Abstract: This summary aims to provide information about the potential use of cannabinoids in the treatment of epilepsy. Background information about the disease and the extent of epilepsy as a health problem is illustrated. The proposed mechanisms behind seizures are discussed, alongside a basic anatomy and physiology of the central nervous system. Finally, the current body of evidence on how cannabinoids could be a valuable addition and/or alternative to current treatments is examined. Cannabidiol has shown to have profound anticonvulsive effects in both animal and human trials, and has a favorable side effect profile. Large scale and multi-disciplinary research is required to validate the use of cannabidiol as an anticonvulsant and to further define its pharmacological action.

Keywords: epilepsy, seizure, epileptogenesis, anticonvulsant, cannabinoids, Cannabidiol

Introduction

Definition of Epilepsy

Epilepsy as a term, describes the enduring predisposition of the brain to generate epileptic seizures. The international league against epilepsy (ILAE) added to this conceptual definition in 2014 (Fisher et al., 2014), stating that to be diagnosed with epilepsy, a patient must fit at least one of three categories;

- A patient must have experienced two unprovoked seizures, at least 24 hours apart
- A patient has experienced one unprovoked seizure, however there is a high chance of recurrence - this allows patients who have been put on treatment after a single seizure to fit the diagnostic criteria
- A patient is diagnosed with an epilepsy syndrome
A **seizure** is the clinical manifestation of excessive and synchronous electrical activity within the brain. The presentation of seizures can vary greatly depending on the specificity of the areas of the brain that are affected, as well as the number of brain regions affected (Fisher et al., 2014).

**Epileptogenesis** is the process whereby the neuronal network in the brain changes over time to promote the development of seizures (Fisher et al., 2014).

**Epidemiology & Impact**

Current figures estimate that there are over 2.5 million people in Europe living with active epilepsy, defined by at least one seizure occurrence during the previous five years. Prevalence differs amongst age groups. Amongst children and adolescents, five out of every 1000 live with epilepsy. On the other hand, six in 1000 people aged 20 to 64 are affected and seven in 1000 people aged 65 or above are affected (Forsgren, Beghi, Oun, & Sillanpaa, 2005).

Every year above 200,000 new diagnoses are made. The oldest age bracket leads incidence figures, as 100 out of every 100,000 people aged 65 or above are diagnosed every year. 70 in every 100,000 children and adolescents are diagnosed, followed by 30 out of every 100,000 in the 20 to 64 year old age group. (Forsgren et al., 2005) (Figure 1).

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**Figure 1:** Incidence and prevalence of epilepsy in Europe. (Forsgren et al., 2005)
An epidemiological study conducted in the Australian state of Tasmania reported a prevalence of 4.34 per 1000 people. The breakdown of the prevalence by age-group is shown in Figure 2 (D’Souza et al., 2012). It can be concluded from the statistics shown that prevalence increases with age.

Despite receiving medical treatments, 20 - 30 % of patients with active epilepsy experience at least one seizure a month and are considered to have drug resistant epilepsy, defined as the inability to achieve a seizure free status despite having trialled two appropriately chosen and well tolerated anti-epileptic medications. There is a lack of large and comprehensive epidemiological data to verify these numbers, though current approximates are that in Europe and the United States 230,000 adult patients and 150,000 paediatric patients are suffering from treatment resistant epilepsy respectively (Kwan et al., 2010).

**Impact**

When analysing the impact of epilepsy, it is important to consider both the direct implications of seizures as well as the impact epilepsy has on the patient’s quality of life (QOL). This involves acknowledging the short and long-term effects resulting from the disease and its treatments. This includes physical, psychological and social burdens.

In epileptic patients, seizures occur suddenly and are associated with a complete loss of control. For patients this means that harmless everyday activities including bathing, cooking, driving or supervising young children pose an unknown threat. The ramifications are a loss of
independence frequently associated with social isolation, employment difficulties and emotional trouble.

