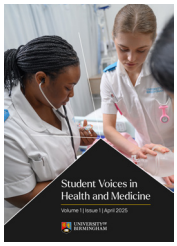
Student Voices in Health and Medicine



How effective are cannabis-based products for paediatric epilepsy?

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Abstract

Epilepsy affects children's development and quality of life and antiepileptic drugs are often ineffective for children with drug resistant epilepsy. Some evidence suggests that cannabis-based products may offer potential benefits for children with drug resistant epilepsy by reducing the frequency of seizures. Epidiolex is a cannabis-based product licenced for a small number of children in the UK but concerns about adverse events (AEs) limit its wider use. This opinion piece considers the effectiveness of cannabis-based products for paediatric drug-resistant epilepsy and the associated risks. Cannabis-based products may have detrimental long-term effects and there are concerns about the safety of certain derivatives. Consequently, while cannabis-based products may be effective for reducing seizures in paediatric epilepsy, a definitive answer about whether benefits outweigh risks remains unclear. This paper concludes that more research is needed to investigate the safety of cannabis-based products. Once a more definitive answer is established, evidence-based education and practice may improve the accessibility and availability of products and offer more families informed choices about treatments for epilepsy.

Keywords: Epilepsy; Children; Cannabis

Introduction

Epilepsy affects one in 200 children in the UK (Nair and O'Dwyer, 2010). Seizures occur due to excessive electrical discharges in brain cells; their location determines the seizure experienced (Nair and O'Dwyer, 2010). There are multiple types of epileptic seizures, epilepsy types and syndromes, with a variety of underlying causes. The International League Against Epilepsy (ILAE) published the most recent definitions in 2017 and defined three diagnostic levels, seizure type, epilepsy type and epilepsy syndrome, emphasising aetiology should be considered at every level (Wirrell et al., 2022).

Treatment for epilepsy involves antiepileptic drugs, which block sodium and calcium channels or enhance the inhibitory neurotransmitter gamma aminobutyric acid (GABA) (Parker et al., 2022). This reduces glutamate release, an excitatory neurotransmitter, preventing seizures from spreading in the brain (Parker et al., 2022). Despite antiepileptic drugs, 30% of children with epilepsy have drug resistant epilepsy, where two or more antiepileptic drugs cannot control seizures (Campos-Bedolla et al., 2022). Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are severe developmental and epileptic encephalopathies that typically begin in childhood and are often resistant to treatment (Ali et al., 2018). This evidence-based opinion piece focuses on these syndromes due to the substantial body of research available on them.

Drug resistant epilepsy affects children's attention, concentration, and memory (Löscher et al., 2020). Learning can be affected by somnolence caused by antiepileptic drugs, due to their possible negative side effects on cognition and attention processes (Lagae, 2006), as well as being affected by post-seizure confusion (postictal state) and interictal epileptiform activity, the discharges that occur in the brain between seizures (Karaoglu et al., 2021). Parents express concerns surrounding behaviour, communication, sleep and social isolation (Kerr et al., 2011). Families caring for a child with drug resistant epilepsy in the UK may carry a large financial burden, due to costs of treatment and ability for parents to continue work alongside caring responsibilities (Ali et al., 2014). Additionally, drug resistant epilepsy syndromes have high mortality (Parker et al., 2022). The impact on quality of life for children and their families and the risks associated with drug resistant epilepsy highlights why there is an urgent need for alternative treatment.

Cannabis for treatment of paediatric epilepsy has been utilised in medicine for over 10,000 years (Billakota et al., 2019). Chinese documents report cannabis as a treatment for epilepsy 4700 years ago and Irish physician O'Shaughnessy introduced the anticonvulsant effects of cannabis to Western medicine in the late 19th Century (Billakota et al., 2019). Small studies then emerged in the 1970s investigating cannabis as a treatment for epilepsy (Russo, 2017). Cannabis contains over 100 cannabinoids, but the two most biologically active and researched are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Ali et al., 2018). CBD is most researched due to its anticonvulsive effects and lack of psychoactive properties, unlike THC, which is psychoactive (Thompson et al., 2020).

Studies have explored compounds with varying ratios of CBD and THC. Whilst THC may have anticonvulsive effects, its psychoactive properties, potential negative impacts, and inconsistent performance in seizure models have made it undesirable for further development (Perucca, 2017). Studies have therefore focused on CBD, although its mechanism of action is poorly understood and research is ongoing (Alsolamy et al., 2023). Several clinical trials assessed CBD as epilepsy treatment in the 90's, but small sampling led to inconsistent results (Billakota et al., 2019). Further research was accelerated by media coverage, in the US, of the successful case of Charlotte Figi in 2014 (Ali et al., 2018). Charlotte, who had DS was started on a low dose of CBD, she experienced >90% reduction in seizures (Maa and Figi, 2014).

