

ISSN:2456-9739

Available Online at <http://www.bjbmr.org>

BRITISH JOURNAL OF BIO-MEDICAL RESEARCH

Cross Ref DOI: <https://doi.org/10.24942/bjbmr.2019.542>

Volume 03, Issue 04, July -August 2019

Review Article

Role of Cannabinoids for Reluctant Epilepsy

Dr. Hoori Shahwar¹, Dr Saera Suhail Kidwai², Professor Shaukat Ali¹¹NMC National Medical Centre, Karachi Pakistan²United Medical And Dental Hospital, Karachi Pakistan

ARTICLE INFO

Article History:

Received on 09th July 2019
Peer Reviewed on 25th July 2019
Revised on 16th August 2019
Published on 30th August 2019

Keywords:

Epilepsy, Endocannabinoid,
anandamide, 2-arachidonoyl
glycerol (2-AG), anti-seizure

ABSTRACT

Records of cannabis usage for medicinal purposes can be traced back to as early as during the 1800 BCE Sumerian context. While similar records of cannabis usage in medicinal purpose exist in other contexts as well, legislations coming up with the development of Phenobarbital in 1912 and Phenytoin in 1937 resulted in gradual decrease in the use of medicinal cannabis. Epilepsy as a refractory disease while been attempted to treat using anti-seizure drugs for at least the last twenty years has not been largely effective in realizing positive outcomes. The utility of cannabis as an alternative treatment for epileptic seizures without the associated side effects of seizure control drugs to the CNS has been focusing upon once again as pieces of evidence have been provided by scholarly research and empirical studies regarding the efficiency exhibited by cannabis in seizure control in children with severe epilepsy. This paper adopted a method of systematic review of scholarly literature and research evidences from various

publication sources focusing in the endocannabinoid system, comparing animal models of seizure and epilepsy and evidences of treatment of epilepsy in human using cannabinoids. The historical case of Charlotte Figi, suffering from prolonged status epilepticus Since 3 months of age was also referred to as one of the most significant evidences of the efficacy of cannabinoids in treatment of epilepsy.

Br J Bio Med Res Copyright©2019, Dr Hoori Shahwar et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material for any purpose, even commercially, provided the original work is properly cited and states its license.

Corresponding Author: Dr Hoori Shahwar , NMC National Medical Center, Karachi Pakistan

INTRODUCTION

According to Schultes, 1973, the use of Cannabis for medicinal purposes and especially in the treatment of epilepsy can be traced back to as early as 1800 B.C.E in Sumeria. Evidences have been identified in various researches regarding the utilization of Indian hemp by Victorian-era neurologists for the treatment of epilepsy for which, significant success was also reported. With the course of time, as legislation such as the Marijuana Tax Act, 1973 was introduced in the United States and with the development of Phenobarbital in 1912 and phenytoin in 1937, the utilization of cannabis in the treatment of epilepsy and other medicinal purposes started to gradually diminish. According to the Friedman and Devinsky, 2015 in spite of the development of more than twenty different drugs for controlling seizures in epileptic patients as well as the availability of several medical therapy interventions, approximately one-third of the epileptic population still continues to suffer from seizures. Even with the development of many anti-seizure drugs during the last twenty years, of which numerous have the novel mechanism of action, they have not contributed to significantly reduce the number of patients suffering from the medically refractory disease. While significant side effects of such anti-seizure drugs have evolved with research and developments, side effects associated with the CNS are more evident in seizure control drugs which affects the quality of life of patients who are treated. As such, recently there has been a significant demand for the development of alternative methods of treatment which would have fewer side effects and the overall treatment will not affect the quality of life of the patients. It is in this context that the utility of cannabis as an alternative treatment for epileptic seizures without the associated side effects of seizure control drugs to the CNS has been focusing upon once again as pieces of evidence have been provided by scholarly research and empirical studies regarding the efficiency exhibited by cannabis in seizure control in children with severe epilepsy. As

such, various states and regions all around the world have also legalized the medical use of cannabis to facilitate the treatment of epileptic seizures as well as for other medicinal usages (Friedman and Devinsky, 2015).

The Endocannabinoid system

Psychoactive side effects of Δ^9 -THC found in the cannabis plant is attributed to the endocannabinoid system which was discovered in the early 1990s and helped in the understanding of the mechanisms that facilitated this psychoactive after effects. Existing research literature in the earliest scope of studies in this context identified evidences of depolarization-induced suppression of excitation or inhibition (DSE or DSI) which is the phenomenon in which short postsynaptic depolarization significantly decreased the release of neurotransmitter from the excitatory terminals onto Purkinje cells in the cerebellum and inhibitory terminals onto pyramidal neurons in the hippocampus (Llano, et al., 1991; Pitler and Alger, 1992). This postsynaptic depolarization was hypothetically assumed to facilitate the release of an unidentified substance which transiently constrained presynaptic neurotransmitter release. Furthermore, with the discovery of nitric oxide, the concept of retrograde signaling compared to a fundamentally anterograde perspective of synaptic signaling was established. The fact that DSE or DSI are mediated by the presence of an endogenous cannabinoid ligand was identified from the implementation of the CB₁R agonist or antagonist which enhanced or restricted the DSE or DSI (Kreitzer and Regehr, 2001). Thus the two endocannabinoids were identified subsequently as the hydrophobic ligands N-arachidonoyl ethanolamide or more commonly known as anandamide and 2-arachidonoyl glycerol (2-AG) (Sugiura et al., 1995).

