Epilepsy among Pediatric Patients: The Use of Cannabidiol and Potential Impacts on Quality of Life

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Abstract

Background: Chronic epilepsy can cause severe impairments with respect to physical, mental, and social aspects of a child's life leading to low self-esteem, anxiety, depression, impaired memory and attention, lack of independence, and social stigma. Controlling seizures and their negative sequelae can be challenging in those with early onset epilepsy as they are often refractory to standard therapies. A further challenge is that all currently available anti-epileptic drugs have been shown to cause adverse cognitive effects and a certain degree of toxicity. However, cannabidiol (CBD), an agent found in cannabis, has been proven effective in reducing seizures in those with severe epilepsy, and has a lower side effect profile than standard treatments. This systematic literature review explores the potential impact of cannabidiol in improving quality of life (QOL) factors among pediatric patients with severe forms of epilepsy with respect to seizure control, alertness, mood/behavior, and language.

Methods: An exhaustive literature search was performed using MEDLINEOvid, Web of Science, and Clinical Key. Keywords included: cannabidiol, epilepsy, child, and quality of life. Eligible studies assessed changes in quality of life factors among pediatric patients with epilepsy since incorporating cannabinoids as a part of their treatment, and were assessed using the GRADE criteria.

Results: Three articles met eligibility criteria. Each cohort study had a different design: observational; retrospective; and prospective. All studies found cannabidiol to effectively reduce seizure frequency and improve alertness, mood/behavior, and language. Unfortunately, however, the overall quality of each reviewed study is very low due to design limitations. Further randomized double-blind control studies can minimize these limitations, and so enhance the quality of evidence available for demonstrating the impact cannabidiol may have on improving quality of life in patients with severe epilepsy.

Conclusion: There is weak evidence to suggest that cannabidiol use in those with severe epilepsy can contribute to improvements in QOL and reduce seizure frequency. Randomized control trials or double-blind case-control studies are needed to more effectively discern CBD's potential impact in improving quality of life in those with severe epilepsy.

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Biography

[redacted for privacy]
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**Results:** Three articles met eligibility criteria. Each cohort study had a different design: observational; retrospective; and prospective. All studies found cannabidiol to effectively reduce seizure frequency and improve alertness, mood/behavior, and language. Unfortunately, however, the overall quality of each reviewed study is very low due to design limitations. Further randomized double-blind control studies can minimize these limitations, and so enhance the quality of evidence available for demonstrating the impact cannabidiol may have on improving quality of life in patients with severe epilepsy.

**Conclusion:** There is weak evidence to suggest that cannabidiol use in those with severe epilepsy can contribute to improvements in QOL and reduce seizure frequency. Randomized control trials or double-blind case-control studies are needed to more effectively discern CBD’s potential impact in improving quality of life in those with severe epilepsy.

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Table 1: Quality assessment of reviewed studies

List of Abbreviations

QOL Quality of life
CBD Cannabidiol
AED Anti-epileptic drug
FDA Food and Drug Administration
THC Tetrahydrocannabinol
U.S. United States
EMR Electronic medical record
OCE Oral cannabis extract
EEG Electroencephalography
QOLCE Quality of Life in Childhood Epilepsy
Background

Epilepsy is a broad term used to define a brain disorder that causes one or more types of seizures, is often due to an underlying cause, and can have a profound impact on one’s quality of life (QOL). In 2015 as many as 3.4 million people in the United States (U.S.) were living with epilepsy, and of those, 470,000 of them were children. A diagnosis of epilepsy can be made if the patient has experienced two or more seizures.\(^1\) During a seizure one may experience changes in muscle tone, loss of consciousness, and/or convulsions that can result in injuries requiring hospital visits. Factors that determine the severity of one’s condition with epilepsy include the type(s) of seizure(s) one experiences, co-existing medical conditions, as well as underlying cause(s) for their epilepsy.\(^1\)

Chronic epilepsy has been shown to cause severe impairments with respect to physical, mental, and social aspects of a child’s life and can lead to low self-esteem, anxiety, depression, impaired memory and attention, lack of independence, and social stigma.\(^2\) Seizure control is crucial at any age but even more so in children due to their increased risk of progressive and detrimental cognitive effects and impairments of quality of life from uncontrolled seizures.\(^3\) Controlling seizures and their negative sequelae can be challenging in those with early onset childhood epilepsy, as this cohort is often refractory to Food and Drug Administration (FDA) approved therapies, ketogenic diets, and/or even corrective surgeries—leading to potentially major cognitive, behavioral and motor delays.\(^4,5\) On the other hand, even those with well controlled epilepsy are not
immune to the complications from having the condition. All currently available anti-epileptic drugs (AEDs) have been shown to cause adverse cognitive effects and toxicity—even more so in children taking additional medications.6

