between patients, the clinical response may be

influenced by the sensitivity of the receptors involved, by the disease mechanism, pharmacogenomic differences and by concomitant drugs.

Exposure-response has been shown in clinical trials; this relationship is positive where 10-20mg/kg/day showed significant clinical efficacy in reducing the number of seizures in the population of children with Dravet syndrome and Lennox–Gastaut syndrome. Dosages up to 25-50 mg/kg/day have also been studied in patients with tuberous sclerosis complex (TSC) epilepsy. Doses of this medication that are higher tend to cause more of a seizure reduction, but they can also cause more of a reaction of somnolence, gastrointestinal issues, decreased appetite and hepatic enzyme elevations. Thus, treatment is always optimised for effectiveness with tolerability by carefully adjusting the dose to each individual patient.

In addition to the above, pediatric patients have physiologic considerations that affect the pharmacokinetics of drug metabolism during childhood development ranging from impact on hepatic metabolism through gastrointestinal absorption, renal elimination and impact on body composition. In addition, these children are often prescribed multiple antiseizure medications, a ketogenic diet and/or a special nutrition plan, which can affect the pharmacokinetics of cannabidiol. It is therefore imperative to have careful clinical monitoring when increasing the dose and during long-term therapy.

Clinically relevant drug interactions have been mostly studied with the association of cannabidiol to clobazam. CBD alters the metabolic pathway of N-desmethylclobazam, the active metabolite of clobazam, by inhibiting CYP2C19 and this results in a decrease in metabolisation and increased plasma levels of N-desmethylclobazam, which may increase the drowsiness, somnolence, and the incidence of these adverse effects. In contrast, liver function should be monitored often when used concomitantly with valproate, as this appears to have an association with hepatic transaminase elevations. However, there have been several reports of interaction with stiripentol, rufinamide, topiramate, zonisamide, brivaracetam and everolimus, especially in children using multiple drug therapy.

In conclusion, the pharmacokinetics and pharmacodynamics of CBD highlight the need for personalized treatment. Because of the known variability in absorption, metabolism, genetic etiology and developmental physiology, as well as co-administered medications, careful monitoring and dose-titration are required. Although these are difficulties, the potential of cannabidiol for drug-resistant epilepsy in children is well supported by its unique multimodal pharmacological profile, and differs greatly from current antiseizure medications. Further work on the pharmacogenomics, exposure-response relationships and assessment of therapeutic drug monitoring should continue to provide the clinical guide for future treatments and outcomes.

CLINICAL EVIDENCE OF CANNABIDIOL IN PEDIATRIC DRUG-RESISTANT EPILEPSY

Dravet syndrome is a developmental and epileptic encephalopathy (DEE) that is one of the most severe types of childhood DEEs. The disorder is usually characterised by the onset of seizures in the first year of life, which are chronic and produce purulent fever; it gets complicated into many kinds of seizures, developmental delay, mental retardation, behavioural problems and motor defecits. In about 80-90% of patients it is found that there are pathogenic mutations that are responsible for defects in inhibitory neurons,

causing hyperexcitability of neurons throughout the brain.

Even if it's treated with conventional antiseizure drugs, seizures don't respond well in many people. Seizures continue causing regression in development and frequent hospitalizations, poor quality of life and increased risk of Sudden Unexpected Death in Epilepsy (SUDEP). In this context, there was a great and pressing need for therapies with new modes of action. The first forerunners in support of cannabidiol were compassionate-use and expanded access programs. Although these were preliminary studies/observational, each of these reports has clinicians reporting that the child's seizure were reduced significantly, reporting a reduction in seizure frequency in children who were previously on multiple antiseizure drugs.

These enhancements in alertness, sleep and conduct of the caregivers additional fueled the fascination with cannabidiol as a remedy. The most significant evidence was provided by the Devinsky and colleagues (2017) study, a randomized controlled trial (RCT) study in which half of the patients received a drug intervention (cannabis) whereas the other half did not receive. Children and young adults with Dravet syndrome that did not respond to treatment were given either cannabidiol or a placebo along with regular antiseizure drugs (ASDs) in this study. Cannabidiol was significantly effective in reducing convulsive seizures (as measured statistically and clinically) while compared with placebo in monthly seizures. Further, significantly more patients responded to the treatment (a 50% or greater reduction in the number of seizures), than is typically considered a response in studies of epilepsy.

No patients were completely free of seizures, but this population of patients is very treatment resistant, and if they became seizure free, it would be a tremendous success. Notably, this was the first research to have high-quality evidence in the form of a randomized trial, and enabled international regulatory approval for the use of CBD. In the following open label extension studies, prolonged (> 16 weeks) treatment continued to show a tendency to further reduce seizures. Consequently, adherence to treatment was relatively good and effectiveness of the treatment was maintained for many years, suggesting a relatively high tolerability and effectiveness of the treatment in many children.