Fortunately, the majority of patients suffering from epilepsy respond to currently available medications: which are able to inhibit seizures. For many, however, seizure freedom comes at a cost. Patients suffer a variety of side effects with currently available medications, which in turn can have a strong impact on their QOL (Table 3). Adverse health effects such as lethargy, reduced cognitive functioning, sensory disturbances and changes in mood are common and accompanied by changes in weight and body hair.

The patients experience low efficacy to available medications are also the ones who suffer the most side effects from those medications. As doses are increased and medications are added, the side effects naturally get more severe.

Current guidelines underline the importance of acknowledging a patient’s treatment resistant status. It is tempting for both clinicians and patients to continue trialling and adding AEDs in the hope that seizure control is achieved, though current statistics suggest that the likelihood of successful seizure control decreases significantly with every unsuccessful AED trial (Perucca & Gilliam, 2012).

Consequently, patients with treatment resistant epilepsy have the highest incidence of neuropsychological and psychiatric problems associated with decreased marriage rates, less employability and the strongest decrease in QOL. This patient population is set to gain the most from the development of novel treatment solutions.

**Anatomy, Histology & Electrophysiology of the Central Nervous System**

**Anatomy**

The central nervous system (CNS) is made up of two principle structures; the brain and the spinal cord (Figure 2). The brain is located within the cranial cavity, commonly referred to as skull, from which the spinal cord exits into the spinal canal.
**Histology**

From a histological point of view the CNS is made up of billions of cells, of which neurons and neuroglial cells are specific and functionally relevant to the nervous system. Neurons are nerve cells, responsible for the transmission of information whereas neuroglial cells have a supportive role.

Neuroglial cells are present in very high numbers in the CNS and mainly have housekeeping purposes. They insulate nerve cells to facilitate electrical transmission, metabolize and inactivate neurotransmitters, maintain the delicate balance of the CNS environment and are responsible for mounting immune responses when damages occur.

Neurons on the other hand transmit information, in the form of electrochemical signals. They can be divided into afferent neurons, efferent neurons and interneurons, depending on whether they carry information towards the CNS, away from the CNS or within the CNS respectively.

Figure 3 illustrates a typical neuron. All neurons possess a cell body or soma, where the production of proteins and other metabolic activities takes place. Extending from the soma are elongated projections called neurites. These communicate with other neurons and can be further
classified as dendrites, which receive and process information and as axons, responsible for the output of information. Every nerve may have many dendrites but only possesses one axon, at the end of which there is the axon terminal responsible for transmitting information onwards (Bear, Connors, & Paradiso, 2007).

**Electrophysiology**

The mechanism underlying the transmission of information is the release of a neurotransmitter from the axon terminal, initiated by action potentials.

At rest, the cell membrane, which separates the inside of the cell from the outside, generates a negatively charged electrical potential. This is referred to as resting membrane potential (Figure 4, Image 1).

In response to chemical stimulation, ligand-gated ion channels (Box 1) open and allow positively charged ions to enter the cell. This decreases the resting membrane potential (Figure 4, Image 2).

If the decrease in charge reaches the threshold potential, voltage-gated ion channels in the proximity open, allowing for a rapid influx of positively charged ions. This depolarizing chain reaction continues along the plasma membrane, and eventually causes the release of neurotransmitter at the axon terminal (Figure 4, Image 3). Immediately after depolarization, the
neuron releases positively charged ions previously held within, to counteract the influx of positive ions and to repolarize the cell (Figure 4, Image 4). Immediately after repolarization the neuron becomes hyperpolarized. This removes it further from the threshold potential and ensures that a second action potential cannot immediately follow (Figure 5, Image 5).

Channels in the neuronal membrane can respond to either changes in charge (voltage-gated ion channels) or to ligands (ligand-gated ion channels). Ligands are chemical messengers which trigger excitatory or inhibitory neuronal responses upon activating specific receptors. Neurotransmitters are ligands, though non-neurotransmitter ligands also exist.

