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REVIEW

Medical Cannabis and Epilepsy: The Evidence

Varinder Kaur[1,*], Hannah Deacon[2], Michael Philip Barnes[2,3,4], David John Nutt[4,5]

[1]Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK
[2]Maple Tree Medical Cannabis Consultancy, Henley-in-Arden, UK
[3]Faculty of Medical Sciences, University of Newcastle, Newcastle Upon Tyne, UK
[4]Drug Science, St. Peters House, London, UK
[5]Department of Brain Sciences, Faculty of Medicine, Imperial College London, London, UK
*Correspondence: varinderkaur11@hotmail.com (Varinder Kaur)

Abstract

Epilepsy is a serious neurological condition that can affect individuals of all ages. Treatment is far from perfect, and roughly 30% of patients can experience seizures that are resistant to antiseizure medications. Interestingly, the cannabis plant, specifically the phytocannabinoids, cannabidiol and delta-9-tetrahydrocannabinol, has been shown to possess anticonvulsant properties and are effective in the treatment of seizures. The clinical evidence base for cannabis for epileptic conditions has been growing in the last few decades with studies aiming to establish the clinical efficacy and safety profile of the plant. Despite the advancements that are being made, clinicians and medical regulatory bodies are still reluctant for epilepsy patients to use cannabis. Thus, it is essential that individuals are educated about the therapeutic properties of cannabis and the clinical evidence base to help patients gain access to cannabis medicines.

Key words: medicinal cannabis; drug resistant epilepsy; cannabidiol; dronabinol

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Introduction

Epilepsy is classified as one of the most common neurological conditions. According to the World Health Organization (WHO), an estimated 4–10 per 1000 people have active epilepsy (Fiest et al, 2017). It affects both sexes, with the condition being slightly more prevalent in men compared to women. It also affects people of all ages, with the condition peaking in the elderly, who also have a higher prevalence of stroke and neurodegenerative diseases. The aetiology of the condition differs according to the social and demographic characteristics of the affected population; approximately half of the epilepsy cases in high-income countries have been reported as having an unknown cause. According to the International League Against Epilepsy (ILAE) (Fisher et al, 2017; Scheffer et al, 2017), there are six known causes of epilepsy which are categorised into the following: genetic, structural, infectious, immune, metabolic and unknown. A patient's epilepsy can be classified into more than one of these categories (Scheffer et al, 2017). It is reported that epilepsy per se does not lead to high mortality rates yet there are significant differences when comparing the mortality rates between the different age

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ranges of individuals, patients with idiopathic and symptomatic seizures and different geographical locations. Patients suffering from drug-resistant epilepsy, nocturnal seizures, and generalized tonic-clonic seizures have a higher incidence of sudden unexpected death in epilepsy (SUDEP) (Beghi, 2020).

The onset of a seizure occurs when there is a disruption of the normal balance between excitation and inhibition levels in the brain (Stafstrom, 2010). This imbalance can arise from alterations at multiple different levels of brain function, including genetic factors, signalling cascades, and widely distributed neuronal circuits. Genetic and acquired factors contribute to the imbalance of excitatory and inhibitory levels. Genetic factors can include abnormal neural circuits, abnormal levels of receptors, such as γ-aminobutyric acid (GABA), and abnormal functions of ionic channels, like potassium channel mutations. Acquired factors like cerebral insults and traumatic brain injury can cause alterations in the circuit functions, resulting in seizures (Stafstrom and Carmant, 2015).

Severe drug-resistant epilepsy affects roughly 30% of patients who have epilepsy and makes them refractory to the available pharmacological therapies (Picot et al, 2008). Drug-resistant epilepsy is an incredibly difficult disorder to manage and proves to be a significant challenge for healthcare professionals (Fattorusso et al, 2021; Ghosh et al, 2021). According to the ILAE, drug-resistant epilepsy is defined as "a failure of two or more sufficient trials of tolerated, chosen, and appropriately used antiepileptic drug regimens, which can be administered as monotherapies or in combination to get relief from seizures" (Kwan et al, 2010). Patients with drug-resistant epilepsy can often have a higher risk to injuries, premature death, are 2 to 10 times more likely to experience SUDEP, and have psychosocial problems. Furthermore, each drug-resistant patient often has a heterogenous clinical and neurobiological background; this makes it difficult to treat this group as a collective and so a complex approach is often taken (Fattorusso et al, 2021). A prognostic evaluation of drug-resistant epilepsy is provided when individuals are diagnosed with specific paediatric epilepsy syndromes, such as Lennox Gastaut Syndrome, Dravet Syndrome and Rasmussen encephalitis, which are very resistant to pharmacological treatment (Dalic and Cook, 2016).

The pathogenesis of drug-resistant epilepsy is unclear and can be multifactorial. Some of the hypothesised mechanisms that are said to underly drug-resistant epilepsy are changes that are made to the drug targets, failure of the drugs to reach their target site, drugs missing their target site and genetic mechanisms. These aforementioned mechanisms can all act together in a patient resulting in the onset of the condition (Ghosh et al, 2021).