The synthesis and subsequent release of these two ligands, anandamide and 2-AG are attributed to the postsynaptic membrane phospholipid precursors via an activity-dependent and on-demand release compared to

conventional vesicular neurotransmitters. According to a number of different research findings in this key context, depolarization of the postsynaptic cell is directly linked to the escalation of the levels of intracellular calcium. This also holds true for direct activation of metabotropic glutamate receptors. The final outcome is the triggering of a second messenger that facilitates the synthesis of endocannabinoids (Alger, 2002; Maejima et al., 2001).

While the ligand anandamide is synthesized by phospholipase D-mediated hydrolysis of N-arachidonoyl-phosphatidylethanolamine and deteriorated by fatty acid amide hydrolase (FAAH) into arachidonic acid and ethanolamine, 2-AG is synthesized by diacylglycerol (DAG) lipase DAGL – α induced hydrolysis of DAG and deteriorated by FAAH into arachidonic acid and glycerol or by

monoacylglycerol lipase (Di Marzo et al., 1994; Stella et al., 1997). Based on the fact that changes in the endocannabinoid pathways are resulted by chronic hyperexcitability, Pertwee, 2000, established that targeting of enzymes facilitating metabolism and cannabinoid receptors is an efficient initiation to develop treatment interventions for a number of neurological diseases (Pertwee, 2000). This led to the rapid approval of CB₁R blocker rimonabant in more than fifty national contexts for treating obesity acting as an anorectic. Furthermore, Cahill, 2007, also established the potential for CB₁R blocker rimonabant in significantly helping tobacco smokers to quit. However, with this was rapidly suspended with the subsequent identification of causing higher levels of depression and suicidal intentions among end users in post-marketing feedbacks (Cahill and Ussher, 2007).

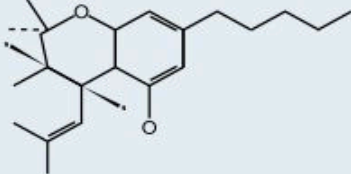
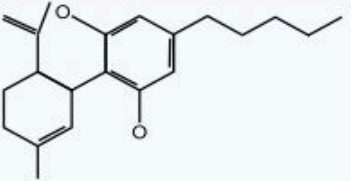
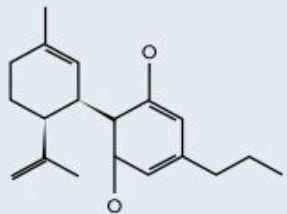
Cannabinoid	Structure	Central Nervous System Targets	Actions
Δ^9 -Tetrahydrocannabinol		CB ₁ R CB ₂ R (microglia) TRPA1 TRPV2 TRPM8 $\alpha_1\beta$ GlyR 5-HT _{3A} R PPAR- γ GPR18 GPR55	Partial agonist Partial agonist Agonist Agonist Antagonist Enhancer Antagonist Activator Agonist Agonist
Cannabidiol		CB ₁ R CB ₂ R (microglia) GPR55 TPRA1 TRPV1-3 TRPV4 TRPM8 5-HT _{1A} R 5-HT _{3A} R α_2 GlyR PPAR- γ Ca _v 3 ion channel Adenosine reuptake	Antagonist Antagonist Antagonist Agonist Agonist Antagonist Enhancer Antagonist Enhancer Activator Inhibitor Inhibitor
Cannabidivarin		TRPA1 TRPM8 TRPV4 TRPV1-3 DAGL- α	Agonist Antagonist Agonist Agonist Inhibitor

Fig.1 Selected Pharmacological features of cannabinoids showing antiseizure effects in Preclinical models