No unexpected safety problems were detected in long-term trials, except for the ones that occurred in the early trials. These data have been corroborated with observational studies done with actual systems in the real world. Variations in dosage or co-medication have been reported in usual practice with a similar response among the 'responders' as in the randomized trial. Other benefits, including improved attention, behavior, communication, sleeping and functional abilities, beyond just seizures are commonly mentioned by many caregivers. The findings from this study were encouraging, however, there were still some limitations to this study.

While the predictors for treatment response remain an undetermined factor, long-term neurodevelopmental effects of cannabidiol treatment have not been well established and the majority of evidence related to cannabidiol evaluations has been conducted in conjunction with other medications. But the studies so far are all definitive that if a child is not controlled even with all the conventional treatments, he or she can benefit from an adjunctive treatment with CBD. Dravet syndrome is one of the most severe types of developmental and epileptic encephalopathy seen in childhood. It is usually seen in the first year

of life, and is often complicated by continued febrile convulsions and eventually progresses to other types of seizures and impaired intelligence, behaviour disorders and motor deficiencies. In about 80-90% of patients, there is a disruption of inhibitory neurons caused by pathogenic mutations in the gene responsible for the synthesis of those inhibitory neurons (SCN1A gene) and more neurons are hyperexcitable throughout the brain.

Although patients receive intensive therapy using standard anti-epilepsy drugs, many many still have seizures. Seizures become persistent, causing developmental regression, increased chances of recurrent admission to hospital and decreased quality of life and sudden unexpected death in epilepsy (SUDEP). Understand the need for therapeutic strategies with alternative modes of activity due to these constraints.Recognise the requirement for newer therapies with novel mechanisms of activity. The first indications of the benefits of CBD were found with the Compassion use and expanded access programs. Although the shortcomings of these studies aren't addressed in this week's project limitations, pediatricians who prescribe any of the medications in the study consistently found that kids experienced a significant drop in the number of seizures after starting a previous drug.

Self-reports from caregivers suggested that there were improvements in alertness, sleep and behaviour further enhanced the interest in using CBD as treatment. Devinsky et al (2017) performed a revolutionary Phase III randomized controlled trial (RCT) as the most important evidence to emerge from the ground. Children and young adults with Dravet syndrome that failed to respond to other antiseizure drugs, were given either cannabidiol or a placebo as well as other antiseizure drugs in this study. The results showed statistically and clinically significant decrease in the number of convulsive seizures per month, when compared with placebo. Furthermore, a higher percentage of patients experienced a clinically significant treatment response – more than half – in the standard benchmarks used to assess the efficacy of epilepsy treatments.

Some patients were completely seizure free but the seizure-free group in the very severely refractory population achieved was significant. Most importantly, the study offered high quality randomized evidence – and therefore set the precedent for international regulatory approval of a cannabinoid therapy – namely cannabis-derived cannabidiol. Longer-term open label extension studies typically revealed continued benefits of reduced seizures. This treatment retention and relatively high benefit observed in the treated group were sustained for some years and clinical effectiveness and relatively good tolerability were observed. Long-term studies additionally did not reveal any unanticipated safety issues apart from those noticed in initial clinical trials. The present studies in different health care systems confirm these.

The "responders" are fairly consistent in the trials while there are some variations in dosing regimens and co-medication in clinical practice. Many caregivers report that their daily life functioning and communication, as well as attention and behaviour, improve as well as seizure reduction, following the treatment. While these promising results are promising, there are a number of caveats. Predictors of treatment responsiveness are not known, long-term neurodevelopmental outcomes are largely unexplored, and most of the evidence in the literature is for the use of CBD in adjunctive vs. monotherapy. Regardless, there's solid evidence available today that can support the

effectiveness of CBD on youngsters whose dread syndrome treats are ineffective.

CANNABIDIOL IN LENNOX–GASTAUT SYNDROME

The Lennox–Gastaut syndrome (LGS) is another developmental and epileptic encephalopathy with multiple seizure types, and also presents with EEG abnormalities, intellectual disability and life-long neurological deficits. LGS on the contrary, has many different underlying causes, including brain structural abnormalities, genetic abnormalities, metabolic diseases, perinatal brain injury and past epileptic encephalopathies. One, if not the most debilitating symptom of LGS is drop seizures, which can be followed by unexpected falls, injuries and loss of independence.

Though multidrug therapy has proven to be effective, some anti-seizure drugs are only partially effective, making adjunctive drugs more effective options. As proof for the use of cannabidiol in LGS, two major, independent, Phase III randomized controlled trials (RCTs), GWPCARE4 and GWPCARE3, have been published. The GWPCARE4 trial results confirm that the addition of adjunctive CBD is significantly more effective than use of a placebo for reducing the drop seizure frequency per month when compared to a naïve CG. The percentage of the patients who had CBD that had clinically meaningful responder rates was higher with a reduction in seizure burden. This study was the first to conclusively demonstrate that a substance in cannabis – CBD – is effective in treating seizures in Lennox–Gastaut syndrome.