In response to AED resistance and the adverse side effects associated with current medications, pharmaceutical companies and other research institutions have explored alternative therapies, such as cannabidiol (CBD). Results from clinical trials7,8 have shown great potential in the use of cannabidiol to reduce both partial and generalized seizures, including in those who are refractory to other forms of treatment. In fact, the FDA approved a cannabidiol drug in June of 2018, Epidiolex, that is an oral solution indicated for treatment of Lennox-Gastaut or Dravet syndromes—2 severe forms of epilepsy. The most common side effects seen in clinical trials for Epidiolex, were mostly mild and included: fatigue, lethargy, elevated liver enzymes, decreased appetite, diarrhea, rash, insomnia, and infections.9

Cannabidiol is a compound found in cannabis, also known as marijuana. Cannabis contains roughly 80 cannabinoids and of those, cannabidiol and tetrahydrocannabinol (THC) are the 2 major components, but the effects of these 2 substances couldn’t be more polar. THC is a psychoactive agent that can be pro-convulsive in those with epilepsy; whereas, cannabidiol is a non-psychoactive agent that has been proven to have anticonvulsant properties in both animal and human studies.8

Although CBD has been proven to provide seizure control in severe forms of epilepsy, there has been little research on the agent’s effects on quality of life. This systematic literature review aims to further explore the use of cannabidiol as a co-agent in
treating various forms of epilepsy and its potential to positively impact QOL specifically with relation to seizure control and over-all improvements in alertness, mood/behavior, and language.

METHODS

An exhaustive literature search was performed using MEDLINE-Ovid, Web of Science, and Clinical Key. The following search terms were used: (cannabidiol or cannabis) AND epilepsy AND (child OR children OR pediatric OR pediatrics) AND ("quality of life" OR alertness OR sleep OR mood OR behavior OR language). Included were studies assessing changes in QOL among pediatric patients with epilepsy since incorporating cannabinoids or cannabis as a therapeutic agent for controlling their seizures. Other inclusion criteria required scholarly research studies performed on humans within the last 5 years in the U.S., and published in the English language. Studies were excluded if researchers did not assess QOL factors, as well as those that limited their research to subjects diagnosed exclusively with a specific seizure disorder. Bibliographies of relevant articles were also searched for further related material. Articles were then graded for quality using the GRADE approach.

RESULTS

The initial search yielded 35 articles for review. After eliminating duplicates 3 articles met the inclusion criteria. The first of those 3 articles was an observational study\textsuperscript{8} using online parent surveys. The second was a retrospective cohort study\textsuperscript{10} that examined the electronic medical records (EMR) of epileptic patients treated with cannabinoids for seizure management. Lastly, the third article was a prospective cohort study\textsuperscript{11} that
assessed parental observed QOL changes pre and post treatment with CBD. (See Table 1).

**First Article: Porter et al (2013)**

This observational study\(^8\) aimed to explore the parental observed response to cannabinoids for their child’s treatment-resistant epilepsy. A separate online survey was administered to validate the survey instrument, and presented to parents of children with a severe form of epilepsy, Dravet Syndrome, and who use an AED called stiripentol but did not use cannabinoids.\(^8\)

The investigators presented a 24-question survey to a Facebook group that supports use of cannabidiol for treatment of seizures in pediatrics, and received nineteen responses that met inclusion criteria. The majority of the children had a severe form of epilepsy, Dravet syndrome (n=13), and the remainder had Doose Syndrome (n=4), Lennox-Gastuat syndrome (n=1), or idiopathic (n=1) causes. All data collected was self-reported by parents and could not be verified. Inclusion criteria consisted of a child diagnosed with epilepsy and who is actively using cannabidiol as part of seizure management. Factors assessed in the survey included diagnosis, seizure types, observed effect of cannabidiol on seizure frequency, and side effects.\(^8\)

In consideration of the profoundly supportive survey results for use of CBD, as well as the study population composed mainly of those with Dravet Syndrome, the same survey was administered to 20 parents of children with a diagnosis of Dravet syndrome who used an approved AED called stiripentol, well known for controlling seizures in this
form of epilepsy, but did not use cannabidiol. The investigators wanted to compare the results of this survey to those seen in clinical trials for stiripentol and found them to be consistent with respect to seizure control and side effects.  