Source: Friedman, D. and Devinsky, O., 2015

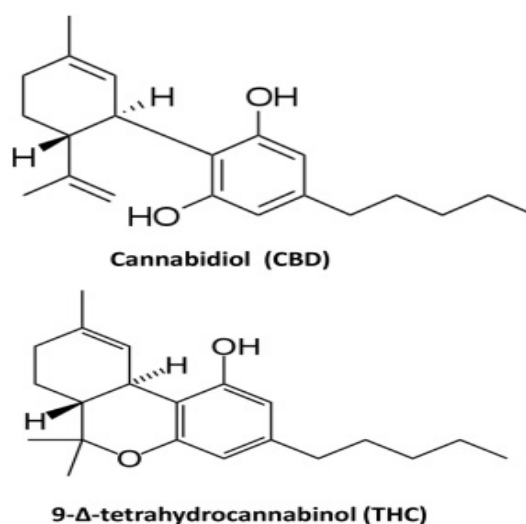


Fig 2. Chemical structure of cannabidiol and Δ 9 -THC

Source: Perucca, E., 2017

The mechanism of the endocannabinoid system is closely related to the binding capacity with CB₁R. Activity-dependent endocannabinoids bind with CB₁R in the presynaptic cell. These CB₁R are fundamentally subunits of G protein-coupled receptors linked to pertussis sensitive Gi/o α . As such, these subunits are activated triggering the disintegration of the $\beta\gamma$ complex thereby decreasing adenylate cyclase generation of cyclic adenosine monophosphate. Furthermore, this activation also inhibits N and P/Q type voltage-gated calcium channels, triggers A-type potassium channels while at the same time inhibiting the vesicular release machinery (Photowala et al., 2006). As a result of all these mechanisms triggered by the activation of Gi/o α subunits, presynaptic cell excitability is drastically reduced while also reducing the release of presynaptic neurotransmitters. Schlicker, 2001 established that CB₁R also have the potential to decrease the abnormal release of more than one presynaptic neuromodulators namely acetylcholine, dopamine and norepinephrine (Schlicker and Kathmann, 2001). One more critical aspect of this activation was also identified in multiple studies. Endocannabinoid signalling has been attributed to regulate regional specific prolonged synaptic plasticity which includes prolonged potentiating and

long-term depression as well (Chevalerey et al., 2006; Piomelli, 2003).

The distribution of CB₁R plays a significant role in the endocannabinoid system mechanism. Distribution is mainly concentrated in the axon terminals in the neocortex in cingulate, frontal and parietal areas of the brain. In addition to this, the hippocampus, amygdala, basal ganglia, thalamus and hypothalamus, nucleus accumbens, substantia nigra, ventral tegmental region, cerebellum and brainstem are the areas of concentration distribution of CB₁R (Katona and Freund, 2008). The denser association of CB₁R are featured at the cortical and hippocampal presynaptic γ -aminobutyric acid (GABA) ergic presynaptic boutons, especially cholecystokinin-positive (CCK+) and parvalbumin-negative GABAergic interneurons. Compared to these areas, glutamatergic axon terminals found in the cortical and subcortical neurons exhibit a lesser number of CB₁ receptors (Wittmann et al., 2007).

Control of neuronal excitability

The cannabis species is the source of more than 545 different naturally occurring compounds of which the most abundantly available are the cannabinoids. Cannabinoids are a molecular family which is comprised of 21 carbon terpenophenolic skeleton and includes several

other metabolites. Of these, cannabinoids, $\Delta 9$ -tetrahydrocannabinol ($\Delta 9$ -THC) and cannabidiol and their corresponding metabolites are the attention of most researchers for clinical research. $\Delta 9$ -THC is attributed to the psychoactive properties of cannabis and hence the fundamental focus for cannabis-based compounds usable in the treatment in epilepsy is on cannabinoids mainly.

The primary cannabinoid receptor in the human CNS is the cannabinoid receptor 1 or CB₁R which is a presynaptic receptor coupled with G protein which functions to activate voltage-gated calcium channels while simultaneously enhancing potassium channel conduction in presynaptic terminals. Clinical research focuses on the role of endocannabinoids during normal brain functioning and diseased conditions have been motivated by the cloning of CB₁R confirming that $\Delta 9$ -THC binds CB₁R effectively and the discovery of two endogenous ligands namely 2-arachidonoyl glycerol (2-AG) and anandamide both of which binds CB₁R (Devane et al., 1992). Both these ligands have a critical role in affecting neuronal excitability in the human brain. While CB₁R gets activated through the activity governed synthesis of 2-AG which affects the retrograde control of synaptic transmission, the other ligand, anandamide also exhibits properties to affect neuronal excitability through the activation of transient receptor potential (TRP) cation channel, member 1 of subfamily V. Furthermore, being modulators of neuronal excitability, endogenous cannabinoids are very well aligned with affecting the initiation, propagation and spread of epileptic seizures (Castillo et al., 2012).

Human subjects suffering from epileptic conditions have been identified to exhibit certain defects in the endocannabinoid system. For instance, Romigi, 2010 identified in a research that newly detected patients who suffered from temporal lobe epileptic conditions exhibited significantly reduced levels of anandamide in cerebrospinal fluid compared to normal human beings without any

epileptic disease (Romigi et al., 2010). Furthermore, Ludányi, 2008 also established from tissue samples of human subjects who underwent surgery for treatment of epilepsy that these patients exhibited significantly lower levels of the CB₁R messenger RNA especially in the glutamatergic terminals in the dentate gyrus compared to tissue samples that were obtained from post-mortem of patients who did not suffer from any kind of epileptic conditions (Ludányi, et al., 2008) Furthermore, this particular 2008 research also identified that there was also a decreased diacylglycerol lipase α (DAGL - α) expression in these patients' tissue sample. DAGL - α is the enzyme that facilitates the on-demand synthesis of 2-AG ligand in the postsynaptic neurons. The outcome of these studies indicates the fact that the endocannabinoid system has a significant role to play in the inhibition of seizures in human subjects suffering from epilepsy.

