

**MEDICAL CANNABIS FOR THE TREATMENT OF
DRUG-RESISTANT EPILEPSY IN CHILDREN:
A HEALTH TECHNOLOGY ASSESSMENT**

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DEDICATION

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ABSTRACT

Interest in the use of medical cannabis for the treatment of drug-resistant epilepsy in children has grown over the last decade; however, little is known about its potential benefits and harms, cost-effectiveness, or the perspectives of key stakeholders. In this thesis, a health technology assessment approach was adopted to assess the intended and unintended consequences of medical cannabis use in the treatment of pediatric drug-resistant epilepsy. This thesis comprises three main sections: (1) a living systematic review of the benefits and harms of medical cannabis for the treatment of pediatric epilepsy, including drug-resistant forms; (2) an economic evaluation of the cost-effectiveness of medical cannabis for the treatment of pediatric drug-resistant epilepsy, and (3) qualitative exploration of the perspectives of neurologists and parents of children with drug-resistant epilepsy about the use of medical cannabis in this population. While neurologists generally perceived medical cannabis as a viable treatment option for drug-resistant epilepsy in children, particularly after other treatments have failed, they identified several gaps in the evidence base, including a lack of long-term studies and a lack of evidence related to cannabinoids other than cannabidiol. This is in keeping with the findings of the living systematic review, which support a beneficial role for medical cannabis in reducing seizures associated with drug-resistant epilepsy, although the certainty of the evidence was moderate at best. Parents described experiencing many barriers to accessing medical cannabis for their children, primarily related to finding a health care provider to authorize its use, the high cost of cannabis-based treatments, and a lack of reimbursement through public or private insurance programs. However, cannabinoid oil may be a more cost-effective treatment for some types of pediatric drug-resistant epilepsy compared with antiepileptic drugs currently reimbursed by some provincial insurance programs. These findings suggest that medical cannabis is a potentially effective and cost-effective treatment for drug-resistant epilepsy that may address an unmet need. However, additional studies are needed to address uncertainty related to the long-term benefits and harms of cannabis-based products, particularly with respect to products available in Canada.

EXECUTIVE SUMMARY

“When you have a kid who's sick and doesn't respond to regular medications, you'll try anything”

Mother of an 11-year-old boy with Dravet syndrome

Children with Dravet syndrome and other forms of drug-resistant epilepsy are in need of an effective treatment to control their seizures, owing to a lack of success with traditional antiepileptic treatments. Beginning in 2013 with the airing of the “Weed” documentary on CNN, which highlighted the case of a 5-year-old girl with Dravet syndrome whose seizures were dramatically reduced by cannabinoid oil, interest has grown rapidly in the use of medical cannabis to treat drug-resistant epilepsy. While parents and the general public have been quick to accept medical cannabis as a treatment for epilepsy in children, health care professionals have been slower to view it as a viable option. Importantly, as of 2016 when cannabinoid oils were introduced into the Canadian medical cannabis system, there had been few clinical studies of its effectiveness and/or safety in this population.

This thesis explores the intended and unintended consequences of adopting medical cannabis as a treatment for pediatric drug-resistant epilepsy, with an overall aim of providing usable evidence to parents, health care providers, and policy makers to inform their decisions about the use of medical cannabis. To meet this aim, three research questions were addressed:

Question 1: What are the benefits and harms of medical cannabis for pediatric drug-resistant epilepsy?

Question 2: Is medical cannabis a cost-effective treatment for pediatric drug-resistant epilepsy compared to current therapeutic options?

Question 3: What are the perspectives of neurologists and parents about the use of medical cannabis for pediatric drug-resistant epilepsy?

This thesis entailed three main sections, each including multiple studies designed to address these research questions: (1) a living systematic review of the benefits and harms of medical cannabis in

the context of pediatric epilepsy; (2) an economic evaluation of the cost-effectiveness of cannabinoid oil compared to other treatments for Dravet syndrome, a severe form of pediatric drug-resistant epilepsy; and (3) two qualitative studies that explored the perspectives of neurologists and parents about the use of medical cannabis for children with drug-resistant epilepsy.

Overview of methods and findings

1. Benefits and harms of medical cannabis. Living systematic review methodology was used to identify, appraise, and synthesize studies involving the use of cannabis-based products in the treatment of pediatric epilepsy, including drug-resistant forms. Unlike traditional systematic reviews, which may be updated infrequently or not at all, living systematic reviews search for new studies at *a priori* defined intervals, thus incorporating new evidence shortly after it becomes available. Here, the initial literature search was performed in April 2018 (baseline review), followed by updates at 6-month intervals (October 2018, May 2019).

In the baseline review, 23 studies involving the treatment of pediatric epilepsy with medical cannabis were identified, including four randomized controlled trials (RCTs) and 19 non-randomized studies (NRS). At that time, most studies involved purified cannabidiol (CBD), which is not available in Canada. Evidence from the RCTs suggested that, compared with placebo, purified CBD reduced the monthly number of seizures experienced by children with Dravet and Lennox-Gastaut syndromes by about 20%. CBD also increased the number of children who had at least 50% fewer seizures from baseline, although there was no statistically significant difference in the number of children who became seizure free nor in quality of life, and gastrointestinal adverse events were common. Findings from the NRS were similar, although most were at high risk of bias. Across all outcomes, the certainty of the evidence ranged from very low to moderate, suggesting that the effect estimates could change with the publication of additional studies. Importantly, a further 33 registered clinical studies were identified in ClinicalTrials.gov, indicating that the literature base would continue to rapidly evolve.

In the first review update (October 2018), an additional seven NRS were identified, published between April and October 2018. The first study of a cannabinoid oil available in Canada was published during this interval. While this was a small, open-label cohort study, the findings similarly supported a beneficial role for cannabinoid oil in the treatment of drug-resistant epilepsy. The remaining studies primarily involved purified CBD and supported earlier findings.

The second review update (May 2019) identified an additional five NRS published between October 2018 and May 2019, bringing the total to 35 studies that have assessed the benefits and harms of cannabis-based products for the treatment of epilepsy in children. The findings from these studies were generally consistent with earlier findings, and the certainty of the evidence did not change for any outcome. Notably, as of May 2019, 32 studies involving treatment of pediatric epilepsy with various cannabis-based products were registered in ClinicalTrials.gov, including six RCTs, further supporting the use of living systematic review methodology to continue to monitor the evidence base.

2. Cost-effectiveness of medical cannabis. Although evidence suggests that cannabis-based products may be effective in reducing seizures, the cost-effectiveness of medical cannabis in this context is not clear. To address this question, a systematic review was conducted to identify any existing economic evaluations of medical cannabis for the treatment of pediatric drug-resistant epilepsy. Finding none, a *de novo* model-based cost-utility analysis was undertaken to evaluate the cost-effectiveness of a cannabinoid oil available in the Canadian medical cannabis system. In this study, the long-term costs and health outcomes associated with cannabinoid oil were compared with two treatments for Dravet syndrome which are currently reimbursed under some provincial drug plans (stiripentol, clobazam plus valproate). A second systematic review was performed to identify and assess model inputs (i.e., health state utility values, health care resource use, productivity losses) for the cost-utility analysis.

In the cost-utility analysis, cannabinoid oil (20:1 CBD to tetrahydrocannabinol [THC]) was found to be cost-effective compared with clobazam plus valproate from the perspective of the Canadian public health care system for the treatment of Dravet syndrome, if a decision maker is willing to pay at least

\$32,399 for each quality-adjusted life year (QALY) gained. Stiripentol was more expensive than cannabinoid oil and produced fewer QALYs, suggesting that it would not be the preferred treatment. From a more broad societal perspective, cannabinoid oil was more cost-effective than stiripentol and clobazam plus valproate at all willingness-to-pay thresholds, primarily owing to lower productivity costs with cannabinoid oil compared to the other treatments.

3. Stakeholder perspectives. Although the use of medical cannabis as a treatment for drug-resistant epilepsy in children is common, little is known about the perspectives of key stakeholders (e.g., neurologists and parents) regarding its use in this population, especially in the Canadian context. Thus, two interview-based qualitative studies were undertaken, with the aim of exploring the perspectives and experiences of neurologists and parents in Canada related to the use of medical cannabis for the treatment of pediatric drug-resistant epilepsy.

In the first study, 12 neurologists who provide care to children with drug-resistant epilepsy in Canada were interviewed. Participants generally perceived medical cannabis as a viable treatment option for pediatric drug-resistant epilepsy but identified important gaps in the available evidence (e.g., lack of long-term studies, lack of evidence related to cannabinoids other than CBD) and implications for their practices. Six themes were generated from the content of the interviews: learning about medical cannabis; perceptions about medical cannabis; discussing medical cannabis with parents; experiences with medical cannabis authorization; barriers to authorizing medical cannabis; and the impact of medical cannabis on clinical care.

In the second study, 19 parents were interviewed, all of whose children had used medical cannabis for treatment of their drug-resistant epilepsy, and an access to care framework was used to explore the barriers they faced when trying to access medical cannabis in Canada. Medical cannabis was viewed as an acceptable treatment option to all parents interviewed, largely because of unmet need stemming from the failure of antiepileptic drugs to control their children's seizures. Obtaining authorization and the cost of cannabinoid oils were important barriers described by parents. Most

encountered resistance from their child's neurologist to discussing or authorizing medical cannabis use, leading many parents to seek authorization from a cannabis clinic. Participants described spending up to \$2000 out-of-pocket per month on medical cannabis and were frustrated that it is not eligible for reimbursement through public or private insurance programs.

Conclusion

Parents of children with drug-resistant epilepsy pursue treatment with medical cannabis because of an unmet medical need. Until recently, however, there had been little clinical evidence to support its use in this population. The evidence available at this time suggests that medical cannabis may be effective in reducing the frequency of seizures for children with drug-resistant epilepsy; however, most evidence relates to purified CBD oil, a product not available in Canada. Small open-label studies have suggested that some Canadian cannabinoid oils are similarly effective and safe; however, these products are not reimbursed by any provincial or private insurance program for the treatment of epilepsy, and the out-of-pocket costs are prohibitive for some parents. However, cannabinoid oils may be a more cost-effective treatment option than some currently reimbursed antiepileptic drugs for treatment of specific epilepsy syndromes. Although medical cannabis has been legal in Canada for almost two decades, parents may still encounter many barriers in accessing medical cannabis for their children, including finding a neurologist to authorize its use, and strategies are needed to ensure that children using medical cannabis receive proper care from health care professionals with training in epilepsy care, antiepileptic drugs, and medical cannabis.

CONTRIBUTION OF THE AUTHORS

Nine manuscripts were prepared as part of this thesis (presented in Chapters 3–5), all of which have been published or submitted for publication.

All manuscripts were led by Jesse Elliott and were co-authored by at least one supervisor (George A Wells; co-supervisors Doug Coyle, Tammy Clifford) and members of the thesis advisory committee (Beth Potter, Bláthnaid McCoy). Jesse is first author on all publications, having been responsible for study design, data collection, analysis, and writing of the manuscripts. All studies were designed in consultation and discussion with members of the thesis advisor committee. Bláthnaid McCoy provided clinical input into all studies, and two family members of children with drug-resistant epilepsy (Christine Alexander, Alexander Repetski) provided input into the design of the living systematic review presented in Chapter 3 and are co-authors of the resulting publications.

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
BCE	Before Common Era
CBD	cannabidiol
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CLAE	Canadian League Against Epilepsy
CUA	cost-utility analysis
DIN	drug identification number
DRE	drug-resistant epilepsy
DS	Dravet syndrome
EEG	electroencephalogram
ER	emergency room
EUnetHTA	European Network for Health Technology Assessment
FIRES	febrile infection-related epilepsy
GABA	gamma-aminobutyric acid
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ILAE	International League Against Epilepsy
IQR	interquartile range
KD	ketogenic diet
LGS	Lennox-Gastaut syndrome
LSR	living systematic review
MD	mean difference
NAC	not adequately controlled
NA	not applicable
NOC	notice of compliance
NR	not reported
NRS	non-randomized study
NSF	not seizure free
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
QALY	quality-adjusted life year

QoL	quality of life
RCT	randomized controlled trial
RD	risk difference
ROB	risk of bias
RR	relative risk
SD	standard deviation
SE	status epilepticus
SF	seizure free
SRQR	Standards for Reporting Qualitative Research
SUDEP	sudden unexpected death in epilepsy
THC	delta-9-tetrahydrocannabinol
TSC	tuberous sclerosis complex
VNS	vagus nerve stimulation

Chapter 1:

Introduction

1.1 Statement of the problem

In Canada, about 19,000 people under the age of 18 have epilepsy.¹ Of these, about one-third have a drug-resistant form (failure of two or more antiepileptic drugs to control their seizures).² The consequences of drug-resistant epilepsy in children are severe and include neurologic damage, cognitive impairment, poor quality of life, and an increased risk of death.³ Drug-resistant epilepsy in children also has a major impact on other family members, with parents experiencing high levels of stress, financial burden, and reduced quality of life.⁴⁻⁶

Interest among parents in the use of medical cannabis as a treatment for epilepsy in children has grown over the last decade, driven at least partly by media reports of children whose severe drug-resistant epilepsy has responded to cannabis.⁷ In 2013, CNN aired a documentary that highlighted Charlotte Figi, a 5-year-old girl from Colorado with Dravet syndrome whose seizures were reduced by more than 90% by treatment with medical cannabis.⁸ Charlotte's case received considerable media attention and has led to hope among parents that cannabis could help control their children's seizures despite the failure of antiepileptic drugs. However, health care professionals have been slower to accept medical cannabis as a treatment for epilepsy. As of 2015, there was a striking difference in opinion between neurologists and the public and patients as to whether the evidence was sufficient to permit the use of medical cannabis in the treatment of epilepsy, with more than two-thirds of neurologists considering the available data on its safety and effectiveness to be insufficient.⁹ In contrast, 98% of respondents from the general public supported use of medical cannabis in cases of drug-resistant epilepsy.⁹

In Canada, the legal medical cannabis system was introduced with the *Marihuana Medical Access Regulations* in 2001, which permitted authorized patients to purchase dried cannabis from Health

Canada. Parents, however, described difficulty in finding a health care provider to authorize medical cannabis, as well as the inability to access a form of cannabis that could be easily administered to their children.¹⁰ The medical cannabis landscape has undergone major transformations since then; importantly, the sale of cannabinoid oils to authorized patients became legal in 2016. However, at that time, there had been no randomized controlled trials (RCTs) of medical cannabis involving children with epilepsy, and anecdotal reports suggested that parents were still facing barriers to accessing medical cannabis at that time.

1.2 Objective

The overall objective of this thesis is to provide comprehensive and up-to-date information about the use of medical cannabis for the treatment of drug-resistant epilepsy in children, with the aim of providing information that could aid parents, health care providers, and policy makers in making decisions about the use of medical cannabis in this population.

1.3 Research questions

In order to meet this objective, this thesis addresses three research questions:

Question 1: What are the benefits and harms of medical cannabis for pediatric drug-resistant epilepsy?

Question 2: Is medical cannabis a cost-effective treatment for pediatric drug-resistant epilepsy compared to current therapeutic options?

Question 3: What are the perspectives of neurologists and parents about the use of medical cannabis for pediatric drug-resistant epilepsy?

1.4 Chapter outlines

This thesis comprises six chapters. Chapter 1 provides an overall introduction and the rationale for the thesis, while Chapter 2 provides an overview of epilepsy, medical cannabis, and the research methodology. Chapters 3, 4, and 5 present manuscripts that address the three research questions; of

note, each of these chapters contains multiple related manuscripts. The final chapter of the thesis, Chapter 6, integrates the major findings from the thesis and considers the implications for clinical practice and policy.

The following section presents a brief overview of each chapter:

Chapter 1. Introduction: This introductory chapter provides a summary of the rationale for the thesis, the overall objectives of the thesis, and a brief description of each subsequent chapter.

Chapter 2. Background: This chapter provides relevant background information about epilepsy and medical cannabis, as well as an overview of the methodologic framework used to guide the thesis.

Chapter 3. Benefits and harms of medical cannabis for pediatric drug-resistant epilepsy: This chapter contains three related manuscripts (**Sections 3.1–3.3**) that describe a living systematic review of the benefits and harms associated with the use of cannabis-based products for the treatment of epilepsy in children. The title of each manuscript is listed below:

Section 3.1: Cannabis for pediatric epilepsy: Protocol for a living systematic review

Section 3.2: Cannabis-based products for pediatric epilepsy: A systematic review

Section 3.3: Cannabis-based products for pediatric epilepsy: An updated systematic review

Chapter 4. Cost-effectiveness of medical cannabis for pediatric drug-resistant epilepsy: This chapter contains four related manuscripts that explore the cost-effectiveness of medical cannabis as a treatment for pediatric drug-resistant epilepsy compared to current therapeutic options. The first three manuscripts in this chapter (**Sections 4.1–4.3**) pertain to systematic reviews intended to identify existing economic evaluations of cannabis-based products for pediatric drug-resistant epilepsy, as well existing decision models for other antiepileptic drugs and inputs (health state utility values, resource use, productivity loss) to inform the *de novo* cost-utility analysis presented in **Section 4.4**. The title of each manuscript is listed below:

Section 4.1: Cost-effectiveness of cannabinoids for pediatric drug-resistant epilepsy:
Protocol for a systematic review of economic evaluations

Section 4.2: Decision models for assessing the cost-effectiveness of treatments for pediatric drug-resistant epilepsy: A systematic review of economic evaluations

Section 4.3: A systematic review of health state utility values, health care resource use, and productivity costs associated with pediatric drug-resistant epilepsy

Section 4.4: Economic evaluation of cannabinoid oil for Dravet syndrome: A cost-utility analysis

Chapter 5. Stakeholder perspectives on the use of medical cannabis for pediatric drug-resistant

epilepsy: This chapter presents the findings of two qualitative studies exploring the perspectives and experiences of neurologists (**Section 5.1**) with the use of medical cannabis as well as the barriers experienced by parents of children with drug-resistant epilepsy when attempting to access medical cannabis (**Section 5.2**). The title of each manuscript is listed below:

Section 5.1: Neurologists' perspectives on medical cannabis for pediatric drug-resistant epilepsy in Canada: A qualitative interview study

Section 5.2: Barriers in accessing medical cannabis for children with drug-resistant epilepsy in Canada: A qualitative study

Chapter 6. Discussion and Conclusion: This summary chapter integrates the findings of the individual manuscripts and considers the implications for policy and practice. Limitations of the thesis are discussed, and recommendations for future studies are proposed.

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Chapter 2:

Background

Overview of Chapter 2. As introduced in Chapter 1, this thesis focuses on the use of medical cannabis as a treatment for drug-resistant epilepsy in children. As such, Chapter 2 provides background information about epilepsy and medical cannabis. Chapter 2 also describes the overarching thesis framework and the methodologies used to address each of the research questions outlined in Chapter 1.

2.1 Epilepsy

“Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition.”¹

The current International League Against Epilepsy (ILAE) definition of epilepsy is based on the occurrence of two or more unprovoked seizures occurring more than 24 hours apart; one unprovoked seizure and a probability of further seizures greater than 60%; or diagnosis of an epilepsy syndrome.¹ Epilepsy is characterized by recurrent seizures caused by brief disturbances of the electrical functions of the brain (i.e., abnormal oscillatory events within neuronal networks), leading to the excessive firing of neurons. Such oscillations are driven by neuronal hyperexcitability (abnormal burst discharges by neurons), a loss of neuronal inhibition (the normal inhibition of the spreading of burst discharges), and neuronal hypersynchrony (synchronous spread of bursts through a group of neurons).² Notably, there are multiple causes of epilepsy, including genetic, infectious, metabolic, immune, and structural (e.g., due to ischemic or traumatic brain injury) causes, which has implications for treatment.³

The ILAE considers three elements in the hierarchical classification of epilepsy: (1) seizure type; (2) epilepsy type; and (3) epilepsy syndrome (Figure 1). At the first level of classification, seizures are

described according to the area of onset (i.e., focal onset, generalized onset, unknown) and symptoms (e.g., motor, non-motor).⁴ Next, epilepsy type (determined by a combination of seizure type, electroencephalogram [EEG] findings, and clinical observation) is described as focal, generalized, combined generalized and focal, or unknown.³ Finally, for some patients, diagnosis of a specific epilepsy syndrome can be made, on the basis of multiple factors including seizure types, EEG and imaging findings, as well as age at onset, seizure triggers, and comorbidities.³

Epilepsy syndromes include “*idiopathic generalized epilepsies*” (further subdivided into childhood absence epilepsy; juvenile absence epilepsy; juvenile myoclonic epilepsy; and generalized tonic–clonic seizures alone) and “*self-limited focal epilepsies*.”³ While some epilepsy syndromes are typically “*pharmacoresponsive*” (i.e., can be controlled by antiepileptic therapy), others are “*pharmacoresistant*” and do not typically respond to antiepileptic therapy (i.e., drug-resistant).^{3,5}

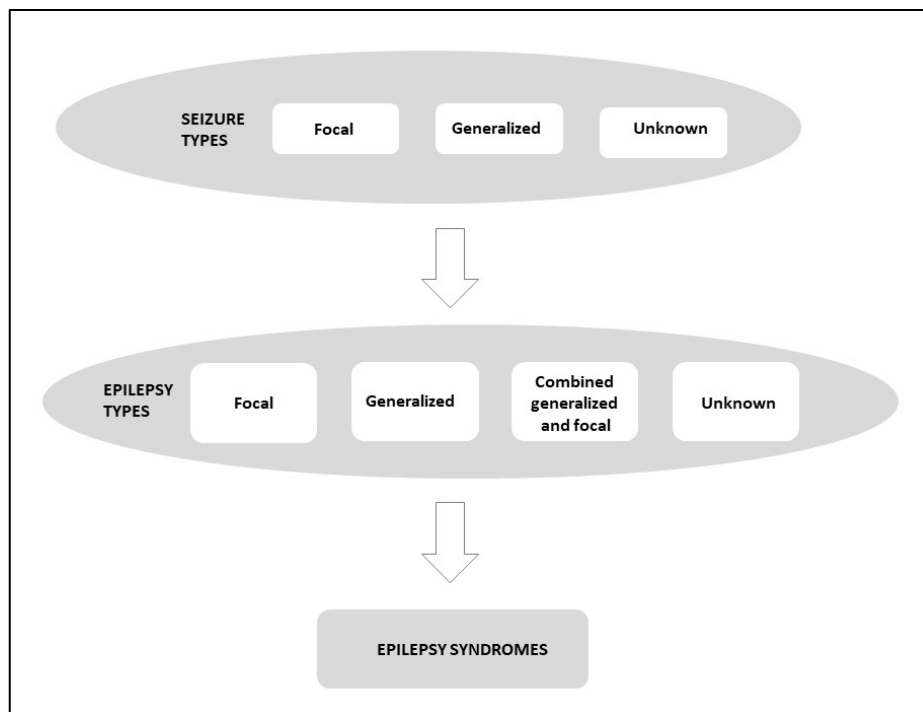


Figure 1: International League Against Epilepsy’s framework for the classification of epilepsy
Adapted from Scheffer 2017.³

2.1.1 Drug-resistant epilepsy

“Epilepsy in which seizures persist and seizure freedom is very unlikely to be attained with further manipulation of AED [antiepileptic drug] therapy. ... it is defined as ‘failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.’”⁵

The definition of drug-resistant epilepsy hinges on whether a patient continues to have seizures despite trying two appropriate antiepileptic drugs.⁵ In this context, an appropriate antiepileptic drug is one that is deemed appropriate for the patient’s epilepsy and seizure type and has been shown to be effective, preferably in a randomized controlled trial.⁵ After failing two appropriate drugs, the likelihood of achieving seizure freedom with subsequent treatment is low.⁶

Drug-resistant epilepsy is also referred to in the literature as “*treatment resistant*,” “*pharmacoresistant*,” “*intractable*,” or “*catastrophic*,” although “*drug resistant*” is the term favoured by the ILAE. All types of epilepsy can be drug resistant, thus the term “*drug resistant*” can be broadly applied across many individual epilepsy syndromes. Several pediatric epilepsy syndromes are typically classified as being associated with drug-resistant seizures, including Dravet syndrome (Severe Myoclonic Epilepsy in Infancy), Lennox-Gastaut syndrome, West syndrome (infantile spasms), Sturge-Weber syndrome, Doose syndrome (epilepsy with myoclonic-astatic seizures), Ohtahara syndrome (early infantile epileptic encephalopathy with suppression burst), and seizures associated with Tuberous Sclerosis Complex.

2.1.2 Epidemiology

About 50 million people worldwide have epilepsy,⁷ including about 139,000 people in Canada.⁸ Based on the 2010/2011 Canadian Community Health Survey, the prevalence of active epilepsy among those aged less than 18 years was 2.9 per 1,000 (95% confidence interval [CI] 2.3 to 3.6), or about 19,000 people.⁸ Prevalence estimates from the 1998/99 cycle of the Canadian National

Longitudinal Survey of Children and Youth were higher (5.26 per 1,000 [95% CI 5.25 to 5.27], with a higher incidence among male children (6.45 per 1,000) than among female children (4.00 per 1,000).⁹ While this estimate is considerably higher than the 2010/2011 estimate from the Canadian Community Health Survey, this may be owing to how questions about epilepsy were asked in the survey: The Canadian Community Health Survey asked respondents about “active epilepsy” (a seizure within the last five years or taking an antiepileptic drug), while the Canadian National Longitudinal Survey of Children and Youth asked ““Does the child have any of the following long-term conditions that have been diagnosed by a health professional?” with a list that included epilepsy.⁹

Prevalence estimates in other countries ranges between 3.2 and 5.1 per 1,000 children in Europe and between 4.7 and 6.3 per 1,000 children in the US.¹⁰ A 2017 systematic review reported a worldwide prevalence of 5.19 per 1,000 (95% CI 3.54 to 7.62) among children aged 0 to 9 years and 8.86 per 1,000 (95% CI 6.58–11.92) among those aged 10 to 19 years, although high heterogeneity between studies was noted.¹¹ Generally, the prevalence may be higher in lower-income countries, possibly owing to higher rates of head injury, meningitis, encephalitis, and cystercerosis.¹⁰ Further, the wide variation in estimates and heterogeneity across studies may be owing to differences in definitions (e.g., active epilepsy vs ever epilepsy), methodology (e.g., door-to-door survey v. administrative database), and ages considered.