The congruence between parental observations and medical observations of stiripentol patients, led the researchers to conclude that parental observations of CBD treated patients were a valid indicators of actual patient outcomes. Those CBD survey results reported CBD to be a well-tolerated agent highly effective in reducing seizure occurrence with minimal adverse effects, and noted improvements with respect to cognition and mood. The majority of parents surveyed observed CBD to be most effective in reducing number of seizures (84%) to the extent that many parents reported being able to wean their child from other AEDs (63%). Additionally, most noted improvements in their child’s mood (79%) and alertness (74%). Data on seizure control for those strictly on stiripentol was not available, but of those surveyed, one third of parents reported noted improvements in their mood (27%) and increased alertness (23%) since initiating stiripentol. Most AEDs are commonly associated with negative side effects related to mood and cognition including, insomnia, irritability, and aggressiveness; however, these tendencies were not observed by parents of those using CBD.  

Several limitations were noted in reviewing this study. First, as the investigators recognize, there is a great selection bias in the study sample, as well as a strong potential for placebo effect as the survey was presented to a Facebook group of parents in support of CBD in epilepsy. Furthermore, parent-reported outcomes are subjectively measured
and unsubstantiated. Another limitation to this study is the level of inconsistency with respect to the different types of cannabis extracts used across the study population as well as dosing and duration of use. Potential confounding variables to the study include the potential contamination of THC in those using cannabidiol enriched cannabis, which is known to have pro-convulsive effects in those with epilepsy.


Investigators reviewed the medical records of 75 children using oral cannabis extracts (OCE) given for seizure management by clinicians at the Children’s Hospital of Colorado as part of this retrospective cohort study.  

Those children included in the study were between the ages of 30 days to 18 years of age, they must have had a diagnosis of epilepsy, and a documented seizure frequency before and after initiating OCE. Additionally, the patient must have been seen at least twice by the medical provider. Patients were excluded from the study if they were not using the prescribed OCE daily. Of those included, patients had a variety of seizure types and forms of epilepsy, including Dravet and Lennox-Gastaut syndromes.

Data collected for review included demographic information, seizure characteristics and frequency, OCE type and dosage, benefits from OCE use, adverse effects, and electroencephalography (EEG) patterns and changes. Patients were considered to be responding to the OCE if parents reported >50% reduction in frequency and supported by their clinician’s documented reports. Factors dependent upon OCE use were analyzed using Fisher’s exact test and binary logistic regression, and “seizure type responses were compared using ANOVA.”
Results from this study demonstrated mild to moderate improvements in QOL factors. A reduction in seizure frequency was observed by 57% of parents, and 33% of the total sample were considered to be true responders. EEG findings were available for eight of the responders but showed no changes since initiating OCE. Other improvements noted by a small subset of parents were in behavior and alertness (33%), language (10%), and motor skills (10%). Some adverse events were documented in 44% of the patients including an increase in seizures (n=10) and fatigue (n=9), developmental regression (n=2), abnormal movements (n=2), status epilepticus (n=1), and death (n=1). There were no observed differences between those on varying strains or type of OCE (e.g. high CBD, CBD plus, THC-A, etc.).

Inconsistencies across this study could have invariably impacted the data. These inconsistencies included the type of product used, duration, and dosing—all of which lacked standardization. Often time dosing data was not available or parents were advised to recommend increasing or decreasing the amount to administer, but the new dosing recommendations were not documented.

**Third Article: Rosenberg et al (2017)**

This was a prospective cohort study\textsuperscript{11} that enrolled 68 patients with intractable epilepsy to an open-label CBD clinical study and measured caregiver reported Quality of Life in Childhood Epilepsy (QOLCE) using diaries and questionnaires. The QOLCE is a 91-item survey that measures five domains of QOL, including, behavior, physical, cognitive, and social function, and has been tested for internal consistency and test-retest reliability.\textsuperscript{11}
Recruited subjects were patients seen at the New York University Epilepsy Center, between the ages of 1-30 years, and deemed eligible if they had four or more motor seizures within a 4-week period. Excluded patients had liver, renal or hematological abnormalities as assessed by baseline labs, progressive disorders, or a medication use history of felbamate or vigabatrin within six months of enrollment. Of the sixty-eight patients enrolled, 80% completed the study and the majority of the patients had either Dravet Syndrome, Lennox-Gastaut, or a genetic generalized epilepsy.11

Upon enrollment, parents/patients were asked to keep a seizure diary over a 4-week period prior to initiating CBD and while continuing to receive their standard treatment. Caregivers completed the QOLCE survey at the pretreatment visit, and then following 12 weeks of CBD treatment.11