Epileptic seizures are attributed to the strong activation of the endocannabinoid system associated with an upregulation of the CB₁R activity which exhibits significant antiseizure properties. Marsicano, in a 2003 research on mice identified that the levels of hippocampal anandamide were increased significantly post seizures induced by the intraperitoneal injection of Kainic acid (Marsicano et al., 2003). Furthermore, Deshpande, 2007 also established from the neuron culture from hippocampus that prolonging seizure-like discharges are induced by CB₁R antagonists while they are eliminated by CB₁R agonists. Compared to wild-type mice, conditional knockout mice which lacks pyramidal cell CB₁R in their forebrain exhibited more severe and prolonged seizures in response to Kainic acid-induced seizures in test samples in a number of research studies (Marsicano et al., 2003; Monory et al., 2006). Contrasted to these results from test samples, Guggenhuber, 2010 established the protective nature of viral vector induced overexpression of CB₁R in hippocampal pyramidal cells (Guggenhuber, 2010). Furthermore, Karanian et al., 2007 also established that reduction of the metabolic deterioration of endocannabinoid

ameliorates experimentally induced seizures (Karanian et al., 2007).

Animal models of seizures and epilepsy

Animal models of seizures and epilepsy provide key shreds of evidence and opportunities to develop human clinical trials in a safe and planned approach to examine the potential antiseizure and antiepileptic effects of cannabinoids. Each of the preclinical paradigms exhibits fundamental benefits and drawbacks while several of them reflect on unique seizure etiologies, semiologies and corresponding electroencephalography patterns. Although exhibiting critical technical challenges, these models provide a better representation of epileptogenesis and drug screening for humans.

A 2015 research studied the implications of incorporating cannabinoids as a potential treatment for epilepsy for developing a basic understanding of the intervention and providing a guide to future clinical research associated with cannabis and epilepsy. To establish this, the authors incorporated some critical preclinical evidence of cannabinoids to be an alternative intervention for epilepsy. The author established this in the light of animal models to highlight the changes in the endocannabinoid system following chronic seizures. The release of endocannabinoid helps in preventing seizure induced neurotoxicity. Trials in wild-type mice associated with Kainic acid (KA) induced seizures showed that it leads to the increment of the anandamide levels while pilocarpine-induced seizures showed pieces of evidence of an increase in the 2-AG levels. This suggests that a neuroprotective, on-demand release of endocannabinoids is facilitated by epileptiform activities. The severity of Kainic acid-induced seizures was found to be decreased as a result of pre-treatment with an anandamide reuptake inhibitor exceptions being mice with a conditional CB₁R deletion in principal forebrain excitatory neurons. Furthermore, it was also identified that protection against Kainic acid-induced hippocampal seizures and the associated issues with balance and coordination can be provided by blocking of the

endocannabinoid catabolic enzyme FAAH. Furthermore, blocking FAAH and DAGL- α increased level of anandamide and 2-AG prevented Kainic acid-induced seizures as well as providing protection against seizure-induced cytotoxicity (Rosenberg et al., 2015).

Hill et al., 2013 established that activated CB₁R receptors as a result of Δ 9 -THC in experimentally induced seizures in animal models helped in the reduction of seizures by CB₁R agonists reduced seizures while others found out that the activation of CB₁R was linked to the convulsing effects for some specific dosages (Hill et al., 2013). In another 2003 research by Wallace et al., findings established that CB₁R antagonists helped in decreasing the threshold for seizure in selected preclinical animal models. These findings suggest that CB₁R activation is linked to the anticonvulsant properties of cannabinoids (Wallace et al., 2003)

Plant-derived non-psychoactive cannabinoid, cannabidiol has also been identified to exhibit antiseizure properties in various in vivo and in vitro models of epilepsy (Devinsky et al., 2014). While Δ 9 -THC is associated with the activation of the CB₁R receptor, the case is not the same for cannabidiol as it does not exert its fundamental neural effects through CB₁R receptor activation. According to Pertwee, 2008, cannabidiol acts as an indirect CB₁R antagonist in higher doses (Pertwee, 2008). A different method compared to Δ 9 -THC is adopted by cannabidiol to modify neuronal excitability where the cannabinoid binds itself with the members of the TRP family of cation channels at low levels thereby antagonising the G protein-coupled receptor 55. As a result, there is a presynaptic release of glutamate which activates 5-hydroxytryptophan 1A receptors. Additionally, there is an inhibition of adenosine reuptake through multiple mechanisms (Sylantsev et al., 2013). Furthermore, antioxidant and anti-inflammatory characteristics have also been found to be exerted by cannabidiol. These properties of cannabidiol which are exhibited without any psychoactive side effects on the

subjects have led to the generation of immense interest to develop it as a potential antiseizure drug for humans. Propyl developments of cannabidiol, cannabidivarin also exhibits anti-seizure properties in both in vitro and in vivo models. Similar to cannabinoid-like cannabidiol, cannabidivarin's antiseizure effects are not dependent on the endocannabinoid system and hence can be deemed to be exhibited through influencing TRP channels or reducing 2-AG synthesis through the inhibition of DAGL- α . Apart from cannabinol and the propyl variant of $\Delta 9$ -THC, $\Delta 9$ -THCV, which exhibited anticonvulsant properties in a few selected studies, no other phytocannabinoids are known to exhibit antiseizure properties at such an extent as cannabidiol (Hill et al., 2013).