The results of the following GWPCARE3 trial were consistent with the above with two doses of 10 and 20 mg/kg/ day. Both doses of treatment were able to decrease seizure frequency relative to placebo and a meaningful decrease in seizures was seen without using the highest dose of treatment possible. Clinically relevant because if the lower doses are used, then there will be less adverse effect without losing its efficacy. Combining the results of these trials together revealed that both the number of drop seizures and the overall severity of seizures (measured across a range of seizures) decreased with both treatments. A clinically significant reduction in seizure frequency was found in approximately 1/3 – nearly 1/2 of treated patients, as patients with long-standing (pharmacoresistant) epilepsy saw a reduction in seizure frequency of at least 50%.

Extension trials over the long term also demonstrated that long-term treatment resulted in a decrease of seizures over the long run period. In randomised trials, the majority of patients who responded clinically at the end of the first periods of treatment maintained a clear clinical response over long periods of time, on a clinically acceptable treatment retention and without signs of progressive treatment toxicity. Results of RCTs have been consistent with those in the real world clinically. Throughout the various epilepsy centres throughout the world, CBD has proven to have an eternal effect of reducing the number of seizures in patients and beneficialising the life of caregivers.

Many families share some of the following findings: reduction of seizure injuries, participation in school, increased alertness and decreased caregiver stress. But not all children become completely seizure-free and there is a considerable variation intra-individually in responsiveness to treatment. Biomarkers to predict response to therapy, and head-to-head comparisons of cannabidiol with other recently approved therapies like fenfluramine, should be the subject of future research. The totality of the evidence so far is quite satisfactory that CBD is an effective, add-on therapy for drop seizures in

Lennox–Gastaut syndrome and for seizures in general.

CANNABIDIOL IN TUBEROUS SCLEROSIS COMPLEX-ASSOCIATED EPILEPSY

Tuberous sclerosis complex (TSC) is a genetic disorder of multiple systems (organs) that occurs because abnormalities occur in one of two genes, TSC1 and/or TSC2 that cause abnormalities in the mammalian target of rapamycin (mTOR) signaling pathway. The neurological involvement is most severe, and present in 80-90% of those affected, and epilepsy is present. Seizures tend to begin in infancy, and commonly are resistant to regular anti-epileptic drugs. In addition to epilepsy, many children will suffer from other forms of developmental delay, such as ASD, intellectual disability and behaviour disorders and seizure control is important to consider for long-term neurological outcomes.

Based on positive results witnessed in the Lennox–Gastaut and Dravet syndromes, the CIIP interest in TSC started. Many additional trials since this initial one demonstrated excellent efficacy of the addition of CBD to children's current anti-seizure medications for the specific case of "epilepsy associated with TSC" in which other anti-seizure medications were not sufficient. Hempel's study into the use of CBD in TSC was a landmark trial that tested the drug on a group of people with the condition and found the two groups that took the drug and that that didn't so numbers of monthly seizures were reduced, though not significantly different from the placebo group.

Adverse effect incidence increased with higher doses (between 25-50mg/kg/day) however, higher doses were suggested to potentially further reduce seizures in some patients, thus requiring individual dose optimization. The longer term extended trials have also shown good seizure control during the longer treatment given. First of all, cannabidiol is also active in multiple and a variety of types of seizures seen in TSC; and in cases of more than one seizure type, it is active in more than one seizure type. Existing evidence is mostly targeted to seizure control; future research should determine if achieving better seizure control results in better cognitive development, adaptive functioning and/or behavior in children with TSC.

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CIIP interest started with good results being seen in Dravet syndrome and Lennox – Gastaut syndrome. Many additional trials since this initial one demonstrated excellent efficacy of the addition of CBD to children's current anti-seizure medications for the specific case of "epilepsy associated with TSC" in which other anti-seizure medications were not sufficient. Hempel's study into the use of CBD in TSC was a landmark trial that tested the drug on a group of people with the condition and found the two groups that took the drug and that that didn't so numbers of monthly seizures were reduced, though not significantly different from the placebo group.

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doses were suggested to potentially further reduce seizures in some patients, thus requiring individual dose optimization. Extensions trials over the long term have shown that seizures can be well controlled all year long. Importantly, cannabidiol also has activity in a variety of the many types of seizures commonly found in TSC—when more than one type of seizure occurs, it is across multiple types of seizures. Existing evidence is mostly targeted to seizure control; future research should determine if achieving better seizure control results in better cognitive development, adaptive functioning and/or behavior in children with TSC.

EVIDENCE IN OTHER PEDIATRIC DRUG-RESISTANT EPILEPSIES

There are interesting reports that CBD may be effective in treating other developmental and epileptic encephalopathy, such as some of the few children who experience success with its use in for Dravet syndrome, Lennox – Gastaut syndrome and Tuberous sclerosis complex. Observational studies and expanded access programs have shown promising results with regard to drugs in children with CDKL5 deficiency disorder, STXBP1 encephalopathy, Doose syndrome (myoclonic-astatic epilepsy), FIRES (Febrile Infection-Related Epilepsy Syndrome), Aicardi syndrome, infantile spasms and several rare genetic epilepsies.