Currently, there is no cure available for epilepsy. As a result, patients receive the mainstay of epilepsy therapy, which is symptomatic pharmacological treatment. Anti-seizure medications (ASMs), previously called antiepileptic drugs, are able to prevent/suppress the generation and severity of an epileptic seizure (Löscher and Klein, 2021). ASMs aim to stop seizures, reduce the number of them, lower the adverse effects that are usually associated with long-term therapy and help patients restore and maintain their normal/usual lifestyle (Goldenberg, 2010). The ASM treatment regimen is not the same for each patient, factors such as the type of

epilepsy, the age of the patient, the severity of the seizures, underlying aetiology, pharmacokinetics and drug-drug interactions, all determine what type of ASM is administered to the individual (Hakami, 2021; Löscher and Klein, 2021).

However, there are a plethora of issues surrounding the use of ASMs which include severe adverse effects, negative psychological effects, social and economic challenges (Mutanana et al, 2020).

Whilst the newer generation of drugs are well tolerated by patients, individuals can still experience a range of side effects with ASMs. The most commonly observed side effects are dizziness, tremors, behavioural changes, mood changes, coordination disturbances, fatigue and cognitive deficits (Löscher and Klein, 2021; Mutanana et al, 2020). These are dose-dependent and can be reversible. Severe adverse effects have been observed, for example, skin rashes, life-threatening allergic reactions, renal stones and aggravation of seizures which can eventually lead to status epilepticus (when inappropriate ASM has been prescribed) (Löscher and Klein, 2021). There has been a lot of attention drawn to the psychobehavioural side effects of ASMs which include aggression, hyperactivity, irritability, psychosis, depression, suicidal thoughts and anxiety (Strzelczyk and Schubert-Bast, 2022). Experiencing these side effects can often lead to lower drug compliance among patients and can cause them to have a lowered quality of life (Löscher and Klein, 2021; Mutanana et al, 2020; Strzelczyk and Schubert-Bast, 2022).

Furthermore, ASMs are unable to stop and reverse the development of drug-resistant epilepsy. Even though new ASMs are being manufactured and produced, achieving "seizure freedom" and having an improved quality of life is not possible for many epileptic patients (Löscher and Klein, 2021). Given the lack of clinical evidence, it is difficult to conclude which ASMs are the most effective by age group as not all ASMs have undergone randomised controlled trials (RCTs) in neonates, children or the elderly. There is a consensus that ASMs effective for focal epilepsies in adults are also applicable to children, as the European Medicines Agency (EMA) stated that focal epilepsies in children >4 years of age have a similar presentation to adolescents and adults. Additionally, it was concluded that the results of ASM trials conducted in adults can be extrapolated, to some extent, to children. However, this may not always be the case as the efficacy of ASMs may vary for different ages, which was suggested in the 2007 Standard and New Antiepileptic Drug Study, where children <16 years of age were found to be more likely to fail treatment in comparison to adults (French and Staley, 2012).

Due to the limited efficacy of ASMs, many patients and clinicians often seek alternative therapies that may be more effective and improve the quality of life. The anticonvulsant properties of cannabis have been reported since ancient times. Anecdotal studies, clinical trials and preclinical studies have all provided evidence supporting the use of cannabis in the treatment of epilepsy yet concerns regarding the long-term safety and efficacy of cannabis still exist (Kirkpatrick and O'callaghan, 2022). A recent study showed that upon using purified Cannabidiol (CBD) as an adjunctive treatment, a 92.2% seizure reduction in children and young adults who suffered from drug-resistant epilepsy with various etiologies, was obtained (Tzadok et al, 2024). Furthermore, Zafar et al (2021) observed an 86% reduction in seizure

frequency in paediatric patients who suffered from drug-resistant epilepsy and were using whole-plant medical cannabis oils.

The main aim of this paper is to provide an overview of medical cannabis and evidence of its use for the management of epilepsy. Additionally, this article explores the mechanism of actions of phytocannabinoids, the entourage effect and discusses the importance of real-world studies.

Background in Cannabis

Evidence has shown that the plant possesses a range of therapeutic properties and has suggested its use as a potentially effective treatment for a variety of medical conditions (Pagano et al, 2022; Rapin et al, 2021). Consequently, the evidence base for the medicinal use of cannabis has been significantly growing over the years (Rapin et al, 2021). Studies have been aiming to establish the safety and efficacy profile of cannabis for the treatment of a range of conditions like epilepsy and chronic pain (Sachs et al, 2015). Despite the advancements made in medical cannabis research, there is still a need for further work to establish the benefits and limitations of this medicine.