**Box 1 Ion-gated channels**

**Figure 4 Stages of an action potential; Copyright © Pearson Education, Inc. publishing as Benjamin Cummings**

**The Neuronal Synapse & Neurotransmitters**

Once an action potential reaches the axon terminal, neurotransmitters are released into the synaptic cleft where they activate ligand-gated channels on the receiving neuron (Figure 3). Neurotransmitters can be either excitatory or inhibitory, depending on whether they increase or decrease the likelihood that an action potential occurs in the receiving neuron.
The main excitatory neurotransmitter is glutamate which acts on NMDA, AMPA and kainate receptors. Glutamate depolarizes the receiving neuron, moving it closer towards the threshold potential and thereby increasing the chance that an action potential occurs.

The main inhibitory neurotransmitter is gamma-amino-butyric acid (GABA). It acts on GABA receptors, resulting in an influx of negatively charged chloride ions which move the neuron further away from the threshold potential. The receiving neuron is therefore hyperpolarized and has a decreased likelihood of firing an action potential.

**Table 1** Two most common excitatory and inhibitory neurotransmitters and target receptors.

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Effect</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>glutamate</td>
<td>excitatory</td>
<td>NMDA, AMPA, kainate</td>
</tr>
<tr>
<td>GABA</td>
<td>inhibitory</td>
<td>GABA</td>
</tr>
</tbody>
</table>

**Excitability of Neurons & Epileptogenesis**

The chance of an action potential occurring is referred to as excitability. Structural, genetic and metabolic changes in the CNS are able to alter excitability and are thought to be the foundation of how the uncontrolled synchronous electrical activity during seizures occurs in the brain. This process is referred to as epileptogenesis (Goldberg & Coulter, 2013).

**Structural Changes**

In order to ensure that only desired neurons are activated, local networks of neurons communicate with each other via interneurons. They inhibit neurons, surrounding a firing neuron, through a process called feed-forward inhibition. Similarly, interneurons can act on the firing neuron itself to terminate firing, a process termed feed-back inhibition. Combined together they enable complex and targeted signalling within the CNS (O’Dell, Das, Wallace, Ray, & Banik, 2012).

It has been proposed that the reorganization of these neuronal connections can lead to seizure generation (Goldberg & Coulter, 2013). This can occur through either degeneration of the existing interneurons responsible for inhibition or the development of self-reinforcing stimulatory circuits. It is thought that the most common cause is prior insult to the CNS including ischemia, haemorrhage and infection (Reeves & Swenson, 1981).
Structural change also occurs at a synaptic level. Synaptic plasticity is the process whereby synapses alter the strength of their influence on the receiving neuron. This can happen through different mechanisms, including widening or shortening of the synaptic cleft, changes in neurotransmitter release capacity and number of receptors on the receiving neuron (Bear et al., 2007).

These changes occur in response synaptic activity; frequently activated synapses become more efficient, increasing the excitability of the target neuron and vice versa.

**Genetic Changes**

The distribution and type of ion channels found on a neuron influence its excitability. However, the way ion channels themselves behave and interact with their surroundings may be modified by activation of non-neurotransmitter mediated messenger systems such as the endocannabinoid system (Krisztina Monory et al., 2006) or other genetic alterations (Goldberg & Coulter, 2013).

Similarly, neurotransmitters secreted at the axon terminal needs to be taken up by either the firing neuron or neuroglial cells in the area. Any reduction in neurotransmitter uptake capacity, as can occur with genetic mutations, will increase the amount of neurotransmitter in the synapse and therefore may increase excitability of the target neuron.

**Metabolic Changes**

The fluid surrounding neurons is called the extracellular fluid and the body carefully controls the ion concentrations within it. If changes occur, the normal exchange of ions between the neuron and the extracellular fluid are altered, causing a change in excitability.

An example of this is dehydration. During dehydration there is a decrease in extracellular fluid volume, which leads to a higher ion concentration. Normally after an action potential fires, neurons repolarize by moving potassium out of the cell into the extracellular fluid. However in a dehydrated state, the increase in, including potassium ions, opposes the neurons ability to repolarize leading to an increase in neuronal excitability (Somjen, 2004).