Similarly, estimates of the incidence of epilepsy in children vary depending on the definition and age group.¹⁰ A 2017 systematic review estimated the pooled worldwide incidence among those aged less than 18 years to be 85.29 per 100,000 children (95% CI 59.54 to 122.19 per 100,000), with higher incidence in lower and middle income countries.¹¹ In Canada, the overall incidence of epilepsy is estimated to be 41 per 100,000 among those aged less than 17 years, with higher incidence in younger age groups (< 1 year: 118 per 100,000; 1–5 years: 48 per 100,000; 6–10 years: 43 per

100,000; 11–16 years: 21 per 100,000).¹² Higher incidence among younger children has also been reported in other jurisdictions.^{13,14}

About one-third of people with epilepsy are thought to have a drug-resistant form.¹⁵ Thus, based on the estimated prevalence of epilepsy in Canada,⁸ about 6000 Canadian children are predicted to have drug-resistant epilepsy. The incidence varies across individual epilepsy syndromes. For example, Dravet syndrome is estimated to occur in between 2.4 and 6.4 per 100,000 children,^{16–18} while Lennox-Gastaut syndrome affects about 2 in 100,000 children.^{19,20}

2.1.3 Consequences of pediatric epilepsy

Epileptic seizures contribute to neurologic damage and cognitive impairment and increase the risk of falls/injuries, status epilepticus, and sudden unexpected death (i.e., sudden unexpected death in epilepsy [SUDEP]).²¹ Up to 50% of children with epilepsy may have a comorbid condition, including cognitive and psychiatric conditions such as autism spectrum disorder or attention deficit and hyperactivity disorder,²² and educational achievement, employment, adult relationships may be negatively impacted later in life.²³ Further, epilepsy affects quality of life among children, with lower health-related quality of life reported among children with epilepsy compared to population controls.^{24,25} While individual trajectories vary after initial diagnosis, children prescribed more antiepileptic drugs may have lower health-related quality of life,²⁴ potentially because more intense drug management is indicative of harder to control seizures. Indeed, among children with drug-resistant epilepsy, use of more antiepileptic drugs and more frequent seizures are associated with lower health-related quality of life.^{26,27}

Childhood epilepsy also affects other family members, with parents of children with epilepsy reporting increased stress and reduced quality of life.²⁸ Parents of children with epilepsy may have lower quality of life relative to healthy controls, similar to that of parents of children with other chronic health conditions.²⁵ Further, degree of seizure control may be related to parental quality of life: better child seizure control has been associated with higher parental quality of life,²⁹ and parents

of children with drug-resistant epilepsy report lower quality of life compared to parents of children with controlled epilepsy.²⁵ Drug-resistant epilepsy may also contribute to a high level of stress among parents and a breakdown of relationships both within and outside the family,³⁰ with lower overall family wellness and more financial concerns among families of children with severe epilepsy.³¹ In addition to parents, the effects of epilepsy may extend to other family members, with lower quality of life and increased behavioural problems and emotional distress reported among siblings of children with severe chronic neurologic conditions.³²

2.1.4 Treatment options for pediatric drug-resistant epilepsy

There is no known cure for epilepsy, and for children with drug-resistant epilepsy, long-term seizure freedom is unlikely to be achieved with subsequent pharmacologic treatment.⁶ Children with drug-resistant epilepsy may experience periods of seizure remission with the use of additional antiepileptic drugs, but this is typically not long-lasting.³³ Thus, the goal of treatment is to reduce the frequency of seizures, as well as to improve and/or prevent decreases in health-related quality of life.²¹

However, because drug-resistant epilepsy comprises many individual epilepsy syndromes, there is no one standard of care,³⁴ and clinical practice guidelines for pediatric drug-resistant epilepsy are largely lacking.³⁵ The presence of comorbid conditions further complicates the treatment of epilepsy, as some treatments may have unintended negative effects on these comorbidities.³⁶ Treatment options for drug-resistant epilepsy include both non-pharmacologic interventions (e.g., resective surgery, ketogenic diet, vagal nerve stimulation) as well as pharmacologic interventions (i.e., antiepileptic drugs). Individual antiepileptic drugs may benefit only small groups of patients because of the rare nature of some epilepsy syndromes, and some drugs have designated orphan drug status in some jurisdictions (e.g., stiripentol for Dravet syndrome³⁷).

In addition to pharmacologic and nonpharmacologic treatments, complementary and alternative medicines are commonly used among people with epilepsy, including among children.^{38–41} The term “*complementary and alternative medicine*” broadly encompasses treatments that fall outside of

conventional medical practice, including (but not limited to) acupuncture, diet-based therapies, homeopathy, and natural health products (e.g., herbs and other products from plants).⁴² Reported estimates for the use of complementary and alternative medicines among children with epilepsy range from 13% to 78%,^{38–41} although a large proportion of parents may not disclose use.^{39,43} Use of complementary and alternative medicines may be higher among children with higher seizure frequency, those for whom conventional treatments have failed to control their seizures, and those who have experienced adverse drug events from conventional antiepileptic drugs.³⁸ Some parents may choose to try complementary and alternative medicines for their children because of a belief that such treatments are more natural or have less side effects than conventional treatments.³⁸ Indeed, some parents of children with epilepsy report trying cannabis as to treat their children's epilepsy because of experiencing unacceptable side effects from conventional antiepileptic drugs.⁴⁴

2.2 Medical cannabis

The cannabis plant (*Cannabis sativa*, *Cannabis indica*, *Cannabis ruderalis*) contains more than 100 different cannabinoid compounds (“*phytocannabinoids*”), of which the most recognized and studied are Δ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The term “*medical cannabis*” may be used to describe the dried buds of the cannabis plant (which contains cannabinoids in various ratios depending on the strain and breeding), as well as products derived from dried cannabis buds (e.g., cannabinoid oils). This is in contrast to synthetic cannabinoids, which are man-made compounds that mimic cannabinoids found in the cannabis plant. At present, one such product is approved by Health Canada for use in Canada: nabilone (synthetic THC) for the treatment of nausea and vomiting associated with chemotherapy.

Unless otherwise stated, the following sections focus on naturally occurring cannabinoids and products derived from the cannabis plant.

2.2.1 History of medical cannabis

The use of cannabis as a medicine dates to at least 2700 BC, when it was included in Chinese pharmacopeias.⁴⁵ Around 1800 BC, cannabis was used to treat ailments including “*nocturnal convulsions*” in the Middle East and for infections and pain relief by the Ancient Egyptians.⁴⁵ The medicinal use of cannabis was introduced to Europe in the late 1830s by Irish physician William O’Shaughnessy, who reported successfully using a cannabis extract to treat a 40-day-old child’s “*nocturnal convulsive episodes*” that had failed to respond to other treatments.⁴⁶ Notably, Sir William Gowers described the use of cannabis to treat refractory seizures in his 1881 book *Epilepsy and Other Convulsive Disorders*.⁴⁷

By the early 1900s, cannabis extracts had been added to the British and American pharmacopeias and were used widely as sedatives, hypnotics, and anticonvulsants.⁴⁸ However, cannabis began to fall out of favour as a medicine around the same time, owing to variation in plant composition, a short and unpredictable shelf life, increasing use of opiates, and increasing availability of synthetic drugs.⁴⁸ By the 1940s, cannabis had been removed from both the British and American pharmacopeias and, by the early 1970s, was moved to Schedule 1 (i.e., no medical use and high potential for abuse) in the US. Notably, cannabis became illegal in Canada in 1923.

Despite this, cannabis research continued. The cannabinoid THC was isolated in 1964, and small studies involving the use of THC began to appear in the literature, along with observational studies of recreational cannabis.⁴⁵ Pharmaceutical cannabis products consisting of synthetic THC were introduced in the 1980s (e.g., nabilone) and, more recently, pharmaceutical companies have introduced products derived from the cannabis plant, including nabiximols (Sativex, an oro-mucosal spray containing purified CBD and THC) and purified CBD (e.g., Epidiolex).

2.2.2 Medical cannabis in Canada

2.2.2.1 Legal status

The medical use of cannabis in Canada became legal in 2001 with introduction of the *Marihuana Medical Access Regulations* (Figure 2). At present, both medical and recreational cannabis are regulated under the *Cannabis Act*, which came into effect October 17, 2018.⁴⁹ Prior to the *Cannabis Act*, medical cannabis was governed by the *Cannabis for Medical Purposes Regulations* (ACMPR). The ACMPR represented an important update from previous cannabis regulations by allowing the sale of cannabinoid oils to authorized patients beginning in mid-2016. Although the *Cannabis Act* replaced the ACMPR, the regulations related to medical cannabis remained largely unchanged. Notably, the next review of these regulations by the Government of Canada is scheduled for 2023.⁴⁹

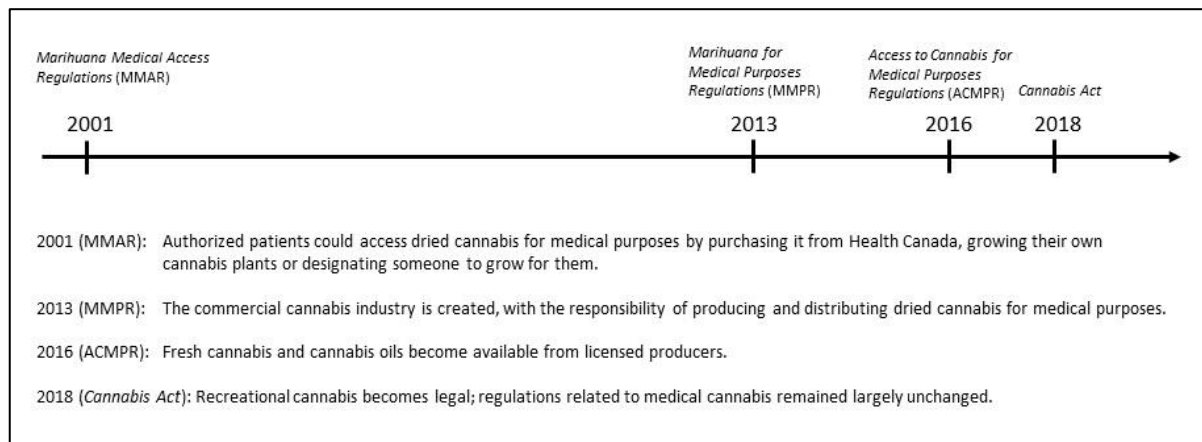


Figure 2: Timeline of medical cannabis regulations in Canada

Under the current regulations, patients who have received authorization from a health care provider (i.e., physician or nurse practitioner) can register with a licensed cannabis producer and can purchase cannabis products including fresh or dried cannabis or cannabis oil (i.e., oil containing cannabinoids extracted from cannabis [cannabinoid oil]).⁴⁹ As of December 31, 2019, a total of 165 producers held a federal license from Health Canada to sell cannabis to authorized patients, including 61 authorized to sell cannabinoid oils.⁵⁰

2.2.2.2 Regulation of medical cannabis

With the introduction of the *Cannabis Act* in 2018, which legalized recreational cannabis (i.e., cannabis for non-medical purposes), a new framework was established that regulates both medical and recreational cannabis products (Table 1). Within this framework, there are three categories of cannabis products: “cannabis for non-medical purposes,” “cannabis for medical purposes,” and “health products containing cannabis.” The category “health products containing cannabis” encompasses pharmaceutical products that contain cannabis; these continue to be regulated by the *Food and Drug Act* and are subject to pre-market safety and efficacy review by Health Canada; notably, approved products are granted market authorization (notice of compliance) and a drug identification number. In contrast, “cannabis for medical purposes” is regulated solely by the *Cannabis Act*, and products in this category are not subject to pre-market safety and efficacy review; as such, these are not issued a notice of compliance or a drug identification number.

2.2.2.3 Medical cannabis use

Based on the 2018 Canadian Cannabis Survey, 13% of Canadians aged 16 years and older have used cannabis for medical purposes.⁵¹ However, most people (66%) who reported medical cannabis use obtained it outside the legal medical system (i.e., without authorization from a healthcare professional), instead accessing cannabis through friends, compassion clubs/dispensaries, online sources, or illicit cannabis dealers.⁵¹ As of June 2019, a total of 363,917 people had registered with a Health Canada-licensed cannabis producer.⁵¹ Because this represents about 1% of the Canadian population, it suggests that a large percentage of Canadians continue to access cannabis for medical purposes outside the legal framework. This is consistent with data from the 2019 National Cannabis Survey, which found that about 1% of people who reported medical cannabis use had obtained medical authorization.⁵²

Table 1: Categories of cannabis products in Canada

	Cannabis for non-medical purposes	Cannabis for medical purposes	Health products containing cannabis
Description	Products obtained from a provincially and territorially licensed retailers, which are supplied by Health-Canada licensed producers	Products obtained from Health-Canada licensed producers (licensed to sell to medical patients), with authorization from a health care practitioner	Prescription drugs containing cannabinoids; e.g., nabiximols (oro-mucosal spray containing purified CBD and THC); nabilone (capsule containing synthetic THC)
Types of products	Fresh, dried, oil, plants, seeds, edibles, concentrates	Fresh, dried, oil, plants, seeds, edibles, concentrates	No restriction on dosage forms
Relevant regulations	<i>Cannabis Act</i>	<i>Cannabis Act</i>	<i>Cannabis Act</i> and the <i>Food and Drug Act</i>
Licensing of cannabis producers	Health Canada	Health Canada	NA
Minimum age for use	18–21 years, depending on province	None	Depending on authorization
Health care practitioner oversight	No	Yes (authorization)	Yes (prescription)
Pre-market review of safety and efficacy	No	No	Yes
Quality and security requirements	Yes, regulated by the <i>Cannabis Act</i>	Yes, regulated by the <i>Cannabis Act</i>	Yes, regulated by the <i>Cannabis Act</i> and the <i>Food and Drug Act</i>
Can make health claims	No	No	Yes, if authorized
Given a drug identification number	No	No	Yes

The number of children in Canada who use cannabis for medical purposes is not clear. Although patients registered with licensed cannabis producers are tracked by Health Canada,⁵¹ the publicly available data are not stratified by age group. Further, both the Canadian Cannabis Survey and the National Cannabis Survey included only those aged 15 years and older. In a 2017 survey of pediatricians by the Canadian Paediatric Surveillance Program, 50% of respondents reported that they had “*encountered patients who had used cannabis for medical purposes, either authorized or not authorized,*” and 38% of respondents reported having been asked to provide authorization in the past year.⁵³

2.2.2.4 Medical cannabis products available in Canada

Since the introduction of the *ACMPR* regulations in mid-2016, authorized patients in Canada have been able to purchase cannabinoid oil (oil extracted from the cannabis plant, containing a mixture of cannabinoids in various ratios), as well as dried or fresh cannabis flower, from licensed producers.⁵⁴ Amendments to the *Cannabis Act* in October 2019 further allow for the sale of cannabis edibles, cannabis extracts, and cannabis topical to authorized patients.⁵⁵ Cannabinoid oils are the form most commonly used by pediatric patients⁵⁶; as such, this thesis focuses specifically on cannabinoid oils, unless otherwise stated. Notably, Epidiolex, a purified CBD oil that recently received approval by the US Food and Drug Administration⁵⁷ and the European Medicines Agency⁵⁸ is not available in Canada at this time.

In contrast to Epidiolex, Canadian cannabinoid oils are whole plant isolates, containing CBD as well as THC in various ratios. Additionally, cannabinoid oils may contain other phytocannabinoids including cannabichromene, cannabigerol, cannabiol and cannabidivarin, as well as flavonoids and terpenes.⁵⁶ There are many cannabinoid oils available in Canada; as of December 31, 2019, there were 61 producers licensed to sell cannabinoid oils to authorized medical patients. Most producers offer multiple products with various ratios and concentrations of CBD and THC, including those high in THC (and low in CBD), balanced oils (approximately equal concentration of CBD and THC), and those high in CBD (and low in THC). The variability between products is further highlighted in Table 2, which shows a selection of high-CBD cannabinoid oils available in Canada. For example, the concentration of cannabinoids is variable across preparations, such that a cannabinoid oil with a 20:1 ratio of CBD to THC from one producer does not necessarily contain the same concentration of CBD as a 20:1 oil from a different producer. Variability may also exist between batches of the same product, with an inconsistent concentration of CBD and THC between batches. These sources of variability may affect dosing, cost, adverse effects, and therapeutic efficacy.⁵⁹

Table 2: Examples of high-CBD, low-THC cannabinoid oils available in Canada

Producer*	Product name	Cannabinoid concentration, mg/ml†		CBD:THC ratio‡	CDN\$		URL
		CBD	THC		Cost per bottle	Cost per mg CBD‡	
MedReleaf	Avidekel Oil†	21–30	<2	15:1	\$150 (40 ml)	\$0.125	shop.medreleaf.com/
Tilray	2:100 Oil	99.8	1.7	59:1	\$390 (40 ml)	\$0.098	tilray.ca/en/products/medical-cannabis.html?cannabinoids=105
	1:25 Oil	24.1	1.0	24:1	\$75 (40 ml)	\$0.078	
Organigram	Shubie Oil	20	0.75	27:1	\$55 (25 ml)	\$0.110	medical.organigram.ca/products
CanniMed	CanniMed Oil 1:20	18.2–20.5	0.9–1.1	19:1	\$130 (60 ml)	\$0.106	cannimed.ca/collections/medical-marijuana-oil
Emblem	Emblem 0:20 CBD oil	13.31	0.63	21:1	\$85 (30 ml)	\$0.213	emblemcannabis.com/product/emblem-020-cbd-oil/

Note: CBD = cannabidiol, THC = tetrahydrocannabinol.
 *Not a comprehensive list: As of December 31, 2019, 61 producers were licensed to sell cannabinoid oils to authorized patients. For an up-to-date list of producers, readers are directed to www.canada.ca/en/health-canada/services/drugs-medication/cannabis/industry-licensees-applicants/licensed-cultivators-processors-sellers.html
 †Concentrations may vary from batch to batch. Concentrations listed here reflect those listed on commercial websites or obtained from customer support staff and are current as of December 10, 2019.
 ‡Based on upper end of CBD range.

2.2.2.5 Guidance for health care providers in Canada

There are no formal regulations in Canada governing when it is appropriate for a health care provider to authorize medical cannabis use.⁵⁹ In the following section, the guidance available from Canadian associations and groups with respect to authorization for pediatric patients is summarized.

Health Canada (year of most-recent guidance document: 2018). Despite licensing cannabis producers to sell cannabis products for medical use, Health Canada cautions that “*Cannabis is not an approved therapeutic product, unless a specific cannabis product has been issued a drug identification number (DIN) and a notice of compliance (NOC).*”⁶⁰ In Health Canada’s *Information for Health Care Professionals* document, pediatric medical use is not specifically addressed, other than in the statement “*Cannabis (especially cannabis administered by smoking or vapourization) containing primarily THC (and especially higher levels of THC with little if any CBD) should not be used in any person under the age of 25, unless the benefit/risk ratio is considered by the physician to*

be favourable. The adverse effects of (THC-predominant) cannabis use on mental health are greater during development, particularly during adolescence (ages 10 to 24), than in adulthood with risks increasing with younger age, frequent use and THC potency.”⁶⁰ An earlier version of this document from 2013 did not differentiate between cannabis in general and that high in THC, stating that “*Cannabis should not be used in any person under the age of 18...The adverse effects of cannabis use on mental health are greater during development, particularly during adolescence, than in adulthood.*”⁶¹ The use of cannabis with a high concentration of CBD is not addressed in either version of the Health Canada guidance document.

Canadian Paediatric Society (2016). In its 2016 position statement, the Canadian Paediatric Society urged caution about the use of medical cannabis in children because of insufficient safety and efficacy data and potential adverse events, recommending evaluation on a case-by-case basis.⁶² Further, they recommend that treatment plans should be developed by health care professionals with experience in both the child’s condition and training in the use of psychoactive drugs in children.⁶² The Canadian Paediatric Society encourages comprehensive discussion with the patient (if possible) and family about their expectations and potential risks of cannabis.⁶² The lead author of the 2016 statement indicated in a news story related to medical cannabis in August 2019 that the statement would be “*getting an update in the coming months*”⁶³; however, as of January 21, 2020, no new statements on medical cannabis had been issued by Canadian Paediatric Society.

Canadian Medical Association (2018). The Canadian Medical Association has long expressed “*strong concerns*” about the authorization of medical cannabis by physicians, stating concerns that physicians should not be asked to act as “*gate keepers for a proposed medical intervention that has not undergone established regulatory review as required for all other prescription medicines.*”⁶⁴ In a 2018 statement, the Canadian Medical Association recognized that “*some individuals suffering from terminal illness or chronic disease for which conventional therapies have not been effective may obtain relief with marijuana used for medical purposes.*”⁶⁵ Notably, the Canadian Medical

Association recently asserted that there should be one system governing both recreational and medical cannabis, stating that after the legalization of recreational cannabis “*Cannabis will be available for those who wish to use it for medicinal purposes, either with or without medical authorization, and for those who wish to use it for other purposes. The medical profession does not need to authorize use once cannabis is legalized, especially given that cannabis has not undergone Health Canada’s usual pharmaceutical regulatory approval process...*”⁶⁵ The Canadian Medical Association refers physicians to their provincial College of Physicians and Surgeons and to the Canadian Medical Protective Association for policies and liability issues, respectively.

The Canadian Medical Protective Association (2019). The Canadian Medical Protective Association’s website provides an overview of the current cannabis regulations in Canada (www.cmpa-acpm.ca/en/advice-publications/browse-articles/2014/medical-marijuana-new-regulations-new-college-guidance-for-canadian-doctors) and refers physicians to the applicable guidelines by their provincial College of Physicians and Surgeons. In addition, Canadian Medical Protective Association reminds physicians “*of the importance of having the necessary clinical knowledge to engage in meaningful discussions with patients about medical marijuana*” and that “*Physicians should not feel obligated to complete the medical document for medical cannabis when they are unfamiliar with its use or management, or when they feel it is medically inappropriate for a patient.*”⁶⁶

College of Physicians and Surgeons (2014-2019). The guidelines for authorizing medicinal cannabis set by the individual Colleges vary by province, and few address authorization for pediatric patients (Table 3). Most caution that physicians should only authorize cannabis use when they have the necessary clinical knowledge to have a meaningful discussion with their patients about the potential benefits and risks of cannabis. Several Colleges stipulate that medical cannabis should only be authorized by the patient’s treating physician and “*only if the physician is actually treating the patient for the medical condition for which marijuana for medical purposes is prescribed.*”

Table 3: Guidance for authorizing medical cannabis for pediatric patients from the Colleges of Physicians and Surgeons, by province.

Province	URL	Date updated	Addresses pediatric use?	Quote related to pediatric use
British Columbia	www.cpsbc.ca/files/pdf/PSG-Cannabis-for-Medical-Purposes.pdf	June 21, 2019	Yes	“Cannabis is generally not appropriate for patients who are under the age of 25”
Alberta	www.cpsa.ca/standardspractice/cannabis-for-medical-purposes/	April 3, 2014	No	—
Yukon	www.yukonmedicalcouncil.ca/pdfs/Marijuana_for_Medical_Purposes.pdf	September 18, 2018	No	—
Saskatchewan	www.cps.sk.ca/iMIS/Documents/Legislation/Legislation/Regulatory%20Bylaws.pdf	September 2019	No	—
Manitoba	https://cpsm.mb.ca/cjj39alckF30a/wp-content/uploads/Standards%20of%20Practice/Standards%20of%20Practice%20of%20Medicine.pdf	June 21, 2019	No	—
Quebec	www.cmq.org/publications-pdf/p-1-2018-09-20-fr-ordonnance-cannabis-fins-medicales.pdf?t=1575309815744	September 2018	Yes	“Généralement, la prescription de cannabis n’est pas appropriée pour les jeunes de moins de 25 ans...”
Ontario	www.cpso.on.ca/Physicians/Policies-Guidance/Policies/Cannabis-for-Medical-Purposes	January 2019	Yes	“As evidence strongly suggests that the risks of cannabis are greater for youth and young adults, physicians must not prescribe cannabis to patients under the age of 25 unless all other conventional therapeutic options have been attempted and have failed to alleviate the patient’s symptoms.”
New Brunswick	http://cpsnb.org/en/medical-act-regulations-and-guidelines/guidelines/444-medical-marijuana	September 2017	No	—
Newfoundland and Labrador	www.cpsnl.ca/WEB/CPSNL/Policies/Advisory_and_Interim_Guideline_-_Medical_Marihuana.aspx	April 1, 2014	No	—
Nova Scotia	https://cpsns.ns.ca/wp-content/uploads/2017/12/Authorization-of-Marijuana-Medical-Purposes.pdf	December 8, 2017	No	—
Prince Edward Island	https://cpspei.ca/wp-content/uploads/2017/03/Marijuana-Prescribing-Nov-3016.pdf	November 30, 2016	No	—

2.2.3 Medical cannabis as a treatment for pediatric epilepsy

Cannabis as a treatment for epilepsy was first described in the mid-1800s,⁴⁷ yet as of 2014, only four randomized controlled trials (RCTs) involving the treatment of epilepsy with cannabis had been published, and none involved children.⁶⁷ However, the clinical knowledge base has changed rapidly since 2014, growing in parallel with interest in the general public.

Public interest. The public was introduced to cannabis as a treatment for epilepsy in 2013 with the airing of the CNN documentary *Weed*. In the accompanying article,⁶⁸ Dr. Sanjay Gupta describes how he changed his opinion on medical cannabis after reviewing the evidence related to its abuse potential and inclusion as a Schedule 1 drug, as well as observing how medical cannabis was affecting the lives of patients. In *Weed*, viewers were introduced to one such patient: Charlotte Figi, a then 5-year-old girl with Dravet syndrome. Because Charlotte's seizures were resistant to conventional antiepileptic drugs, Charlotte's parents searched online for other options, finding a video of another parent giving cannabinoid oil to a young child. Charlotte's parents purchased high-CBD cannabis after obtaining authorization from two physicians (in accordance with Colorado law) and administered her oil distilled from dried cannabis, resulting in a reduction in her seizures from about 300 to 1 per week. Following airing of the CNN documentary, as well as other similar reports in the media, many families moved to Colorado from other states to access medical cannabis to treat their children's epilepsy,⁶⁹ and, by 2015, an international online survey found that 95% of respondents from the general public felt that there was sufficient evidence to recommend its use in cases of severe epilepsy.⁷⁰

Clinical research. Researchers began to take notice of medical cannabis as a treatment for epilepsy around the same time as the airing of the *Weed* documentary, initially publishing descriptive studies of cannabis use among children with epilepsy. In the first such study, which was a small online survey in 2013, a total of 19 parents of children with drug-resistant epilepsy described giving their children "*CBD-enriched cannabis*" after the failure of an average of 12 antiepileptic drugs.⁷¹ Most parents (84%) reported that medical cannabis had reduced their children's seizures, with fewer side effects compared with other antiepileptic drugs.⁷¹ In a similar survey by the same group in 2015, a total of 117 parents of children with drug-resistant epilepsy described giving their children "*CBD-enriched oil-based extracts*."⁷² Again, the majority of parents (85%) reported a reduction in seizure frequency with use of a cannabis product, and 14% reported that their children's seizures had completely stopped.⁷² While the authors acknowledged the inherent biases in online surveys, they

used the results of these studies to call for “*formal studies to determine safety, optimal dosing, tolerability, and efficacy of a standardized cannabidiol preparation in different populations of children and adults with epilepsy.*”⁷¹

The first interventional study involving medical cannabis in children with drug-resistant epilepsy was published in 2015, describing the preliminary findings from a subset of 13 children with drug-resistant epilepsy participating in an expanded access program involving purified CBD (Epidiolex; a 99% pure CBD extract at a concentration of 100 mg/mL in a sesame oil-based solution).⁷³ This was the first publication involving Epidiolex, although it was quickly followed by publication of preliminary results from 162 patients aged 1–30 years (mean age 10.5 years) participating in the expanded access program across 11 centres in the US.⁷⁴ In this study, participants who had received Epidiolex (up to 50 mg/kg/d; mean dose 22.9 mg/kg/d) for 12 weeks had a 34.6% reduction in the median number of monthly seizures (interquartile range [IQR] –66.7% to –9.8%).⁷⁴ In total, 2% of participants were completely seizure free during the treatment period, and 37% of participants had a seizure reduction of at least 50% from baseline.⁷⁴ Adverse events were common, however, with 79% of participants experiencing at least one adverse event and 30% experiencing a serious adverse event, including status epilepticus, diarrhea, pneumonia, or weight loss, and one death was reported.⁷⁴

Randomized controlled trials. To date, four randomized controlled trials^{75–78} involving medical cannabis have been published, all involving Epidiolex. The first RCT,⁷⁵ published in early 2017, involved 120 children with Dravet syndrome (mean age 9.8 years) who were randomized to receive Epidiolex (20 mg/kg/d) or placebo for 14 weeks, in addition to stable antiepileptic therapy (range 1–5 antiepileptic drugs). Among those who received Epidiolex, the median frequency of total seizures per month was reduced by 28.6% compared with 9% in the placebo group (adjusted median difference: –19.2%, 95% CI –39% to –1%), and 5% of children became seizure free.⁷⁵ Again, adverse events were common, affecting 93% of patients in the Epidiolex group (v. 73% in the placebo group); these included vomiting, fatigue, pyrexia, upper respiratory tract infection, decreased appetite, convulsion,

lethargy, somnolence, and diarrhea. In 2018, three additional short-term RCTs (up to 14 weeks) were published,^{76–78} involving children with Dravet or Lennox-Gastaut syndromes. Based on the results of these RCTs and the expanded access program, Epidiolex received approval from the Food and Drug Administration in 2018⁵⁷ and the European Commission in 2019.⁵⁸

2.2.3.1 Canadian medical cannabis products for treatment of pediatric epilepsy

Epidiolex is not available in Canada, and as of December 31, 2019, it was not under review by Health Canada. The cannabinoid oils available in Canada differ from Epidiolex in important ways (i.e., they contain both CBD and THC), and experts caution that the evidence from Epidiolex does not readily translate to the cannabinoid oils available in Canada.⁵⁹ In the following section, studies evaluating the benefits and harms associated with Canadian medical cannabis products in the context of pediatric epilepsy are briefly reviewed.