However, the rate of responders varies greatly and many kids may have seizures controlled when they stop taking so many antiseizure drugs. A few small observational studies have studied the use of CBD for: Focal Epilepsies, Generalized Epilepsies and Mixed Epilepsy Syndromes.

To date there is less evidence, however the range of pharmaceutical activity of CBD has the potential to promise a host of types of seizures. The conclusions are tentative since the studies available so far generally are limited to few patients, varied patient populations, uncontrolled study designs, and varying doses and treatment schemes. Therefore, less commonly, it is recommended that cannabidiol be used in epilepsy syndromes for non-approved uses. Randomized controlled trials are needed to establish the efficacy and optimal dose and safety of these treatments in such populations and their efficacy in long-term settings.

OVERALL CLINICAL EFFECTIVENESS

The majority the evidence, together a few observations, is consistent.

The first is that in a large number of children with severe drug-resistant epilepsy who were unresponsive to various medications, CBD was found to have clinically meaningful antiseizure effects. While not many patients become completely seizure-free, being able to get a 50% or more reduction in seizures tends to greatly improve their quality of life and also greatly benefits their caregivers.

Second, treatment has a broader impact than just a reduction in seizures. In clinical trials and their clinical experience, better sleep, behaviour, alertness, communication, daily functioning and well-being for caregivers are frequently reported. The results highlight the importance of using more holistic patient-centred outcomes than seizures in assessing treatment of epilepsy.

Third, the long-term extension trials of the randomized controlled trials and clinical use of cannabidiol has proven its durability and reproducibility of the potential benefits in a range of healthcare environments.

To sum up, when it comes to the treatment of epilepsy, a CBD treatment is not a single pill cure, but should be used as a supplement to the rest of the treatment. An individualized treatment should be used; the treatment needs to be closely monitored for adverse effects and drug interactions, regular liver function tests should be performed, and treatment should be supplemented with other medication and non-medication therapy.

Overall, the results are quite promising for the use of CBD as one of the most promising therapeutic advances used in the treatment of drug-resistant epilepsy in children. CBD's mechanism of action, its wide-ranging effect and the relatively high level of its safety make it a likely future adjunctive treatment option for children with refractory epilepsy of high severity.

SAFETY AND TOLERABILITY OF CANNABIDIOL

For the successful incorporation into epilepsy management, the efficacy of cannabidiol (CBD) in the treatment of pediatric epilepsy as well as its safety and tolerability is of great importance. Because children with DR epilepsy typically must take several antiseizure drugs throughout their lives, the safety of these drugs is a concern. The findings of RCTs and open label extension trials, expanded access programs, and real-world studies indicate successful tolerance of CBD. Adverse events occur relatively commonly, but are usually mild to moderate and dosage-dependent and can be easily controlled by careful dosage adjustment and clinical monitoring.

The majority of adverse events are seen in the first few weeks of therapy or when doses are increased and they often resolve with ongoing treatment or a decrease in dose. Rarely do children experience adverse effects and in only a small number of children, therapy can be permanently discontinued; most children can be treated effectively if therapy is indicated and supervised by a qualified health care professional. Somnolence/excessive drowsiness is the most frequent side effect that occurs, particularly when used with clobazam. In this interaction, a decrease in the activity of the CYP2C19 enzyme would lead to an increase of N-desmethylclobazam, the active metabolite of clobazam.

Treatment may include sedation, which in some cases will reduce the seizures, but make it more difficult to learn or function. If clinically relevant sedation occurs, dosage changes usually are enough to alleviate symptoms without stopping the use of cannabidiol. The gastrointestinal side effect is another common side effect mentioned. These are some examples, such as stomach discomfort and decreased appetite, diarrhea, nausea or vomiting. Problems with the gastrointestinal tract usually go away or are managed with a dose change. For some children, loss of appetite or loss of weight is a problem and frequent monitoring of nutritional status is relevant for children with preexisting feeding issues or for younger children.

Other effects noticed during trials include: fatigue, lethargy, dizziness, pyrexia, irritability and upper respiratory tract infections. However, positive identification of adverse effects attributable to the medication administration and not to the presence of severe neurological disorders or use of multiple medications can be complex because many children with drug resistant epilepsy have underlying complex medical conditions. Among the clinical safety issues that have been noted with cannabidiol use is elevation of hepatic transaminases.

Elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are more common in those patients who are given

concurrent valproate therapy. The mode of interaction is unknown, although recent evidence suggests it is pharmacodynamic, not pharmacokinetic interaction. Most of the time, there are no symptoms and the liver function returns to normal when the level of the drug in the body is lowered or stopped for a brief period of time. Liver injury rarely occurs, but is mild and frequently recommended every day, particularly at the beginning and the growth of treatment. Caution may be warranted to the barest degree, and they might require a smaller dose if they already have a liver ailment.