Other metabolic changes induced by fever, infections, and alcohol can also influence excitability in a similar fashion.
Classification of Seizures

As previously mentioned, seizures are the physical manifestation of uncontrolled synchronous electrical activity in the brain. The activity may begin in one small area of the brain, or widely distributed neuronal networks, where very high levels of firing, secondary to one or more excitatory favouring mechanisms described above, recruit surrounding neurons by overriding the inhibitory mechanisms normally in place (Jefferys, 2009).

Because it is difficult to distinguish between the underlying seizure pathologies, physical signs are used for classification.

When the electrical activity begins in a localized region, they are referred to as partial seizures. The signs of a partial seizure will vary depending on the location. Examples include repetitive to complex involuntary movements, the vocalization of sounds and the perception of odd tastes and smells (Bear et al., 2007). Patients may remain conscious during partial seizures, though if consciousness is lost the label 'complex' partial seizure (or ‘focal dyscognitive’) applies (Mayo Clinic).

Partial seizures can spread to both hemispheres in the brain to become secondary generalized or alternatively a seizure may begin generalized, by mechanisms that are not fully understood.

Generalized seizures commence in and rapidly engage widely distributed bi-hemispheric networks can manifest in convulsive or non-convulsive seizures. One special type of generalized seizures are absence seizures, most frequent in children. These only manifest through brief moments of inactivity and inattentiveness (Reeves & Swenson, 1981).

Epilepsy Syndromes

Providing a patient with the diagnosis of an epilepsy syndrome aids in pointing towards the underlying pathology and provides an indication of the course of the illness. They are characterized by the type of presenting seizure, the age of onset and the associated EEG characteristics (Panayiotopoulos, 2005). The syndromes (Table 2) also provide direction when administering medications, as some epilepsy syndromes have been found to respond negatively or positively to the different types of anti-epileptic drugs.
**Dravet Syndrome**

Dravet syndrome typically presents within the first year of life and is linked to a genetic mutation on the SCN1A gene (Dravet, Bureau, Oguni, Fukuyama, & Cokar, 2005). Affected children have had a normal development until then but start presenting with seizures, often associated with fevers or infections. The type of seizures can vary, however they are often intractable and response to medication is very poor.

Within one year, physical and behavioural development begins to cease and regress. By the age of four most affected children have reached a steady state of intellectual disability, behavioural disorders, neurological deficits and frequent seizures. The mortality rate for this disease is around 16% (Dravet et al., 2005).

**Lennox-Gastaut syndrome**

Lennox-Gastaut syndrome typically presents between the third and fifth year of life. The cause is unknown, and likely can be either acquired or genetic (Beaumanoir & Blume, 2005). Affected children may have had a normal neonatal and birth history, however structural brain
abnormalities secondary to injury such as infections, malformations and tumours are common (Beaumanoir & Blume, 2005). The types of seizures vary and similar to Dravet syndrome, they respond very poorly to medication.

Soon after onset, cognitive development begins to slow and regress, accompanied by severe behavioural issues with autistic features (Beaumanoir & Blume, 2005). Seizures usually cannot be controlled, continuing throughout life.

**Epileptic Encephalopathies**

Both these syndromes belong to a group of epilepsies referred to as the ‘epileptic encephalopathies’ (Table 2). In these, it is implied seizures themselves, rather than just their underlying cause, contribute to progressive changes in the CNS and worsening of health outcomes in affected individuals (Dulac, 2001).

The development of medications able to reduce and stop seizures is a high priority for patients affected by these syndromes, their families and health care professionals. Long term outcomes would drastically improve and the burden on the health care system would decrease.

**Drug resistant epilepsies**

Drug resistant epilepsy is an additional disease classification describing patients in whom seizures cannot be controlled with current anti-epileptic medication (Kwan et al., 2010). This includes patients suffering from many different epilepsy syndromes, although some syndromes are more liable to be drug resistant than others (Table 2).