The first study of a Canadian medical cannabis product for the treatment of epilepsy was published in 2018 (NCT02983695).⁷⁹ In this study, based at The Hospital for Sick Kids in Toronto, 20 children with Dravet syndrome (mean age 10.5 years) were administered cannabinoid oil for up to 20 weeks. The intervention in this study was a cannabinoid oil commercially available from a Health Canada-licensed cannabis producer (TIL-TC150 [Tilray]; www.tilray.ca/en/tilray-2100-oil.html), with a 50:1 ratio of CBD to THC. In this open-label, single-group cohort study, all children were administered TIL-TC150 at a starting dose of 2 mg/kg/d CBD, with titration up to 16 mg/kg/d (maximum THC dose 0.32 mg/kg/d) on a background of stable antiepileptic treatment (range 1–4 antiepileptic drugs per participant). During the last four weeks of treatment, motor seizures were reduced by 70.6% compared with the before treatment period, while 63% of participants had at least a 50% seizure reduction, two participants became seizure free, and quality of life was significantly improved relative to baseline. Adverse events were common (95% of participants), including one death (sudden unexpected death in epilepsy). All other adverse events were described by the authors as mild, and most were transient and resolved during the first 8 weeks of treatment; these included somnolence,

diarrhea, constipation, poor balance, and anorexia. Elevated levels of liver enzymes (alanine amino transferase, aspartate amino-transferase, gamma-glutamyl transferase), as well as elevated blood levels of valproate, were also observed, which had also been noted in the Epidiolex studies.

The second study involving a Canadian medical cannabis product for the treatment of epilepsy is ongoing at the University of Saskatchewan (CARE-E; NCT03024827); preliminary results from this study were published in July 2019.⁸⁰ In this open-label single-group cohort study, seven children with drug-resistant epileptic encephalopathy (Dravet or Lennox Gastaut syndrome; aged 1–10 years) were administered cannabinoid oil for up to 5 months. The intervention is commercially available from a Health Canada-licensed cannabis producer (CanniMed Oil 1:20 [CanniMed];

www.cannimed.ca/collections/medical-marijuana-oil) and has a 20:1 ratio of CBD to THC.

Participants were administered the 20:1 oil at a starting dose of 2–3 mg/kg/ day CBD, with titration up to 10–12 mg/kg/d on a background of stable antiepileptic treatment (range 2–4 antiepileptic drugs per participant). At the highest dose, all participants experienced a reduction in seizures (mean 74%), with five participants having a decrease of at least 50% from baseline. Improved quality of life was reported for all participants relative to baseline, although adverse events were common, including sleepiness/lethargy, irritability, nausea/vomiting, and diarrhea, and elevated levels of liver enzymes were reported.

2.2.3.2 Guidance for Canadian health care providers

As described in Section 2.2.2.5, there is little guidance available to Canadian health care professionals about the use of medical cannabis in children. Of the associations whose positions are described in Section 2.2.2.5, only the Canadian Paediatric Society specifically mentions epilepsy, stating that “*While anecdotal evidence and biological plausibility suggest that cannabis and its derivatives may be an effective treatment for refractory epilepsy in children, its efficacy in this population should be carefully evaluated over the long-term, using appropriately supported and well-designed research into developmental effects, including neuroimaging.*”⁶² Notably, this

statement was released prior to the publication of the Epidiolex RCTs or the two studies involving cannabinoid oils available in Canada.

The Canadian League Against Epilepsy recently released a position statement on the use of medical cannabis in the treatment of epilepsy, with recommendations specific to the Canadian context.⁵⁹ The authors note the lack of evidence related to the medical cannabis products available in Canada and caution that purified CBD (i.e., Epidiolex) and cannabinoid oils containing both CBD and THC are not equivalent. The authors recommended that, for patients who wish to use medical cannabis, their care be managed by “*a physician knowledgeable and experienced with epilepsy care and anti-seizure medications, preferably with experience in CBD-THC cannabis oil.*” Other important considerations include proper baseline assessment of the patient for contraindications and monitoring of potential drug interactions. The authors also encourage “*clinicians and researchers to continue to seek further knowledge and education about this therapeutic approach*” and call for additional research.⁵⁹

2.2.3.3 How the intervention might work

The endocannabinoid system. The endogenous cannabinoid system (the “*endocannabinoid system*”) is a widespread neuromodulatory system composed of G protein-coupled cannabinoid receptors (CB1, CB2) as well as endogenous cannabinoids (“*endocannabinoids*”; arachidonoyl ethanolamide [anandamide], 2-arachidonoyl glycerol [2-AG]), and the enzymes involved in the synthesis and degradation of endocannabinoids.⁸¹ Endocannabinoids, as well as exogenous cannabinoids (phytocannabinoids) interact with the CB1 and CB2 receptors, both of which are expressed in the central and peripheral nervous system.⁸² CB1 expression is highest in the central nervous system, particularly in the hippocampus, basal ganglia, cerebellum, and olfactory bulb, with lower expression in the cerebral cortex, septum, amygdala, and hypothalamus.⁸² CB1 receptors are predominantly found at pre-synaptic axon terminals, where their activation by endocannabinoids inhibits the release of a range of different neurotransmitters via suppression of voltage-gated calcium channels and activation of potassium channels.⁸³ The CB2 receptor is most abundantly expressed in the immune

system, with lower expression in the central and peripheral nervous systems as well as in the cardiovascular system, gastrointestinal tract, liver, adipose tissue, bone, and reproductive system.⁸² Importantly, the endocannabinoid system may play a role in regulating neuronal network oscillations and preventing excessive neuronal hyperexcitability.⁶

Phytocannabinoids and epilepsy. Over 140 different phytocannabinoids have been identified in cannabis, which may have different biologic effects.⁶ Of these, the best known and most studied are THC and CBD. THC has a high affinity for both the CB1 and CB2 receptor and competes with the endocannabinoids anandamide and 2-AG for binding, and activation of CB1 by THC is believed to be responsible for its psychotropic effects.⁶ In the context of epilepsy, THC has been reported to have both pro- and anti-convulsant activity, which may depend on dosage, species, and seizure type.⁶ Notably, THC may reduce seizure activity via interaction with the CB1 receptor, reducing glutamate release from the presynaptic axon terminal.⁸⁴ However, owing to its psychotropic effects, THC alone may have limited applicability in the treatment of epilepsy, especially in children.

Compared with THC, the molecular activity of CBD is not well understood and may be mediated by targets other than the CB1 and CB2 receptors. In contrast to THC, CBD has a low affinity for the CB1 receptor, which is the predominant form expressed in the brain. Other targets of CB1 may include serotonin receptors, transient receptor potential (TRP) channels, and G protein-coupled receptors.⁸³ Activation of the TRP receptors by CBD may modulate the flow of sodium and calcium into neurons, thus decreasing neuronal excitability in response to stimulation.⁶ Additionally, the anticonvulsant activity of CBD may be a result of the increased production of gamma-aminobutyric acid (GABA) in pre-synaptic GABAergic neurons.⁶ Owing largely to CBD's lack of psychotropic activity, the use of purified CBD and high-CBD concentration products have become the primary focus of research into cannabis-based treatments for pediatric epilepsy.

2.2.4 Summary

While there has been increasing interest in medical cannabis by the general public and parents of children with drug-resistant epilepsy, clinical research lags behind public opinion, especially with respect to the medical cannabis products available in Canada. Despite this, stakeholders, including parents, clinicians, and policy makers, must make decisions about the use of cannabis in the care of children with drug-resistant epilepsy. In order to inform their decision making, an up-to-date assessment of the evidence is needed. In this thesis, a health technology assessment approach has been used to address three research questions:

Question 1: What are the benefits and harms of medical cannabis for pediatric drug-resistant epilepsy?

Question 2: Is medical cannabis a cost-effective treatment for pediatric drug-resistant epilepsy compared to current therapeutic options?

Question 3: What are the perspectives of neurologists and parents about the use of medical cannabis for pediatric drug-resistant epilepsy?

The following section provides a brief overview of health technology assessment (HTA) and the methodologies used to address these research questions.

2.3 Health technology assessment

Health technology assessment is *“A multidisciplinary process that uses explicit and scientifically robust methods to assess the value of using a health technology at different points in its lifecycle. The process is comparative, systematic, transparent and involves multiple stakeholders. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.”*⁸⁵

In this context, *“health technology”* encompasses any intervention, health product or service intended to prevent, diagnose or treat medical conditions as well as those intended to promote health, provide rehabilitation, or organize health care delivery.⁸⁵ Importantly, HTA comprises the structured

assessment of the intended and unintended consequences of adopting a health technology, including the clinical effectiveness, safety, and economic implications, as well as the ethical, legal and social implications.

In 2006, the European Network for Health Technology Assessment (EUnetHTA) undertook development of a framework for the conduct and reporting of HTAs in order to standardize production and reporting of HTAs across jurisdictions and technologies.⁸⁶ The most recent version of the model (HTA Core Model version 3, hereafter called the “*Core Model*”) was released in 2016.⁸⁷ In this thesis, the Core Model served as a framework for the evaluation of the clinical effectiveness, safety, and cost-effectiveness of medical cannabis, including incorporating the perspectives of key stakeholders.

2.3.1 HTA Framework

The Core Model comprises nine domains (Table 4). In this thesis, Domains 1, 2 and 9 are addressed in Chapter 2 (Background). Chapter 3 addresses the safety (Domain 3) and clinical effectiveness (Domain 4) of medical cannabis for the treatment of pediatric drug-resistant epilepsy, while Chapter 4 considers the economic implications of its use (Domain 5). Organizational issues (Domain 7) and patient and social aspects (Domain 8) are addressed in Chapter 5 through qualitative studies that explore the perspectives of key stakeholders (neurologists, parents of children with drug-resistant epilepsy). A full ethical analysis (Domain 6) was beyond the scope of this thesis; however, ethical issues related to the medical use of cannabis in children with drug-resistant epilepsy are identified as part of the concluding chapter (Chapter 6).

Table 4: HTA Core Model and its relation to the thesis research questions

Domain	Domain description ⁸⁷	Thesis chapter	Research Question
Health problem and current use of the health technology (Domain 1)	“This domain describes the target conditions, target groups, epidemiology and the availability and patterns of use of the technology in question... addresses the burden – both on individuals and on the society – caused by the health problem, the alternatives to the technology in question, as well as the regulatory status of the technology and the requirements for its use.”	Chapter 2 (Background)	NA
Description of the health technology (Domain 2)	“...this domain describes the technology (or a sequence of technologies) and its technical characteristics, i.e. when it was developed and introduced, for what purpose(s); who will use the technology, in what manner, for what condition(s)...”		
Legal aspects (Domain 9)	“The objective of the Legal Aspects domain is to assist the HTA doers in detecting rules and regulations which need to be taken into consideration when evaluating the implications and consequences of implementing a health technology.”		
Safety (Domain 3)	“...HTA should cover those safety issues that are important to patients, or otherwise likely to be important in guiding the decisions of health care providers and policy makers.”	Chapter 3	What are the benefits and harms of medical cannabis for pediatric drug-resistant epilepsy?
Clinical effectiveness (Domain 4)	“The effectiveness domain in a health technology assessment considers two questions: Can this technology work, and does this technology work in practice?”		
Costs and economic evaluation (Domain 5)	“The aim of the Costs and Economic Evaluation domain ... is to inform value-for-money judgements about health technologies with information about costs, health-related outcomes and economic efficiency”	Chapter 4	Is medical cannabis a cost-effective treatment for pediatric drug-resistant epilepsy compared to current therapeutic options?
Organizational aspects (Domain 7)	“The domain of Organisational Aspects considers the ways in which different kinds of resources (e.g. material artefacts, human skills and knowledge, money, attitudes, work culture) need to be mobilised and organised when implementing a technology, and the consequences they may further on produce in the organisation and the health care system as a whole.”	Chapter 5	What are the perspectives of neurologists and parents about the use of medical cannabis for pediatric drug-resistant epilepsy?

Domain	Domain description ⁸⁷	Thesis chapter	Research Question
Patient and social aspects (Domain 8)	“The Patients and Social Aspects domain takes patients or individuals in whose care a health technology is used as a point of reference in an HTA. Patients Aspects relate to issues relevant to <i>patients, individuals and caregivers</i> ... Social Aspects are related to <i>social groups</i> , that is specific groupings of patients or individuals that may be of specific interest in an HTA”		
Ethical analysis	“the Ethical Analysis domain considers prevalent social and moral norms and values relevant to the technology in question. It involves an understanding of the consequences of implementing or not a healthcare technology in two aspects: with regard to the prevailing societal values and with regard to the norms and values that the technology itself constructs when put into use”	Chapter 6	Not addressed by a research question; however, ethical issues are identified in Chapter 6

In the following sections, the methodologies and relevant guidance used to address each of the three research questions are briefly described.

2.3.2 Living systematic review (Safety, Clinical effectiveness)

“People using the health services have already waited too long for the available evidence to be assembled and kept up to date.”⁸⁸

A core function of HTA is to evaluate the safety and effectiveness of the health technology, in order to *“benefit individual patients and to inform policy makers.”⁸⁷* This evaluation typically takes the form of a systematic review of relevant studies.⁸⁷ In this thesis, living systematic review methodology was used to assess the safety and effectiveness of medical cannabis as a treatment for pediatric epilepsy, including drug-resistant epilepsy.

What is a living systematic review? Systematic reviews *“seek to collate all evidence that fits pre-specified eligibility criteria in order to address a specific research question”* by use of explicit and systematic methods that aim to minimize bias.⁸⁹ Living systematic reviews are a type of systematic review that is frequently updated at *a priori* defined intervals, such that new evidence is incorporated in the review shortly after it becomes available.⁹⁰ Thus, living systematic reviews are not a distinct

methodology but are a type of systematic review that employs standard systematic review methods but has the distinction of being frequently updated (Table 5).⁹⁰ Notably, living systematic reviews differ from updated standard systematic reviews in that the update frequency is explicit and determined *a priori*.⁹⁰

Table 5: Comparison of key features of living systematic reviews with standard and updated systematic reviews*

Characteristic	Living systematic reviews	Standard systematic reviews	Updated standard systematic reviews
Literature search is updated to consider new evidence	YES	NO	YES
Explicit pre-defined update frequency	YES	NA	NO
Explicit pre-defined methods describing when and how to incorporate new evidence	YES	NA	NO
Continuous evidence surveillance	YES	NA	NO
New evidence is flagged for reader or incorporated into review	YES	NA	NO
Use of standard systematic review methods (e.g., screening, data extraction, risk of bias assessment)	YES	YES	YES
*Adapted from Synnot 2017. ⁹¹			

Living systematic reviews are a relatively new development in the field of evidence synthesis, despite calls being made as early as 1993 for systematic reviews to be kept up to date in order to inform health care decisions.⁸⁸ However, keeping systematic reviews up to date is challenging, as the number of papers published per year steadily increases.⁹² Yet few systematic reviews are updated,^{93,94} and the estimated time from publication of a new study until its inclusion in a systematic review is about 6.5 years.⁹⁵ This is particularly concerning, given that within one year of publication, 15% of reviews will have failed to include new evidence that could have changed the review's conclusion about an intervention's safety or effectiveness; this number jumps to 23% by 2 years after publication.⁹² As such, health care decisions may be being made on the basis of outdated or harmful information. Recognizing this, living systematic reviews were proposed in 2014 as a way of keeping systematic reviews up to date.⁹⁵

It is important to note, however, that not all review topics are suitable for the use of living systematic review methodology. The choice of whether to undertake a living systematic review should be based on the importance of the topic for decision making, whether there is certainty in the existing evidence, and whether new evidence will be forthcoming.⁹⁰

Guidance. Because living systematic reviews are a relatively new development in the field of evidence synthesis, there is little guidance for their conduct. The Cochrane Collaboration's Living Evidence Network provided interim guidance in 2017 for authors of Cochrane living systematic reviews,⁹¹ as well as a series of introductory articles in the *Journal of Clinical Epidemiology*.^{90,96–98} The main consideration with living systematic reviews is when to update the search: this decision should consider the balance between updating too frequently (i.e., potentially wasting resources) or too infrequently (i.e., potentially allowing the review to become outdated).⁹⁹ Based on the Cochrane guidance, living systematic reviews “*must include ongoing evidence surveillance and be continually updated,*” at a suggested frequency of monthly literature searching.⁹¹ However, in the series of articles in the *Journal of Clinical Epidemiology*, the same author group acknowledges that there are “*many logistical hurdles*” to this approach and that there should be a “*balance between currency and feasibility,*” thus proposing that new evidence should be incorporated within six months of publication.⁹⁰ Based on these considerations, the living systematic review undertaken as part of this thesis was updated at six-month intervals.

At the time of each living systematic review update, any newly identified records should be screened against the inclusion criteria, with three possible outcomes:

1. No new studies are found;
2. New studies are found, but the new information is likely to have a negligible effect on the effect estimate or the certainty of the evidence;
3. New studies are found, and new information is likely to affect the effect estimate or the certainty of the evidence.⁹⁰

In the first two scenarios, no additional action is required beyond making the findings transparent. In the third scenario, data should be extracted from the newly identified new studies and integrated into any previous evidence syntheses, risk of bias should be assessed, and the updated findings disseminated.⁹⁰

The goal of the Safety and Clinical Effectiveness domains of the HTA Core Model is to address safety issues important to patients, health care providers, and policy makers, as well as to assess whether the intervention can work in practice, respectively. Because the use of cannabis in the treatment of pediatric epilepsy is an active area of research, the review described in Chapter 3 was conceived as a living systematic review. Although it is not a Cochrane review, the general guidance provided by the Cochrane Living Evidence Network was followed in its conception and conduct.

2.3.3 Economic evaluation (Costs and economic evaluation)

“The basic tasks of any economic evaluation are to identify, measure, value, and compare costs and consequences of the alternatives being considered.”¹⁰⁰

In the context of HTA, economic evaluations are used to systematically evaluate the costs and consequences associated with adopting a new health technology, compared to the next best currently available option(s) (Figure 3). Implicit in this concept is the idea of choice and scarcity of resources; that is, despite an almost unlimited list of health care “wants,” resources are not infinite, and decision makers must choose between the available options. Indeed, there is frequently a mismatch between what is technically possible and economically feasible.⁸⁷ Thus, the goal of the Costs and Economic Evaluation domain of the Core Model is to provide evidence to inform these decisions. In this thesis, an economic evaluation of the use of medical cannabis as a treatment for pediatric drug-resistant epilepsy was undertaken (Chapter 4). This comprised a systematic

review of existing economic evaluations and a *de novo* cost-utility analysis of medical cannabis compared with alternative antiepileptic treatments.

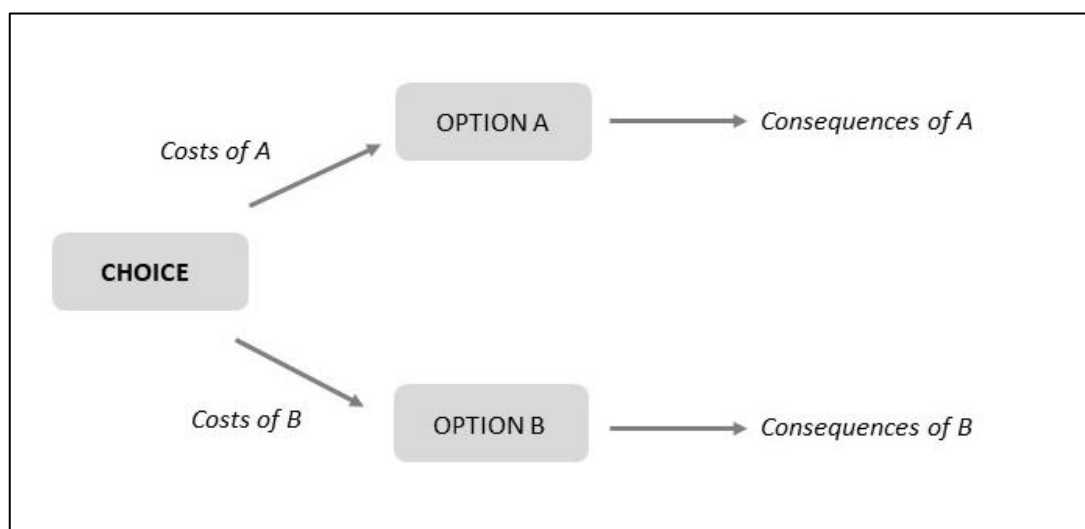


Figure 3: Comparison between options in an economic evaluation. Adapted from Drummond 2015.¹⁰⁰

What is cost-utility analysis?

Cost-utility analysis is one of four types of “full” economic evaluation (Table 6), each of which involve a “*comparative analysis of alternative courses of action in terms of both their costs and consequences.*”¹⁰⁰ Compared with the other types of full economic evaluation, however, cost-utility analysis allows for the most broad consideration of health benefits, by use of an overall summary measure (quality-adjusted life years [QALYs]) that can be compared across different outcomes or disease areas.¹⁰⁰ Further, cost-utility analyses allow preferences for health states to be incorporated through the use of utility weights in the calculation of the QALY.¹⁰⁰

Table 6: Types of economic evaluations*

Analysis method	Valuation		Cost–Outcome comparison	Limitations
	Costs	Outcomes (consequences)		
Cost-minimization	Dollars	NA	None	Each intervention is assumed to be equally effective
Cost-benefit	Dollars	Dollars	Net costs	Health outcomes must be expressed in monetary terms
Cost-effectiveness	Dollars	Natural units (e.g., life years)	Costs per unit of outcome gained	Outcomes must be the same for each treatment
Cost-utility	Dollars	QALYs	Costs per QALY gained	Different methods for measuring utility may give different values for the same health state*
Note: QALY = quality-adjusted life year. *Adapted from Drummond 2015. ¹⁰⁰				

Cost-utility analyses, as well as other forms of economic evaluation, can take the form of trial-based or model-based evaluations. In trial-based evaluations, a single RCT is used to provide all information for the evaluation, including the costs and outcomes associated with each treatment option.¹⁰¹ However, this approach has several limitations, including the potential failure to consider all relevant treatment options in the RCT, a short duration of treatment and/or observation, a lack of generalizability or relevance to the decision context, and a failure to measure all important costs and/or outcomes.¹⁰¹ In contrast, model-based evaluations can address these concerns by considering all relevant evidence.¹⁰¹ In the context of medical cannabis, few RCTs involving children with drug-resistant epilepsy have been conducted, and none have involved cannabis products available in Canada. As such, model-based cost-utility analysis was chosen as the form of the economic evaluation undertaken as part of this thesis. Further, a series of systematic reviews were undertaken to identify relevant evidence to inform the decision model (i.e., effectiveness and safety, resource use, utility values, productivity costs).

Guidance. The most recent version of the “*Guidelines for the Economic Evaluation of Health Technologies*”¹⁰² was followed in the design and conduct of the cost-utility analysis described in Section 4.4. These guidelines provide a series of recommendations related to the conduct of

economic evaluations, with the aim of “*providing best practices for those undertaking economic evaluations of health care technologies in Canada in order to produce credible standardized economic information that is relevant and useful for decision makers in Canada’s publicly funded health care system.*”¹⁰²

The Canadian guidelines assume that the goal of health care decision makers is to improve the overall health of the population (i.e., social decision-making viewpoint) and that the role of an economic evaluation is to inform such decisions.¹⁰² The guidelines set out the methods to be used in a “*reference case*” analysis (Table 7) in order to promote comparability across evaluations of different interventions and disease areas, with alternative methods considered in secondary and sensitivity analyses.

Table 7: Guidance for Canadian economic evaluations of health care technologies*

Domain	Guidance
Decision problem	Specify the interventions, setting, perspective, costs, outcomes, time horizon and target population
Types of evaluations	Conduct a cost-utility analysis capturing health outcomes in terms of quality-adjusted life years
Target population	Identify the population(s) for which the interventions are to be used; conduct stratified analysis if distinct subgroups are identified
Comparators	Compare all relevant interventions, including “current care” (i.e., the interventions presently used in the Canadian context)
Perspective	Adopt the perspective of a publicly funded health care payer
Time horizon	Select a time horizon long enough to capture all relevant differences in the future costs and outcomes associated with the interventions
Discounting	Discount costs and outcomes at a rate of 1.5% per year
Measurement and valuation of health	- Identify, measure, and value all relevant health outcomes based on the perspective of the publicly funded health care payer - Use health preferences that reflect the general Canadian population - Obtain health preferences from an indirect method of measurement based on a generic classification system
Resource use and costs	- Identify, measure, and value all relevant resources and costs based on the perspective of the publicly funded health care payer - Estimate Canadian resources and costs using data that reflect the jurisdiction of interest
Analysis	- Derive expected values of costs and outcomes for each intervention through probabilistic analysis, incorporating potential correlation among parameters - Calculate ICERs - For evaluations with more than two interventions, calculate ICERs sequentially

Domain	Guidance
Uncertainty	• Address methodological uncertainty by comparing the reference case results to those from a non-reference case analysis • Summarize decision uncertainty, using such items as CEACs and CEAFs • Use scenario analysis to address structural uncertainty
Equity	• Weight all outcomes equally regardless of the characteristics of people receiving the interventions
Note: CEAC = cost-effectiveness acceptability curve, CEAF = cost-effectiveness acceptability frontiers, ICER = incremental cost-effectiveness ratio. *Adapted from CADTH 2017. ¹⁰²	

2.3.4 Qualitative analysis (Organizational issues, Patient and social aspects)

“Patients’ perspectives on their illnesses and the technology under study provide a unique insight into the influence and impact of the technology.”⁸⁷

The inclusion of patient perspectives in HTA can provide an understanding of how patients and other stakeholders perceive the health condition being studied and how they make decisions about the technology being considered.⁸⁷ Additionally, stakeholders can provide an understanding of the organizational aspects of a technology; that is, how the technology affects work flow for health care providers or the flow of patients through the health care system; education and/or training needs for patients or care providers; communication needs between different types of care providers or between providers and patients; and barriers that may impede access to the technology.⁸⁷

The inclusion of patient perspectives in an HTA is considered essential within the EUnetHTA framework. The Core Model stipulates that stakeholder perspectives should be studied through a “systematic and methodologically robust process,”⁸⁷ which typically takes the form of a systematic review of qualitative studies or through primary qualitative research. Prior to this thesis, there had been no qualitative study of the perspectives of key stakeholders (namely, parents, neurologists) in Canada with respect to the use of cannabis as a treatment for pediatric drug-resistant epilepsy. Thus, two primary qualitative studies were undertaken as part of this thesis (Chapter 5), in order to explore the perspectives of parents and neurologists about the use

of medical cannabis in this context. Both studies were guided by interpretive description methodology.

What is interpretive description?

Interpretive description is one of many methodologies that can be used for qualitative research.