Cannabinoids in the treatment of epilepsy in human subjects

Literary evidence from as early as 2900 BCE has revealed the use of cannabis for the treatment of seizures in Sumerian texts as well as in Arabian documents dating back to the twelfth century (Russo et al., 2008; Lozano, 2001). In the contemporary history of the evolution of medical sciences, in 1854, cannabis was listed by the US Dispensatory for the treatment of a number of conditions including neuralgia, depression, pain, spasms, sleeplessness and tetanus among others (Szaflarski and Bebin, 2014). Furthermore, cannabis usage for its analgesic, anti-inflammatory properties, capacity to escalate appetite and other properties was attributed to this. William O' Shaughnessy, a British surgeon utilised and reported the use of cannabis in the treatment of a number of issues associated with epilepsy and established that most patients reported an alleviation of the pain with significant appetite increment for all of the patients while at the same time exhibiting mental wellbeing properties and acting like an aphrodisiac for some (Abel, 2013; O'Shaughnessy, 1843). Furthermore, W.Gowers, English neurologist from the latter half of the nineteenth century, established the effect of *Cannabis indica* to treat the seizures

of a patient for whom bromide treatments failed to control seizures with controlled doses of 3 times each day for up to 6 months (Gowers, 1881).

Due to the non-psychoactive properties of CBD compared to THC, the former has been more extensively studied and currently utilised in selected cases for the treatment of various conditions including epilepsy. For instance, Devinsky et al., 2016, performed tests using Epidiolex which is a purified formulation for CBD in children and adolescents who suffered from drug-resistant epileptic conditions. The research returned a significant 36.5% decrease in seizures with the use of purified CBD. The dose of CBD received by the patients varied significantly with some of the subjects having administered up to 25mg/kg/day dose of Epidiolex. The research also evaluated the post-intervention quality of life of the patients using Quality of Life in Childhood Epilepsy Scores and established that there has been a significant enhancement in the scores compared to standard scores using seizure control drugs. Quality of life improved in terms of decrease of fatigue level of the children and enhancement of social behaviour and interaction. Only some insignificant side effects were identified in some of the patients in the form of somnolence, diarrhoea and fatigue (Devinsky et al., 2016). In a very recent 2017 research by Devinsky, randomized controlled trials of the same purified formulation of CBD was used by the researchers to be administered in a sampled population of children and adolescents who suffered from Dravet's syndrome. 120 subjects were administered the intervention in randomized trials at the dose of 20mg/kg/day or placebo added to their anticonvulsant regimen. The results of the trials provided empirical evidence of a decrease in the frequency of convulsive seizures per month. The reduction in the frequency was significant from an average frequency of 12.4 to 5.9 with the use of Epidiolex. Compared to these results exhibited in the CBD group, the reduction in the frequency of seizures was nominal in the control group decreasing from an average of

14.9 to just 14.1. No statistical difference could be identified for the patients in terms of the number of nonconvulsive seizures and the quality of life indicators. Adverse effects were limited to diarrhoea, nausea, and somnolence and heightened liver enzyme productions only in the CBD group with a frequency of less than 10% (Devinsky et al., 2017).

Efficacy of cannabis as an anti-seizure drug has also been established by Tzadok et al., 2016, who performed clinical trials on a sample size of 74 children who suffered from drug-resistant epileptic conditions and were administered gradually increasing doses of CBD enriched low THC content oil. Only 7% of the sampled patients had to cease the administration of the intervention due to severe adverse effects while more than 50% of the participants exhibited a higher than 50% decrease in the frequency of epileptic seizures. Furthermore, the research also identified that the response rate to the CBD enriched oil based intervention was exhibited more in the case of patients who suffered from epileptic encephalopathy (Tzadok et al., 2016). Ostrovsky and Ehrlich, administered cannabidiol treatment in randomised controlled trials to a sample population of 171 patients including majority of children (n=113) as well as adults (n = 58) to establish the efficacy of addition of cannabidiol based interventions to treat seizures in the patients who all suffered from treatment-resistant Lennox Gastaut syndrome (LGS) and established that cannabidiol as an add-on therapy shows promising potential to reduce the frequency of seizures. The sampled population was grouped in the intervention group (n=86) and placebo group (n=85). During the initial phase, the median frequency of drop seizures was found to be reduced by 43.9% in the intervention group receiving an initial dose of 2.5mg/kg/day of 100mg/ml liquefied formulation of purified cannabidiol. Over the next 2 weeks, the dose was increased to 20mg/kg prolonged for a period of 12 weeks followed by a medication taper of up to 10 days. 44% of the patients exhibited a 50% reduction in drop seizure frequency compared to just 24% reductions in

the control group. Furthermore, the cannabidiol intervention group also exhibited a significant drop rate of the number of seizures of all types compared to the control group. Compared to baseline statistics, patients, as well as caregivers in the study, reported significant improvement in the overall condition of the patient after the intervention period was over (Ostrovsky and Ehrlich, 2018).