During CBD treatment, each patient received a 99% oil-based CBD extract in a consistent composition and mixed with 100mg/mL sesame oil. Initial CBD dosing was 2-5mg/kg/day divided and administered twice daily via by mouth or gastric tube. The dosage was then titrated by 2-5mg/kg/week until either intolerant or the maximum dose of 50mg/kg/day was achieved. Also during the treatment phase, patients maintained their treatment at enrollment and no new medications were initiated.11

Responses to the survey were graded on a 5-point Likert scale and the overall QOL was calculated using the sum of the subscores. Those subscores were then linearly converted to a 100-point scale. Overall baseline and post-treatment scores were compared using a paired t test, which were then compared individually and between responders. Seizure frequency was documented and compared during the 4-week pre-treatment and 12-week treatment periods for all patients—these results were compared using a
Wilcoxon rank sum test. Percentage seizure reduction and changes in QOLCE scores were analyzed using simple linear regression analysis to assess for any association.\textsuperscript{11}

Results showed a 50\% reduction in mean monthly seizures from baseline to end of treatment. Overall caregiver-reported QOLCE scores demonstrated statistically significant improvements in the areas of: energy/fatigue, memory or cognitive functioning, behavior and social interactions, as well as overall QOL. Interestingly, no association was found between changes in QOLCE and seizure frequency, nor was there an association found between number of adverse effects and QOLCE scores. Adverse events included fatigue or drowsiness (n=28) and psychiatric events (n=10).\textsuperscript{11}

In this open-label prospective study, neither investigators nor participants were blinded—thus, risking placebo or over-exaggerated effects. Furthermore, as the investigators state, the repeated exposure to the same QOL survey could have contributed to falsely elevated scores not related to the true effects of the treatment. Moreover, the lack of a comparison or control group challenges the over-all results of CBD’s seizure reducing potential or its ability to improve measures of QOL among patients with severe epilepsy.

**DISCUSSION**

Chronic epilepsy can cause profound and irreversible impacts on a patient’s quality of life across a multitude of domains, including impairments on their cognitive and social function.\textsuperscript{3} Furthermore, standard AEDs can have toxic and cognitive effects and an even greater potential in doing so in patients on additional medications. Therefore, attaining seizure control and mitigating the potential effects of AEDs, especially during a patient’s developmental years, has the potential to provide meaningful life-long benefits.
Clinical trials have revealed CBD’s potential to help provide seizure control in those patients with severe forms of epilepsy that are refractory to standard anti-epileptic drugs.\textsuperscript{3} This finding was observed consistently within the studies examined in this systematic review.\textsuperscript{8,10,11} Furthermore, those same studies collectively demonstrated CBD’s potential to improve quality of life with respect to alertness, mood/behavior, and language in a similar patient profile. An adverse effect of cannabidiol noted across all studies was somnolence or fatigue.\textsuperscript{8,10,11} This effect seems contrary to the noted benefits of improved alertness or cognitive functioning, but is consistent with what has been observed in clinical trials.\textsuperscript{9} As seen in Table 1, the quality of the studies was graded to be very low, but synergistically they show the potential for CBD to improve QOL amongst pediatric patients with severe epilepsy. Therefore, results of the individual studies should be interpreted with caution.

In appraising the reviewed studies, many significant limitations were noted, including lack of double blinding, selection bias, and inconsistencies within each study including, type of CBD used, dosage administered, duration of CBD use, and the potential for performance bias due to heightened expectations. All studies had small sample sizes which can further decrease statistical power. Additionally, only 1 of the studies reviewed used a validated instrument for measuring subjective outcomes of interest (Roseburg et al).

\textbf{CONCLUSION}

There is weak evidence to suggest that cannabidiol use in those with severe epilepsy can contribute to improvements in QOL and reduce seizure frequency. However,
it is unclear if improvements to quality of life are due to decrease in seizure frequency or from cannabidiol.

Further studies are needed to more effectively discern CBD’s potential impact in improving QOL using randomized control clinical trials or double-blind case-control studies. Additionally, standard dosing of CBD and validated instruments for measuring outcomes should be utilized to further improve the quality of evidence.
References


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a Selection bias in Porter et al study
b Cannabinoid dosing and type used within and across all studies was variable
c Qualitative outcome based on parent report and not measured consistently across all studies
d The Porter et al study was funded by the publisher (NIH)
e Rosenberg et al study lacked blinding