On 1 November 2018, public pressure and campaigning saw the legalisation of medical cannabis in the UK, yet according to a recent YouGov survey, almost 50% of the respondents were unaware of the law change in 2021 (Erridge et al, 2022; Schlag et al, 2020). Since the change of the law, patients in the UK have had limited access to cannabis on the National Health Service (NHS) and it was reported that since 2018 (up to 2024) only 5 full spectrum prescriptions had been made available (Schlag et al, 2020). Many have spoken out and have expressed that, although medical cannabis has been legalised, it remains almost impossible to access without seeking out the private sector (Nutt et al, 2020).

The National Institute for Health and Care Excellence (NICE) (2019) published guidelines (last updated in 2021 (National Institute for Health and Care Excellence (NICE), 2021)) covering the cannabis-based medicinal products (CBMPs) that can be prescribed for intractable nausea and vomiting, chronic pain, spasticity, and severe treatment-resistant epilepsy. Other associations such as the British Paediatric Neurology Association (BPNA) (2021) have also published guidelines regarding the use of CBMP use in epileptic children and young people. The Medical Cannabis Clinicians Society (MCCS) (2021) has also produced a guide for prescribers. Whilst this shows that the sector is heading in the right direction and is recognising the scientific value of CBMPs for the treatment of diseases, many of the guidelines have been criticised by campaigners and doctors for being too restrictive (Schlag et al, 2022).

Most of the NICE guidelines evidence base consists of RCTs and evidence that assesses patient-reported outcomes (PROs) has been disregarded (Schlag et al, 2022). PROs are crucial as they allow researchers to gain insight into the patient's experience with the administered treatment that the clinical measurements may not be able to represent (Mercieca-Bebber et al, 2018). Additionally, the lack

of education and training on prescribing cannabis medicines means that healthcare professionals prescribing decisions and confidence are negatively impacted.

Despite medical cannabis being approved for use in the UK in 2018, the number of prescriptions that were made available on the NHS still remains incredibly low. The NHS seems reluctant to fund CBMPs and as a result, the vast majority of patients resort to private cannabis clinics to access unlicensed CBMPs for their medical conditions (Schlag et al, 2022). Private clinics can cost families with epileptic children an average of up to $25,000 per annum (Schlag et al, 2021; Schlag et al, 2020). Patients from low/middle-income economic backgrounds may therefore be placed at a disadvantage and are unable to access a treatment that could be of great benefit to them. There is a lack of RCTs supporting the cost-effectiveness of CBMPs that is required by NICE to provide a rationale for the NHS paying for medical cannabis (Schlag et al, 2022).

Mechanism of Actions of Phytocannabinoids in Epilepsy

The endocannabinoid system is a widespread neuromodulatory system found in the human body, consisting of cannabinoid receptors, their respective ligands, endogenous cannabinoids (endocannabinoids), and the enzymes that synthesize and degrade them (Lu and Mackie, 2016).

The cannabinoid receptors primarily mediate the effects of endocannabinoids. There are two main subtypes of cannabinoid receptors: cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2). CB_1 receptors are highly expressed in the central nervous system (CNS), particularly in areas such as the basal ganglia, hippocampus, the cortex. CB_2 receptors have a lower expression, in comparison to CB_1 receptors, in the CNS and are mainly expressed in the peripheral tissue and the immune system (Haspula and Clark, 2020; Kirkpatrick and O'callaghan, 2022). Other receptors found in the endocannabinoid system include the transient receptor potential vanilloid (TRPV) receptor family, metabotropic receptors like G-Protein Coupled Receptor 3 (GPR3), GPR6, GRP12, GPR19 and GPR55, peroxisome proliferator-activated receptors and other receptors, enzymes and proteins (Lu and Mackie, 2016; Rezende et al, 2023).

The cannabis plant contains over 500 active chemical compounds and around 150 phytocannabinoids have been discovered, of which cannabidiol (CBD) and (–)-trans-Δ^9-tetrahydrocannabinol (THC) are the most well-researched (Rock and Parker, 2021). CBD has been shown to possess antiepileptic properties and can act via multiple molecular targets. Preclinical studies have demonstrated that CBD can antagonize GPR55, which can inhibit the release of intracellular calcium resulting in a decrease in excitatory currents and seizure activity. Additionally, CBD desensitizes the transient receptor potential vanilloid 1 (TRPV1) channels, to cause a decrease in the extracellular calcium influx and neurotransmission. CBD can also reduce the reuptake of adenosine by inhibiting equilibrative nucleoside transporters, which reduces neurotransmission and hyperexcitability (Nichol et al, 2019). Over-

all, CBD's antiepileptic mechanisms of actions are incredibly complex and despite the many advances made in research to uncover them, they are still not fully elucidated.