The case of Charlotte Figi

The most well-known efficacy of the use of cannabinoids in contemporary medicinal usage is not complete without referring to the case of Charlotte Figi who suffered from prolonged status epilepticus at 3 months of age. After suffering from frequent bouts of febrile and afebrile epileptic seizures, she was diagnosed with Dravet Syndrome (DNA variant I) after her transition to a Level 4 Epilepsy centre. Giving suffering and undergoing treatment for her conditions, at 5 years of age, through a history of medication failure, the Charlotte was experiencing up to 50 generalised tonic-clonic seizures on an average daily. After the failure of all probable medicinal interventions, Charlotte was administered with initial doses of sublingual preparation of CBD extract. Compared to a baseline statistic of more than 300 convulsions per week, Charlotte responded to a three months intervention of high concentration CBD extracts exhibiting a more than 90% reduction in the generalised tonic-clonic seizures. Furthermore, for a 5 year old girl whose cognitive and motor functions has been rendered non-functional requiring continuous support for walking and talking and requiring a feeding tube for nutrition and water, the quality of life was significantly improved after 20 months of the intervention able to eat and drink on her own and exhibiting only 2-3 nocturnal seizures per month (Maa and Figi, 2014).

CONCLUSION

Even though cannabinoid usage in the treatment of epilepsy alongside other disorders exhibits a side effect profile, most of the information available in the scope of cannabinoid side effect profile in prolonged

usage is attributed to research works that focus on the recreational use of cannabinoids. These side effects use memory impairment, motor performance and judgements. While CBD does not exhibit any psychoactive properties, high THC content is associated with psychoactive properties. Prolonged usage, therefore, bears the risk of addiction which is again very nominal occurring with only 9% of long terms users. Compared to these recreational usage studies, data obtained from randomised clinical trials which mainly focus on the administration of purified formulations of cannabinoids and using CBD instead of Δ^9 -THC in order to eliminate the risk of psychoactive side effects that are exhibited by THC. Systematic collection of data regarding safety identified from a research that included 1619 patients in numerous short-term placebo-controlled researches receiving CBD treatment for pain and tremor and spasticity attributed to multiple sclerosis identified that 6.9% of the patients in the intervention group withdrew due to side effects. The commonest adverse effects in all the trials were nausea, weaknesses, mood changes, psychosis, hallucinations, suicidal intentions and fatigue. Even with these, no reports of death occurring from overdose of cannabinoids were reported with the administration of cannabinoid-based medications (Friedman and Devinsky, 2015). As such, it can be safely envisaged that the safety of cannabis-based medicines in human trials is yet to be identified as a critical issue due to the lack of any evidence of the clinical use of cannabinoids. Furthermore, the review of numerous literary sources in this chapter also provides evidence regarding the efficacy of cannabinoids that do not exhibit psychoactive properties in the treatment of refractory and childhood-onset epilepsy as well as in other cases of Dravet Syndrome and LGS affected patients. All of the clinical trials identified in this review exhibited significant drop rate in all types of seizures whether administered independently or alongside other antiseizure drugs concomitant to the use of controlled doses of cannabinoids. With multiple nations

around the world approving the use of cannabinoids in medicinal purposes from around the world, and considering the high efficacy of cannabinoids in treating epileptic seizures and other forms of medical disorder while improving the quality of life for most patients, it is imperative that third world countries like Pakistan and India also acknowledge the efficacy of the naturally occurring compounds and develop appropriate legislation to legalise and approve the use of the same for medicinal purposes. According to a 2003 research, overall prevalence of epilepsy in Pakistan was estimated to be almost at 10 out of 1000 persons. The prevalence is higher in the sub-30 year age group (Khatri et al., 2003). Considering the pieces of evidence produced and analysed in this review, it is imminent that cannabis-based medicines are approved for trials, research and development and subsequent commercial production and utilisation in the medical field with the most urgent eagerness in Pakistan.

REFERENCES

1. Abel, E.L., 2013. *Marihuana: the first twelve thousand years*. Springer Science & Business Media.
2. Alger, B.E., 2002. Retrograde signalling in the regulation of synaptic transmission: focus on endocannabinoids. *Progress in neurobiology*, 68(4), pp.247-286.
3. Cahill, K. and Ussher, M.H., 2007. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. *Cochrane database of systematic reviews*, (3).
4. Castillo, P.E., Younts, T.J., Chávez, A.E. and Hashimoto, Y., 2012. Endocannabinoid signalling and synaptic function. *Neuron*, 76(1), pp.70-81.
5. Chevaleyre, V., Takahashi, K.A. and Castillo, P.E., 2006. Endocannabinoid-mediated synaptic plasticity in the CNS. *Annu. Rev. Neurosci.*, 29, pp.37-76.
6. Deshpande, L.S., Sombati, S., Blair, R.E., Carter, D.S., Martin, B.R. and DeLorenzo, R.J., 2007. Cannabinoid CB1 receptor antagonists cause status epilepticus-like