Importantly, there have been no clinically significant cognitive deficits that have been demonstrated in clinical studies involving use of cannabidiol. Purified CBD has no effect on behavioural disinhibition or euphoria/intoxication like tetrahydrocannabinol (THC). In fact, it has been noted that many caregivers report improvements in their child's attention span, alertness, behaviour and sleep patterns following successful control of seizures despite the fact that they were intermittently sedate throughout the process of treatment. Reassuring safety data has been available from long-term studies that have been conducted over several years. However, there are no observations of long-term treatment for acute or chronic toxicities or organ dysfunctions. There is now some evidence indicating that long-term safety of pharmaceutical grade CBD oil is promising, but monitoring is essential.

DRUG–DRUG INTERACTIONS

A consideration in the use of cannabidiol with children who have drug-resistant epilepsy is drug interactions due to their tendency to be on multiple anti seizures medications. Both the kidney and liver enzymes are involved in the metabolism of CBD and it could inhibit multiple enzymes, so there may be clinically relevant pharmacokinetic interactions.

The interaction with clobazam seems to be the most well documented. Therefore, CBD may lead to increased plasma levels of clobazam, and may inhibit its metabolism by CYP2C19, which can cause increased concentrations of the active metabolite of clobazam, N-desmethylclobazam. This interaction may be helpful in controlling seizures, and is also very likely to cause somnolence, fatigue and sedation.

So, if fiveedation is seen, caution should be taken in the administration of clobazam including reducing doses. Co-administration of cannabidiol and valproate is especially problematic however with regard to increased rates of hepatic enzyme elevations. The use of two products concomitantly has not been reported to be related to significant change in plasma levels of valproate, however, may be related to increased transaminase levels. This combination should therefore require initial and periodic measurement of liver function tests (LFTs). Stiripentol, rufinamide, topiramate, zonisamide, brivaracetam and everolimus are several other antiseizure drugs whose use has been associated with other drug interactions.

Generally these interactions are not clinically significant, but will be considered when optimising and monitoring doses. However, when a child is prescribed three or more antiseizures simultaneously, the evaluation of the entire medication regimen is particularly important, and the clinician needs to carefully review the child's treatment history prior to initiating a child's treatment with cannabidiol. The significance of close clinical monitoring, titration of dose and individual therapy will remain vital to help to minimize adverse interactions, while maximizing therapeutic benefit.

DOSING STRATEGIES AND CLINICAL MONITORING

When using CBD, it is crucial you always begin with a low dose and work up to get the correct amount of CBD in your body, as well as minimise the risk of unwanted side effects occurring. As a general rule, treatment is begun at 2.5mg/kg twice daily (5mg/kg a day) or so. After determining the tolerability of this dose the dose is slowly increased to a typical maintenance dose of 10 mg/kg/day in 1-2 weeks. Otherwise, a further increase in dosage to the standard dose for Lennox–Gastaut syndrome and Dravet syndrome of 20 mg/kg/day may be recommended if the level of tolerance is good.

Tuberous sclerosis complex (TSC) associated epilepsy: testing has been done in clinical trials and a dosage of up to 25-50 mg/kg/day is recommended; amounts higher than 20 mg/kg/day should always be individualized to account for the therapeutic benefits and side effects. Why: There is significant variation between people as to the response to medication – doses are customized. Some children are going to respond significantly in terms of therapeutic response to a low dosage and others are going to respond significantly to Wegen high dosage.

Thus, the point of therapeutic goals is not the dosage that is given, but the clinical response. One other factor is mutual administration as far as the amount of food. Administration with meals or non-meals should be delayed for each administration of CBD as this produces a much larger pharmacokinetic variability. A careful clinical monitoring should be carried out as the support of the therapy. Liver function tests (ALT, AST, AP, and TBili), body weight, and nutritional status assessment, seizure frequency, current medication history, and relevant laboratory tests should be performed as baseline studies.

Liver function tests are performed again approximately at the start of treatment, at about 1 month, 3 months and 6 months after the start, and at regular intervals thereafter (as clinically determined). In patients who need valproate to be co-administered with other medications or where there is pre-existing liver disease, a higher frequency of tests is recommended. Regularly reviewing the frequency and severity of the seizures, quality of life, behaviour, performance in school, appetite, growth and weight, gastrointestinal disturbances, daytime alertness and ability to take the medication should be planned for routine review. One of the best ways to determine the effectiveness of treatment and keep track of doses is to maintain a seizure diary.

REGULATORY STATUS OF CANNABIDIOL

The FDA approval of purified CBD is a huge stride in the direction of treating epilepsy. Several significant randomized controlled trials demonstrated a substantial decrease in seizures, with few side effects, leading to the U.S. and European regulatory bodies approving CBD as the first treatment to be used for children with drug-resistant forms of epilepsy.