The current definition of drug resistant epilepsy includes patients for which at least two appropriately chosen AEDs have failed to eliminate the occurrence of seizures (Kwan et al., 2010). To adequately manage affected patients, early recognition is vital in order to avoid a futile cycle of medication trials leading to patients suffering from disabling side effects in the absence of gained medication benefits.

Current guidelines suggest doses should be kept an effective minimum while discontinuing sedative and cognitive impairing AEDs, and assessing whether they are suitable for epilepsy surgery (Sirven, Pedley, & Wilterdink, 2011). If they are not suitable for epilepsy surgery, in many cases it needs to be accepting that currently available AEDs will not control seizures and maximizing patients QOL health outcomes need to be prioritized (Sirven et al., 2011).
Simultaneously research needs to be conducted into the currently unknown mechanism of drug resistance as well as novel drug solutions.

**Treatments**

The two overlying principles through which anti-epileptic drugs (AEDs) reduce synchronous and uncontrolled firing of neurons, are increasing neuronal inhibition and prolonging neuronal inactivation after firing. However, all AEDs work on multiple targets in the CNS, many of which are unknown.

Sodium channels exist in three different states: resting, open and inactivated. After an action potential fires, sodium channels are in an inactivated state, preventing them from reopening. AEDs including phenytoin and carbamazepine bind to and inhibit sodium channels in their inactivated state, thereby prolonging the time before a neuron can fire again (Rogawski, 2004). Thus they are able to target areas where high frequency firing occurs, while still allowing normal signalling to occur within the CNS.

Benzodiazepines and barbiturates on the other hand work by directly activating or potentiating inhibitory GABA receptors (Rogawski, 2004). These include clonazepam, clobazam and phenobarbitone.

Lastly the breakdown of GABA in the neuronal synapse can be inhibited. This increases availability of the inhibitory neurotransmitter and therefore increases inhibition (Rogawski, 2004). Sodium valproate is an example of this drug, although this drug also likely acts by other, currently poorly understood, mechanisms.

The choice of the prescribed drug is based on an individual basis, depending on the epilepsy syndrome, a patient’s age, their life circumstances and other prescribed medication. The choice of AED should be based on the known effectiveness of a drug for a specific epilepsy syndrome as well as the side effect and risk profile, which needs to be adjusted to the patient’s individual life situation, age and other illnesses.

Table 3 summarizes the most common AEDs and their side effects.
### Table 3: Common Drugs Used to Treat Epilepsies and Related Side Effects.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Cosmetic changes (gum overgrowth, coarsening of facies, hirsutism), peripheral neuropathy, hypersensitivity reactions</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Hyponatremia, Leukopenia, drug eruptions, weight gain</td>
</tr>
<tr>
<td>Sodium Valproate</td>
<td>Weight gain, endocrine changes, tremor, hair loss, thrombocytopenia, hyperammonemia, hepatotoxicity, pancreatitis</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>Behavioral changes and cognitive effects, Dupytren’s contractures, peripheral neuropathy</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Sedation, hypersalivation</td>
</tr>
</tbody>
</table>

The assessment of how effective a medication is at improving patients’ holistic wellbeing can be measured through changes in patients' QOL. The most commonly used tool for this is the quality of life in epilepsy inventory (Vickrey, 1993). The document, which covers emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry and medication effects is able to guide treatment but can also be utilized to assess newly developed drugs.

**Cannabinoids and Seizures - a growing body of evidence**

Anecdotal evidence supporting the anticonvulsant use of cannabinoids dates back to the 18th century, though to date only a small number of animal and human trials have been conducted. While many different cannabinoids exist, Cannabidiol (CBD) has attracted the highest levels of interest to date. Results provide promise that CBD could have a high level of efficacy and improved side effect profile (it is considered a safe molecule), compared to currently available AEDs. Furthermore, CBD may be a novel treatment solution for drug resistant epileptic syndromes such as Dravet syndrome and Lennox-Gastaut syndrome, where current AEDs have failed.