THC has been shown to display variable anticonvulsant effects with some *in vivo* studies indicating that it has proconvulsive effects whereas other stating that it has antiepileptic effects (Pertwee, 2008). A review paper highlighted that across 34 studies from 6 animal species, THC demonstrated anticonvulsant effects in 61.8% of seizure models, proconvulsant effects in 2.9% of seizure models, mixed effects in 2.9% of seizure models and no significant effect in 32.4% of seizure models (Rosenberg et al, 2015). The antiepileptic property of THC is primarily mediated by the CB_1 receptor, which is also responsible for its psychoactive effects. This receptor has the ability to regulate the glutaminergic excitatory activity of the brain and once activated it depresses synaptic transmission of glutamate (Colizzi et al, 2016; Monory et al, 2006). It also inhibits the receptors and transporter's function, reduces the activity of enzymes and after prolonged exposure, the glutamate synaptic plasticity can become disrupted (Colizzi et al, 2016). Furthermore, research has also shown that THC is an allosteric modulator of type μ and δ opioid receptors—this inhibits neurotransmitter release which means the glutamatergic N-methyl-D-aspartate (NMDA) receptors are unable to be activated, resulting in seizure reduction (Senn et al, 2020). Overall, several preclinical *in vivo* studies using acute seizure models and *in vitro* studies have displayed THC's antiepileptic effects (Rosenberg et al, 2015).

CBMPs are medicinal products that are produced from the cannabis plant. In the UK, the only licensed CBMP for intractable epilepsy remains to be Epidyolex—which contains 99.8% CBD, and <0.4% THC. A wide range of second-generation (unlicensed) CBMPs are available for medicinal purposes through private cannabis clinics in the UK, and each differ in their formulation, THC: CBD ratio and recommended dosage.

The Entourage Effect

It is likely that whole-plant cannabis extracts are more effective and tolerable in comparison to purified single components of the plant (Morano et al, 2020), yet more studies are needed to corroborate this (Pamplona et al, 2018). A recent study by Zafar et al (2021) found that there was an 86% reduction in seizure frequency in children with severe treatment-resistant epilepsy upon treatment with whole-plant medicinal cannabis products. Additionally, a study investigating the anti-cancer properties of cannabis discovered that a whole plant extract had a greater anti-tumoral effect compared to just pure THC (Blasco-Benito et al, 2018). It was concluded that this enhanced outcome was attributed to the interaction of multiple compounds affecting several targets and mechanisms of action in the whole-plant cannabis extract. Several studies have gone on to further show that whole plant extracts are more effective than single compound products due to the complex synergistic interactions that take place between the active and inactive molecules of the cannabis plant and have coined this phenomenon 'the entourage effect' (Morano et

al, 2020; Rosenberg et al, 2015; Mechoulam and Ben-Shabat, 1999; Russo, 2011). The entourage effect was originally applied to a group of endogenous compounds that are structurally similar to endocannabinoids and potentiated the effects of the cannabinoid receptors. However, since then, this concept has been expanded and can be applied to plants other than cannabis (Rosenberg et al, 2015). Research has shown that phytocannabinoids not only interact with each other but can additionally interact with lipophilic molecules and terpenes/terpenoids that are found in the cannabis plant. These interactions could play a crucial role in enhancing the pharmacological actions and effects of phytocannabinoids (Morano et al, 2020).

The concentration of active/non-active compounds co-administered with THC, such as entourage compounds, can greatly impact its pharmacological effects (Maccarrone et al, 2023). CBD has been reported to function as an entourage compound as it can bind to the CB_1 receptor to impact the bioavailability of THC. It has also been shown to inhibit hepatic enzymes belonging to the cytochrome P450 family, which can slow down the conversion of THC into its potent, psychoactive metabolite. As a result, CBD can reportedly affect the pharmacokinetics of THC. Not only does CBD impact the functions of phytocannabinoids, but CBD can also inhibit the degradation of arachidonoylethanolamine, an endocannabinoid, by inhibiting fatty acid amide hydrolase (André et al, 2024). Terpenes are another class of active compounds that are found within the cannabis plant. They are also referred to as entourage compounds as they can enhance the permeability of the blood-brain barrier, which can improve the pharmacokinetic properties of phytocannabinoids (Boggs et al, 2018).

Despite the current research suggesting a combined therapeutic benefit between the active components of the cannabis plant, the evidence supporting whether the effects are additive or synergistic remains unknown. Thus, further work is required to better understand this phenomenon to support the use of whole-plant cannabis extracts in treating patients.

Real-World Evidence (RWE)

RCTs have been considered as the gold standard when investigating the efficacy of medical products (Akobeng, 2005), however, in relation to CBMPs, they have led to very restrictive and limiting guidelines in the UK (Schlag et al, 2022). RCTs are necessary, yet they have several limitations including the high cost to conduct them, their time-consuming nature, the lack of ecological validity to real-life situations, limited long-term patient safety data that is obtained and limited generalisability to individuals from various backgrounds (Banerjee et al, 2022; Schlag et al, 2022).