In 2018, the United States Food and Drug Administration (FDA) approved pharmaceutical-grade cannabidiol oral solution (Epidiolex®) as a previously unapproved add-on treatment for people 2 years of age and older with Dravet syndrome who have seizures, or Lennox–Gastaut syndrome who have seizures. It's the first time that the FDA has approved a purified cannabis-derived medication. Later, the European Medicines Agency (EMA) has also approved it for these indications, which has been adding to the global acceptance of treatment with CBD-epilepsy.

In 2020, the approval for seizures was extended for use in patients who have tuberous sclerosis complex (TSC), because of growing evidence of efficacy. Today, national guidelines for epilepsy have officially approved the use of CBD as a second-line treatment for children who still have seizures despite optimized conventional treatment and are suffering from Dravet syndrome, Lennox–Gastaut syndrome and Tuberous Sclerosis Complex. The recommendations are directed towards patient selection, follow-up and multi-disciplinary treatment.

It is generally accepted that using CBD is a good way to treat a wide variety of health problems, but not everyone has access to it because of the increased expense of treatment, reimbursement policies, regulatory challenges and disparities in the healthcare system. Challenges are yet to be met in ensuring equitable access particularly, in low and middle-income countries.

CLINICAL SIGNIFICANCE

The FDA's approval of a purified CBD is a great addition to the treatment of epilepsy. Following that, several influential randomized controlled trials revealed CBD's effectiveness against seizures with little to no adverse effects, leading U.S. and European regulators to four years ago approve it as a successful drug for some forms of drug-resistant childhood epilepsy. In 2018, the FDA approved the pharmaceutical grade formulation of CBD oral solution (Epidiolex®) to treat seizures in patients with Dravet syndrome older than 2 years of age and Lennox–Gastaut syndrome older than 2 years of age to be used as an add-on to other medications.

This is the first purified form of cannabis medicine to become FDA approved. Later, this was confirmed by the European Medicines Agency (EMA) on these indications, further solidifying the world's approval of the epilepsy indication with cannabis based products. In 2020 increased clinical evidence of efficacy led to extension of the approval for use in seizures in patients with tuberous sclerosis complex (TSC).

In the case of epilepsy it's now accepted in the international guidelines that children with Dravet syndrome, Lennox–Gastaut syndrome and tuberous sclerosis complex who have been on the best conventional treatment and still have seizures could benefit from the use of cannabidiol as an adjunctive drug. The recommendations focus upon patient selection, the monitoring and multi-disciplinary treatment.

In addition to being a valuable treatment for numerous illnesses, the adoption of pharmaceutical grade CBD has been unevenly distributed around the world owing to the potential costs of using cannabis, restricted policies on reimbursement, restricted regulatory availability and an inconsistent healthcare infrastructure. However, there are much to be done in the areas of research and preventive measures, especially in low or middle income nations, to make it accessible across a level playing field.

FUTURE PERSPECTIVES

The research study that has grown beyond scale is focused on the positive impacts of CBD on children with difficult to treat epilepsy that is resistant to both drug treatment and standard conventional therapy.Study of how valuable CBD can be to children with drug resistant epilepsy (that does not respond to conventional symptoms) has been getting faster. Despite these strides, there remain intriguing questions that will not be addressed without further research. There is a need for continued research to better tailor administration of treatments, identify patient groups and comprehend the long term impacts of

CBD on neurological growth. Predicting treatment response is among one of the key areas of future research. If seizures get reduced during clinical trials, there can be significant differences in the percentage of reduction of seizures experienced by people receiving the same dose of cannabis or cannabidiol.

Those kids that make a tremendous amount of improvement make up a large percentage while those that make a little make up another, and the rest of the kids don't make any improvement. The variability suggests that a single drug might not affect the course of an individual's therapy, depending on genetic and/or different types of epilepsy, blood levels of the drug, the sensitivity of the receptor or the severity of the condition. In the future, doctors may be able to use pharmacogenomics to see if CBD has more of an effect on some patients and could find a more personalized epilepsy treatment that might use CBD. Another study area that will be of great interest is the longer term neurodevelopmental effects of CBD.

It is now confirmed to have a substantial effect on decreasing the number of seizures, but effects on better cognitive, language, behaviour, education and adaptive functioning are yet to be determined. Future studies need to incorporate the standardized neurodevelopmental and QOL evaluations in the primary outcome of epilepsy treatment in children. Optimisation of dosing strategies is another main stream of research. Currently, the dosages are based primarily on weight, but a vast amount of inter-individual difference in the way CBD is absorbed, metabolized and therapeutically responded to has been found.

Further pharmacokinetics/pharmacodynamics (PK/PD) studies could help to create individualized dosing based on optimal exposure levels for best results. The need for therapeutic drug monitoring is also another area worthy of further exploration, but, at present, there is no clear range of therapeutic levels. There have been a few interest notes about new clinical uses of CBD, too. Evidence for its use in Dravet syndrome, Lennox–Gastaut syndrome and tuberous sclerosis complex (TSC) epilepsy are good and there is some preliminary observational evidence in other developmental and epileptic encephalopathies, such as CDKL5 deficiency disorder, STXBP1 encephalopathy, Doose syndrome, FIRES, Aicardi syndrome and other rare genetic epilepsies.