**Figure 5**: Chemical structure of cannabidiol (CBD) with the typical C_{21} terpenophenolic structure which characterizes the cannabinoid class of compounds. CAS no.: 13956-29-1
Mechanism

The specific mechanism of action of the anticonvulsant effects of CBD is complicated and still relatively unclear, although it is understood that the endocannabinoid system (ECS) is involved. The ECS is involved in the fine tuning of neuronal excitability and is therefore likely to be implicated in epileptogenesis, providing a potential target for treatment (Krisztina Monory et al., 2006).

During epileptogenesis, there is a change in endocannabinoid tone and expression of the ECS receptors, CB1 and CB2 (K. Monory et al., 2006). In a study investigating the expression levels of the CB1 receptors in the hippocampus, a decrease in CB1 receptors expression was found on glutamatergic synapses and a change in ratio was seen on GABAergic synapses (Katona et al., 2006). In another study, an upregulation of CB1 receptors was observed in human hippocampi (Maglóczky et al., 2010).

CBD has shown little affinity and efficacy at CB1 and CB2 receptors (McPartland, Duncan, Di Marzo, & Pertwee, 2015) but it is proposed that CBD affects endocannabinoid tone via interaction with other molecular targets. CBD has shown to inhibit AEA hydrolysis by FAAH and increase AEA and 2-AG levels (McPartland et al., 2015). Therefore, it might cause increased inhibition by increasing endocannabinoid tone in glutamatergic or other epileptic regions. CBD has also shown to be an agonist a 5-HT1A receptors, which could cause inhibition of excitatory nerves via membrane hyperpolarization (E. Russo, Burnett, Hall, & Parker, 2005). Additionally, CBD is able to act as an indirect agonist at A2A receptors, by inhibiting adenosine uptake and subsequently enhancing the inhibitory effects of adenosinergic tone (Nicholas A. Jones et al.). Very recent evidence has shown that cannabidiol might exert its anticonvulsant effect through voltage gated sodium channels, and blocking resurgent current as a result (Patel, Barbosa, Brustovetsky, Brustovetsky, & Cummins, 2016).

It can be concluded that CBD’s mechanism of action is not specific to one receptor or molecular target and exerts its anticonvulsant effects via a poly-pharmacodynamic profile.

Animal Trials

N. A. Jones et al. (2012) examined the administration of CBD to rats before inducing temporal lobe and partial seizures. Compared to controls, rats that had received CBD experienced less seizures and the administration of 10mg/kg significantly reduced mortality rates. Rodents were
also assessed for motor function under the influence of CBD at doses up to 200mg/kg. In contrast to the decrease in motor function caused by currently licensed AEDs, animals were still able to complete all tests accurately and in the same time as controls.

Further highlighting the therapeutic potential, Turkanis et al 1979 compared CBD to phenytoin and ethosuximide, two first line AEDs. After establishing that the dose of CBD did not produce any unwanted motor impairment, seizures were artificially generated with electricity. The amount of current required to generate a seizure was recorded. The groups exposed to CBD and phenytoin required the highest current, and additionally seizure activity in the CBD group was shorter and less strong.

Compared to current AEDs, CBD was also found to be lacking the undesired excitatory properties, which can initiate seizures if given in the wrong setting.

**Human trials**

To date controlled human trials examining the anticonvulsant effects of CBD are lacking. Cunha et al 1980 administered either 400mg of CBD or a placebo, daily for 18 days to 15 patients suffering from secondary generalized seizures. Of the eight patients receiving CBD, four showed strong reductions in seizure activity and three a moderate reduction, compared to only one patient in the placebo group showing improvement. All patients were resistant to available AEDs, however they continued to take their prior medication regime throughout the study. Blood tests, neurological examinations and psychiatric evaluations revealed no toxicity or side effects besides mild sedation. Mechoulam et al 1978 saw similar results after administering nine patients either 200 mg CBD or a placebo daily. Two out of the four patients receiving CBD showed remarkable improvements, becoming completely seizure free during the three-month trial.