It is worth highlighting that RCTs with CBMPs are possible and there have been several that have been conducted (Solmi et al, 2023), however, there are many challenges that limit their use. Whole cannabis products do not lend themselves well to RCT assessment, which is a major issue as the current cannabis evidence base repeatedly emphasises that more RCTs should be conducted. The complex pharmacology and heterogeneity of the cannabis plant means that one pharmaceuti-

cal product that undergoes RCT assessment is not representative of the wide variety of the CBMPs that are available. Additionally, the route of administration can vary for different CBMPs and consequently affects factors such as bioavailability, drug elimination etc. (Banerjee et al, 2022). Again, this highlights that using RCTs to assess the efficacy of CBMPs may result in the failure to identify the appropriate CBMP that can be used for each clinical scenario (World Health Organization, 2015). The design of an RCT requires the use of a placebo, this presents as an obstacle for CBMP assessment as there is no appropriate placebo that has been identified. Thus, without adequate blinding, the RCT assessment will not be able to draw accurate and reliable conclusions regarding the treatment effects (Banerjee et al, 2022).

A major challenge that is associated with CBMPs is the high cost of both their production and importation, as a result, they tend to be very expensive (Banerjee et al, 2022; Schlag et al, 2020). The majority of the clinical trials that have been conducted with CBMPs have been funded privately, which is not ideal as it can introduce potential reporting bias (Banerjee et al, 2022; Dreyer et al, 2020). Currently, research mainly focuses on compounds that are under patent compared to CBMPs, as a large return can be gained on investment for pharmaceutical companies. There are issues with patenting whole plant extracts especially cannabis, as each plant can be highly heterogenous due to the varying cannabinoid composition, and diversity between the crops. These factors further contribute to the reluctance of the UK government to license plant-based medicines (Banerjee et al, 2022; Schlag et al, 2022). It should be highlighted that GW Pharmaceuticals (now Jazz Pharmaceuticals) have conducted RCTs for the use of CBD in Lennox Gastaut Syndrome and Dravet Syndrome, which took nearly 20 years to complete, however when the company did apply for CBMPs to be made available through the NHS, it was disregarded due to the lack of cost-effectiveness (which has now been changed) (Schlag et al, 2022).

Additionally, RCTs are often used to measure the safety of compounds, however, they fail to obtain long-term patient safety data, with the most well-known example being thalidomide (Schlag et al, 2022). There have been thousands of years of documented evidence which has highlighted the safety of cannabis in real life, unfortunately, this evidence has been disregarded (Nutt, 2022).

CBMPs are unable to be developed through the standard drug development pipeline due to the aforementioned challenges and as a result, their uses have not yet been fully explored. Consequently, novel methods of collecting evidence for CBMPs efficacy need to be used to allow better-informed decisions regarding regulations, guidelines and clinical trials to be made. RWE has been proposed as a solution to assess the clinical efficacy of CBMPs in a suitable and appropriate manner. Incorporating RWE means that the quality and design of RCTs and clinical evidence can be significantly improved (Banerjee et al, 2022; Schlag et al, 2022).

RWE is evidence that has been extracted from health data obtained from insurance records, registries, electronic health records and non-interventional studies (Baumfeld Andre et al, 2020). This data is usually beneficial for the monitoring of post-approval pharmacovigilance of medications (Ehrenstein et al, 2013) and research has shown that using this type of population-based data is helpful in the iden-

tification of safety events, which aids the development of harm-reduction strategies (Baumfeld Andre et al, 2020). Although using RWE is currently not normalised, it has the potential to be an invaluable aid when making regulatory decisions (Szigeti et al, 2023).

Recently, RWE has become more prevalent and integrated into the cannabis literature base (Banerjee et al, 2022; Schlag et al, 2022). Previously, state-level records have been used to assess cannabis use, however, over the past few years, collecting data from clinical registries/databases has become more common, with these databases containing evidence on pharmacovigilance and patient-reported outcomes (PROs). There are a number of experimental and observational study designs that are able to produce RWE from real-world data. Examples of RWE studies include registry analysis, regional/national survey studies, analysis of clinic/dispensary data, claims database analysis and government record analysis (Banerjee et al, 2022). These observational studies can take the form of cross-sectional, case-control or cohort studies, and data collection can be done either prospectively (data is collected at that present time) or retrospectively (data previously collected is analysed) (Dang, 2023).

A first-of-its-kind comprehensive, prospective registry, the UK Medical Cannabis Registry, was set up in December 2019 to help collate the prescribing outcomes of cannabis (Sapphire Medical Clinics, 2019). Additionally, another prominent observational registry, Project Twenty21 (T21) was set up in the UK in August 2020 and more recently in Australia, to recognise the potential effectiveness of medicinal cannabis (Zafar et al, 2020). These registries have obtained crucial data and have shed light on the advantages of using RWE to study medical cannabis. Having medical cannabis registries is essential as they help provide the foundations for clinical trials and contain high-quality data that is obtained at lower costs (Schlag et al, 2022).