Epidiolex, a CBD-only component, is licenced for children in the UK with DS and LGS over the age of two (National Institute for Health and Care Excellence (NICE), 2019). However, adverse events (AEs) and

unknown physiological effects cause concern for physicians and there is currently limited access in the NHS (Fischer et al., 2020). NICE (2019) suggests there is not enough evidence to determine whether CBD and THC are safe and effective, calling for more research. This opinion piece investigates the effectiveness of cannabis-based products for paediatric epilepsy, using studies published between 2012 and 2023. The children within the studies had drug resistant epilepsy, more specifically LGS and DS and were 1-18 years old.

Seizure Frequency

Many studies have found that cannabis-based products can reduce seizure frequency. A retrospective study by Tzadok et al. (2016) observed that 52% of children between the ages of 1-18 in Israel experienced >50% reduction in seizure frequency, while a later study led by the same author (Tzadok et al, 2022) reported a reduction in only 40% of participants. Similarly, Caraballo and Valenzuela (2021), in another retrospective study found a >50% reduction in half of the children in their Canadian study, who were aged between 16-22 months. However, as retrospective studies, data were not collected in a predesignated proforma, consequently some data may be missing, reducing internal validity (Hess, 2004).

Scheffer et al. (2021) observed a 44% reduction in seizure frequency in children aged 3-18 in Australia and New Zealand. However, whilst specifying this was a non-randomised controlled trial, there was no control group. Instead, it was described as a 'before and after' study, but failed to elaborate, resulting in ambiguity. Despite this, Paulus et al. (2013) justifies studies without control when there is insufficient evidence in literature to suggest the intervention is associated with the outcome. This rationale could apply to cannabis-based products, as they represent a relatively new and emerging area of treatment for paediatric epilepsy (Alsolamy et al., 2023).

An open label prospective study in the US found 56% of children aged 1-17 had >50% reduction in seizures (Sands et al., 2018). Similarly, Caraballo et al.'s (2022) prospective cohort study observed a 78% reduction for children aged 2-17 in Argentina. Although these studies observed a reduction in seizure frequency, prospective design involved a long follow up period, which can increase the risk of dropouts and threaten internal validity due to attrition bias (Deeks et al., 2003). Furthermore, Tzadok et al. (2022) found 36% of participants developed a tolerance to treatment, necessitating an increase in dose. Despite the uncertainty surrounding the validity of these studies, the overall weight of evidence supports the conclusion that cannabis-based products are clearly related to a reduction in seizure frequency.

Positive Effects

Many studies have found positive effects, the most common being improved alertness, observed in 39% (Tzadok et al., 2022), 56% (Tzadok et al., 2016), 40% (Scheffer et al., 2021) and 59% (Caraballo et al., 2022) of participants. Children also experienced improvements in communication, with 25% (Tzadok et al., 2022; Tzadok et al., 2016), 38% (Scheffer et al., 2021) and 39% (Caraballo et al., 2022) showing progress over the course of the study periods. Other effects noted across studies included improvements to sleep, behaviour, school attendance and reduced duration of postictal symptoms (those which occur between a seizure subsiding and the child's return to baseline) (Scheffer et al., 2021; Tzadok et al., 2022; Caraballo et al., 2022) Consequently, based on the available evidence, cannabis-based products may improve children's quality of life.

Adverse events

Although studies suggest cannabis-based products effectively reduce seizure frequency and induce positive effects, all reported adverse events. Understanding adverse events is vital to ensure that unrecognised risks are identified promptly, and action can be taken to ensure medicines are used safely (NICE, 2024). Adverse events were reported by 87% (Tzadok et al., 2022), 45% (Tzadok et al., 2016), 96% (Scheffer et al., 2021) and 80% (Sands et al., 2018) of participants. The most common included: somnolence, diarrhoea, vomiting, behavioural disturbances and weight loss. Three studies reported serious adverse events in 23% (Sands et al., 2018), 14% (Knupp et al., 2019) and 21% (Scheffer et al., 2021) of participants. Examples of serious adverse events across studies included status epilepticus and catatonic psychosis.

Interactions

Drug interactions with other antiepileptic drugs were reported. Scheffer et al. (2021) reported somnolence was more common in children taking clobazam, additionally, these children experienced less seizure improvement than other participants. Sands et al. (2018) observed behavioural changes in children taking clobazam, alongside valproic acid; three developed elevated alanine aminotransferase levels (a liver enzyme), which normalised with CBD dose reduction. Caraballo et al. (2022) reported that clobazam increased somnolence, which was reversed by reducing the dose of clobazam. However, both Caraballo et al. (2022) and Scheffer et al. (2021) found no significant changes in alanine aminotransferase levels. However, the small sample sizes in all studies, threatens both internal and external validity, suggesting that conclusions from these findings may have limited reliability (Smith and Noble, 2014). Consequently, there is uncertainty surrounding interactions, coupled with the presence of adverse events that raises significant questions about the safety and clinical application of cannabis-based products for children.