Although qualitative methodologies share many similarities (e.g., focus on words rather than numbers, generate rich and thick description of a phenomenon), there are important difference between methodologies that can help determine which methodology is suitable to address a given research question (Table 8).¹⁰³ Notably, there is no hierarchy of qualitative research methodologies that are appropriate for HTA.⁸⁷ Thus, the choice of methodology should be based on a consideration of the characteristics of the methodology and the research question being addressed.⁸⁷

Table 8: Comparison of common qualitative methodologies*

Characteristic	Phenomenology	Grounded theory	Ethnography	Case study	Interpretive description
Focus	Understanding the “essence of the experience”	Developing theory	Describing and interpreting a culture-sharing group	Developing an in-depth description and analysis of a case	Understanding clinical phenomena; addressing knowledge needs of the intended audience
Type of problem best suited for the design	Describing the essence of a lived phenomenon	Grounding theory in the views of participants	Describing and interpreting shared patterns of culture of a group	Providing an in-depth understanding of a case	Providing meaningful description of clinical phenomena by describing commonalities and differences between participant experiences
Beliefs about prior knowledge	Prior knowledge is “bracketed” or set aside	Literature review is performed after analysis	Initial theory guides the study	Prior knowledge is used to inform the study design and analysis	Prior knowledge (e.g., from clinical experience or literature review) is used to inform study design and analysis
Unit of analysis	Several individuals with shared experiences	A process, action, or interaction involving many individuals	A group that shares the same culture	An event, program, activity, or more than one individual	Several individuals with shared experiences
Data sources	Primarily interviews	Primarily interviews	Primarily participant observation; may include interviews	Multiple sources, including interviews, observations, documents	Multiple sources, including interviews, focus groups, observations, documents

*Adapted from Creswell 2013.¹⁰³ Characteristics of interpretive description were obtained from Thorne 2016.¹⁰⁴

Traditional qualitative methodologies (e.g., grounded theory, ethnography, phenomenology), which originate from within the social sciences, are each associated with their own focus and set of methods. For example, the aim of grounded theory is to generate theory about a process or action;¹⁰³ this theory is built from the data following rules related to maximal sampling variation and theoretical saturation and the use of a specific coding process.¹⁰⁵ Although some aspects of grounded theory methodology may hold appeal to health researchers (e.g., focus on understanding a phenomenon involving many individuals, with data typically obtained through participant interviews), the intent of qualitative applied health research is typically to describe a phenomenon but not to extend the findings to the level of theory.¹⁰⁴ However, researchers who adopt some but not all methods of a methodology or who mix methods from different methodologies may be accused of “methods slurring,” which undermines the credibility of applied qualitative health research.^{106,107}

To combat this, interpretive description was proposed as a “*non-categorical qualitative alternative*” that could be used to address clinically relevant health-related questions.¹⁰⁸ The aims of interpretive description are to provide meaningful descriptions of clinical phenomena, including commonalities and differences between participant experiences.¹⁰⁹ Interpretive description is not an entirely novel or distinctive approach from the other methodologies; indeed, interpretive description is a pragmatic approach that allows methods to be borrowed from traditional methodologies. Notably, since the first publication related to interpretive description in 1997,¹⁰⁸ this methodology has been used by many groups to address research questions important in clinical care,^{110–117} including to study the experiences of parents of children with complex health conditions.^{110,111,113}

Guidance. Interpretive description does not have a set of prescribed methods. Instead, interpretive description serves as “*an organizing logic with which to generate meaningful scholarly products that have application and knowledge translation built into them from the outset for the specific needs of applied fields.*”¹⁰⁴ General guidance for the conduct of interpretive description studies is provided in the 2016 text “*Interpretive Description: Qualitative Research for Applied Practice.*”¹⁰⁴ Interpretive

description is intended to be a pragmatic methodology, serving as a framework “*within which a fairly wide range of options for design decisions ... can be enacted in a coherent and fully justifiable manner.*” Notably, no one method is considered better than another within this methodology, and researchers are encouraged to choose from among the methods common within the other methodologies (e.g., sampling, data collection, analysis strategies), provided that the methods chosen are internally consistent with each other and with the aim of the study.¹⁰⁴ The two interpretative description qualitative studies presented in Chapter 5 were designed to address questions of clinical importance in the context of caring for children with drug-resistant epilepsy. Thus, the study methods were chosen with the intent of obtaining a range of insights and perspectives about the use of medical cannabis and such that the findings “*ring true*” to the study population and have application potential in clinical practice.¹⁰⁴

2.4 Summary

In this chapter, background information about the health condition (pediatric drug-resistant epilepsy) and the health technology (medical cannabis) has been described. The following three chapters (Chapters 3–5) present a series of nine manuscripts that each address one of three research questions by use of the methodologies introduced within this chapter.

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Chapter 3:

Benefits and harms of medical cannabis for pediatric drug-resistant epilepsy

CHAPTER OVERVIEW

Chapter 3 addresses the first research question: *What are the benefits and harms of medical cannabis for pediatric drug-resistant epilepsy?*

Before this thesis was undertaken, there had been no comprehensive study of the benefits and harms of medical cannabis for the treatment of pediatric epilepsy, or more specifically, for the treatment of pediatric drug-resistant epilepsy. As such, the objective of this chapter was to identify and assess all studies, including randomized controlled trials and non-randomized studies, involving use of medical cannabis to treat epilepsy in children, in order to gain an understanding of its potential benefits and harms. Because this is an active area of research, this study was designed as a living systematic review that was updated at set intervals throughout the duration of the thesis. (Note: the living systematic review will continue to be maintained beyond the updates presented in this thesis; however, only the baseline review and the first two updates were undertaken as part of the thesis).

Chapter 3 contains three manuscripts (**Sections 3.1–3.3**), all of which have been published. Each manuscript is briefly described below, and a more fulsome description is found on the first page of each section.

CHAPTER CONTENTS

Section 3.1 presents the protocol for a living systematic review to assess the benefits and harms of cannabis-based products for the treatment of pediatric epilepsy. This manuscript was published in *Systematic Reviews*.

Section 3.2 presents the results of the baseline systematic review of the benefits and harms of cannabis-based products for pediatric epilepsy. In the baseline review, studies published from database inception to April 2018 were identified, appraised, and synthesized. This manuscript was published in *Epilepsia*.

Section 3.3 describes the state of the literature one year after the baseline systematic review. This manuscript includes studies identified as part of the baseline review (Section 3.2), as well as the first two updates (October 2018, May 2019); as such, it provides an up-to-date summary of the evidence base as of May 2019. This manuscript was published in *Seizure*.

Section 3.1

Cannabis for pediatric epilepsy: Protocol for a living systematic review

SECTION OVERVIEW

This section presents a manuscript that describes the protocol for a living systematic review of the benefits and harms of cannabis-based products for treatment of pediatric epilepsy. The findings of this review are described in **Sections 3.2** and **3.3**.

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Supporting material

Supplementary file 1: PRISMA-P checklist

Supplementary file 2: Search strategy

Author roles and contributions

JE, TC, DC, BP, and GW conceived the study. BS designed the search strategy. JE drafted the protocol, which was revised by all authors. BM provided clinical input, while CA and AR provided patient and family perspectives. All authors have approved the version of the manuscript submitted for publication

RELATED THESIS APPENDICES

Appendix G: Published manuscripts. The PDF of the published manuscript is presented in Appendix G.

Cannabis for pediatric epilepsy: Protocol for a living systematic review

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Keywords: pediatric epilepsy, cannabis, cannabinoids, cannabidiol, seizure, efficacy, safety, living systematic review, meta-analysis

Abstract

Background: Pediatric epilepsy, including treatment-resistant forms, has a major effect on the quality of life, morbidity, and mortality of affected children. Interest has been growing in the use of medical cannabis as a treatment for pediatric epilepsy, yet there has been no comprehensive review of the benefits and harms of cannabis use in this population. In this systematic review, we will search for, synthesize, and assess the published and grey literature in order to provide usable and relevant information to parents, clinicians, and policy makers.

Methods: We will perform a living systematic review of studies involving the use of cannabis to treat pediatric epilepsy. We will search the published and grey literature for studies involving children with any type of epilepsy taking any form of cannabis. Studies will be selected for inclusion by two independent reviewers. The primary outcome is seizure freedom. Secondary outcomes are seizure frequency, quality of life (child, caregiver), quality and quantity of sleep, status epilepticus, tonic-clonic seizures, death (all-cause, sudden unexpected death in epilepsy), gastrointestinal adverse events (diarrhea, vomiting), and visits to the emergency room. The quality of each included study will be assessed. If data are sufficient in quantity and sufficiently similar, we will conduct pairwise random-effects meta-analysis. We will repeat the literature search every 6 months to identify studies published after the previous search date. Sequential meta-analysis will be performed as necessary to update the review findings.

Discussion: Our review aims to provide a comprehensive and up-to-date summary of the available evidence to inform decisions about the use of cannabis in children with treatment-resistant epilepsy. The results of this review will be of use to parents, clinicians, and policy makers as they navigate this rapidly evolving area.

PROSPERO registration no.: CRD42018084755

Background

Interest in the use of cannabis for pediatric epilepsy has grown over the last decade, driven in part by media reports of children whose treatment-resistant epilepsy has responded to cannabis [1]. The well-publicized case of Charlotte Figi, whose parents started her on medical cannabis at age 5, is not unique,[2] and many parents of children with treatment-resistant epilepsy have reported turning to alternative treatments,[3] both with and without the aid of medical professionals. In particular, parents of children with treatment-resistant epilepsy (an inadequate response to two or more adequate trials of antiepileptic drugs[4]), which affects between 28% and 37% of people with epilepsy,[5] have expressed great interest in the use of cannabis for the treatment of their children's epilepsy.[3] Indeed, pediatric treatment-resistant epilepsy has potentially catastrophic consequences, including cognitive delay, behavioural problems, autism, poor quality of life, and early death [6–9].

Despite recorded medicinal use of cannabis dating back to the 2nd century BCE [10], there has been relatively little research into its effectiveness or safety, likely owing to its illegal status in many jurisdictions. In adults, cannabis has been reported to be effective in the treatment of nausea and vomiting due to chemotherapy, chronic pain, spasticity associated with multiple sclerosis, sleep disorders, and Tourette syndrome, with inconclusive evidence for its use in appetite stimulation in patients with HIV/AIDS, anxiety disorders, and glaucoma [11]. There is relatively little clinical evidence to support the use of cannabis in the treatment of pediatric epilepsy, and there are large discrepancies between the beliefs of health care professionals and the general public with respect to its effectiveness and safety [12]. A 2014 Cochrane review of the use of cannabinoids for treatment of epilepsy included four small low-quality randomized controlled trials (RCTs), none of which involved children [13]. At the time of this review, the authors concluded that there was insufficient evidence to make reliable conclusions about the efficacy or long-term safety of cannabinoids for the treatment of epilepsy [13]. However, the evidence base in this area is changing rapidly, and recently

published studies have suggested a beneficial effect of cannabis in this population [14,15], although the mechanisms underlying this response are not clear.[16]

The use of cannabis in the treatment of pediatric epilepsy is an ideal topic for a living systematic review because it is a priority for decision-making, there is little certainty in the existing evidence base, and there is rapidly accumulating evidence.[17] Living systematic reviews are a relatively new approach to continually updating systematic reviews, with new evidence being incorporated as it becomes available.[17] Unlike traditional systematic review updates, which may be undertaken infrequently, living systematic reviewers search for new studies at *a priori* defined intervals and follow a set protocol for determining whether updated analysis and publication are warranted. At present, 37 studies involving the use of various forms of cannabis for treatment of pediatric epilepsy are registered in ClinicalTrials.gov, suggesting that there will be an abundance of new data in the coming years.

In this living systematic review, we will comprehensively search the published and grey literature for studies that have evaluated the benefits and harms of cannabis for pediatric treatment-resistant epilepsy. The results of our review will be of use to parents, clinicians, and policy makers in making treatment decisions for children with epilepsy.

Methods/design

This systematic review protocol has been submitted to PROSPERO (CRD42018084755) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (Online supplementary file 1) [18].

Patient involvement: Two family members of children with epilepsy were involved in selecting the outcome measures for inclusion in this systematic review and are co-authors of this protocol (C.A., A.R.).

Search strategy: A search of the published and grey literature will be performed by an experienced medical information specialist to identify studies involving the use of cannabis for treatment of pediatric epilepsy. The search strategy was developed in consultation with an experienced medical information specialist and the research team (Online supplementary file 2). The search will be peer reviewed by another librarian by use of the Peer Review of Electronic Search Strategies (PRESS) checklist [19]. Using the OVID platform, we will search Ovid MEDLINE®, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase Classic + Embase, and PsycINFO. We will also search the Cochrane Library on Wiley. The search strategies will use a combination of controlled vocabulary (e.g., “Epilepsy”, “Cannabinoids”, “Medical Marijuana”) and keywords (e.g., “seizure”, “cannabis”, “THC”). Vocabulary and syntax will be adjusted across databases. No date or language restrictions will be imposed. Grey literature will be searched by use of CADTH’s Grey Matters Light,[20] Google Scholar, and the clinical trials registries ClinicalTrials.gov and the ICTRP Search Portal of the World Health Organization.

Eligibility criteria: Studies will be eligible for inclusion if they meet the population, intervention, comparator, and study design criteria described below. Studies will not be selected based on reported outcomes.

Population: Children (aged 18 years or younger) with any form of epilepsy. Studies that report mixed populations of children and adults will be included if they report data separately for participants aged less than 19 years or if, based on descriptive statistics, we can determine that at least 60% of patients are aged less than 19 years.

Intervention: Any type of cannabis (synthetic or natural), cannabitol, cannabidiol (CBD), tetrahydrocannabinol (THC), or combinations of these agents. The intervention may be administered by any route (e.g., oral, inhalation), include any strain of cannabis, and any ratio of THC to CBD.

Comparators: Eligible comparators include pharmacologic and non-pharmacologic treatments for epilepsy, including antiepileptic drugs, diet therapy, vagus nerve stimulation, and resective brain surgery. Comparators may also include placebo, usual care, or no treatment.

Outcomes: The primary outcome is seizure freedom. Secondary outcomes are seizure frequency, quality of life (child, caregiver), quality and/or quantity of sleep, status epilepticus, tonic-clonic seizures, death (all-cause, sudden unexpected death in epilepsy), gastrointestinal adverse events (diarrhea, vomiting), and visits to the emergency room. Study eligibility will not be evaluated based on reported outcomes.

Study designs: Eligible study designs are RCTs (including cross-over and N-of-1 trials), quasi-randomized controlled trials, controlled before-after, non-randomized controlled trials, historically or concurrently controlled cohort series [prospective or retrospective], case-control studies, uncontrolled cohort studies, case series involving at least 5 patients, and cross-sectional studies. Conference abstracts and clinical trial registrations will be eligible for inclusion.

Screening and selection procedure: Two independent reviewers will screen the title and abstract of each identified record and assess eligibility against the above criteria. The full-text of any record deemed potentially relevant by at least one reviewer will be examined in detail and evaluated for eligibility by two independent reviewers. Disagreements on eligibility will be resolved by discussion. Studies will not be excluded based on treatment duration, and no language exclusions will be applied. All screening and data extraction will be performed using standardized and piloted forms in Distiller SR (Evidence Partners).

Data extraction: Data will be extracted by one reviewer and checked for accuracy by a second reviewer. Data to be extracted includes study characteristics (e.g., first author, year of publication,

study design, country of study), participant characteristics (e.g., age, sex, epilepsy syndrome, ethnicity, comedications, comorbidities), intervention and comparator details (e.g., type of treatment, dose, route of administration, duration), and outcome data at the longest duration of follow-up. Event counts will be extracted for dichotomous outcomes (seizure freedom, improvement or worsening of sleep, status epilepticus, deaths, diarrhea, vomiting, visits to the emergency room). Data for continuous outcomes (seizure frequency, quality of life, quality and/or quantity of sleep) will be extracted as mean or median change from baseline or difference between groups after treatment. If available, the number of participants who achieve at least a 50% reduction in seizures from baseline will be extracted. Estimates of variability (e.g., standard deviation, standard error, 95% confidence intervals) will be extracted. First-period data as well as end-of-study effects will be extracted from cross-over studies. Additional information will be extracted, including the number of cases and controls (case-control studies), adjusted odds ratios, relative risk or hazard ratios, and 95% confidence intervals, as reported by study authors. No data will be extracted from studies that do not present study-specific data (e.g., odds ratios, 95% confidence intervals) or provide sufficient information for calculation of an outcome measure (event counts and denominators).

Quality and risk of bias assessment: The quality of included studies that report at least one outcome of interest will be assessed by use of the Cochrane Collaboration's Risk of Bias tool (ROB v. 2.0) for RCTs [21]. The Institute of Health Economics Quality Appraisal Checklist for Case Series Studies [22] or SIGN50 [23] will be used for other study designs as appropriate. Other quality assessment tools will be identified as needed depending on designs of the included studies. Quality will be assessed by two independent reviewers, and disagreements will be resolved by discussion.

Data synthesis: First, we will provide a descriptive summary of study selection, study and patient characteristics, and the results of the quality assessment.

Second, we will assess whether the data are sufficient in quantity and sufficiently homogeneous to be pooled via random-effects meta-analyses (i.e., minimal clinical, methodological, statistical

heterogeneity). We will assess clinical heterogeneity by examining the patient characteristics of the included studies, and methodological heterogeneity by assessing the study characteristics. Statistical heterogeneity will be assessed by use of the I^2 statistic. If substantial heterogeneity is present ($I^2 > 75\%$), we will explore this by subgroup analyses. At I^2 values above 75%, pooled data will not be reported, and descriptive summaries of the study-level findings will be presented. The primary analysis will involve data from RCTs involving children (at least 80% of participants aged less than 19 years) with any type of epilepsy, and data from other study designs will be evaluated in secondary analyses if deemed appropriate. Other secondary analyses will involve (a) studies including participants with treatment-resistant epilepsy or (b) studies in which at least 60% of the population is aged less than 19 years. If data are sufficient and sufficiently similar, meta-analysis will be performed by use of RevMan (v.5.3; Cochrane Collaboration). If there are insufficient data for meta-analysis, we will report descriptive summaries for each outcome. The findings of conference abstracts will be summarized descriptively.

Additional analyses: If sufficient data are available, sensitivity analyses will be performed to test the robustness of the estimates. For example, we will look at the impact of excluding studies with high risk of bias or poor methodological quality. We will also assess the impact of comedications, study location, and cannabis strain, dose, level of THC or ratio of THC to CBD or route of administration, depending on data availability. Subgroup analyses will investigate the effect of epilepsy syndrome (e.g., Dravet syndrome, Lennox-Gastaut syndrome), age, and sex. Publication bias will be assessed by visual inspection of funnel plots for outcomes that have data from at least 10 studies [24].

Quality of the evidence: The quality of the evidence will be assessed for each outcome by use of the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group method [25].

Update plan: In keeping with current recommendations for the conduct of living systematic reviews,[17] the literature search will be repeated at regular *a priori* defined intervals to identify

newly available studies. Published and grey literature searches will be updated every 6 months, and any records identified after the date of last update will be screened for inclusion as described above. This frequency of updating was chosen to maximize the visibility of new information for decision makers but to minimize the resources required.[17] There are three potential update scenarios: 1) no new evidence is located, 2) new evidence is located but is not sufficient to trigger updated analysis and publication, or 3) new evidence is located and new analysis and dissemination is required.[17] If new studies that meet the eligibility requirements are located, the reviewer team will decide, in consultation with a clinical expert (B.M.), whether updated analyses are required, with consideration of balancing the needs of decision makers with the available resources.[17] If required, meta-analyses will be updated by use of trial sequential analyses (type I error: 0.05; power: 80%; assumed effect size: moderate Cohen's effect size [0.5 standard deviations]) for living systematic reviews.[26]

Discussion

Pediatric epilepsy has a major impact on quality of life for patients and their families. Interest in the use of cannabis as a treatment for pediatric epilepsy and, in particular, for treatment-resistant epilepsy has grown over the last decade, driven in part by media reports of children whose treatment-resistant epilepsy has responded to cannabis after the failure of conventional treatments.[1] This living systematic review will provide a comprehensive summary of the current evidence for the use of cannabis for the treatment of pediatric epilepsy and will incorporate new evidence as it becomes available. The results will be of use to decision makers, including parents of affected children, clinicians, and policy makers.

Abbreviations: CBD = cannabidiol, RCT = randomized controlled trial, THC = tetrahydrocannabinol.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Not applicable.

Competing interests. Bláthnaid McCoy is principal investigator in a study of cannabinoids for Dravet syndrome. Alexander Repetski is director of communications at a licensed cannabis producer. None declared by any other author.

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Author's contributions: JE, TC, DC, BP, and GW conceived the study. BS designed and will execute the search strategy. JE drafted the protocol, which was revised by all authors. BM provided clinical input, while CA and AR provided patient and family perspectives. JE and DD will select the studies for inclusion and perform data extraction. All authors have approved the version of the manuscript submitted for publication.

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Additional Files

Supplementary file 1: PRISMA-P checklist

Supplementary file 2: Search strategy

Supplementary file 1: PRISMA-P checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols)

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file 2
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	

management			
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

Supplementary file 2: Search strategy

Ovid Multifile: Database: Embase Classic+Embase <1947 to 2017 December 13>, Ovid MEDLINE(R) ALL <1946 to December 14, 2017>, PsycINFO <1806 to December Week 2 2017>

Search Strategy:

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1  exp Epilepsy/ (413158)
2  (epileps* or epilept*).tw,kf. (354209)
3  seizure*.tw,kf. (308442)
4  convulsi*.tw,kf. (73122)
5  falling sickness*.tw,kf. (61)
6  comitial disease*.tw,kf. (3)
7  (petit mal or grand mal or absence status).tw,kf. (8405)
8  Landau-Kleffner Syndrome*.tw,kf. (1213)
9  Lennox Gastaut Syndrome*.tw,kf. (3397)
10 Dravet Syndrome*.tw,kf. (2044)
11 West syndrome*.tw,kf. (2852)
12 Doose syndrome*.tw,kf. (167)
13 Ohtahara syndrome*.tw,kf. (499)
14 Sturge-Weber Syndrome/ (3596)
15 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kf. (8090)
16 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw,kf. (776)
17 SMEI.tw,kf. (461)
18 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw,kf. (1137)
19 Lafora.tw,kf. (1430)
20 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kf. (735)
21 ((infantile or nodding) adj2 spasm?).tw,kf. (6276)
22 ((flexor or "in flexion") adj2 spasm?).tw,kf. (332)
23 ((lightning or salaam) adj2 attack?).tw,kf. (16)
24 hypsarrhythmi*.tw,kf. (2063)
25 or/1-24 [EPILEPSY] (627889)
26 Adolescent/ (3482184)
27 exp Child/ (4584752)
28 exp Infant/ (2191998)
29 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kf. (5312514)
30 (newborn* or neonat*).tw,kf. (874968)
31 (pediatric* or paediatric*).tw,kf. (811013)
32 or/26-31 (9306058)
33 25 and 32 [PEDIATRIC EPILEPSY] (223050)
34 Cannabis/ (43738)
35 exp Cannabinoids/ (76752)
36 Medical Marijuana/ (1233)
37 Marijuana Smoking/ (6987)
38 ("c.indica" or cannabi* or bhang or cannador or charas or eucannabinolide* or ganja or ganjah or hash or hashish or hemp or marihuana* or marijuana*).tw,kf. (112741)
39 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw,kf. (79)
40 (dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetranabinex).tw,kf. (23589)
41 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kf. (22)
42 or/34-41 (144274)
43 33 and 42 [CANNABIS - PEDIATRIC EPILEPSY] (670)
44 exp Animals/ not (exp Animals/ and Humans/) (16160986)
45 43 not 44 [ANIMAL-ONLY REMOVED] (453)
46 45 use medall (185)
47 exp epilepsy/ (413158)
48 (epileps* or epilept*).tw,kw. (359359)
49 seizure*.tw,kw. (310739)
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50 convulsi*.tw,kw. (74278)
 51 falling sickness*.tw,kw. (64)
 52 comitial disease*.tw,kw. (3)
 53 (petit mal or grand mal or absence status).tw,kw. (8283)
 54 Landau-Kleffner Syndrome*.tw,kw. (1248)
 55 Lennox Gastaut Syndrome*.tw,kw. (3450)
 56 Dravet Syndrome*.tw,kw. (2094)
 57 West syndrome*.tw,kw. (2980)
 58 Doose syndrome*.tw,kw. (181)
 59 Ohtahara syndrome*.tw,kw. (513)
 60 sturge-weber syndrome/ (3596)
 61 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kw. (8213)
 62 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw,kw. (785)
 63 SMEI.tw,kw. (485)
 64 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw,kw. (1167)
 65 Lafora.tw,kw. (1443)
 66 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kw. (740)
 67 ((infantile or nodding) adj2 spasm?).tw,kw. (6422)
 68 ((flexor or "in flexion") adj2 spasm?).tw,kw. (332)
 69 ((lightning or salaam) adj2 attack?).tw,kw. (16)
 70 hypsarrhythmi*.tw,kw. (2094)
 71 or/47-70 [EPILEPSY] (630155)
 72 juvenile/ (38711)
 73 exp adolescent/ (3482352)
 74 exp child/ (4584752)
 75 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kw. (5321220)
 76 (newborn* or neonat*).tw,kw. (870009)
 77 (pediatric* or paediatric*).tw,kw. (831059)
 78 or/72-77 (9154566)
 79 71 and 78 [PEDIATRIC EPILEPSY] (221973)
 80 cannabis/ (43738)
 81 exp cannabinoid/ (63688)
 82 medical cannabis/ (1625)
 83 exp "cannabis use"/ (7317)
 84 ("c.indica" or cannabi* or bhang or cannador or charas or eucannabinolide* or ganja or ganjah or hash or hashish or hemp or marihuana* or marijuana*).tw,kw. (113719)
 85 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw,kw. (79)
 86 (dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetranabinex).tw,kw. (23862)
 87 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kw. (22)
 88 or/80-87 (143934)
 89 79 and 88 [CANNABIS - PEDIATRIC EPILEPSY] (678)
 90 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (48509001)
 91 exp human/ or exp human experimentation/ or exp human experiment/ (37777771)
 92 90 not 91 (10732950)
 93 89 not 92 [ANIMAL-ONLY REMOVED] (631)
 94 93 use emczd [EMBASE RECORDS] (399)
 95 exp Epilepsy/ (413158)
 96 Status Epilepticus/ (17946)
 97 (epileps* or epilept*).tw. (350570)
 98 seizure*.tw. (307670)
 99 convulsi*.tw. (71469)
 100 falling sickness*.tw. (59)
 101 comitial disease*.tw. (3)
 102 Grand Mal Seizures/ (196)
 103 Petit Mal Seizures/ (127)
 104 (petit mal or grand mal or absence status).tw. (8218)

105 Landau-Kleffner Syndrome*.tw. (1210)
 106 Lennox Gastaut Syndrome*.tw. (3379)
 107 Dravet Syndrome*.tw. (2019)
 108 West syndrome*.tw. (2812)
 109 Doose syndrome*.tw. (160)
 110 Ohtahara syndrome*.tw. (494)
 111 ((sturge* or weber) adj2 (disease* or syndrome*)).tw. (8041)
 112 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw. (775)
 113 SMEI.tw. (456)
 114 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw. (1127)
 115 Lafora.tw. (1421)
 116 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw. (730)
 117 ((infantile or nodding) adj2 spasm?).tw. (6224)
 118 ((flexor or "in flexion") adj2 spasm?).tw. (332)
 119 ((lightning or salaam) adj2 attack?).tw. (15)
 120 hypsarrhythmi*.tw. (2024)
 121 or/95-120 [EPILEPSY] (626451)
 122 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw. (5256005)
 123 (newborn* or neonat*).tw. (860199)
 124 (pediatric* or paediatric*).tw. (800591)
 125 or/122-124 (6005033)
 126 121 and 125 [PEDIATRIC EPILEPSY] (158962)
 127 exp Cannabis/ (46269)
 128 exp Cannabinoids/ (76752)
 129 Marijuana Usage/ (2514)
 130 ("c.indica" or cannabi* or bhang or cannador or charas or eucannabinolide* or ganja or ganjah or hash or hashish or hemp or marihuana* or marijuana*).tw. (112358)
 131 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw. (79)
 132 (dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetranabinex).tw. (23463)
 133 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw. (22)
 134 or/127-133 (143233)
 135 126 and 134 [CANNABIS - PEDIATRIC EPILEPSY] (510)
 136 exp Animals/ not (exp Animals/ and Humans/) (16160986)
 137 135 not 136 [ANIMAL-ONLY REMOVED] (333)
 138 137 use medall,emczd (279)
 139 137 not 138 [PSYCINFO RECORDS] (54)
 140 46 or 94 or 139 [ALL DATABASES] (638)
 141 remove duplicates from 140 (441) [TOTAL UNIQUE RECORDS]
 142 141 use medall [MEDLINE UNIQUE RECORDS] (138)
 143 141 use emczd [EMBASE UNIQUE RECORDS] (270)
 144 141 not (142 or 143) [PSYCINFO UNIQUE RECORDS] (33)

Section 3.2

Cannabis-based products for pediatric epilepsy: A systematic review

SECTION OVERVIEW

This section presents a manuscript that describes the findings of the baseline systematic review of the benefits and harms of cannabis-based products for treatment of pediatric epilepsy including, but not limited to, drug-resistant epilepsy. The protocol described in **Section 3.1** was followed in order to identify and appraise studies, extract and summarize the data, and assess the certainty of the evidence. Literature searching was performed in April 2018; as such, this manuscript describes the state of the evidence related to the use of medical cannabis for the treatment of pediatric epilepsy as of April 2018. In the subsequent section (**Section 3.3**), the state of the evidence as of May 2019 is described.