- activity in the hippocampal neuronal culture model of acquired epilepsy. *Neuroscience letters*, 411(1), pp.11-16.
7. Devane, W.A., Hanus, L., Breuer, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A. and Mechoulam, R., 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, 258(5090), pp.1946-1949.
 8. Devinsky, O., Cilio, M.R., Cross, H., Fernandez-Ruiz, J., French, J., Hill, C., Katz, R., Di Marzo, V., Jutras-Aswad, D., Notcutt, W.G. and Martinez-Orgado, J., 2014. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*, 55(6), pp.791-802.
 9. Devinsky, O., Cross, J.H., Laux, L., Marsh, E., Miller, I., Nabbout, R., Scheffer, I.E., Thiele, E.A. and Wright, S., 2017. The trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *New England Journal of Medicine*, 376(21), pp.2011-2020.
 10. Devinsky, O., Marsh, E., Friedman, D., Thiele, E., Laux, L., Sullivan, J., Miller, I., Flamini, R., Wilfong, A., Filloux, F. and Wong, M., 2016. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *The Lancet Neurology*, 15(3), pp.270-278.
 11. Di Marzo, V., Fontana, A., Cadas, H., Schinelli, S., Cimino, G., Schwartz, J.C. and Piomelli, D., 1994. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature*, 372(6507), p.686.
 12. Friedman, D. and Devinsky, O., 2015. Cannabinoids in the treatment of epilepsy. *New England Journal of Medicine*, 373(11), pp.1048-1058.
 13. Gowers, W.R., 1881. Epilepsy and other chronic convulsive disorders. *London: Churchill*, 223.
 14. Guggenhuber, S., Monory, K., Lutz, B. and Klugmann, M., 2010. AAV vector-mediated overexpression of CB1 cannabinoid receptor in pyramidal neurons of the hippocampus protects against seizure-induced excitotoxicity. *PloS one*, 5(12), p.e15707.
 15. Hill, A.J., Hill, T. and Whalley, B., 2013. The development of cannabinoid-based therapies for epilepsy. In *Endocannabinoids: molecular, pharmacological, behavioural and clinical features* (pp. 164-204). Bentham Science, Oak Park, IL.
 16. Karanian, D.A., Karim, S.L., Wood, J.T., Williams, J.S., Lin, S., Makriyannis, A. and Bahr, B.A., 2007. Endocannabinoid enhancement protects against kainic acid-induced seizures and associated brain damage. *Journal of Pharmacology and Experimental Therapeutics*, 322(3), pp.1059-1066.
 17. Katona, I. and Freund, T.F., 2008. Endocannabinoid signalling as a synaptic circuit breaker in neurological disease. *Nature medicine*, 14(9), p.923.
 18. Khatri, I.A., Iannaccone, S.T., Ilyas, M.S., Abdullah, M. and Saleem, S., 2003. Epidemiology of epilepsy in Pakistan: a review of the literature. *JPMMA. The Journal of the Pakistan Medical Association*, 53(12), pp.594-597.
 19. Kreitzer, A.C. and Regehr, W.G., 2001. Cerebellar depolarization-induced suppression of inhibition is mediated by endogenous cannabinoids. *Journal of Neuroscience*, 21(20), pp.RC174-RC174.
 20. Llano, I.S.A.B.E.L., Marty, A.L.A.I.N., Armstrong, C.M. and Konnerth, A., 1991. Synaptic and agonist-induced excitatory currents of Purkinje cells in rat cerebellar slices. *The Journal of Physiology*, 434(1), pp.183-213.
 21. Lozano, I., 2001. The therapeutic use of Cannabis sativa (L.) in Arabic medicine. *Journal of Cannabis Therapeutics*, 1(1), pp.63-70.
 22. Ludányi, A., Eröss, L., Czirják, S., Vajda, J., Halász, P., Watanabe, M., Palkovits, M., Maglóczy, Z., Freund, T.F. and Katona, I., 2008. Downregulation of the CB1