One of the advantages of RWE, in comparison to RCTs, is that they have a broader inclusion criterion, for example, they are able to account for factors such as variations in doses of CBMPs, comorbid illness, age and gender, use of other pharmaceuticals and previous use/current use of cannabis (Banerjee et al, 2022; Schlag et al, 2022). All of these allow RWE to have improved ecological validity and greater generalisability to real-life settings (Schlag et al, 2022). Furthermore, RWE studies tend to have a slightly longer follow-up period, which is beneficial as it can allow rare adverse events, that are not usually identified in conventional RCTs, to be reported. Thus, one of the primary roles of RWE in the context of medical cannabis is to increase overall pharmacovigilance understanding of them (Banerjee et al, 2022).

RWE studies are beneficial for collecting data on individuals that have rare epilepsy syndromes as RCTs often fail to recruit patients afflicted by rare illnesses due to some trials being conducted at specific sites only and the strict inclusion criteria of studies (Banerjee et al, 2022; Schlag et al, 2022). RWE studies also allow information that would not usually be reported in RCTs to be uncovered as patients may withhold sensitive information due to the fear of repercussions (Banerjee et al, 2022). Data obtained from RWE can help design more patient-centred studies

and improve clinical trial efficiency by improving the inclusion/exclusion criteria (Banerjee et al, 2022). Coupling RCTs and RWE would be especially valuable when investigating rare diseases such as rare epilepsy syndromes, where normally patient recruitment presents a significant challenge (Zafar et al, 2021).

Case study research is a prime example of RWE that can be used to provide a unique insight into the use of cannabis for the treatment of illnesses that are difficult to treat such as rare childhood epilepsy syndromes (Schlag et al, 2022). This is incredibly useful as many RCTs fail to design studies where patients with rare diseases are included as the population affected is too small (Zafar et al, 2020; Zafar et al, 2021) and, in some cases, it is not profitable enough to invest into. Case studies are invaluable assets to research as they can help develop clinical expertise and new approaches to aid with the prescribing process. Previous case study reports that were conducted on the prescribing of medical cannabis have highlighted several issues and as a result have helped reduce and overcome these barriers. Overall, case studies are indispensable as they help provide high-quality evidence, with increased ecological validity, for the use of medical cannabis in the treatment of difficult-to-treat illnesses like intractable epilepsy (Schlag et al, 2022).

Despite the many advantages of RWE, there are still some inherent limitations that need to be highlighted. One of the major issues that is repeatedly emphasised is the lack of controls, the presence of confounding variables and the lack of randomisation, which all make it difficult to draw causative relationships between the factors (Banerjee et al, 2022; Schlag et al, 2022). Yet, interestingly this can also be considered as a strength of RWE (U.S Food & Drug Administration, 2018), as in real life, factors are not controlled, and so it means that the evidence collated from RWE studies has greater generalisability to clinical settings. However, RCTs are still imperative for establishing a causative relationship between medication and treatment outcomes. Furthermore, the quality of evidence from electronic medical records and insurance records can vary and lack the appropriate outcome measures alongside focusing only on specific endpoint measures. Researchers are trying to overcome this issue by incorporating PROs into their studies to understand more about CBMPs effect on quality of life and effect on symptom reduction, yet more consistency and quality are needed (Banerjee et al, 2022; Schlag et al, 2022).

Summary of the Clinical Evidence Base

A publication released by Kaur et al (2024) Consultants summarised 90 papers on cannabis and epilepsy published since 1949 (see **Supplementary References**). The great majority have been published in the last 10 years and the recent legalisation of cannabis for medical purposes worldwide has seen a rapid increase in publications on the topic. There have been 10 double-blind, placebo-controlled studies but the majority have been real-world publications—observational studies, case series, open-label studies and case reports. Real-world studies must be acknowledged as valid evidence given the very real difficulties of conducting double-blind, placebo-controlled studies for the full spectrum cannabis product, except in the case of isolates which can be treated in a similar fashion to pharmaceuticals.

All the RCTs that have been conducted have focussed on the active components of the cannabis plant, primarily on CBD. To our knowledge, there have been no RCTs that have been conducted on whole-plant cannabis products (full-spectrum cannabis). It should be emphasised that full-spectrum cannabis does not lend itself to assessment by the double-blind placebo-controlled procedure due to its complexity and the lack of an adequate placebo, which has been highlighted by the Medical Cannabis Clinicians Society several times (Medical Cannabis Clinicians Society (MCCS) and Drug Science, 2021). Non-RCT studies that have been carried out to investigate the efficacy of full-spectrum cannabis products should not be disregarded on the basis of study design as they may hold significant data.

Numbers and Studies

The total number of patients discussed in these papers (see **Supplementary References**) amounts to 8660 which confirms that there is now a considerable body of efficacy and safety data for the use of cannabis in epilepsy. Most patients are children but there are significant numbers of adults reported in many of the papers (Kaur et al, 2024). Cannabis can be administered and utilised as a treatment for both paediatric and adult populations. Yet, the majority of the literature base has shown that cannabis, particularly CBD therapy has a higher efficacy and a more significant reduction in the frequency and severity of seizures is observed in paediatrics compared to the adult population. This is mainly thought to be due to a greater distribution of CBD in younger paediatric patients (Osman et al, 2024). However, there is a lack of systematic clinical trials being conducted that will enable a direct, competitive comparison between the two patient populations.