MANUSCRIPT STATUS

This manuscript has been published:

Elliott J, DeJean D, Clifford T, Coyle D, Potter B, Skidmore B, Alexander C, Repetski A, Shukla V, McCoy B, Wells GA. Cannabis-based products for pediatric epilepsy: A systematic review. *Epilepsia*. 2019;60(1):6-19.

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Appendix 10: Evidence summary — Seizure frequency

Appendix 11: Evidence summary — Tonic-clonic seizure frequency

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Appendix 13: Evidence summary — Quality of life (children)
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Author roles and contributions

JE, TC, DC, BP, CA, AR, BM and GW designed the study. BS developed and executed the search strategy. BM provided clinical input. CA and AR provided patient and family perspectives. JE and DD selected studies for inclusion and assessed risk of bias. JE extracted study data, which were checked by DD. JE and VS assessed the certainty of the evidence using GRADE criteria. JE analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors provided comments on the draft and approved the version of the manuscript submitted for publication.

RELATED THESIS APPENDICES

Appendix A: Abstracts accepted for oral presentation. Findings from Section 3.2 were presented at the Society for Medical Decision Making, 40th North American Meeting (2018) and at the 2019 CADTH Symposium.

Elliott J, DeJean D, Clifford T, Coyle D, Potter B, Skidmore B, Alexander C, Repetski A, McCoy B, Wells GA. Cannabis for the treatment of pediatric epilepsy: The case for a living systematic review. Society for Medical Decision Making, 40th North American Meeting, Montreal, Quebec (October 2018).

Elliott J, DeJean D, Clifford T, Coyle D, Potter B, Skidmore B, Alexander C, Repetski A, McCoy B, Wells GA. How living systematic reviews can support health care decision-making: The case of cannabis for pediatric epilepsy. CADTH Symposium, Edmonton, Alberta (April 2019).

Appendix B: Abstracts accepted for poster presentation. Findings from Section 3.2 were presented at 2018 Innovations in the Science of Cannabis Conference at the Michael DeGroote Centre for Medicinal Cannabis Research.

Elliott J, DeJean D, Clifford T, Coyle D, Potter B, Skidmore B, Alexander C, Repetski A, McCoy B, Wells GA. Cannabis for pediatric epilepsy: A living systematic review. Innovations in the Science of Cannabis Conference, Hamilton, Ontario (February 2018).

Appendix G: Published manuscripts. The PDF of the published manuscript is presented in Appendix G.

Cannabis-based products for pediatric epilepsy: A systematic review

Jesse Elliott,^{1,2} Deirdre DeJean,³ Tammy Clifford,^{1,4} Doug Coyle,¹ Beth K Potter,¹ Becky Skidmore,⁵
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Keywords: pediatric drug-resistant epilepsy, cannabis, cannabidiol, seizure, efficacy, safety, systematic
review

Number of text pages: 15

Number of words: 3980

Number of references: 50

Number of figures: 1

Number of tables: 4

SUMMARY

Objective: To assess the benefits and harms of cannabis-based products for pediatric epilepsy.

Methods: We identified in this living systematic review randomized controlled trials (RCTs) and non-randomized studies (NRS) involving children with epilepsy treated with cannabis-based products. We searched MEDLINE, Embase, PsycINFO, Cochrane Library, and grey literature (April 25, 2018). The primary outcome was seizure freedom; secondary outcomes were seizure frequency (total, $\geq 50\%$ reduction), quality of life, sleep, status epilepticus, death, gastrointestinal adverse events, and visits to the emergency room. Data were pooled by random-effects meta-analysis. Risk of bias was assessed for each study. GRADE was used to assess the quality of evidence for each outcome.

Results: Four RCTs and 19 NRS were included, primarily involving cannabidiol. All RCTs were at low risk of bias, while all NRS were at high risk. Among RCTs, there was no statistically significant difference between cannabidiol and placebo in seizure freedom (relative risk [RR] 6.77, 95%CI 0.36 to 128.38; 1 RCT), quality of life (mean difference [MD] 0.6, 95%CI -2.6 to 3.9 ; 3 RCTs), sleep disruption (MD -0.3 , 95%CI -0.8 to 0.2 ; 3 RCTs), or vomiting (RR 1.00, 95%CI 0.51 to 1.96; 4 RCTs). There was a statistically significant reduction in the median frequency of monthly seizures with cannabidiol compared with placebo (-19.8% , 95%CI -27.0% to -12.6% ; 3 RCTs) and an increase in number of participants with at least a 50% reduction in seizures (RR 1.76, 95%CI 1.07 to 2.88; 1 RCT) and diarrhea (RR 2.25, 95%CI 1.38 to 3.68; 3 RCTs). Death and status epilepticus were infrequently reported.

Significance: Evidence from high-quality RCTs suggests that cannabidiol probably reduces seizures among children with drug-resistant epilepsy (moderate certainty). At this time, the evidence base is primarily limited to cannabidiol, and these findings should not be extended to all cannabis-based products.

PROSPERO: CRD42018084755

Keywords: pediatric drug-resistant epilepsy, cannabis, cannabidiol, seizure, efficacy, safety, living systematic review

Key points:

- Few RCTs have assessed the use of cannabis-based treatments for pediatric epilepsy.
- Evidence from short-duration high-quality RCTs suggests that cannabidiol may be effective in reducing seizures among children with drug-resistant epilepsy.
- All available evidence from RCTs is related to one pharmaceutical cannabidiol product, and should not be extended to all cannabis-based products.

INTRODUCTION

Epilepsy affects an estimated 50 million people worldwide¹; of those, about one-third have a drug-resistant form² (failure of two or more adequate trials of antiepileptic drugs [AEDs]³). Consequences of drug-resistant epilepsy (DRE) during childhood are catastrophic, with frequent seizures impairing neurological and cognitive development, impacting quality of life,⁴ and contributing high costs to the health care system.⁵ Although AEDs are the mainstay of treatment, these are often ineffective at reducing seizures and are associated with multiple adverse events.⁶

Interest has been steadily growing in the use of cannabis-based treatments for pediatric epilepsy,⁷ partly owing to media reports of successful cases.⁸ Nine-delta-tetrahydrocannabinol (THC) and cannabidiol (CBD) have received greatest attention as potential antiepileptic agents. In practice, the psychoactive properties of THC may limit its potential as an antiepileptic treatment, especially in children. In contrast, CBD has little psychoactive effect and, in animal models, is protective against multiple seizure types.⁷ Yet until recently, there had been relatively little clinical research into the effectiveness and safety of cannabis-based treatments for epilepsy, and there are large discrepancies between the beliefs of neurologists and the general public as to whether there is sufficient evidence of effectiveness and safety.⁹ A 2014 Cochrane review¹⁰ included four RCTs that assessed the use of cannabinoids in adults with epilepsy, reporting that no reliable conclusions could be made about its efficacy and safety.¹⁰ However, recent randomized controlled trials (RCTs) and non-randomized studies (NRS) have suggested a beneficial effect of CBD in the treatment of epilepsy in children,^{11–15} and the US Food and Drug Administration recently approved the first cannabis-based product (Epidiolex), a pharmaceutical-grade cannabidiol extract, for the treatment of Dravet and Lennox-Gastaut syndrome.¹⁶

In the present study, we performed a systematic review to identify studies involving the use of cannabis and cannabis-based products as treatment for pediatric epilepsy. Systematic review methodology provides a lens through which the evidence from various types of studies can be viewed and compared, in order to assess their quality and applicability to stakeholders (e.g., caregivers, clinicians, policymakers).¹⁷

Objective and significance

The aim of this study is to provide an up-to-date comprehensive summary of the evidence assessing the use of cannabis-based treatments for epilepsy in children. Because the evidence-base is rapidly changing, living systematic review methodology will be used to provide parents, clinicians, and policy makers with up-to-date evidence to inform their decision-making.

METHODS

The systematic review protocol was developed using guidance from the PRISMA-P statement,¹⁸ registered in PROSPERO (CRD42018084755), and published.¹⁹ Two family members (C.A., A.R.) of children with epilepsy and a pediatric neurologist (B.M.) with experience caring for children with DRE were involved in protocol development. Screening and data extraction were performed using Distiller SR (Evidence Partners). This report follows the PRISMA guidelines (Appendix 1).²⁰

Eligibility criteria

We included RCTs and NRS examining the use of cannabis as a treatment for any type of epilepsy in children (≤ 18 yr). Interventions included any type of cannabis-based product, including CBD, cannabidiol, THC, or their combinations, administered by any route (e.g., oral, inhalation). Eligible comparators included pharmacologic (i.e., AEDs) and non-pharmacologic (e.g., diet therapy, vagus nerve stimulation, resective brain surgery) treatments, as well as placebo, usual care, or no treatment.

Outcomes

The outcomes were chosen in consultation with a practising neurologist (B.M.) and two patient family representatives (C.A., A.R.). The primary outcome was seizure freedom. Secondary outcomes were seizure frequency (total, tonic-clonic, $\geq 50\%$ reduction from baseline), quality of life (child, caregiver), sleep, status epilepticus, death (all-cause, sudden unexpected death in epilepsy [SUDEP]), gastrointestinal adverse events (vomiting, diarrhea), and visits to the emergency room. Quality of life could be measured by any instrument designed to assess quality of life in children or their adult caregivers. Impact on sleep

could be assessed by use of an instrument or reported as the number of children who experienced a sleep improvement or impairment. Studies were not selected for inclusion based on reported outcomes.

Search strategy, screening, data extraction

We searched Ovid MEDLINE, Embase, PsycINFO on Ovid, and the Cochrane Library on Wiley from inception to April 25, 2018, with no language or date restrictions (Appendix 2). Grey literature was identified using CADTH's Grey Matters Light,²¹ Google Scholar, ClinicalTrials.gov, and the ICTRP Search Portal. Two independent reviewers (J.E., D.D.) screened the title and abstract of each record and the full text of any record deemed potentially relevant. Data were extracted from primary reports and companion publications by one reviewer and checked for completeness and accuracy by a second reviewer. Disagreements were resolved by discussion.

Risk of bias and quality of the evidence

Risk of bias (RoB) was assessed by two reviewers (J.E., D.D) for each study that reported at least one outcome of interest. For RCTs, bias was assessed by use of the Cochrane Collaboration's RoB tool²²; to be considered at overall low RoB, a study must have been at low risk for each of the following domains: allocation concealment, blinding (participants, outcome assessors, investigators) for subjective outcomes, and incomplete outcome data. The potential for bias in NRS was assessed by use of the SIGN50 Checklist (comparative cohort studies),²³ the NIH Quality Assessment Tool for Before–After (Pre–Post) Studies with No Control Group (single-arm cohort studies),²⁴ and the Joanna-Briggs Institute Checklist for Analytic Cross Sectional Studies.²⁵ To facilitate comparison across tools, we judged overall RoB according to the most serious risk across all domains, regardless of assessment tool. Two independent reviewers (J.E., V.S.) assessed the quality/certainty of the evidence for each outcome by use of the GRADE method.²⁶ Disagreements were resolved by discussion.

Data synthesis

The full analysis plan is available.¹⁹ Descriptive summaries are provided for study selection, study and patient characteristics, and quality assessment. Data from RCTs were pooled by random-effects meta-

analyses by use of RevMan (v.5.3; Cochrane Collaboration) or Comprehensive Meta-Analysis (v. 2.2.064; Biostat) and reported as relative risk (RR), risk difference (RD), mean difference (MDs), or median difference and 95% confidence intervals (CIs). For NRS, the proportion of participants who experienced an outcome was pooled by use of the *metaprop* command in STATA using the Freeman-Tukey double arcsine transformation,²⁷ and the data are reported as percentage of those exposed and 95%CIs. Where multiple time points were reported, data from the longest duration of follow-up were analyzed. Clinical and statistical heterogeneity were investigated by examining study and patient characteristics and the I^2 statistic, respectively. I^2 values above 75% were considered to represent substantial heterogeneity.

RESULTS

Study selection and characteristics

In total, 631 records were screened after removing duplicates (Figure 1). Subsequently, 142 records were screened in full-text format, with 92 records meeting the eligibility criteria (Appendix 3). Of these, 25 records corresponded to 23 unique published studies (four RCTs,^{12,28–30} 19 NRS^{11,13–15,31–45}). An additional 33 records corresponded to trial registration records in ClinicalTrial.gov without reported results, and 34 corresponded to conference abstracts. See Appendix 4 for full list of excluded studies.

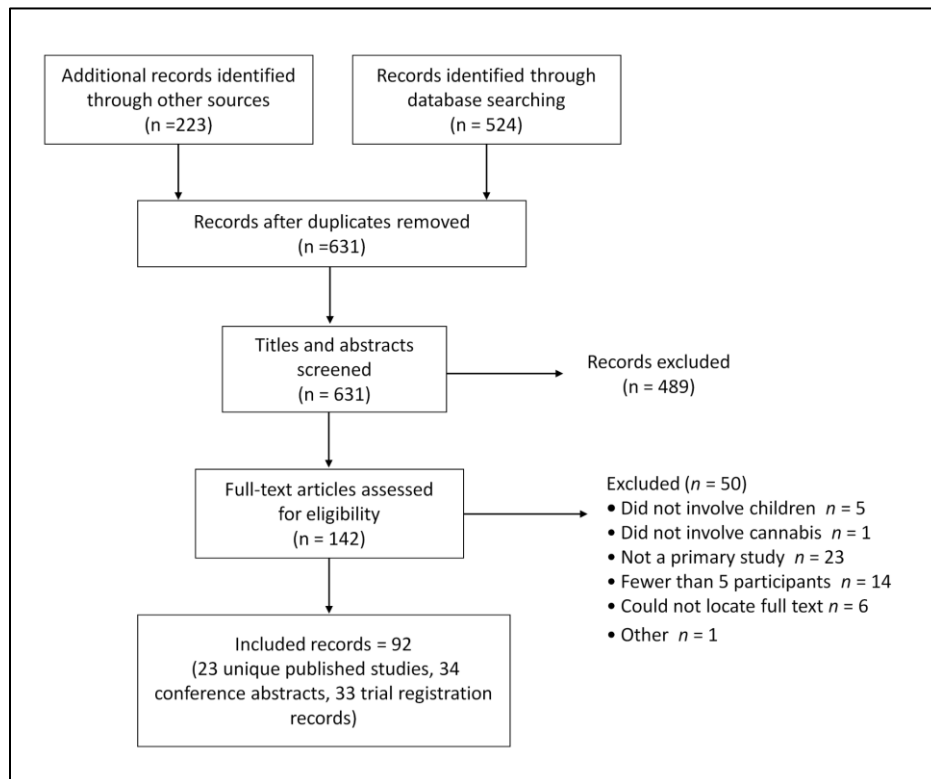


Figure 1: PRISMA flow diagram showing selection of studies.

The four RCTs^{12,28–30} included a total of 550 participants (range 34–225), with either Dravet^{12,28} or Lennox-Gastaut^{29,30} syndrome (Table 1) randomized to placebo or oral CBD (5–20 mg/kg/d) for up to 14 weeks. The mean age in each study was between 7 and 16 years, with an approximately equal number of male and female children taking multiple AEDs at baseline (Table 2). The baseline frequency of total seizures was variable across RCTs (Table 2).

Table 1: Characteristics of included randomized controlled trials

Author, yr, page no. (NCT record)	Design features	Population	Inclusion criteria	Treatments (no. randomized)	Duration	No. centres; country	Funding source	Risk of bias†
Devinsky 2018, p. e1204 (NCT02091206; GWPCARE1 Part A) ²⁸	Double-blind, placebo controlled RCT	Dravet syndrome	4–10 yr, taking ≥ 1 AED and experiencing < 4 convulsive seizures during a 4-wk baseline period, stable medications or interventions (inc. ketogenic diet and VNS) for 4 wk	• Oral cannabidiol solution* 5 mg/kg/d (10), 10 mg/kg/d (8), 20 mg/kg/d (9); given in 2 divided doses • Placebo (7)	3-wk treatment, 10-day taper, 4-wk follow-up	12 centres; US, UK	GW Research Limited	Low
Devinsky 2017, p. 2011 (NCT02091375; GWPCARE1 Part B) ¹²	Double-blind, placebo controlled RCT	Dravet syndrome	2–18 yr, taking ≥ 1 AED, ≥ 4 convulsive seizures during the 28-day baseline period, stable medications or interventions (inc. ketogenic diet and VNS) for 4 wk	• Oral cannabidiol solution,* up to 20 mg/kg/d (61); given in 2 divided doses • Placebo (59)	14-week treatment period (2 wk escalation, 12 wk maintenance), 10-day taper, 4-wk follow-up	23 centres; US and Europe	GW Pharmaceuticals	Low
Devinsky 2018, p. 1888 (NCT02224560; GWPCARE3) ²⁹	Double-blind, placebo controlled RCT	Lennox-Gastaut syndrome	2–55 yr, with an electroencephalogram that showed a pattern of slow spike-and-wave complexes and ≥ 2 types of generalized seizures, inc. drop seizures, for ≥ 6 mo, with use of 1–4 AEDs and ≥ 2 drop seizures per wk during the 28-d baseline period	• Oral cannabidiol solution,* 10 mg/kg/d (73), 20 mg/kg/d (76); given in 2 divided doses • Placebo (76)	14 wk (2 wk escalation, 12 wk treatment), 4-wk follow-up	30 centres; US, Spain, UK, France	GW Pharmaceuticals	Low
Thiele 2018, p. 1085 (NCT02224690; GWPCARE4) ³⁰	Double-blind, placebo controlled RCT	Lennox-Gastaut syndrome	2–55 yr, >1 type of generalised seizure, inc. drop seizures, for at least 6 mo; taking 1–4 AEDs, and ≥ 2 drop seizures per wk during the 4-wk baseline period; stable medications or interventions (inc. ketogenic diet and VNS) for 4 wk	• Oral cannabidiol solution,* 20 mg/kg/d (86); given in 2 divided doses • Placebo (85)	14 wk (2 wk escalation, 12 wk treatment), taper period, 4-wk follow-up	24 centres; US, Netherlands, Poland	GW Pharmaceuticals	Low
Note: AED = antiepileptic drug, RCT = randomized controlled trial, VNS = vagus nerve stimulation *Epidiolex (GW Pharmaceuticals). †Low risk of bias for each of allocation concealment, blinding, and outcome data reporting.								

Table 2: Characteristics of participants in the included randomized controlled trials

Author, yr, page no.	Treatments (no. randomized)	Baseline total seizure frequency, median (IQR), mo	Age, yr, mean (SD)	Male, no. (%)	BMI or weight, mean (SD)*	No. of concomitant AEDs, mean (SD)*	No. previous AEDs, mean (SD)*	Ketogenic diet, no. (%)	VNS, no. (%)
Devinsky 2018, p. e1204 ²⁸	• Placebo (7) • CBD 5 mg/kg/d (10) • CBD 10 mg/kg/d (8) • CBD 20 mg/kg/d (9)	NR	7.0 (0.9) 7.2 (1.9) 7.4 (2.1) 8.7 (1.8)	5 (71) 5 (50) 3 (38) 3 (33)	BMI: 18.7 (4.0) 18.9 (4.4) 16.1 (1.5) 16.1 (2.3) Weight: NR	2.1 (0.9) 2.6 (1.1) 2.8 (0.5) 2.8 (0.8)	NR	0 1 (10) 2 (25) 3 (33)	0 1 (10) 0 1 (11)
Devinsky 2017, p. 2011 ¹²	• Placebo (59) • CBD 20 mg/kg/d (61)	41.5 (NR) 24.0 (NR)	9.8 (4.8) 9.7 (4.7)	27 (46) 35 (47)	BMI: 19.1 (4.7) 18.3 (4.5) Weight: NR	2.9 (1.0) 3.0 (1.1)	4.6 (3.3) 4.6 (4.3)	4 (7) 6 (10)	9 (15) 6 (10)
Devinsky 2018, p. 1888 ²⁹	• Placebo (76) • CBD 10 mg/kg/d (73) • CBD 20 mg/kg/d (76)	180.6 (90.4–431.3) 165.0 (81.3–359.0) 174.3 (82.7–392.4)	15.3 (9.3) 15.4 (9.5) 16.0 (10.8)	44 (58) 40 (55) 45 (59)	NR	Median (range) 3 (1–5) 3 (1–5) 3 (0–5)	Median (range) 6 (1–22) 6 (0–21) 6 (1–18)	6 (8) 6 (8) 6 (8)	21 (28) 15 (21) 17 (22)
Thiele 2018, p. 1085 ³⁰	• Placebo (85) • CBD 20 mg/kg/d (86)	176.7 (68.6–359.5) 144.6 (72.0–385.7)	15.3 (9.8) 15.5 (8.7)	43 (51) 45 (52)	NR	Median (IQR) 3 (1–4) 3 (1–5)	Median (IQR) 6 (0–28) 6 (1–18)	10 (12) 4 (5)	25 (29) 26 (30)
Note: CBD = cannabidiol, IQR = interquartile range, NR = not reported, SD = standard deviation, VNS = vagus nerve stimulation. *Unless otherwise stated									

Of the 19 NRS, two were comparative cohort studies (one prospective, one retrospective),^{31,35} 12 were single-group cohort studies (eight prospective, four retrospective),^{13–15,32,34,37,38,40–44} four were cross-sectional surveys,^{11,36,39,45} and one was a case series³³ (Appendix 5). In total, the NRS involved 1,115 participants (range 5–214) with variable baseline seizure frequency, and variable treatment durations (10 days to 57 months). Fourteen NRS included participants with multiple forms of DRE (Appendix 5),^{11,13–15,31,34–42} while some studies focused on specific syndromes, including Dravet syndrome,¹² tuberous sclerosis complex (TSC),⁴⁴ Sturge-Weber syndrome,³² and Febrile Infection-Related Epilepsy (FIRES).⁴³ The range of mean ages of included participants, where available, was between 7 and 14 years (Appendix 6). The types of cannabis-based interventions varied among studies, although more than half involved CBD (68%). Not all interventions were well described and some included “artisanal” products,³⁸ products from illicit cannabis suppliers,³⁹ or home-made extracts.¹¹ Most cannabis-based products were administered orally, although one study¹⁴ involved use of inhaled cannabis by some participants.

Risk of bias

All four RCTs were at overall low RoB (Appendix 7); however, selective outcome reporting was a potential concern in three RCTs,^{12,29,30} with discrepancies noted between the protocol or ClinicalTrials.gov record and the published report.

The overall RoB was considered high for all NRS, owing to at least one of the following: lack of a control group, lack of blinding and subjective outcomes, self-selection or unclear selection of participants, inconsistency in interventions across participants, or a lack of detail about the interventions (Appendix 5).

Summary of results

In total, four RCTs^{12,28–30} and 17 NRS^{11,13–15,31,32,34–40,42–45} reported at least one outcome of interest and form the evidence base for this review. The evidence summary, including GRADE assessment, is shown in Table 3 and 4. The full GRADE assessment is provided in Appendix 8.

Table 3: Evidence summary

Outcome	Randomized controlled trials					Non-randomized studies				
	No. of studies	No. of participants	Effect estimate (95%CI), cannabidiol v. placebo	I ²	GRADE assessment	No. of studies	No. of participants	Proportion of those exposed to a cannabis-based product (95%CI)*	I ²	GRADE assessment
Primary outcome										
Seizure freedom	1	120	RR 6.77 (0.36 to 128.38) RD 0.05 (−0.01 to 0.11)	NA	Low	14	761	7% (4% to 11%)	72%	Very low
Secondary outcomes†										
Total Seizure frequency	3	516	Median reduction in monthly seizures v. placebo: −19.8% (−27.0% to −12.6%)	0%	Moderate	6	316	NA**	NA	Very low
Tonic–clonic seizure frequency	3	321	Median reduction in monthly seizures v. placebo: −27.5% (−38.7% to −16.3%)	0%	Moderate	2	95	NA**	NA	Very low
Treatment response‡	1	171	RR 1.76 (1.07 to 2.88) RD 0.16 (0.03 to 0.29)	NA	Moderate	12	641	48% (39% to 57%)	79%	Very low
Quality of life: Child	3	516	Pooled mean difference 0.6 (−2.6 to 3.9)¶	0%	Moderate	1	48	Mean difference before–after: 8.12 (SD 9.85)¶	NA	Very low
Sleep Disruption	3	516	Pooled mean difference: −0.3 (−0.8 to 0.2)§	0%	Moderate	0	NA	NA	NA	NA
Improved sleep	0	NA	NA	NA	NA	5	368	44% (15% to 72%)	98%	Very low
Impaired sleep	1	171	Sleep apnea reported for 1 participant (1.2%) in the CBD group; none in the placebo group	NA	NA	5	140	4% (0% to 7%)	6%	Very low
Status epilepticus	3	516	RR 1.39 (0.55 to 3.47) RD 0.01 (−0.02 to 0.03)	0%	Low	3	283	4% (0% to 8%)	NA	Very low
Death	1	171	1 death reported in the CBD group (n = 86); zero deaths in the placebo group (n= 85)	NA	Low	5	314	1% (0% to 2%)	0%	Very low
Gastrointestinal AEs	4	550	RR 1.54 (0.92 to 2.58) RD 0.12 (−0.01 to 0.24)	52%	Low	11	682	8% (4% to 12%)	69%	Very low
Note: AE = adverse event, CBD = cannabidiol, CI = confidence interval, RD = risk difference, RR = relative risk. *Unless otherwise stated †None of the included studies assessed caregiver quality of life or visits to the emergency department ‡≥50% reduction in seizure frequency relative to baseline period. ¶Quality of Life in Childhood Epilepsy scale §Assessed by use of the Sleep Disruption Rating Scale (negative value favours CBD). **Data reported in a variety of ways precluded pooling; see Appendix 9 and 10.										

Table 4: GRADE evidence profile for critical outcomes

Certainty assessment							No. events/ no. of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	Standard care	Relative (95% CI)	Absolute (95% CI)	
Seizure freedom (total seizures) (treatment duration: 14 weeks; number of patients with zero seizures during treatment)											
1	RCTs	not serious	not serious	not serious	very serious ^{a,b,c}	none	3/61 (4.9%)	0/59 (0.0%)	RR 6.77 (0.36 to 128.38) ^d	—	⊕⊕○○ LOW
Treatment response (treatment duration: 14 weeks; number of participants with at least a 50% reduction in total seizures from baseline)											
1	RCTs	not serious	not serious	not serious	serious ^a	none	32/86 (37.2%)	18/85 (21.2%)	RR 1.76 (1.07 to 2.88)	161 more per 1,000 (from 15 more to 398 more)	⊕⊕⊕○ MODERATE
Gastrointestinal adverse events (treatment duration: 3 to 14 weeks; number of children with vomiting or diarrhea or both)											
4	RCTs	not serious	serious ^e	not serious	serious ^{a,b}	none	89/323 (27.6%)	45/227 (19.8%)	RR 1.54 (0.92 to 2.58)	107 more per 1,000 (from 16 fewer to 313 more)	⊕⊕○○ LOW

Note I: CI = confidence interval, MD = mean difference, RCT = randomized controlled trials, RR = relative risk.

Note II: The full GRADE assessment of all outcomes is reported in Appendix 8.

a. Number of participants is less than the optimal information size.

b. 95%CI includes important benefits and harms.

c. Rare event; confidence intervals may be misleading because of fragility.

d. Risk difference: 5% (95% –1% to 11%).

e. Heterogeneity (*I*²): 52%.

Primary outcome

Seizure freedom

Fifteen studies reported results related to freedom from all seizure types after administration of a cannabis-based product (Appendix 8), including one RCT¹² and 14 NRS (six prospective single-arm cohort studies,^{13,14,32,42–44} four retrospective single-arm cohort studies,^{15,34,38,40} one comparative retrospective cohort study,³⁵ three cross-sectional studies^{11,36,45}).

Among children with Dravet syndrome who received CBD in one RCT,¹² 5% (3/61) experienced freedom from all seizures, while no children in the placebo group (n = 59) became seizure free during a 14-week treatment period (RD 5%, 95%CI –1% to 11%; low certainty). Among the NRS, estimates of seizure freedom ranged from 1% to 20% (pooled proportion 7%, 95%CI 4% to 11%; duration: 8 wk to 33 mo), with the highest estimates observed among cross-sectional studies (very low certainty; Appendix 9).