These early observations in the clinical context must be translated into clinical recommendations that are based on evidence, and for this at least large multicentre randomized controlled trials are warranted. Another area that may be of interest is the potential from of CBD for its neuroprotective and anti-inflammatory properties. According to scientific evidence, CBT exerts an effect on reducing oxidative stress, managing neuroinflammation and stopping damage to the neurons by seizures. This indicates that CBD does not just prevent seizures, but does in addition have an impact on the process of the disease. However, there is no clear evidence to give an idea that it could affect the disease in humans.

This situation is still unresolved, and further prospective studies, using more powerful tools like neuroimaging, molecular and cognitive tests, must be conducted to unravel this. New patented therapies for the next generation of cannabinoids are also in the process of being developed. Additionally, targeted development of more selective compounds against specific molecular pathways associated with epileptogenesis and with a low side effect profile could be possible with the help of better understanding of the pharmacology of cannabinoids. The latter types of therapies could be used alongside, or even in place of, existing

cannabis preparations, in the future. Finally, a significant improvement of health service access should be achieved, globally.

Although the therapy has been approved in several countries, access to a therapy is impeded by high costs of therapy, inconsistent reimbursement policies and the limited availability of the therapy. Having a policy change to health systems, make the treatment affordable, and improve the education of clinicians will be key to ensuring equitable access to this much needed treatment.

CURRENT RESEARCH GAPS

Driven by the growth of the research study, the scientists' sole direction is the focus on what is great about CBD and its positive effects on kids suffering from troublesome to address epilepsy that is resistant to drug treatment and various conventional therapies.Study of how valuable CBD can be to children with drug resistant epilepsy (that does not respond to conventional symptoms) has been getting faster. Nevertheless, many new questions await answers, and that can only come as a result of further research. Further studies are required to fine-tune the use of these treatments, as well as to determine who can benefit and understand the long-term effects of using CBD in the neurological growth of patients. One of the main areas for study in the future is to predict or forecast treatment response. If seizures get reduced during clinical trials, there can be significant differences in the percentage of reduction of seizures experienced by people receiving the same dose of cannabis or cannabidiol.

Those kids that make a tremendous amount of improvement make up a large percentage while those that make a little make up another, and the rest of the kids don't make any improvement. The difference implies that for some people one drug may not influence the course of their therapy depending on genetic and/or other types of epilepsy; blood levels of the drug, sensitivity of the receptor or severity of the epilepsy. Additionally, future studies with doctors could determine whether everyone is responsive to the treatment effects that CBD might have and a customised treatment pathway for epilepsy might be developed which incorporates CBD. Other areas of interest that will be explored are the longer term neurodevelopmental effects of CBD.

Now proven to have significant impact on reducing seizure frequency, further research is required to assess the impact on improved cognitive, language, behavior, education and adaptive functioning. On-going studies should consider using the standardized neurodevelopmental and QOL assessments as the primary outcome measure of the treatment of epilepsy in children. The optimisation of dosing strategies, is another major research avenue. Currently, all dosages are given mainly according to weight; however, a significant variation of how individuals absorb, metabolize and respond to CBD has been discovered.

Additional pharmacokinetics/pharmacodynamics (PK/PD) studies may be utilized to develop a personalized dose according to the optimal exposure in order to maximize the drug's effects. Another aspect which may be explored is the need for therapeutic drug monitoring: At this time, there is no clear range of therapeutic levels. There's been some interest on new ways CBD might be used in the clinic, too. Evidence for its use in Dravet syndrome, Lennox–Gastaut syndrome and tuberous sclerosis complex (TSC) epilepsy are good and there is some preliminary observational evidence in other developmental and epileptic encephalopathies, such as CDKL5 deficiency disorder, STXBP1 encephalopathy, Doose

syndrome, FIRES, Aicardi syndrome and other rare genetic epilepsies.

Such initial experiences in the clinical setting will have to be translated to clinical practice based evidence which require, at the very minimum, large multicentre and randomized controlled trials. Another area that may be of interest is the potential from of CBD for its neuroprotective and anti-inflammatory properties. Based on scientific studies, CBT has an impact on reducing oxidative stress, controlling neuro-inflammation and preventing it from causing damage to the neurons during seizure events. This means that CBD isn't simply benefiting in blocking seizures from happening, but additionally affecting the actions of the disease. However there is no clear indication that this will have an effect on the disease in humans.