More recently GW Pharmaceuticals have begun clinical trials with Epidiolex™, a plant derived pure CBD formulation. Epidiolex has received an orphan drug designation by the U.S. Food and Drug Administration for the treatment of Dravet and Lennox-Gastaut syndromes, and Phase 3 Clinical trials are currently underway. Preliminary results for the Phase 3 trial have shown a 36.5% reduction in monthly motor seizures (Devinsky et al., 2016).

**Pediatric Epilepsy and CBD**

Without seeing any benefit from currently available medications, parents of children with treatment resistant epilepsy increasingly take it upon themselves to gain access and administer
CBD to their children. Anecdotal evidence from these experiences are highly promising for the efficacy and safety of CBD in children with drug resistant epilepsies.

Porter and Jacobson 2013 surveyed 19 parents on an online forum dedicated to the topic. On average, each child had tried 12 AEDs and was suffering from treatment resistant epilepsy for at least three years. Dravet syndrome was the most common disease, affecting 13 of the 19 children. 16 parents reported a reduction in the number of seizures, including two children who became completely seizure free. Eight children saw a reduction in seizures of more than 80%, three children of more than 50% and a further three children of more than 25%. Parents were asked to report on side effects. Drowsiness and fatigue affected seven and three children respectively. However more than 70% of the children experienced improved sleep, improved mood and an increase in alertness.

There are obvious issues with parents taking control over administering medications. The cannabis extracts used by parents are not of a medical grade standard and have a high variation in their content of cannabinoids. It is not possible to get access to a pure CBD formulation, therefore administrations would also contain THC, the main psychoactive ingredient in cannabis which can be either pro-convulsive or anti-convulsive dependent on dose, background and other factors.

**Charlotte’s Web**

Nevertheless, there have been cases where patients wish to gain access to cannabinoid derived medications have led to horticultural advances.

Charlotte’s Web is a specific “characterized” extract of the cannabis plant, produced by the Stanley brothers in Colorado, which has a very high CBD content while only containing very low levels of THC. The name stems from a pediatric patient who was suffering from Dravet syndrome. The girl was experiencing nearly 300 seizures each week and her parents found someone that could supply an extract of cannabis promising to contain high levels of the desired CBD. Following the administration of the extract she improved significantly, experiencing only four seizures monthly. Her case gained world-wide media attention and subsequently the extract was named Charlotte’s Web.
Cannabidivarin and Δ9-THCV

To date there is limited research on the anticonvulsant properties other cannabinoids.

Hill et al. 2012 and Hill et al. 2013 conducted animal studies, demonstrating anticonvulsant effects of cannabidivarin (CBDV). Similarly, to CBD, CBDV does not act on CB₁ receptors but rather through its antagonistic action on TRPM8 and agonistic action at TRPV1-4 and TRPA1 channels, as suggested by Cascio and Pertwee 2014.

On the other hand, the anticonvulsant properties of Δ9-THCV, demonstrated by Hill et al. 2010, were shown to work through direct antagonistic action on CB₁ receptors by Cascio and Pertwee 2014.

Synergistic therapy of multiple cannabinoids could therefore have a more potent and effective anticonvulsive effect then one cannabinoid alone. A retrospective study describing the effect of cannabidiol (CBD)-enriched medical cannabis significant positive effect on seizure load. 66 out of the 74 children reported reduction in seizure frequency (Tzadok et al., 2016). Comparatively, these results are much more significant than those seen with pure cannabidiol (see above).

This could be due to the ‘entourage effect’ (E. B. Russo, 2011) seen from the synergic effect of multiple cannabis components. Further characterization and research is required to find and justify potential combinations of cannabis-derived compounds that may be efficacious for treating intractable epileptic conditions.

Future Directions

The next step forward will need to see patient communities, researchers and governments come together in order to lay a foundation on which research can be conducted. Efficacy, dosing and safety will need to be formally assessed based on current evidence and clinical trials. Further a formal assessment needs to be conducted, whether fast tracking the involvement of patients suffering from highly drug resistant epilepsy syndromes in clinical trials is viable.
References