Cannabis has been shown to be highly effective against childhood drug-resistant epilepsy syndromes such as Dravet Syndrome, Lennox Gastaut Syndrome and Tuberous Sclerosis. A study conducted by Devinsky et al (2017), discovered a 48.7% reduction in convulsive seizure frequency and a 45.7% reduction in total seizure frequency in Dravet Syndrome patients. A similar outcome has also previously been reported in a cohort of patients with Lennox Gastaut Syndrome, where an RCT reported a 41.9% reduction in drop-seizure frequency from baseline measurements (Devinsky et al, 2018a). Due to the increasing amount of evidence supporting the use of CBD as an effective therapy, Epidyolex was consequently approved for use as an add-on therapy for these epilepsy syndromes in the UK in 2019 (Wechsler et al, 2024). However, the evidence base is now starting to evolve and the use of cannabis for other rarer epilepsy syndromes such as infantile spasms, Doose, Rett, Sturge Weber, Cyclin-Dependent Kinase-Like 5 (*CDKL5*), Aicardi, Chromosome 15q11.2-13.1 duplication syndrome (Dup15q), Potassium Sodium Channel Subfamily T Member 1 (*KCNT1*) and Synaptic Ras GTPase Activating Protein 1 (*SYNGAP1*), amongst others, is now started to be reported on Kaur et al (2024). One open-label study reported that highly purified CBD reduced the median number of seizures by half upon 3 months of use in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndrome (Devinsky et al, 2018b). Overall, there is no noticeable difference in efficacy or side effect profile of CBD between the syndromes, which confirms that cannabis (particularly CBD) is a general anti-

convulsant and, as would be expected, not an anti-convulsant only for a few specific syndromes (Devinsky et al, 2018b; Kaur et al, 2024; Rosenberg et al, 2015).

Dose and Cannabinoid Type

The current evidence base focuses on the use of CBD as an anti-convulsant—either as an isolate or as the main anti-convulsant in full-spectrum products (Kaur et al, 2024). A few papers mention the use of additional THC and few mention studies on other minor anti-convulsant cannabinoids (Crippa et al, 2016; Erridge et al, 2023; Lorenz, 2004; McCoy et al, 2018; Nowicki et al, 2022). However, the published evidence on the efficacy and safety of the minor cannabinoids (and terpenes) is lacking.

Most studies employ a "start low and go slow" dose escalation regime. Most clinicians suggest a starting regime of 5 mg/kg CBD and slowly escalate over 1–2 months to a final dose of about 20 mg/kg. Some have gone higher—up to 50 mg/kg. However, it is important to emphasise that full-spectrum products will need a lower dosage than isolate products. The final, stable dose of full-spectrum products from the literature is about 10 mg/kg but with significant personalised variability. This dose, from the literature, produces similar efficacy to the higher doses needed for isolates but with less side effects, which is not surprising as many side effects are dose-dependent. The literature has mentioned adult doses indicate a total CBD load of about 300–500 mg daily (Lawson et al, 2022; Arzimanoglou et al, 2020; Medical Cannabis Clinicians Society (MCCS), 2021).

The literature has indicated better efficacy with additional THC (in other words using full spectrum products) and the dose most quoted for additional THC is around 0.5 mg/kg. Once again it is important to slowly escalate the dose as the literature is clear that there is significant dose variability (Nowicki et al, 2022; Erridge et al, 2023; Medical Cannabis Clinicians Society (MCCS), 2021; Lorenz, 2004; McCoy et al, 2018).

Tolerance is rarely mentioned but just one paper mentions about 10% tolerance rate at 11 months (Tzadok et al, 2022). The current evidence base consists of studies that were conducted over a shorter trial period, which emphasizes the importance of longer-term real-world longitudinal studies in order to help gather more data regarding the long-term safety and efficacy of cannabis medicines (Kaur et al, 2024). Despite this, there have been a few studies that have followed patients for up to 3–4 years with no drop of efficacy (Caraballo et al, 2022; Devinsky et al, 2019; Sands et al, 2019; Scheffer et al, 2021; Szaflarski et al, 2018). However, due to these studies being open-label expanded access observational studies, and not RCTs, they have not been given as much importance as they should have received.

Efficacy

There is surprising consensus in the literature regarding the efficacy of CBD for epilepsy (Kirkpatrick and O'callaghan, 2022). Around 75–80% of patients have been observed to have a reduction in seizures. Given that the patients have, by definition, drug-resistant epilepsy that is a remarkable statistic. Around 40–50% of patients achieve a seizure reduction of at least 50%. A few (around 5–10%) achieve

Table 1. Summary of the additional benefits from cannabis prescription (other than reduction in seizure frequency) in all patient populations.