However, this is still not clarified and more prospective studies are needed, employing the more potent tools as neuroimaging, molecular and cognitive tests to further unravel this. In addition to that, innovative, novel patented drugs for the next generation of cannabinoids are being developed. Furthermore, targeted development of more selective compounds, directed specifically to these molecular pathways involved in epileptogenesis and designed to have a low side effect profile may be possible with the help of better understanding of the pharmacology of cannabinoids. The latter types of therapies could be used alongside, or even in place of, existing cannabis preparations, in the future. Last, but not least, there needs to be an improvement of the access to health services, internationally.

While therapy is approved on several countries, the implementation of a therapy is hindered by high costs of therapy, non-standardized reimbursement systems and the lack of the implementation on a given country. Implementing a policy and making treatment affordable, and enhancing clinician education, will be critical toward equitable access to this much needed treatment.

LIMITATIONS OF THE CURRENT EVIDENCE

Several conclusions were possible to draw from the literature reviewed but some lessons must be learned. Most of these are relevant to the use of a CBD product, specifically for selected pediatric epilepsies.

The results reported vary widely between studies, depending on several factors such as study design, patients studied, epilepsy syndromes, duration of treatment, doses of cannabidiol, other drugs that are prescribed at the same time as the CBD and metrics used to report outcomes. This varies between studies and makes it difficult to draw conclusions between them and to decide on best practice.

Many of the observational studies are also non-placebo controlled and therefore are subject to selection bias, reporting bias and to concomitant therapy bias. Further, it is likely that sustained efficacy estimates are somewhat over-optimistic because people that are treated that do very well will be more likely to be included in long term extension trials.

Other drawbacks include the continued emphasis on the number of seizures. Although seizures are known to be important, additional research efforts are needed to examine other meaningful measures that benefit impacted families like cognition and behavior, school performance, socio-demotional functioning, caregiver well-being, and quality of life.

Despite such limitations, a consistency in the results obtained in RCTs, long term extension trials, and real-world trials allows for a high level of confidence in overall conclusions about the use of cannabidiol therapy.

CONCLUSION

One of the more challenging aspects of pediatric care is that of epilepsy not sensitive to treatment. Unfortunately 1/3 of children that develop epilepsy will still have seizures even if they are on a well chosen AED and these children are at risk of developmental delay, cognitive impairment, behavioural and psychosocial problems, reduced quality of life and mortality. Many of these cases are very severe, such as Dravet syndrome, Lennox–Gastaut syndrome or tuberous sclerosis complex-associated epilepsy; in this case, a significant proportion of these children remain critically ill medically for life, and are treated by many specialists.

One of the greatest strides in the treatment of childhood epilepsy in the past 10 years has been the introduction and use of cannabidiol. Unlike with conventional AEDs, that generally target a small number of molecular targets, CBD has a unique pharmacological action profile with multiple modes of action, such as the modulation of neuronal excitability, intracellular calcium homeostasis, the adenosine signaling, the GPR55 receptor, the TRP channel, neuroinflammation and oxidative stress. With its biological rationale these mechanisms add to an idea that it could be effective in highly refractory epilepsy syndromes.

Dramatic evidence and consistency have been emerging which increases the benefits of cannabidiol. Multiple randomized controlled trials, open-label extension studies, expanded access programs, systematic reviews and real world, observational studies have demonstrated the reduction in the number of seizures in children with Dravet syndrome, Lennox–Gastaut syndrome and tuberous sclerosis complex. Many teachers have indicated that not only is there a cessation of seizing but that other benefits like increased alertness, behaviour, sleep, communications and activities of daily living are also noted.

Another benefit of CBD is that it's one of the more safe products as well. Adverse events, particularly somnolence, gastrointestinal disturbances, decreased appetite and hepatic transaminase elevations, tend to occur more frequently, but can be controlled by careful attention to slow dosing titration, monitoring and managing drug interactions. The liver function should be monitored on a regular basis, and care should be taken in patients receiving clobazam and valproate therapy.

While these encouraging findings are promising for the future of using CBD to treat pediatric drug-resistant epilepsy, it shouldn't be thought of as the end-all, be-all solution. The outcome for treatment varies from one person to another, and a number of people may not be free from the convulsions altogether; there are sparse data available about neurodevelopment and disease modification in the long term. Other challenges include accessibility to healthcare globally, and treatment cost and regulatory clearance.

Predictors of the response to therapy, optimized individual dosing of the therapy, investigation of new epilepsy syndromes, long-term neurodevelopmental disorders, and the disease-modifying effect of treatment with CBD should be studied in the future. An optimized therapeutic benefit will require cross-pollination between the different healthcare stakeholders involved, such as clinicians, researchers, regulatory and healthcare policymakers.

Current data suggest that the use of pharmaceutical-grade CBD as an adjunctive treatment is effective and tolerated for some in children with drug-resistant epilepsy. Since it came out it has significantly improved the treatment options of a large number of children suffering from intractable epilepsy and has improved outcomes for many children and families. While knowledge of the pharmacology of cannabinoids is continually evolving, cannabidiol has the potential to play a growing role in the treatment and management of paediatric epilepsy – and of precision medicine.

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