Secondary outcomes

Seizure frequency

Nine studies assessed the effect of cannabis-based products on seizure frequency, including three RCTs^{12,29,30} and six NRS (four single-group prospective cohort studies,^{13,42–44} one comparative retrospective cohort study,³⁵ one cross-sectional study³⁹) (Appendix 10). Among the RCTs, the pooled median difference in monthly seizure frequency between CBD and placebo was –19.8% (95%CI –27.0% to –12.6%; moderate certainty; 14 wk). Among the NRS, the reported reduction in total seizures with use of a cannabis-based product was between 30% and 90% (duration: 8 wk to > 16 mo; very low certainty).

Five studies reported the effect of cannabis-based products on the frequency of tonic–clonic seizures (three RCTs,^{12,29,30} two prospective single-arm cohorts^{13,44}) (Appendix 11). The pooled median difference in monthly seizure frequency between CBD and placebo in the RCTs was –26.7% (95%CI –38.8% to –14.8%; moderate certainty; duration: 14 wk). Among the NRS, Devinsky and colleagues¹³ reported a non-statistically significant reduction in the median frequency of monthly tonic-clonic seizures with CBD

among 89 children with any type of DRE (–16%, 95% –60.1% to 35.3%; duration: 12 wk), while Hess and colleagues⁴⁴ reported a significant median reduction in weekly tonic–clonic seizures (–91.4%, 95%CI –100% to –13.9%; duration: 12 mo) among 6 children with TSC (very low certainty).

Thirteen studies assessed treatment response ($\geq 50\%$ reduction in seizure frequency from baseline), including one RCT³⁰ and 12 NRS studies (six prospective single-arm cohort studies,^{13,14,32,42–44} three retrospective single-arm cohort studies,^{15,34,40} one comparative retrospective cohort study,³⁵ two cross-sectional studies^{11,36}) (Appendix 12). Among children with Lennox-Gastaut syndrome in one RCT, 37% (23/86) of children randomized to CBD had a 50% or greater reduction in seizure frequency, compared with 21% (18/85) of children randomized to placebo (RR 1.76, 95%CI 1.07 to 2.88; moderate certainty; duration: 14 wk).³⁰ Among NRS, estimates of treatment response ranged from 24% to 100% (duration: 8 wk to 57 mo; very low certainty).

Quality of life

Five studies (three RCTs,^{12,29,30} two prospective single-arm cohort studies^{13,46}) assessed quality of life among affected children (Appendix 13). In the RCTs, there was no statistically significant difference in overall score on the Quality of Life in Childhood Epilepsy scale between CBD and placebo groups (MD 0.6, 95%CI –2.6 to 3.9; moderate certainty; duration: 14 wk). Both single-arm cohort studies reported statistically significant improvements in quality of life relative to the baseline period after treatment with CBD (duration: 12 to 82 weeks; very low certainty).^{32,37}

None of the included studies assessed caregiver quality of life.

Sleep

Twelve studies (three RCTs,^{12,29,30} nine NRS^{11,31,32,34,36,40,42,44,45}) reported changes in sleep, including improvement or impairment, after administration of a cannabis-based product (Appendix 14). In the RCTs, there was no statistically significant difference in Sleep Disruption Rating scale score between CBD and placebo (MD –0.3, 95%CI –0.8 to 0.2; moderate certainty; duration: 14 wk). One child (1.2%)

with Lennox-Gastaut syndrome who received CBD was reported to have ongoing treatment-related sleep apnea at the end of the trial.³⁰ Sleep apnea was also reported in one NRS,³¹ with one child (4.8%) who received 40 mg/kg/d CBD experiencing sleep apnea.

Improved sleep was reported in five NRS (two retrospective cohort studies,^{34,40} three cross-sectional studies^{11,36,45}; duration: 2 wk to 57 mo), with a higher proportion reported in cross-sectional studies (68%, 95%CI 46% to 90%) compared with retrospective cohort studies (8%, 95%CI 4% to 11%) (very low certainty; Appendix 14). Impaired sleep was reported in five NRS (four prospective cohort studies,^{31,32,42,44} one cross-sectional survey¹¹), affecting 4% (95%CI 0% to 7%) of children who received a cannabis-based product (duration: 10 d to 82 wk; very low certainty).

Status epilepticus

Status epilepticus was reported in six studies, including three RCTs^{12,29,30} and three NRS (two prospective cohort studies,^{13,14} one retrospective cohort study⁴⁶) (Appendix 15). In the RCTs,^{12,29,30} the RR of status epilepticus was 1.39 (95%CI 0.55 to 3.47; low certainty; duration: 14 wk). Among the NRS, the pooled prevalence of status epilepticus was 4% (95%CI 0% to 8%; duration: 12 wk to 33 mo; very low certainty).

Death

Deaths were reported among children who received a cannabis-based product in six studies (one RCT,³⁰ two prospective cohort studies,^{13,43} three retrospective cohort studies^{34,38,46}) (Appendix 16); an additional three studies^{12,28,31} reported that no deaths had occurred during the treatment period). Thiele and colleagues³⁰ reported the death of one participant with Lennox-Gastaut syndrome who received CBD (20 mg/kg/d; n = 86) during their 14-week RCT; the death was attributed to respiratory failure and deemed by study authors to be unrelated to treatment. No deaths were reported in the placebo group (n = 85) (low certainty). An additional six deaths from various causes (including two reports of SUDEP) were reported in five NRS^{13,34,38,43,46} (n = 313; duration: 1 to 29 mo; very low certainty).

Gastrointestinal adverse events

Diarrhea or vomiting were reported in four RCTs^{12,28–30} and nine NRS (six prospective cohort studies,^{13,14,31,32,43,44} three cross-sectional studies^{11,36,45}; Appendix 17). An additional two NRS^{15,40} reported gastrointestinal events without specifying the specific adverse events. In the RCTs, the pooled RR was 1.54 (95%CI 0.92 to 2.58) for any gastrointestinal adverse event, 1.00 (95%CI 0.51 to 1.96) for vomiting, and 2.25 (95%CI 1.38 to 3.68) for diarrhea (low certainty; duration: 3 to 14 wk).

Among the NRS, the pooled proportion of participants who experienced at least one of vomiting or diarrhea was 8% (95%CI 4% to 12%; very low certainty; Appendix 17). A similar proportion of children were reported to have had vomiting (5%, 95%CI 2% to 8%) and diarrhea (7%, 95%CI 2% to 12%). The estimated incidence of both outcomes was highest for prospective cohort studies (vomiting: 7%, 95%CI 3% to 11%; diarrhea: 9%, 95%CI 3% to 16%), while estimates were considerably lower for cross-sectional studies (vomiting: 3%, 95%CI 1% to 7%; diarrhea: 2%, 95%CI 0% to 12%) (duration: 10 d to 57 mo).

Visits to the ER

No studies reported visits to the emergency room during the study period.

Sensitivity analyses

Type of cannabis-based product

To date, all RCTs involved oral CBD (5–20 mg/kg/d). Similarly, most of the NRS (68%) involved CBD. Although some NRS involved the use of non-CBD-based treatments, such studies typically included use of more than one product of varying composition (Appendix 5), precluding assessment of the effect of individual formulations. Data were insufficient to assess the impact of cannabis strain, level of THC, or THC:CBD ratio.

Co-mediations

Two NRS^{35,42} assessed the effect of concomitant CBD and clobazam. Among children with DRE taking CBD and clobazam, the level of clobazam increased by 60% after four weeks of treatment, while *N*-desmethyclobazam levels increased by 500% (n = 13).⁴² Nine of these children (69%) experienced $\geq 50\%$ reduction in seizures from baseline, with a mean reduction of 51% in seizure frequency; two children (15%) became seizure free. The authors noted that the observed adverse events were similar to those seen in patients with high clobazam doses (e.g., drowsiness) and were alleviated by clobazam dose reduction.⁴² A similar proportion of children were reported to have experienced seizure freedom when administered various artisanal CBD products in addition to clobazam (9%); seizure freedom was reported for 14% of children who received CBD alone and 11% who received clobazam alone.³⁵ A higher proportion of children taking concomitant CBD and clobazam experienced seizure freedom (44%), compared with either alone (CBD: 33%; clobazam: 38%).³⁵

Subgroups analyses

Few studies have assessed cannabis-based treatments in specific epilepsy syndromes, with the exception of four RCTs involving participants with Dravet syndrome^{12,28} or Lennox-Gastaut syndrome^{29,30} and three NRS involving participants with TSC,⁴⁴ Sturge-Weber syndrome,³² or FIRES.⁴³ In general, available evidence suggests that CBD reduces seizure frequency across epilepsy syndromes (Appendix 18); however, these findings are predominately based on small open-label studies at high RoB, and no data are available for other cannabis-based products. No data were available to assess the outcomes among different age groups or by sex.

Ongoing studies

We identified 33 yet-unpublished studies registered in ClinicalTrials.gov, in varying stages of completion (Appendix 19). An additional 34 conference abstracts were identified, of which 14 represent potentially unpublished studies (Appendix 20).

DISCUSSION

Despite recorded medical use of cannabis dating back to 2nd century BCE,⁴⁷ until recently there had been few clinical studies of its effectiveness and safety, especially among children. However, the last few years have seen a sharp increase in the number of clinical studies involving cannabis for pediatric epilepsy. We undertook this systematic review to provide an up-to-date, comprehensive summary of the available evidence to support decision-making by parents, clinicians, and policy makers.

The evidence from four recently-published high-quality RCTs suggests that CBD is probably reduces seizures in children with DRE, without a corresponding increase in seizure freedom or quality of life (moderate to low certainty of evidence). In particular, all of the included RCTs involve the use of Epidiolex, and the findings should not be extrapolated to other preparations. The effects of CBD and other cannabis-based products on other outcomes are less clear, and our understanding of the potential benefits and harms in this population will be refined as data from ongoing studies becomes available. In particular, there is currently limited clinical information about the benefits and harms of cannabis-based products with high THC content.

The use of clobazam by children with DRE is common: in the included RCTs, up to 66% of children received clobazam in addition to CBD.^{12,28–30} Cannabidiol is an inhibitor of multiple CYP enzymes, notably CYP3A4 and CYP2C19, which are involved in the clearance of N-desmethyloclobazam, the active metabolite of clobazam.⁴⁸ As such, inhibition of CYP enzymes by CBD has the potential to increase the serum concentration of clobazam and other antiepileptic drugs. Indeed, elevated clobazam and N-desmethyloclobazam levels have been reported among children with DRE who received both CBD and clobazam,^{28,42} which may have implications for both efficacy and safety. A higher rate of seizure freedom has been reported among children who received concomitant CBD and clobazam than either agent alone,³⁵ and increased somnolence has been noted among children who received both CBD and clobazam compared to those who received clobazam alone.¹² Others have noted that the adverse events observed

among children taking both CBD and clobazam are similar to those seen at high CLB doses, and that reduction of clobazam may be sufficient to alleviate adverse events.⁴²

A previous systematic review⁴⁹ involving children and adults with epilepsy similarly found that CBD was more effective than placebo at improving treatment response and reducing seizure frequency. In contrast with our findings, Stockings and colleagues⁴⁹ reported that CBD increased seizure freedom and improved quality of life. These apparent discrepancies are likely related to methodological differences. In their analysis of seizure freedom, Stockings and colleagues⁴⁹ combined estimates of freedom from all seizures with freedom from drop or convulsive seizures, while our assessment included only studies that reported freedom from all seizures. Although we found no statistically significant difference between groups, this finding was based on one RCT, and the publication of additional studies assessing freedom from all seizures will help to clarify whether there is a beneficial effect of CBD.

Similarly, methodological differences may be responsible for the discrepant findings in quality of life between the Stockings⁴⁹ review and our analysis. Stockings and colleagues⁴⁹ assessed quality of life by use of the Caregiver Global Impression of Change score, which assesses whether, in the caregiver's opinion, the child's overall condition has improved. In our review, we used the Quality of Life in Childhood Epilepsy score, which has been validated for use by parents of children with DRE to assess health-related quality of life and is sensitive to seizure severity and medication effects.⁵⁰

Parents of children with DRE have reported that “unacceptable AED side effects” and the belief that cannabis-based products are “more natural” and more effective are motivating factors for their willingness to enroll their child in a trial of cannabinoids for epilepsy.³⁹ However, a previous review⁴⁹ reported an increased risk of adverse events and serious adverse events among children and adults who received CBD compared with placebo, and we found that the risk of diarrhea was significantly higher among children who received CBD. As such, the decision to administer CBD or other cannabis-based

products should be based on shared decision-making between parents and health care providers, with consideration of both the potential benefits and harms.

Strengths and limitations

The protocol for this review was published *a priori*,¹⁹ and we followed rigorous systematic review methodology. To ensure the relevance of our findings to decision-making, two family members of children with epilepsy and a pediatric neurologist were collaborators on this project. Because there is little certainty in the evidence-base, and because there are a number of ongoing studies, this review will be updated at six-month intervals to include new evidence as it becomes available, and updates will be posted online at cannabisandepilepsy.blogspot.com

Several limitations should be considered. First, most included NRS were at high risk of at least one important source of bias (e.g., selection, performance, ascertainment) and the certainty of the evidence from such studies is very low owing to the high risk of bias. Although NRS may be important sources of evidence for understanding of real-world effectiveness and informing health care decision-making,⁵¹ such biases affect the ability to evaluate effectiveness and safety. However, the findings were generally consistent between the included RCTs and NRS, although the magnitude of treatment benefit was often greater among NRS. This was expected, given the high rate of placebo response in pediatric epilepsy studies⁵² combined with the use of subjective outcomes and a lack of blinding. Indeed, in the placebo arm of the included RCTs, the percentage reduction in seizures was between 9% and 18.5% and the responder rate was 21% (Appendix 10, Appendix 12), which is consistent with the reported placebo responder rate of 19.7% from a pooled analysis of double-blind RCTs involving children with refractory epilepsy.⁵² Given this high responder rate among participants who received placebo in the RCTs, in the non-randomized studies involving only one treatment arm, it is difficult to separate the effect of the cannabis-based intervention from a possible placebo response.

Second, there was considerable heterogeneity among in terms of the interventions and duration of treatment. All included RCTs involved Epidiolex, a pharmaceutical-grade CBD preparation recently approved by the US Food and Drug Administration for Dravet and Lennox-Gastaut syndromes.¹⁶ Whether the observed effects extend to other cannabis-based products is unknown. Similarly, almost half of the NRS involved Epidiolex, while others involved multiple cannabis-based products, which were often poorly described. All included RCTs had relatively short treatment durations (up to 14 weeks); thus, it is not clear whether the observed effects are sustained over a longer duration. Although the NRS involved up to 57 months of treatment, the available data did not allow for an assessment of maintenance of effect.

Third, the effects of cannabis-based products on individual epilepsy syndromes is currently limited and is primarily related to Dravet^{12,28} and Lennox-Gastaut syndromes.^{29,30} Evidence from NRS suggests that CBD may also be effective in TSC,⁴⁴ Sturge-Weber syndrome,³² and FIRES⁴³; however, these studies were based on few participants and were subject to important biases.

Fourth, in most studies, cannabis-based products were added to an established regimen of antiepileptic therapies, including concomitant AEDs, in children with DRE. As such, whether cannabis-based products are effective as first-line therapy for newly diagnosed epilepsy is unknown. Additionally, although some studies required that the type and dose of AEDs be held constant, AED treatments were more fluid in other studies, particularly retrospective studies, with additional interventions added or removed during the treatment period, potentially confounding the results.³⁵ Interactions between some AEDs (e.g., clobazam) and CBD have been suggested,⁴² although this has yet to be investigated in well-controlled long-term studies.

Fifth, although seizure freedom, the primary outcome of this review, was identified by family members and a practising neurologist as being of utmost importance, it may not be an attainable outcome for children with DRE. In this population, a reduced burden of seizures and the avoidance of status epilepticus may be more realistic goals, with a 50% reduction in seizures being a desirable outcome. As

such, it is not unsurprising that a small proportion of children with Dravet syndrome experienced seizure freedom with CBD treatment.¹² However, the observed reduction in seizure frequency and increased number of children with Dravet or Lennox Gastaut syndrome with $\geq 50\%$ reduction in seizures is a clinically important finding.

Conclusion

Evidence from recent high-quality RCTs suggests that CBD is effective in reducing seizure burden among children with drug-resistant Dravet and Lennox-Gastaut syndrome (moderate certainty); however, few children experienced complete seizure freedom. Although the evidence is currently limited, children with other DRE syndromes may experience similar benefit. These findings should not be extended to all cannabis-based products, especially those of unknown composition.

Declarations

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Ethical publication statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author's contributions: JE, TC, DC, BP, CA, AR, BM and GW designed the study. BS developed and executed the search strategy. JE and DD selected studies for inclusion and extracted data. JE and VS assessed the certainty of the evidence using GRADE criteria. JE analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication.

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39. Suraev AS, Todd L, Bowen MT, et al. An Australian nationwide survey on medicinal cannabis use for epilepsy: History of antiepileptic drug treatment predicts medicinal cannabis use. *Epilepsy Behav.* 2017;70(Pt B):334.
40. Treat L, Chapman KE, Colborn KL, Knupp KG. Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients. *Epilepsia.* 2017;58(1):123.
41. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP, Program UABCBD. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia.* 2017;58(9):1586.
42. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia.* 2015;56:1246-1251.
43. Gofshteyn JS, Wilfong A, Devinsky O, et al. Cannabidiol as a potential treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES) in the acute and chronic phases. *J Child Neurol.* 2017;32(1):35.
44. Hess EJ, Moody KA, Geffrey AL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. *Epilepsia.* 2016;57(10):1617.
45. Hussain SA, Zhou R, Jacobson C, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome. *Epilepsy Behav.* 2015;47:138-141.
46. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy Behav.* 2015;45:49-52.
47. Friedman D, Sirven JI. Historical perspective on the medical use of cannabis for epilepsy: Ancient times to the 1980s. *Epilepsy Behav.* 2016;70:298-301.
48. Bornheim LM, Everhart ET, Li J, Correia MA. Characterization of cannabidiol-mediated cytochrome P450 inactivation. *Biochem Pharmacol.* 1993;45(6):1323-1331.
49. Stockings E, Zagig D, Campbell G, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *J Neurol Neurosurg Psychiatry.* 2018;89(7):741-753.
50. Sabaz M, Cairns DR, Lawson J a, Nheu N, Bleasel a F, Bye a M. Validation of a new quality of life measure for children with epilepsy. *Epilepsia.* 2000;41(6):765-774.
51. Griffiths EA, Macaulay R, Vadlamudi NK, Uddin J, Samuels ER. The role of non-comparative evidence in health technology assessment decisions. *Value Heal.* 2017;20(10):1245-1251.

52. Zaccara G, Giovannelli F, Franco V, Cincotta M, Tramacere L, Verrotti A. Adverse events, placebo and nocebo effects in placebo-treated paediatric patients with refractory focal epilepsies. Analysis of double-blind studies. *Epilepsy Res.* 2014;108:1685-1693.

Appendix 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3,5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,7, published protocol

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Appendix 2: Literature search

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2017 December 13>, Ovid MEDLINE(R) ALL <1946 to December 14, 2017>, PsycINFO <1806 to December Week 2 2017> Note: The numbers below pertain to an initial search run December 15, 2017; the search was subsequently updated April 25, 2018.

Search Strategy:

- 1 exp Epilepsy/ (413158)
- 2 (epileps* or epilept*).tw,kf. (354209)
- 3 seizure*.tw,kf. (308442)
- 4 convulsi*.tw,kf. (73122)
- 5 falling sickness*.tw,kf. (61)
- 6 comitial disease*.tw,kf. (3)
- 7 (petit mal or grand mal or absence status).tw,kf. (8405)
- 8 Landau-Kleffner Syndrome*.tw,kf. (1213)
- 9 Lennox Gastaut Syndrome*.tw,kf. (3397)
- 10 Dravet Syndrome*.tw,kf. (2044)
- 11 West syndrome*.tw,kf. (2852)
- 12 Doose syndrome*.tw,kf. (167)
- 13 Ohtahara syndrome*.tw,kf. (499)
- 14 Sturge-Weber Syndrome/ (3596)
- 15 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kf. (8090)
- 16 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw,kf. (776)
- 17 SMEI.tw,kf. (461)
- 18 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw,kf. (1137)
- 19 Lafora.tw,kf. (1430)
- 20 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kf. (735)
- 21 ((infantile or nodding) adj2 spasm?).tw,kf. (6276)
- 22 ((flexor or "in flexion") adj2 spasm?).tw,kf. (332)
- 23 ((lightning or salaam) adj2 attack?).tw,kf. (16)
- 24 hypsarrhythmi*.tw,kf. (2063)
- 25 or/1-24 [EPILEPSY] (627889)
- 26 Adolescent/ (3482184)
- 27 exp Child/ (4584752)
- 28 exp Infant/ (2191998)
- 29 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kf. (5312514)
- 30 (newborn* or neonat*).tw,kf. (874968)
- 31 (pediatric* or paediatric*).tw,kf. (811013)
- 32 or/26-31 (9306058)
- 33 25 and 32 [PEDIATRIC EPILEPSY] (223050)
- 34 Cannabis/ (43738)
- 35 exp Cannabinoids/ (76752)
- 36 Medical Marijuana/ (1233)
- 37 Marijuana Smoking/ (6987)
- 38 ("c.indica" or cannabi* or bhang or cannador or charas or eucannabinolide* or ganja or ganjah or hash or hashish or hemp or marihuana* or marijuana*).tw,kf. (112741)
- 39 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw,kf. (79)
- 40 (dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetranabinex).tw,kf. (23589)
- 41 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kf. (22)
- 42 or/34-41 (144274)
- 43 33 and 42 [CANNABIS - PEDIATRIC EPILEPSY] (670)
- 44 exp Animals/ not (exp Animals/ and Humans/) (16160986)

45 43 not 44 [ANIMAL-ONLY REMOVED] (453)
 46 45 use medall (185)
 47 exp epilepsy/ (413158)
 48 (epileps* or epilept*).tw,kw. (359359)
 49 seizure*.tw,kw. (310739)
 50 convulsi*.tw,kw. (74278)
 51 falling sickness*.tw,kw. (64)
 52 comitial disease*.tw,kw. (3)
 53 (petit mal or grand mal or absence status).tw,kw. (8283)
 54 Landau-Kleffner Syndrome*.tw,kw. (1248)
 55 Lennox Gastaut Syndrome*.tw,kw. (3450)
 56 Dravet Syndrome*.tw,kw. (2094)
 57 West syndrome*.tw,kw. (2980)
 58 Doose syndrome*.tw,kw. (181)
 59 Ohtahara syndrome*.tw,kw. (513)
 60 sturge-weber syndrome/ (3596)
 61 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kw. (8213)
 62 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw,kw. (785)
 63 SMEI.tw,kw. (485)
 64 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw,kw. (1167)
 65 Lafora.tw,kw. (1443)
 66 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kw. (740)
 67 ((infantile or nodding) adj2 spasm?).tw,kw. (6422)
 68 ((flexor or "in flexion") adj2 spasm?).tw,kw. (332)
 69 ((lightning or salaam) adj2 attack?).tw,kw. (16)
 70 hypsarrhythmi*.tw,kw. (2094)
 71 or/47-70 [EPILEPSY] (630155)
 72 juvenile/ (38711)
 73 exp adolescent/ (3482352)
 74 exp child/ (4584752)
 75 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kw. (5321220)
 76 (newborn* or neonat*).tw,kw. (870009)
 77 (pediatric* or paediatric*).tw,kw. (831059)
 78 or/72-77 (9154566)
 79 71 and 78 [PEDIATRIC EPILEPSY] (221973)
 80 cannabis/ (43738)
 81 exp cannabinoid/ (63688)
 82 medical cannabis/ (1625)
 83 exp "cannabis use"/ (7317)
 84 ("c.indica" or cannabi* or bhang or cannador or charas or eucannabinolide* or ganja or ganjah or hash or hashish or hemp or marihuana* or marijuana*).tw,kw. (113719)
 85 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw,kw. (79)
 86 (dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetranabinex).tw,kw. (23862)
 87 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kw. (22)
 88 or/80-87 (143934)
 89 79 and 88 [CANNABIS - PEDIATRIC EPILEPSY] (678)
 90 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (48509001)
 91 exp human/ or exp human experimentation/ or exp human experiment/ (37777771)
 92 90 not 91 (10732950)
 93 89 not 92 [ANIMAL-ONLY REMOVED] (631)
 94 93 use emczd [EMBASE RECORDS] (399)
 95 exp Epilepsy/ (413158)
 96 Status Epilepticus/ (17946)
 97 (epileps* or epilept*).tw. (350570)
 98 seizure*.tw. (307670)
 99 convulsi*.tw. (71469)

100 falling sickness*.tw. (59)
 101 comitial disease*.tw. (3)
 102 Grand Mal Seizures/ (196)
 103 Petit Mal Seizures/ (127)
 104 (petit mal or grand mal or absence status).tw. (8218)
 105 Landau-Kleffner Syndrome*.tw. (1210)
 106 Lennox Gastaut Syndrome*.tw. (3379)
 107 Dravet Syndrome*.tw. (2019)
 108 West syndrome*.tw. (2812)
 109 Doose syndrome*.tw. (160)
 110 Ohtahara syndrome*.tw. (494)
 111 ((sturge* or weber) adj2 (disease* or syndrome*)).tw. (8041)
 112 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw. (775)
 113 SMEI.tw. (456)
 114 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw. (1127)
 115 Lafora.tw. (1421)
 116 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw. (730)
 117 ((infantile or nodding) adj2 spasm?).tw. (6224)
 118 ((flexor or "in flexion") adj2 spasm?).tw. (332)
 119 ((lightning or salaam) adj2 attack?).tw. (15)
 120 hypsarrhythmi*.tw. (2024)
 121 or/95-120 [EPILEPSY] (626451)
 122 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw. (5256005)
 123 (newborn* or neonat*).tw. (860199)
 124 (pediatric* or paediatric*).tw. (800591)
 125 or/122-124 (6005033)
 126 121 and 125 [PEDIATRIC EPILEPSY] (158962)
 127 exp Cannabis/ (46269)
 128 exp Cannabinoids/ (76752)
 129 Marijuana Usage/ (2514)
 130 ("c.indica" or cannabi* or bhang or cannador or charas or eucannabinolide* or ganja or ganjah or hash or hashish or hemp or marihuana* or marijuana*).tw. (112358)
 131 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw. (79)
 132 (dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetranabinex).tw. (23463)
 133 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw. (22)
 134 or/127-133 (143233)
 135 126 and 134 [CANNABIS - PEDIATRIC EPILEPSY] (510)
 136 exp Animals/ not (exp Animals/ and Humans/) (16160986)
 137 135 not 136 [ANIMAL-ONLY REMOVED] (333)
 138 137 use medall,emczd (279)
 139 137 not 138 [PSYCINFO RECORDS] (54)
 140 46 or 94 or 139 [ALL DATABASES] (638)
 141 remove duplicates from 140 (441) [TOTAL UNIQUE RECORDS]
 142 141 use medall [MEDLINE UNIQUE RECORDS] (138)
 143 141 use emczd [EMBASE UNIQUE RECORDS] (270)
 144 141 not (142 or 143) [PSYCINFO UNIQUE RECORDS] (33)

Appendix 3: Included records (k = 92)

Published and grey literature reports (k = 25)

Note: companion publications are listed following the parent publication and are indented.