- cannabinoid receptor and related molecular elements of the endocannabinoid system in the epileptic human hippocampus. *Journal of Neuroscience*, 28(12), pp.2976-2990.
23. Maa, E. and Figi, P., 2014. The case for medical marijuana in epilepsy. *Epilepsia*, 55(6), pp.783-786.
 24. Maejima, T., Ohno-Shosaku, T. and Kano, M., 2001. Endogenous cannabinoid as a retrograde messenger from depolarized postsynaptic neurons to presynaptic terminals. *Neuroscience research*, 40(3), pp.205-210.
 25. Marsicano, G., Goodenough, S., Monory, K., Hermann, H., Eder, M., Cannich, A., Azad, S.C., Cascio, M.G., Gutiérrez, S.O., van der Stelt, M. and López-Rodríguez, M.L., 2003. CB1 cannabinoid receptors and on-demand defence against excitotoxicity. *Science*, 302(5642), pp.84-88.
 26. Monory, K., Massa, F., Egertová, M., Eder, M., Blaudzun, H., Westenbroek, R., Kelsch, W., Jacob, W., Marsch, R., Ekker, M. and Long, J., 2006. The endocannabinoid system controls key epileptogenic circuits in the hippocampus. *Neuron*, 51(4), pp.455-466.
 27. O'Shaughnessy, W.B., 1843. On the preparations of the Indian hemp, or Gunjah: Cannabis indica their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. *Provincial Medical Journal and Retrospect of the Medical Sciences*, 5(123), p.363.
 28. Ostrovsky, D.A. and Ehrlich, A., 2018. Addition of cannabidiol to current antiepileptic therapy reduces drop seizures in children and adults with a treatment-resistant Lennox-Gastaut syndrome. *Explore The Journal of Science and Healing*.
 29. Pertwee, R.G., 2000. Cannabinoid receptor ligands: clinical and neuropharmacological considerations, relevant to future drug discovery and development. *Expert opinion on investigational drugs*, 9(7), pp.1553-1571.
 30. Pertwee, R.G., 2008. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ 9-tetrahydrocannabinol, cannabidiol and Δ 9-tetrahydrocannabivarin. *British journal of pharmacology*, 153(2), pp.199-215.
 31. Perucca, E., 2017. Cannabinoids in the treatment of epilepsy: hard evidence at last?. *Journal of epilepsy research*, 7(2), p.61.
 32. Photowala, H., Blackmer, T., Schwartz, E., Hamm, H.E. and Alford, S., 2006. G protein $\beta\gamma$ -subunits activated by serotonin mediate presynaptic inhibition by regulating vesicle fusion properties. *Proceedings of the National Academy of Sciences*, 103(11), pp.4281-4286.
 33. Piomelli, D., 2003. The molecular logic of endocannabinoid signalling. *Nature Reviews Neuroscience*, 4(11), p.873.
 34. Pitler, T.A. and Alger, B.E., 1992. Postsynaptic spike firing reduces synaptic GABAA responses in hippocampal pyramidal cells. *Journal of Neuroscience*, 12(10), pp.4122-4132.
 35. Romigi, A., Bari, M., Placidi, F., Marciani, M.G., Malaponti, M., Torelli, F., Izzi, F., Prosperetti, C., Zannino, S., Corte, F. and Chiamonte, C., 2010. Cerebrospinal fluid levels of the endocannabinoid anandamide are reduced in patients with untreated newly diagnosed temporal lobe epilepsy. *Epilepsia*, 51(5), pp.768-772.
 36. Rosenberg, E.C., Tsien, R.W., Whalley, B.J. and Devinsky, O., 2015. Cannabinoids and epilepsy. *Neurotherapeutics*, 12(4), pp.747-768.
 37. Russo, E.B., Jiang, H.E., Li, X., Sutton, A., Carboni, A., Del Bianco, F., Mandolino, G., Potter, D.J., Zhao, Y.X., Bera, S. and Zhang, Y.B., 2008. Phytochemical and genetic analyses of ancient cannabis from Central Asia. *Journal of experimental botany*, 59(15), pp.4171-4182.
 38. Schlicker, E. and Kathmann, M., 2001. Modulation of transmitter release via presynaptic cannabinoid receptors. *Trends*

- in *pharmacological sciences*, 22(11), pp.565-572.
39. Stella, N., Schweitzer, P. and Piomelli, D., 1997. A second endogenous cannabinoid that modulates long-term potentiation. *Nature*, 388(6644), p.773.
 40. Sugiura, T., Kondo, S., Sukagawa, A., Nakane, S., Shinoda, A., Itoh, K., Yamashita, A. and Waku, K., 1995. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochemical and biophysical research communications*, 215(1), pp.89-97.
 41. Sylantsev, S., Jensen, T.P., Ross, R.A. and Rusakov, D.A., 2013. Cannabinoid-and lysophosphatidylinositol-sensitive receptor GPR55 boosts neurotransmitter release at central synapses. *Proceedings of the National Academy of Sciences*, p.201211204.
 42. Szaflarski, J.P. and Bebin, E.M., 2014. Cannabis, cannabidiol, and epilepsy—from receptors to clinical response. *Epilepsy & Behavior*, 41, pp.277-282.
 43. Tzadok, M., Uliel-Siboni, S., Linder, I., Kramer, U., Epstein, O., Menascu, S., Nissenkorn, A., Yosef, O.B., Hyman, E., Granot, D. and Dor, M., 2016. CBD-enriched medical cannabis for intractable pediatric epilepsy: the current Israeli experience. *Seizure*, 35, pp.41-44.
 44. Wallace, M.J., Blair, R.E., Falenski, K.W., Martin, B.R. and DeLorenzo, R.J., 2003. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *Journal of Pharmacology and Experimental Therapeutics*, 307(1), pp.129-137.
 45. Wittmann, G., Deli, L., Kalló, I., Hrabovszky, E., Watanabe, M., Liposits, Z. and Fekete, C., 2007. Distribution of type 1 cannabinoid receptor (CB1)-immunoreactive axons in the mouse hypothalamus. *Journal of Comparative Neurology*, 503(2), pp.270-279.

How to cite this article:

Dr Hoori Shahwar, Dr Saera Suhail Kidwai, Professor Shaukat Ali. *Role of Cannabinoids for Reluctant Epilepsy.* Br J Bio Med Res , Vol.03, Issue 04, Pg.1042 - 1053, July - August 2019. ISSN:2456-9739 Cross Ref DOI : <https://doi.org/10.24942/bjbmr.2019.542>

Source of Support: Nil

Conflict of Interest: None declared.

Your next submission with **British BioMedicine Publishers** will reach you the below assets

- Quality Editorial service
- Swift Peer Review
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats (Pdf, E-pub, Full Text)
- Unceasing customer service
- Immediate, unrestricted online access
- Global archiving of articles



Track the below URL for one-step submission

<http://www.britishbiomedicine.com/manuscript-submission.aspx>