Benefits	Outcome
ASM use	Reduction in other ASMs: The average number of ASMs on admission to these trials is around 4, although the children will often have been prescribed many more ASMs in the past—up to 12 being reported. Many children can reduce the total number of ASMs by about 1–2, with concomitant reduction in side effects. A few children can come off all other ASMs but that seems rare
Mood	Around 40% of parents report this improvement in their child
Alertness	Improved—around 30%
Sleep	Improved—around 20%
Appetite	Improved—around 10%
Behaviour	Improved
Communication	Improved
Emotional stability	Improved
Non-verbal communication	Improved
Motor skills and cognitive learning	Improved
Spasticity	Improved

ASM, anti-seizure medication.

seizure freedom. Around 10–15% report no change in frequency and a small number seem to have worsened seizures. The latter is difficult to attribute to CBD given that the patients will have seizures in any case, which often vary in frequency (Kaur et al, 2024). It seems likely that in some cases the increased frequency may be due to higher THC levels in some full-spectrum products given that THC at low doses is anti-convulsant but is pro-convulsant at higher doses (Pertwee, 2008).

Other Benefits

Additional benefits from cannabis prescription, other than reduction in seizure frequency, that have been noted have been summarized in Table 1 (Kaur et al, 2024; Schlag et al, 2021).

Side Effects

There is considerable consensus on the side effect profile (as observed in Table 2). Many side effects seem dose-dependent, emphasizing the importance of a slow titration regime. Most side effects seem to be mild and well tolerated and cessation of therapy due to side effects is unusual (Fazlollahi et al, 2023; Kaur et al, 2024).

Psychosis has only been reported in 2 papers and in two cases it was a recurring issue prior to cannabis therapy (Hausman-Kedem et al, 2018; Sands et al, 2019). However, screening patients for a history of psychosis is important prior to treatment. It should be noted that CBD is anti-psychotic.

It has been suggested that THC can negatively impact the neurodevelopment of adolescents and children, as a result, many clinicians are reluctant to prescribe

Table 2. Summary of the side effect profile of cannabis—isolate products and whole-cannabis extracts in all patient populations.

Side effect	Outcome
Somnolence, fatigue and sleepiness	Increased in around 15–25% but dose-dependent
Appetite	Reduced in around 10–20%
Gastrointestinal disturbance (diarrhea, abdominal pains, nausea and vomiting)	Increased in around 10–30%
Temperature	Increased
Dry mouth	Increased
Liver enzymes	Increased—usually reversible and more common with concomitant sodium valproate
Seizures	Increased in some cases

CBMPs to children and young adults who suffer from intractable epilepsy. The BPNA have expressed concerns that "chronic high exposure to THC during recreational cannabis affects the brain development, structure and mental health" (British Paediatric Neurology Association (BPNA), 2021). However, there has been no evidence showing that THC medical products cause long-term cognitive damage in epilepsy patients (Medical Cannabis Clinicians Society (MCCS) and Drug Science, 2021). Additionally, the clinical evidence base discussed in the Kaur et al (2024) publication included studies where patients were using a wide range of CBMPs (which contained varying proportions of THC) and found that there was no negative impact on brain development, structure, and mental health of children.

Conclusion

Cannabis is a highly personalised medicine and is an effective therapy for children with severe treatment-resistant epilepsy. Many patients who have been treated with cannabis have been shown to experience a significant reduction in seizures, an improved quality of life and an overall reduction in seizure severity. Despite this, patients are still struggling to access cannabis products via the NHS, as doctors refuse to prescribe cannabis due to restrictive guidelines, and concerns regarding the long-term adverse effects of cannabis medicines. It is crucial that healthcare professionals, scientists, and members of the public are educated about the pharmacology of cannabis as well as learning about the clinical evidence base on cannabis and epilepsy—which is constantly evolving. Public healthcare bodies and clinicians need to help patients gain access to medications that are essential for their quality of life and sometimes even their survival.

Key Points

- The cannabis plant possesses anticonvulsant properties which makes it highly effective for the treatment of intractable epilepsy.
- The pre-clinical and clinical evidence base on cannabis for epilepsy has been growing over the decades.
- Clinicians are apprehensive about prescribing cannabis for epileptic conditions due to perceived limited long-term safety, efficacy profiles and restrictive guidelines.
- Healthcare professionals need to be educated regarding the use of cannabis for epilepsy to aid prescribing decisions.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

VK: Conceptualization, Data Curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. MPB: Conceptualization, Data Curation, Formal analysis, Investigation, Methodology, Project Administration, Supervision, Writing – original draft, Writing – review & editing. HD: Conceptualization, Data Curation, Formal analysis, Investigation, Methodology, Project Administration, Supervision, Writing – original draft, Writing – review & editing. DJN: Conceptualization, Data Curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Hannah Deacon and Michael Philip Barnes are affiliated with Maple Tree Medical Cannabis Consultancy. They confirm that they have no conflict of interest with

any company related to epilepsy or paediatric prescribing. Other authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0903.

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