1. Aguirre-Velazquez CG. Report from a survey of parents regarding the use of cannabidiol (medicinal cannabis) in Mexican children with refractory epilepsy. *Neurol Res Int.* 2017;2017; 2985729
2. Cannabidiol oral solution in pediatric participants with treatment-resistant seizure disorders. ClinicalTrials.gov identifier: NCT02324673. <https://clinicaltrials.gov/ct2/show/NCT02324673>. Updated June 23, 2017. Accessed May 10, 2018.
3. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *New England Journal of Medicine.* 2017;376:2011.
4. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: An open-label interventional trial. *Lancet Neurology.* 2016;15:270.
5. Devinsky O, Patel AD, Thiele EA, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology.* 2018; 90:e1204.
6. Gaston TE, Bebin EM, Cutter GR, et al. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia.* 2017;58:1586.
7. Szaflarski M, Hansen B, Bebin EM, et al. Social correlates of health status, quality of life, and mood states in patients treated with cannabidiol for epilepsy. *Epilepsy and Behavior.* 2017;70:364.
8. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia.* 2015;56:1246.
9. Gofshteyn JS, Wilfong A, Devinsky O, et al. Cannabidiol as a potential treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES) in the acute and chronic phases. *Journal of Child Neurology.* 2017;32:35.
10. Devinsky O, Patel AD, Cross H, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *New England Journal of Medicine.* 2018;378:1888.
11. Hausman-Kedem M, Menascu S, Kramer U. Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents – An observational, longitudinal study. *Brain & Development.* 2018 Apr 16. S0387-7604(18)30112-8. doi: 10.1016/j.braindev.2018.03.013.
12. Hess EJ, Moody KA, Geffrey AL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. *Epilepsia.* 2016;57:1617.
13. Hussain SA, Zhou R, Jacobson C, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome. *Epilepsy Behav.* 2015;47:138.
14. Kaplan EH, Offermann EA, Sievers JW, et al. Cannabidiol treatment for refractory seizures in Sturge-Weber syndrome. *Pediatric Neurology.* 2017;71:18.
15. Lorenz R. On the application of cannabis in paediatrics and epileptology. *Neuroendocrinol Lett.* 2004;25:40.
16. Neubauer D, Perkovic BM, Osredkar D. Cannabidiol for treatment of refractory childhood epilepsies: Experience from a single tertiary epilepsy center in Slovenia. *Epilepsy Behav.* 2018; 81:79.
17. Porcari GS, Fu C, Doll ED, et al. Efficacy of artisanal preparations of cannabidiol for the treatment of epilepsy: Practical experiences in a tertiary medical center. *Epilepsy Behav.* 2018;80:240.
18. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav.* 2013; 29:574.
19. Rosenberg EC, Louik J, Conway E, et al. Quality of life in childhood epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. *Epilepsia.* 2017;58:e96.

20. Sulak D, Saneto R, Goldstein B. The current status of artisanal cannabis for the treatment of epilepsy in the United States. *Epilepsy and Behavior*. 2017;70:328.
21. Suraev AS, Todd L, Bowen MT, et al. An Australian nationwide survey on medicinal cannabis use for epilepsy: History of antiepileptic drug treatment predicts medicinal cannabis use. *Epilepsy Behav*. 2017;70:334.
22. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): A randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet*. 2018;391:1085.
23. Treat L, Chapman KE, Colborn KL, et al. Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients. *Epilepsia*. 2017;58:123.
24. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy Behav*. 2015;45:49.
25. Tzadok M, Uliel-Siboni S, Linder I, et al. CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience. *Seizure*. 2016;35:41.

Conference abstracts (k = 34)

Matched* to an included published study. Note: Abstracts were matched to published studies based on study name, registration number, authors, study and population characteristics or reported data.

1. Bruno PL, Geoffrey AL, Pollack SF, Thiele EA. Effect of cannabidiol on the antiepileptic drug clobazam. *Epilepsy Curr* 2015;15:383.
2. Cross JH, Devinsky O, Laux L, et al. Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet syndrome: Results of a multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE1). International Epilepsy Congress, Barcelona Spain, 2-6 September 2017; *Epilepsia*. Supplement 5;S12
3. Cross JH, Devinsky O, Marsh E, et al. Cannabidiol(CBD) reduces convulsive seizure frequency in Dravet syndrome: results of a multi-center, randomized, controlled trial (GWPCARE1). *Neurology* 2017;Conference(16 Suppl 1).
4. Devinsky O, Cross JH, Laux L, et al. Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet syndrome: Results of a multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE1). *Neurotherapeutics* 2017;Conference(3):824.
5. Devinsky O, Sullivan J, Friedman D, et al. Efficacy and safety of Epidiolex (cannabidiol) in children and young adults with treatment-resistant epilepsy: Initial data from an expanded access program. *Epilepsy Curr* 2015;15:532.
6. Friedman D, Cilio MR, Tilton N, et al. The effect of Epidiolex (cannabidiol) on serum levels of concomitant anti-epileptic drugs in children and young adults with treatment-resistant epilepsy in an expanded access program. *Epilepsy Curr* 2015;15:332.
7. Geoffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* 2015;56:1246-1251.
8. Gofshteyn J, Wilfong A, Devinsky O, et al. The use of cannabidiol for the treatment of febrile infection related epilepsy syndrome (FIRES). *Ann Neurol* 2016;Conference:S323.
9. Kaplan E, Sievers J, Comi A. Investigator IND trial of cannabidiol in Sturge-Weber syndrome. *Ann Neurol* 2016;Conference:S320.
10. Mazurkiewicz-Beldzinska M, Thiele EA, Benbadis S, et al. Treatment with cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE4). *Epilepsia*. 2017; Conference:S55

11. Patel A, Devinsky O, Cross JH, et al. Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): results of a dose-ranging, multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE3). *Neurology*. 2017; Conference:e100.
12. Press C, Knupp K, Chapman K. Parental reporting of response to oral cannabis extracts as adjunctive treatment for medically refractory epilepsy. *Epilepsy Curr* 2015;15:153.
13. Tzadok M, Linder I, Kramer U, et al. CBD-Enriched medical cannabis for intractable pediatric epilepsy. *Epilepsia* 2016;Conference:169.
14. Wright S, Devinsky O, Thiele EA, et al. Cannabidiol (CBD) in Dravet Syndrome: A randomised, dose-ranging pharmacokinetics and safety trial (GWPCARE1). *Epilepsia*. 2017; Conference:S56
15. Zhou R, Jacobson C, Weng J, et al. Potential efficacy of cannabidiol for treatment of refractory infantile spasms and Lennox-Gastaut syndrome. *Epilepsy Curr* 2015;15:360.
16. Zuberi S, Patel AD, Wilfong A, et al. Cannabidiol (CBD) significantly reduces drop-seizure frequency in Lennox-Gastaut syndrome (LGS): Pooled efficacy and safety results from two randomized controlled trials. *Developmental Medicine and Child Neurology*. 2017; Conference:18
17. Zuberi S, Devinsky O, Patel A, et al. Cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a dose-ranging, multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE3). *Epilepsia*. 2017; Conference:S13
18. French J, Thiele E, Mazurkiewicz-Beldzinska M, et al. Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a multi-center, randomized, double-blind, placebo controlled trial (GWPCARE4). *Neurology* 2017;Conference(16 Suppl 1).
19. Thiele EA, Mazurkiewicz-Beldzinska M, Benbadis S, et al. Treatment with cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox Gastaut Syndrome (LGS): Results of a multi - Center, randomized, double-blind, Placebo-controlled trial (GWPCARE4). *Neurotherapeutics* 2017;Conference(3):824.
20. Patel A, Devinsky O, Thiele E, et al. A dose ranging safety and pharmacokinetic study of cannabidiol (CBD) in children with Dravet syndrome (GWPCARE1). *Neurology* 2017;Conference(16 Suppl 1).

Unmatched (potentially unpublished studies)

1. Gedde MM, Maa E. Whole cannabis extract of high concentration cannabidiol may calm seizures in highly refractory pediatric epilepsies. *Epilepsy Curr* 2014;14:449.
2. Kuester G, Gazmuri AM, Ahumada A, Bobadilla P. Clinical response to oral cannabis extracts in severe refractory epilepsy: Preliminary experience in Chilean patients. *Epilepsia* 2016;Conference:147.
3. Linder I, Tzadok M, Menascu S, Ben-Zeev B, Lerman ST, Kramer U. Treatment of pediatric intractable epilepsy with vaporized cannabidiol (CBD) and DELTA9-Tetrahydrocannabinol (THC) - Preliminary findings of the Israeli pediatric medical cannabis (MC) cohort. *Epilepsia* 2016;Conference:108.
4. Lodi M, Viri M, Meloni M, et al. Looking for prescription of Hemp Oil, Omega 6 and Omega 3 in children with drug-resistant epilepsy. *Boll - Lega Ital Contro L'Epilessia* 2013;(145):164.
5. Morgan AK, Pan J, Bruno P, Geffrey A, Pollack S, Thiele E. Impact of cannabidiol on quality of life in pediatric drug resistant epilepsy. *Epilepsy Curr* 2015;15:370.
6. Schimpfossli M, Berweck S, Betzler C, et al. Retrospective analysis of tetrahydrocannabinol based on 31 neurologically critically ill children. *Neuropediatrics* 2015;Conference.
7. Vezyroglou K, Eltze C, Varadkar S, et al. Efficacy and safety of cannabidiol as add-on therapy in drug-resistant epilepsy, a single center experience. *Eur J Paediatr Neurol* 2017;Conference(Supplement 1):e87.
8. Vezyroglou K, Eltze C, Varadkar S, et al. Cannabidiol as add on therapy in children with complex epilepsy. *Dev Med Child Neurol* 2017;Conference:17.
9. Wilson CA, Spigarelli M, Sweney M, et al. Efficacy, adverse effects, and additional benefits of Epidiolex in children and young adults with treatment resistant epilepsy. *Ann Neurol* 2015;78:S180.

10. Devinsky O, Nabbout R, Miller I, et al. Maintenance of long-term safety and efficacy of cannabidiol (CBD) treatment in dravet syndrome (DS): Results of the open-label extension (OLE) trial (GWPCARE 5). *Developmental Medicine and Child Neurology*. 2017; American Epilepsy Society: December 1-5, Washington DC, USA.S4:126.
11. Mimura PM, Lima MTAD, Picoli RL, et al. Seguti. Follow-up of patients with refractory epilepsy treated with cannabidiol. *Journal of the Neurological Sciences*. 2017; Conference:683
12. Morales SJG, Benavides AO, Bastida ME. Use of cannabidiol (RSHO) in the treatment of refractory epilepsy (Lennox-Gastaut Syndrome), experience of 38 cases. *Epilepsia*. 2017; Conference:S53
13. Szaflarski JP, Bebin EM, Gaston G, et al. Improvements in seizure frequency parallel improvements in seizure severity in an open label study of cannabidiol. *Epilepsia*. 2017; Conference:S158
14. Abati E, Hess E, Morgan A, et al. Cannabidiol treatment of refractory epileptic spasms: An open-label study. American Epilepsy Society; 2015.

Registry records (Clinical trials.gov k = 32; ICTRP k = 1)

1. GWPCARE5 - An open label extension study of cannabidiol (GWP42003-P) in children and young adults with Dravet or Lennox-Gastaut syndromes. [http://ClinicalTrials.gov identifier: NCT02224573](http://ClinicalTrials.gov/ct2/show/NCT02224573). <https://clinicaltrials.gov/ct2/show/NCT02224573>. Updated October 24, 2017. Accessed April 24, 2018.
2. GWPCARE2 A study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome. [http://ClinicalTrials.gov identifier: NCT02224703](http://ClinicalTrials.gov/ct2/show/NCT02224703). <https://clinicaltrials.gov/ct2/show/NCT02224703>. Updated October 12, 2016. Accessed April 24, 2018.
3. Genetic analysis between Charlotte's Web responders versus non-responders in a Dravet population. [http://ClinicalTrials.gov identifier: NCT02229032](http://ClinicalTrials.gov/ct2/show/NCT02229032). <https://clinicaltrials.gov/ct2/show/NCT02229032>. Updated December 15, 2017. Accessed April 24, 2018.
4. Cannabidiol (CBD) to 27 patients (aged 2 years - 19 years) with drug resistant epilepsy. [http://ClinicalTrials.gov identifier: NCT02286986](http://ClinicalTrials.gov/ct2/show/NCT02286986). <https://clinicaltrials.gov/ct2/show/NCT02286986>. Updated April 12, 2017. Accessed April 24, 2018.
5. Cannabidiol oral solution as an adjunctive treatment for treatment-resistant seizure disorder. [http://ClinicalTrials.gov identifier: NCT02318602](http://ClinicalTrials.gov/ct2/show/NCT02318602). <https://clinicaltrials.gov/ct2/show/NCT02318602>. Updated February 5, 2018. Accessed April 24, 2018.
6. Cannabidiol expanded access study in medically refractory Sturge-Weber syndrome. [http://ClinicalTrials.gov identifier: NCT02332655](http://ClinicalTrials.gov/ct2/show/NCT02332655). <https://clinicaltrials.gov/ct2/show/NCT02332655>. Updated March 1, 2018. Accessed April 24, 2018.
7. Epidiolex and drug resistant epilepsy in children. [http://ClinicalTrials.gov identifier: NCT02397863](http://ClinicalTrials.gov/ct2/show/NCT02397863). <https://clinicaltrials.gov/ct2/show/NCT02397863>. Updated April 24, 2015. Accessed April 24, 2018.
8. Cannabidiol (CBD) and pediatric epilepsy. [http://ClinicalTrials.gov identifier: NCT02447198](http://ClinicalTrials.gov/ct2/show/NCT02447198). <https://clinicaltrials.gov/ct2/show/NCT02447198>. Updated September 20, 2017. Accessed April 24, 2018.
9. Treatment of drug resistant epilepsy. [http://ClinicalTrials.gov identifier: NCT02461706](http://ClinicalTrials.gov/ct2/show/NCT02461706). <https://clinicaltrials.gov/ct2/show/NCT02461706>. Updated March 2, 2018. Accessed April 24, 2018.
10. The use of medicinal cannabinoids as adjunctive treatment for medically refractory epilepsy. [http://ClinicalTrials.gov identifier: NCT02523183](http://ClinicalTrials.gov/ct2/show/NCT02523183). <https://clinicaltrials.gov/ct2/show/NCT02523183>. Updated January 17, 2018. Accessed April 24, 2018.
11. An open-label extension trial of cannabidiol (GWP42003-P, CBD) for seizures in Tuberous Sclerosis Complex (GWPCARE6). [http://ClinicalTrials.gov identifier: NCT02544750](http://ClinicalTrials.gov/ct2/show/NCT02544750). <https://clinicaltrials.gov/ct2/show/NCT02544750>. Updated October 24, 2017. Accessed April 24, 2018.
12. A randomized controlled trial of cannabidiol (GWP42003-P, CBD) for seizures in Tuberous Sclerosis Complex (GWPCARE6). [http://ClinicalTrials.gov identifier: NCT02544763](http://ClinicalTrials.gov/ct2/show/NCT02544763). <https://clinicaltrials.gov/ct2/show/NCT02544763>. Updated October 24, 2017. Accessed April 24, 2018.

13. Cannabidiol oral solution for treatment of refractory Infantile Spasms. <http://ClinicalTrials.gov> identifier: NCT02551731. <https://clinicaltrials.gov/ct2/show/NCT02551731>. Updated February 5, 2018. Accessed April 24, 2018.
14. Cannabidiol for pediatric epilepsy (compassionate use). <http://ClinicalTrials.gov> identifier: NCT02556008. <https://clinicaltrials.gov/ct2/show/NCT02556008>. Updated May 3, 2017. Accessed April 24, 2018.
15. A study to investigate possible drug-drug interactions between stiripentol or valproate and cannabidiol in patients with epilepsy. <http://ClinicalTrials.gov> identifier: NCT02607891. <https://clinicaltrials.gov/ct2/show/NCT02607891>. Updated November 1, 2017. Accessed April 24, 2018.
16. An open-label extension trial to investigate possible drug-drug interactions between stiripentol or valproate and cannabidiol in patients with epilepsy. <http://ClinicalTrials.gov> identifier: NCT02607904. <https://clinicaltrials.gov/ct2/show/NCT02607904>. Updated November 1, 2017. Accessed April 24, 2018.
17. Safety and tolerability of cannabidiol in subjects with drug resistant epilepsy. <http://ClinicalTrials.gov> identifier: NCT02660255. <https://clinicaltrials.gov/ct2/show/NCT02660255>. Updated May 3, 2017. Accessed April 24, 2018.
18. University of Alabama at Birmingham (UAB) adult CBD program. <http://ClinicalTrials.gov> identifier: NCT02700412. <https://clinicaltrials.gov/ct2/show/NCT02700412>. Updated September 26, 2017. Accessed April 24, 2018.
19. A double-blind trial to evaluate efficacy and safety of cannabidiol as an add-on therapy for treatment in refractory epilepsy. <http://ClinicalTrials.gov> identifier: NCT02783092. <https://clinicaltrials.gov/ct2/show/NCT02783092>. Updated April 18, 2018. Accessed April 24, 2018.
20. The effects of cannabidiol (CBD) on electrical and autonomic cardiac function in children with severe epilepsy. <http://ClinicalTrials.gov> identifier: NCT02815540. <https://clinicaltrials.gov/ct2/show/NCT02815540>. Updated June 28, 2016. Accessed April 24, 2018.
21. The pharmacokinetics of cannabidiol (CBD) and its effects in children with severe epilepsy. <http://ClinicalTrials.gov> identifier: NCT02910297. <https://clinicaltrials.gov/ct2/show/NCT02910297>. Updated February 21, 2018. Accessed April 24, 2018.
22. Trial of cannabidiol (CBD; GWP42003-P) for Infantile Spasms (GWPCARE7). <http://ClinicalTrials.gov> identifier: NCT02953548. <https://clinicaltrials.gov/ct2/show/NCT02953548>. Updated October 24, 2017. Accessed April 24, 2018.
23. Phase 3 trial of cannabidiol (CBD; GWP42003-P) for Infantile Spasms: Open-label extension phase (GWPCARE7). <http://ClinicalTrials.gov> identifier: NCT02954887. <https://clinicaltrials.gov/ct2/show/NCT02954887>. Updated October 24, 2017. Accessed April 24, 2018.
24. Cannabinoid therapy for pediatric epilepsy. <http://ClinicalTrials.gov> identifier: NCT02983695. <https://clinicaltrials.gov/ct2/show/NCT02983695>. Updated December 4, 2017. Accessed April 24, 2018.
25. A study to evaluate the safety, tolerability and efficacy of oral administration of PTL101 (cannabidiol) as an adjunctive treatment for pediatric intractable epilepsy. <http://ClinicalTrials.gov> identifier: NCT02987114. <https://clinicaltrials.gov/ct2/show/NCT02987114>. Updated September 15, 2017. Accessed April 24, 2018.
26. Study of cannabidiol for drug-resistant epilepsies. <http://ClinicalTrials.gov> identifier: NCT03014440. <https://clinicaltrials.gov/ct2/show/NCT03014440>. Updated April 4, 2017. Accessed April 24, 2018.
27. Cannabidiol in children with refractory epileptic encephalopathy. <http://ClinicalTrials.gov> identifier: NCT03024827. <https://clinicaltrials.gov/ct2/show/NCT03024827>. Updated February 5, 2018. Accessed April 24, 2018.
28. Expanded use of cannabidiol oral solution. <http://ClinicalTrials.gov> identifier: NCT03196934. <https://clinicaltrials.gov/ct2/show/NCT03196934>. Updated June 23, 2017. Accessed April 24, 2018.
29. Cannabidiol oral solution in pediatric participants with treatment-resistant childhood absence seizures. <http://ClinicalTrials.gov> identifier: NCT03336242. <https://clinicaltrials.gov/ct2/show/NCT03336242>. Updated April 24, 2018. Accessed April 24, 2018.

30. Long-term safety of pharmaceutical grade synthetic cannabidiol oral solution in pediatric participants with treatment-resistant childhood absence seizures. <http://ClinicalTrials.gov> identifier: NCT03355300. <https://clinicaltrials.gov/ct2/show/NCT03355300>. Updated April 24, 2018. Accessed April 24, 2018.
31. A study to assess the safety and tolerability of ZX008 in children and young adults with DS or LGS currently taking CBD. <http://ClinicalTrials.gov> identifier: NCT03467113. <https://clinicaltrials.gov/ct2/show/NCT03467113>. Updated March 15, 2018. Accessed April 24, 2018.
32. A study to assess the efficacy, safety, and tolerability of cannabidiol oral solution with vigabatrin as initial therapy in participants with infantile spasms. <http://ClinicalTrials.gov> identifier: NCT03421496. <https://clinicaltrials.gov/ct2/show/NCT03421496>. Updated April 3, 2018. Accessed April 24, 2018.
33. Open label study to assess the safety and efficacy of ZYN002 administered as a transdermal gel to children and adolescents (3 to <18 years) with developmental and epileptic encephalopathy (BELIEVE 1). ANZCTR register identifier: ACTRN1261800051620. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12618000516280. Updated April 9, 2018. Accessed April 24, 2018.

Appendix 4: Excluded studies (k = 50)

Population (k = 5) (Does not involve children with epilepsy [<60% children or data not reported separately for children])

1. Blimkin L, Libzon S, Bar-Lev SL, et al. Medical cannabis in children with complex motor disorders. *European Journal of Paediatric Neurology*. 2017; Conference:e219
2. Malphrus AD, Messinger M. Evaluating the association between dronabinol use and occurrence of seizures. *Epilepsia*. 2015;56:91.
3. Sexton S, Cuttler C, Finnell JS, et al. A Cross-sectional survey of medical cannabis users: Patterns of use and perceived efficacy. *Cannabis and Cannabinoid Research*. 2016;1:131.
4. Todd L, Burford J, Vithanage J, et al. Attitudes and experiences of medicinal cannabis use in epilepsy. *Epilepsia*. 2017; Conference:S20.
5. Warren PP, Bebin EM, Nabors LB, et al. The use of cannabidiol for seizure management in patients with brain tumor-related epilepsy. *Neurocase*. 2017; 23:287.

Does not involve cannabis (k = 1)

1. Beattie JF, Thompson MD, Parks PH, et al. Caregiver-reported religious beliefs and complementary and alternative medicine use among children admitted to an epilepsy monitoring unit. *Epilepsy Behav*. 2017; 69:139.

Fewer than 5 participants (k = 14)

1. Bravo GA, Izquierdo AY, Monteiro GC, et al. Adult phenotype of Dravet syndrome associated with STXBP1 (syntaxin binding protein 1) mutation and good response to cannabidiol treatment. *European Journal of Neurology*. 2017;Conference:159.
2. Crippa JAS, Crippa ACS, Hallak JEC, et al. DELTA9-THC intoxication by cannabidiol-enriched cannabis extract in two children with refractory epilepsy: Full remission after switching to purified cannabidiol. *Frontiers in Pharmacology*. 2016;7.
3. Cukiert C, Cukiert A, Burattini J, et al. West syndrome associated to unilateral mesial temporal sclerosis. *Epilepsia*. 2015;Conference:68.
4. Fucci N, Pascali VL. Detection of JWH-073 and cannabis congeners in hair: Application in pediatric patient. *Therapeutic Drug Monitoring*. 2016;38:140.
5. Gold J, Sattar S, Wang S, et al. Resolution of seizures and normalization of EEG after initiation of CBD in a patient with Doose syndrome. *Epilepsy Currents*. 2015;15:232.
6. Kariyanna PT, Chhibar P, Yi J. Where dope-hope delivered: A success story of medical marijuana (MM) in intractable seizures. *Annals of Neurology*. 2015;78:S42.
7. Linder I, Nezer-Kanner I, Eden A, et al. *EEF1A2* (eukaryotic elongation factor 1, alfa-2) related early infantile epileptic encephalopathy and myoclonic astatic epilepsy. *Epilepsia*. 2016; Conference:93.
8. Lopez C, Wilfong A, Ngo TK, et al. Prospective, controlled trial of cannabidiol in a case of FIRES. *Epilepsy Currents*. 2015;15:534.
9. Lorenz R. A casuistic rationale for the treatment of spastic and myocloni in a childhood neurodegenerative disease: neuronal ceroid lipofuscinosis of the type Jansky-Bielschowsky. *Neuroendocrinol Lett*. 2002;23:387.
10. Poisson K, Wong M, Lee C, et al. Response to cannabidiol in epilepsy of infancy with migrating focal seizures associated with *KCNT1* mutations. *Annals of Neurology*. 2016; Conference:S324.

11. Riley D, Oscapella E. The Terry Parker case: marijuana for epilepsy — and soon for HIV/AIDS? *Can HIV AIDS Policy Law Newsl.* 1997;3-4:20.
12. Rosemergy I, Adler J, Psirides A. Cannabidiol oil in the treatment of super refractory status epilepticus. A case report. *Seizure.* 2016;35:56.
13. Saade D, Joshi C. Pure cannabidiol in the treatment of malignant migrating partial seizures in infancy: a case report. *Pediatric Neurology.* 2015;52:544.
14. Silveira LP, Bayer DL, Crippa ACS, et al. . Patient diagnosed with epilepsy due to mutation in the cdk15 gene treated with cannabidiol therapy. *Developmental Medicine and Child Neurology.* 2017;Conference:98.

Not a primary study (k = 23)

1. Buechi S. Efficacy of cannabidiol: clinical studies with cannabidiol and cannabidiol-containing extracts. *Schweizerische Zeitschrift für GanzheitsMedizin.* 2017;29:367.
2. Chen KA, Farrar MA, Cardamone M, et al. Cannabis for paediatric epilepsy: challenges and conundrums. *Medical Journal of Australia.* 2018;208:132.
3. Clearing the haze around medicinal cannabis. *The Lancet Neurology.* 2018;17:193.
4. Cortesi M, Fusar-Poli P. Potential therapeutical effects of cannabidiol in children with pharmacoresistant epilepsy. *Medical Hypotheses.* 2007;68:920.
5. Cressey D. The cannabis experiment. *Nature.* 2015;524:280.
6. Dan B. Cannabinoids in paediatric neurology. *Developmental Medicine and Child Neurology.* 2015;57:984.
7. Eisenstein M. Showdown at the cannabis corral. *Nature.* 2015;525:S15.
8. Hausman-Kedem M, Kramer U. Efficacy of medical cannabis for treatment of refractory epilepsy in children and adolescents with emphasis on the Israeli experience. *Israel Medical Association Journal.* 2017;19:76.
9. Hawkes N. Cannabis based drug shows promise in children with resistant epilepsy. *BMJ (Online).* 2017;357:j2564.
10. Ho KS, Wassman ER. A case for cannabidiol in Wolf-Hirschhorn syndrome seizure management. *American Journal of Medical Genetics, Part A.* 2017;173:324.
11. Koo CM, Kang HC. Could cannabidiol be a treatment option for intractable childhood and adolescent epilepsy? *J Epilepsy Res.* 2017; 7(1):16-20.
12. Koubeissi M. Anticonvulsant effects of cannabidiol in Dravet syndrome. *Epilepsy Currents.* 2017;17:281.
13. Lutz B, Monory K. Bench to bedside: Soothing the seizures of children. *Nature Medicine.* 2008;14:721.
14. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine.* 2018;49:12.
15. McCall C. Momentum grows for medical use of cannabis. *Lancet.* 2015;386:1615.
16. Mellis C. Cannabidiol for drug-resistant seizures in the Dravet syndrome. *Journal of Paediatrics and Child Health.* 2018;54:101.
17. Moore Y, Robinson R. Cannabidiol reduced frequency of convulsive seizures in drug resistant Dravet syndrome. *Arch Dis Child Educ Pract Ed.* 2017; Sep 22. doi: 10.1136/archdischild-2017-313700
18. Perucca E. Cannabinoids in the treatment of epilepsy: Hard evidence at last? *Journal of Epilepsy Research* 2017;7:61.
19. Shelley K, Wright S, Wyton S, et al. When the drugs don't work. *Developmental Medicine and Child Neurology.* 2016;Conference:44.
20. Sirven JI. Medical marijuana for epilepsy: Winds of change. *Epilepsy and Behavior.* 2013; 29:435.

21. Stockings E, Zagic D, Campbell G, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *Journal of Neurology Neurosurgery and Psychiatry*. 2018;0:1–13. doi:10.1136/jnnp-2017-317168.
22. Verrotti A, Castagnino M, Maccarrone M, et al. Plant-derived and endogenous cannabinoids in epilepsy. *Clinical Drug Investigation*. 2016;36:331.
23. Williams CM, Jones NA, Whalley BJ. Cannabis and epilepsy. *Handbook of cannabis*. 2014;547.