Aetiology

Some studies explored the relationship between seizure aetiology (the cause or origin of epilepsy) and response to cannabis-based products. Scheffer et al. (2021) reported that 43% of children with DS and 39% in LGS responded to treatment. In a comparable study, Caraballo et al. (2022) observed that 84% of children with LGS achieved >50% reduction in seizures and all children with DS in this study became seizure free. Knupp et al. (2019) suggested there may be differences in response between children with DS and LGS, but did not explore this further, limiting the strength of their conclusions and suggesting there may be an association between aetiology and effectiveness of cannabis-based products. Similarly, Tzadok et al. (2016) observed a 23% response rate in children with DS, compared to 88% in those with LGS, but their later study (Tzadok et al., 2022) concluded that seizure aetiology was not associated with a response. These conflicting findings highlight the uncertainty around whether cannabis-based products are more effective for certain types of drug-resistant epilepsy. Whilst some evidence suggests variability in response based on epilepsy syndrome, further research is needed to clarify these associations.

Discussion

Overall, the evidence suggests cannabis-based products may be effective in treatment of epilepsy, due to seizure reduction and positive effects. Conversely, adverse events and drug interactions, alongside methodological limitations in studies mean a definitive answer regarding the safe use of these medications for all children with drug resistant epilepsy is unclear.

Based on the available evidence, it is clear cannabis-based products are somewhat effective for children

with LGS and DS in reducing seizure frequency and may have positive effects, which include improvements to fatigue, social interaction, mood and cognition (Rosenberg et al., 2017., Porcari et al., 2018). However, observations within these presentations of epilepsy and all aetiologies need further examination because studies are currently small, and literature is focused on DS and LGS (Treves et al., 2021).

There is evidence of an association between CBD and adverse events, such as gastrointestinal, sleep disturbances and nausea, as well as interactions between CBD and clobazam (Pamplona et al., 2018). Additionally, some children experienced elevated alanine aminotransferase levels and adverse mental events, and current understanding is limited surrounding the long-term effects of cannabis on the developing brain and liver (Fischer et al., 2020). Evidence is largely inconclusive and suggests AEs, interactions and long-term developmental outcome measures remain unclear. Consequently, healthcare professionals are reluctant to prescribe CBD in the NHS, limiting access for families and leading to some families choosing to purchase products privately or using unlicensed medications (Calapai et al., 2023).

The studies investigated here used products containing varying amounts of CBD and THC, however Treves et al. (2021) suggested benefits of CBD are annulled in products containing THC. Ali, Scheffer and Sadleir (2018) expressed concerns about long-term effects THC can have on the developing brain, suggesting the manufacturing quality of cannabis-based products is variable, with many not meeting standards for medical use. This raises concerns for parents purchasing unlicensed medications. Additionally, Klotz et al. (2020) outlined that the benefits of cannabis-based products have been oversold and parents often have disproportionate expectations. Consequently, the various derivatives of cannabis require study to determine their safety.

Implications

There are several ethical considerations salient to the use of cannabis-based products, related to social context and misconceptions (Glickman and Sisti, 2019). Whilst fundamental to discuss within this topic, the small scope of this piece restricts the extent to which concepts can be discussed.

The uncertainty surrounding which derivatives of cannabis are safe to use and the long-term effects, specifically on the brain and liver presents a significant gap in current knowledge and understanding. Further research is therefore required to determine which products are safe over an extended period.

The concerns of healthcare professionals, their reluctance to prescribe cannabis-based products and unrealistic expectations of parents has some current implications for education. While further research is currently required, healthcare professionals need to ensure they remain up to date with emerging evidence to ensure they can provide evidence-based information to families. Understanding the current and emerging evidence base will ensure clinicians and parents are well-informed and in equipoise, used to describe individuals that are not biased to outcomes and are prepared it may not be what they expected (Dewar et al., 2023). More research in this area has potential to improve the future accessibility of prescriptions of CBD. Consequently, the risks associated with families purchasing unlicensed medications containing harmful derivatives will be reduced. Increased research and education have implications for nurses who will be better able to help parents and children make informed treatment choices.

Conclusion

Considering evidence, I believe it is unclear how effective cannabis-based products are for paediatric epilepsy. Findings suggest cannabis-based products reduce seizure frequency and induce positive effects. However, there are AEs, concerns surrounding long-term impacts and questions regarding the safety of

products containing THC. Consequently, further research should be conducted investigating the effect cannabis-based products have over a more sustained period and consider products containing which derivatives are safe. Subsequent evidence-based education for healthcare professionals and parents should be introduced, to inform individuals of the advantages and disadvantages and increase knowledge. These advancements may lead to increased accessibility and enable nurses to help families make informed decisions. Despite uncertainties, cannabis-based products may have benefits within paediatric epilepsy. Further research is of utmost importance to answer current questions, to better understand risks and ultimately continue to improve the lives of children with epilepsy.

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