Could not locate full text (k = 6)

1. Gaston T, Bebin E, Szaflarski J. Importance of monitoring clobazam and N-desmethyclobazam levels in treatment with cannabidiol (CBD) for epilepsy. *Neurology*. 2016; 86.
2. Park Y, Flamini R, Pearlman E, et al. Update from the Georgia intermediate expanded access study. *Neurology*. 2016;86.
3. Perry L, Szaflarski J, Bebin E. Investigating the effect of cannabidiol on the EEG. *Neurology*. 2016;86.
4. Szaflarski J, Bebin E, DeWolfe J, et al. Seizure response to cannabidiol in a state-sponsored open-label program. *Neurology*. 2016;86.
5. Treat L, Chapman K, Colborn K, et al. Duration of use of oral cannabis extract in pediatric epilepsy. *Neurology*. 2016; 86.
6. Kramer U. Cannabis for treatment of children with severe epilepsy – promising results. The International Medical Cannabis Conference; 2016; Tel Aviv, Israel.

Other (k = 1)

1. *FDA Briefing Document: Peripheral and Central Nervous System Drugs Advisor Committee Meeting: Cannabidiol. April 19 2018*. Available: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM604736.pdf (Accessed May 10, 2018). [Note: Studies included within this record are included in this systematic review as stand-alone publications]

Appendix 5: Study characteristics — Non-randomized studies

Author, yr (companion studies)	Design features	Population	Inclusion criteria	Treatments (no. in group)	Duration of cannabis treatment	No. centres; country	Funding source	Risk of bias (primary reason)
INSYS 2017 ¹ (NCT02324673)	Prospective, comparative, open-label cohort	Drug-resistant epilepsy	1–17 yr with treatment- resistant seizure disorder	Oral CBD solution • 10 mg/kg/d (20) • 20 mg/kg/d (20) • 40 mg/kg/d (21)	10 d	10 centres; US	INSYS Therapeutics	High (insufficient information to judge most of the criteria at this time; outcome assessment was unblinded, lack of a control group)
Hausman-Kedem 2018 ²	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	1–20 yr with refractory epilepsy (failure of ≥ 4 AEDs, including ketogenic diet or VNS) with stable doses of AEDs for at least 4 wk	• CBD-enriched cannabis oil from whole plant mixture with 20:1 CBD:THC ratio, up to 50 mg/kg/d of CBD (max THC dose 1.35 mg/kg/d) (57*); 30% of patients were transferred to or added inhaled CBD- enriched cannabis during the observation period	Median (range): 18 (3–33) mo; mean (SD): 15.6 (7.23) mo	1 centre; Israel	No funding	High (potential selection bias; unblinded outcome assessment; lack of a comparison group; important variation in the intervention; unclear time of outcome assessment; unclear analysis population)
Gaston 2017 ³ (NCT02695537) (Szaflarski 2017 ⁴)	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	>1 yr to 19 yr, failure of ≥ 4 AEDs at an adequate dose, including ≥ 1 trial of 2 concomitant AEDs, stable VNS settings and ketogenic diet for ≥ 3 mo	• Oral CBD solution, up to 50 mg/kg/d, given in 2 divided doses (42)	12 mo	1 centre; US	State of Alabama, UAB Epilepsy Center, Greenwich Biosciences†	NA (no reported outcomes of interest)
Gofshteyn 2017 ⁵	Prospective, single-group, open-label cohort	FIRES (acute or chronic)	Children with prior failed treatment response	• Oral CBD solution, up to 25 mg/kg/day (7)‡	48 wk	5 centres; US	GW Pharmaceuticals†	High (potential selection bias; inclusion/ exclusion criteria not described; unblinded outcome assessment; lack of a comparison group; small sample size)
Kaplan 2017 ⁶	Prospective, single-group, open-label cohort	Sturge-Weber syndrome with brain involvement	1 mo to 45 yr, diagnosis of drug-resistant epilepsy (failure of ≥ 2 AEDs), ≥ 1 quantifiable	• Oral CBD solution, up to 25 mg/kg/d, given in 2 divided doses (5)	Up to 82 wk	NR; US	Faneca 66 Foundation and Celebrate Hope Foundation; GW	High (potential selection bias; unblinded outcome assessment; lack of a comparison group; small

Author, yr (companion studies)	Design features	Population	Inclusion criteria	Treatments (no. in group)	Duration of cannabis treatment	No. centres; country	Funding source	Risk of bias (primary reason)
			defined seizure with motor signs per mo for ≥ 3 mo, use of 1–5 AEDs at a stable dose for ≥ 4 wk before enrollment, stable VNS and ketogenic or Atkins diet for ≥ 3 mo				Pharmaceuticals†	sample size)
Rosenberg 2017 ⁷	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	1–30 yr, ≥ 4 countable seizures with a motor component per 4 wk period; receiving stable doses of AEDs, diet therapy or VNS settings for ≥ 4 wk before enrolment	• Oral CBD solution, up to 50 mg/kg/d, given in 2 divided doses (48¶)	12 wk	1 centre, US	GW Pharmaceuticals†	High (potential selection bias; unblinded outcome assessment; lack of a comparison group; small sample size; single centre; outcome assessed at a single time point)
Devinsky 2016 ⁸	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	1–30 yr, ≥ 4 countable seizures with a motor component per 4 wk period; receiving stable doses of AEDs, diet therapy or VNS settings for ≥ 4 wk before enrolment	• Oral CBD solution, up to 50 mg/kg/d, given in 2 divided doses (214)	12 wk	11 centres; US	GW Pharmaceuticals; Epilepsy Therapy Project of the Epilepsy Foundation; Finding a Cure for Epilepsy and Seizures	High (potential selection bias; unblinded outcome assessment; lack of a comparison group)
Hess 2016 ⁹	Prospective, single-group, open-label cohort	TSC and drug-resistant epilepsy	Taking 1–7 AEDs at stable doses for ≥ 2 wk, and stable VNS settings and ketogenic diet ratios for ≥ 4 wk	• Oral CBD solution, up to 50 mg/kg/d, given in 2 divided doses (18**)	Up to 12 mo	1 centre; US	Herscot Center for Tuberous Sclerosis Complex, GW Pharmaceuticals†	High (potential selection bias; unblinded outcome assessment; lack of a comparison group; small sample size; single centre)
Geffrey 2015 ¹⁰	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	4–19 yr, with concomitant use of CLO and CBD	• Oral CBD solution, up to 25 mg/kg/day (13)	8 wk	1 centre; US	Pediatric Epilepsy Program at Massachusetts General Hospital, GW Pharmaceuticals†	High (potential selection bias; unblinded outcome assessment; lack of a comparison group; small sample size; single centre)

Author, yr (companion studies)	Design features	Population	Inclusion criteria	Treatments (no. in group)	Duration of cannabis treatment	No. centres; country	Funding source	Risk of bias (primary reason)
Neubauer 2018 ¹¹	Retrospective, single-group cohort	Drug-resistant epilepsy	Children, adolescents, young adults who were given CBD for treatment of refractory epilepsy	• CBD, up to 16 mg/kg/d (70)	Median (range): 14.0 mo (6.0–29.3)	1 centre; Slovenia	NR	High (potential selection bias; unblinded outcome assessment; lack of a comparison group; single centre; funding source not reported; unclear timing of outcome assessment)
Porcari 2018 ¹²	Retrospective comparative cohort	Drug-resistant epilepsy	< 19 yr with epilepsy	• CBD up to 50 mg/kg/d (48) • CBD + CLO (54) • CLO 1.5 (1.4) mg/kg/d (74) Artisanal CBD: 10 different products with varying CBD content	Mean (SD), yr CBD: 1.1 (0.8) CBD + CLO: 1.3 (1.0) CLO treatment: 2.5 (1.9)	1 centre; US	None	High (Unblinded outcome assessment; unclear time of outcome assessment relative to treatment duration; unclear if the outcome was assessed only once; important differences in the intervention)
Treat 2017 ¹³ (Press 2015 ¹⁴)	Retrospective, single-group cohort	Drug-resistant epilepsy	30 d to 18 yr, diagnosed epilepsy and documented seizure frequency before initiation of cannabis, daily use of an oral cannabis extract	• CBD, CBD + other oral cannabis extract, THCA only, or "other" (119++)	Mean (range): 11.7 (0.3–57) mo	1 centre; US	NR	High (Potential selection bias; unblinded outcome assessment; lack of a comparison group; single centre; funding source not reported; unclear timing of outcome assessment)
Sulak 2017 ¹⁵	Retrospective, single-group cohort; case-series	Drug-resistant epilepsy	NR	• Artisanal or hemp-based CBD and/or other related products (CBD, THC, THCA) (cohort: 47++; case series: 4)	NR	1 centre; US	No funding	High (limited methods provided with insufficient detail; high potential for selection bias; likely unblinded outcome assessment; variation in treatment and duration)
Tzadok 2016 ¹⁶	Retrospective, single-group cohort	Drug-resistant epilepsy	1–18 yr, daily seizures refractory to > 7 "appropriate" AEDs and other treatment modes (VNS, surgery, ketogenic diet)	• CBD-enriched cannabis oil, 1 to 20 mg/kg/d (20:1 CBD to THC ratio) (74)	Median (range): 5.5 (3–12) mo	4 centres; Israel	NR	High (potential selection bias; unblinded outcome assessment; lack of a comparison group; funding source not reported; unclear timing of outcome assessment)

Author, yr (companion studies)	Design features	Population	Inclusion criteria	Treatments (no. in group)	Duration of cannabis treatment	No. centres; country	Funding source	Risk of bias (primary reason)
Aguirre-Velazquez 2017 ¹⁷	Cross-sectional	Drug-resistant epilepsy	Children with a diagnosis of treatment-resistant epilepsy without controlled symptoms and current use of medical cannabis (CBD alone or in combination) Respondent: Parent, Online survey, invitations via email or Facebook group about the use of medical cannabis in children	• RSHO-X; CBD (<0.1% THC); combination of CBD + THC (e.g., Charlotte's web); home-made cannabis extracts (43)	Range <1 to 12 mo	NA; Mexico	NR	High (selection bias; unblinded outcome assessment based on parent recall; differences in exposure (cannabis) and duration of treatment; unclear time of outcome assessment relative to treatment duration; no comparison group)
Suraev 2017 ¹⁸	Cross-sectional	Children with epilepsy	Epilepsy, with or without current or prior use of medical cannabis Respondent: Parent or guardian Control: no cannabis use Online survey link distributed by Epilepsy Action Australia	• Cannabis products obtained from illegal suppliers with unknown composition (51); • No cannabis use (340)	Mean (SD): 15.75 (15.65) mo	NA; Australia	The Lambert Initiative for Cannabinoid Therapeutics, The University of Sydney, Epilepsy Action Australia	High (possible selection bias; unblinded outcome assessment based on parent recall; differences in exposure (cannabis) and duration of treatment; unclear time of outcome assessment relative to treatment duration)
Hussain 2015 ¹⁹	Cross-sectional	Drug-resistant epilepsy	Child with epilepsy and use of a cannabinoid product Respondent: Parent or guardian, Online survey advertised online, including via the Infantile Spasms Community and the Lennox-Gastaut Foundation	• CBD-enriched oil-based extracts 2–3 times/d; of parents who knew the CBC:THC ratio, 83.5% reported ratios of at least 15:1; few parents were able to provide specific CBD dosages (median 4.3 mg/kg/d; IQR 2.9–7.5) (117)	Median (IQR): 6.8 (3.8–9.8) mo	NA; US ^{¶¶¶}	Epilepsy Therapy Project, the Milken Family Foundation, the Hughes Family Foundation, UCLA Children's Discovery and Innovation Institute	High (possible selection bias; unblinded outcome assessment based on parent recall; lack of a control group; differences in exposure (cannabis) and duration of treatment; unclear time of outcome assessment relative to treatment duration)
Porter 2013 ²⁰	Cross-sectional	Drug-resistant epilepsy	Children with a diagnosis of treatment-resistant epilepsy and CBD-	• CBD, ranging from less than 0.5 mg/kg/d to 28.6 mg/kg/d, with reported	Range: 2 wk to > 1 yr	NA; US ^{¶¶¶}	Stanford University	High (Possible selection bias; unblinded outcome assessment based on

Author, yr (companion studies)	Design features	Population	Inclusion criteria	Treatments (no. in group)	Duration of cannabis treatment	No. centres; country	Funding source	Risk of bias (primary reason)
			enriched cannabis use Respondent: Parent Control: children with stiripentol use Survey administered in a Facebook group composed of parents supporting the use of CBD	THC dose in the products between 0 and 0.8 mg/kg/d (19); • Stiripentol, dose NR (22)			Institutional Epilepsy Training grant, National Center for Research Resources, National Center for Advancing Translational Sciences, National Institutes of Health	parent recall; control group selected from a different source population, demographic information not reported for comparison group; differences in exposure and duration of treatment; unclear time of outcome assessment relative to treatment duration)
Lorenz 2004 ²¹	Case series	Neurodegener ative disease, mitochondrio- pathy, posthypoxic- state, epilepsy, posttraumatic reaction	NR	• THC (Dronabinol, Marinol), 0.04 to 0.12 mg/kg/d, administered orally (7 patients) or via percutaneous gastroenterostomy tube (1 patient) (8) †††	NR	NR; Germany***	NR	NA (no reported outcomes of interest)

Note: AED = antiepileptic drugs, FIRES = Febrile Infection-Related Epilepsy syndrome, CLO = clobazam, IQR = interquartile range, THC = tetrahydrocannabinol, THCA = tetrahydrocannabinolic acid, VNS = vagus nerve stimulation

*18 participants were also included in Tzadok 2016.¹⁶

†Provided CBD solution (Epidiolex).

‡1 patient was also included in Devinsky 2016.⁸

¶24 of 48 patients in this cohort were included in Devinsky 2016.⁸

**5 patients were also included in Devinsky 2016.⁸

††Data extracted for longest follow-up time (reported in Treat 2017¹³)

‡‡Washington cohort only.

¶¶Obtained REB approval at a US institution.

***Based on author affiliation.

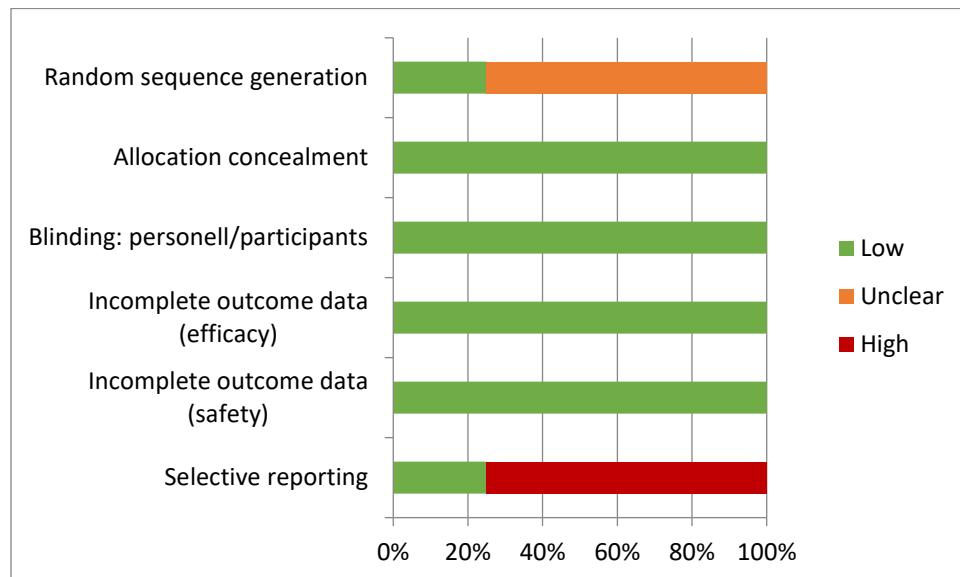
†††Six of eight included children had epilepsy.

Appendix 6: Participant characteristics — Non-randomized studies

Author, yr, page no.	Treatments*	Age, yr, mean (SD)†	Male, %	BMI or weight at baseline, mean (SD)†	No. of concomitant AEDs, mean (SD)†	No. previous AEDs	Other interventions
INSYS 2017 ¹ (NCT02324673)	•CBD 10 mg/kg/d • CBD 20 mg/kg/d •CBD 40 mg/kg/d	7.5 (5.3) 7.7 (5.2) 7.8 (5.4)	50% 65% 48%	NR	NR	NR	NR
Hausman-Kedem 2018 ²	• CBD	9.6 (4.9)	NR	NR	Up to 4	Range 3–17	Ketogenic diet: 33% VNS: 31% Epilepsy surgery: 5%
Devinsky 2016 ⁸	• CBD	Median (range): 10.5 (0.9–26.2)	49%	NR	Median (range): 3 (0–7)	NR	Ketogenic diet: 8% VNS 10%
Rosenberg 2017 ⁷	• CBD	Median (range): 11.7 (3.1–27.2)	48%	NR	Median (range): 3 (1–5)	NR	NR
Geffrey 2015 ¹⁰	• CBD	Mean (range): 10.7 (4–19)	54%	NR	Range: 1–3	NR	NR
Hess 2016 ⁹	• CBD	14 (range 2–31)	50%	NR	Median (range): 3 (1–7)	Median (range): 7 (4–11)	Diet therapy: 61% VNS: 61% Epilepsy surgery: 67%
Kaplan 2017 ⁶	• CBD	8 yr 10 mo (6 yr, 4 mo)	20%	NR	Range: 1–4	Range: 2–7	NR
Gofshteyn 2017 ⁵	• CBD	NR	71.4%	NR	Range: 4–9	Mean: 7.1 Median (range): 7 (4–9)	Ketogenic diet: 85.7% VNS: 28.6% Anesthetics 71.4% Alternative treatments: 100%‡
Neubauer 2018 ¹¹	• CBD	Median (range) 8.0 (0.5–23.0)	57%	NR	Median (range): 2 (1–4)	Median (range): 3 (1–14)¶	Ketogenic diet: 0 VNS: 6%
Porcari 2018 ¹²	• CBD • CBD + CLO • CLO	Mean (range), yr 10.4 (1.1–18) 7.8 (1.4–16) 8.5(1.4–18)	52% 56% 54%	NR	4.5 (2.7) 6.5 (2.3) 6.1 (2.1) (reported as “total AED exposure”: unclear if concomitant or previous)		Diet therapy: 19% 35% 41% VNS: 8% 13% 21%

Author, yr, page no.	Treatments*	Age, yr, mean (SD)†	Male, %	BMI or weight at baseline, mean (SD)†	No. of concomitant AEDs, mean (SD)†	No. previous AEDs	Other interventions
							Surgery: 0% 11% 12%
Suraev 2017 ¹⁸	• CBD • No CBD	Range 0–17 yr	NR	NR	NR	Mean (SD): CBD use: 7.64 (5.9) No CBD use: 4.65 (4.3)	Ketogenic diet: CBD use: 23.5% No CBD use: 9.2%
Tzadok 2016 ¹⁶	• CBD	NR	NR	NR	NR	NR	Ketogenic diet: 39% VNS: 47% Epilepsy surgery: 4%
Treat 2017 ¹³	• Mixed cannabis-based treatments	7.5 (range 0.6–18)	NR	NR	NR	NR	NR
Sulak 2017 ¹⁵	• Mixed cannabis-based treatments	Range 2–18 yr	43%	NR	2.5 (NR)	Mean: 2.5	NR
Aguirre-Velazquez 2017 ¹⁷	• Mixed cannabis-based treatments	7.6 (SD 4.3)	62.7%	NR	Range: 1 to > 10	Range 1–10	NR
Hussain 2015 ¹⁹	• Mixed cannabis-based treatments	Median (IQR) 6.0 (3.0–10.0)	NR	NR	NR	Median (IQR): 8 (4.0–12.0)	Ketogenic diet: 45.3% VNS: 17.9% Resective surgery: 11.1%
Porter 2013 ²⁰	• CBD	Range 2–16 yr	33%	NR	NR	Mean (range): 12 (4–17)	NR
Note: AED = antiepileptic drug, CBD = cannabidiol, CLO = clobazam, IQR = interquartile range, NR = not reported, VNS = vagus nerve stimulation. *Described in Appendix 5. †Unless otherwise stated. ‡Intravenous immunoglobulin, plasmapheresis, steroids, cooling, RituXimab, cyclophosphamide ¶AEDs and/or VNS. **Unclear if prior or concomitant use.							

Appendix 7: Risk of bias — Randomized controlled trials ($k = 4$)



Appendix 8: GRADE assessment, by outcome

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	standard care	Relative (95% CI)	Absolute (95% CI)		
Randomized controlled trials												
Seizure freedom (total seizures) (treatment duration: 14 weeks; number of patients with zero seizures during treatment)												
1	randomised trials	not serious	not serious	not serious	very serious ^{a,b,c}	none	3/61 (4.9%)	0/59 (0.0%)	RR 6.77 (0.36 to 128.38) ^d	—	⊕⊕○○ LOW	CRITICAL
Total seizure frequency (treatment duration: 14 weeks; median % reduction in monthly seizures from baseline)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	296	220	-	-19.8% (-27.0% to -12.6%)	⊕⊕⊕○ MODERATE	
Tonic-clonic seizure frequency (treatment duration: 14 weeks; median % reduction in monthly seizures from baseline)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	219	171	-	-26.7% (-38.6% to -14.6%)	⊕⊕⊕○ MODERATE	
Treatment response (treatment duration: 14 weeks; number of participants with at least a 50% reduction in total seizures from baseline)												
1	randomised trials	not serious	not serious	not serious	serious ^a	none	32/86 (37.2%)	18/85 (21.2%)	RR 1.76 (1.07 to 2.88)	161 more per 1,000 (from 15 more to 398 more)	⊕⊕⊕○ MODERATE	CRITICAL
Quality of life (child) (treatment duration: 14 weeks; Quality of Life in Childhood Epilepsy Scale, range: 0 to 100)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	296	220	-	MD 0.6 higher (2.6 lower to 3.9 higher)	⊕⊕⊕○ MODERATE	
Sleep disruption (treatment duration: 14 weeks; Sleep Disruption Rating Scale; range: 0 to 10)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	296	220	-	MD 0.3 lower (0.8 lower to 0.2 higher)	⊕⊕⊕○ MODERATE	
Status epilepticus (treatment duration: 12 weeks; number of children with status epilepticus during the treatment period)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	standard care	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	15/296 (5.1%)	7/220 (3.2%)	RR 1.39 (0.55 to 3.47)	12 more per 1,000 (from 14 fewer to 79 more)	⊕⊕○○ LOW	
Death (treatment duration: 14 weeks; number of deaths during the treatment period)												
1	randomised trials	not serious	not serious	not serious	very serious ^{c,e}	none	1/86 (1.2%)	0/85 (0.0%)	not estimable		⊕⊕○○ LOW	
Gastrointestinal adverse events (treatment duration: 3 to 14 weeks; number of children with vomiting or diarrhea or both)												
4	randomised trials	not serious	serious ^f	not serious	serious ^{a,b}	none	89/323 (27.6%)	45/227 (19.8%)	RR 1.54 (0.92 to 2.58)	107 more per 1,000 (from 16 fewer to 313 more)	⊕⊕○○ LOW	CRITICAL
Observational studies												
Seizure freedom (total seizures) (treatment duration: 2 to 29 months; number of patients with zero seizures during treatment)												
14	observational studies	very serious ^g	serious ^h	serious ⁱ	not serious	none	The estimate of seizures freedom ranged from 1% to 29% (pooled proportion 7%, 95%CI 4% to 11%)			⊕○○○ VERY LOW	CRITICAL	
Total seizure frequency (treatment duration: range 12 weeks to 2.5 years; % reduction in seizures from baseline)												
5	observational studies	very serious ^j	very serious ^k	serious ⁱ	very serious ^e	none	The reduction in total seizures among NRS with use of cannabis products between 30% and 90%; difference in reporting precluded pooling of effect estimates			⊕○○○ VERY LOW		
Tonic-clonic seizure frequency (treatment duration: 12 weeks to 12 months; % reduction in seizures from baseline)												
2	observational studies	very serious ^l	serious ^{k,m}	very serious ^{m,n}	serious ^e	none	Devinsky et al (2016) reported median frequency of monthly tonic-clonic seizures with any type of drug resistant epilepsy (–16%, 95%CI –60.1% to 35.3%, n=89) while Hess et al (2016) reported weekly reduction of tonic–clonic seizures: –91.4%, 95%CI –100 to –13.9%, n=6) in participants with tuberous sclerosis complex			-		
Treatment response (treatment duration: 3 to 16 months; at least a 50% reduction in total seizures from baseline)												
12	observational studies	very serious ^o	very serious ^p	serious ⁱ	not serious	none			not estimable		⊕○○○ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	standard care	Relative (95% CI)	Absolute (95% CI)		
Quality of life (child) (treatment duration: 12 to 82 weeks; assessed with: score from 0 to 100)												
2	observational studies	very serious ^q	serious ⁿ	serious ⁿ	very serious ^r	none	Rosenberg et al (2017) reported a mean improvement of 8.12 points (SD 9.5; p<0.001) on the Quality of Life in Childhood Epilepsy scale after treatment with cannabidiol. A second study (Kaplan et al, 2018) reported improved QoL for all participants, with no numerical data reported.				⊕○○○ VERY LOW	
Improved sleep (treatment duration: 2 weeks to 14 months; number of children with improved sleep)												
5	observational studies	very serious ^s	very serious	serious ⁱ	not serious	none	Pooled proportion of children who experienced an improvement in sleep (a) 8% (95%CI 4% to 11%) based on pooled analysis of 2 retrospective cohort study (b) 68% (95%CI 46% to 90%) based on pooled analysis of 3 cross-sectional surveys				⊕○○○ VERY LOW	
Impaired sleep (treatment duration: 10 days to 82 weeks; number of children with impaired sleep)												
5	observational studies	very serious ^t	not serious ^u	serious ⁱ	serious ^a	none	Pooled proportion of children with impaired sleep: 4% (95%CI 0% to 7%)				⊕○○○ VERY LOW	
Status epilepticus (treatment duration: 12 weeks to 18 months; number of children with status epilepticus)												
3	observational studies	very serious ^v	not serious ^w	serious ⁱ	serious ^{a,c}	none	Pooled prevalence of status epilepticus: 4% (95% 0% to 8%)				⊕○○○ VERY LOW	
Death (treatment duration: range 12 weeks to 14 months; number of deaths)												
5	observational studies	very serious ^x	not serious ^k	serious ⁱ	very serious ^{a,c}	none	6 deaths from various causes (including 2 reports of SUDEP) were reported in 5 NRS				⊕○○○ VERY LOW	
Gastrointestinal adverse events (treatment duration: 10 days to 82 weeks; number of children with vomiting or diarrhea or both)												
9	observational studies	very serious ^y	serious ^z	serious ⁱ	not serious	none	Proportion of patients experienced at least one of vomiting or diarrhea: 8% (95%CI 4% to 12%); vomiting alone: 5% (95%CI 2% to 8%); diarrhea alone: 7% (95%CI 2% to 12%)				⊕○○○ VERY LOW	
Quality of life (caregiver)												
0									not estimable		-	
Visits to the emergency department												
0									not estimable		-	

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	standard care	Relative (95% CI)	Absolute (95% CI)		
Note: CI = confidence interval, RR = relative risk, MD = mean difference a. Number of participants is less than the optimal information size b. 95%CI includes important benefits and harms c. Rare event; confidence intervals may be misleading because of fragility d. Risk difference: 5% (95% –1% to 11%) e. Small sample size f. Heterogeneity (I^2): 52% g. Mix of different observational study designs (6 prospective cohort studies, 5 retrospective cohort studies, 3 cross-sectional surveys); risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in intervention h. Heterogeneity (I^2): 75.1%, with differences in effect estimate between study designs i. Differences in patient populations, differences in exposure (type, dose of cannabis-based products), and differences in the duration of treatment across studies j. Mix of different observational study designs (1 comparative retrospective cohort, 4 single-group prospective cohorts, and 1cross sectional study); risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in intervention k. Not pooled l. Two single-arm prospective cohort studies; risk of selection bias, unblinded outcome assessment, lack of a comparison group m. Considerable differences in point estimates and confidence intervals between the two studies, which involved different study populations n. Different patient populations, different duration of treatment across studies o. Mix of different observational designs (6 prospective cohort studies, 4 retrospective cohort studies, 2 cross-sectional studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention p. Heterogeneity (I^2) = 78.3% q. Two prospective single-group cohort studies; high risk of selection bias, unblinded outcome assessment, lack of a comparison group r. Numerical data only reported for one of two studies, with a reported effect size smaller than the standard deviation; small sample size s. Mix of different observational designs (2 retrospective cohort studies, 3 cross-sectional studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention t. Mix of different observational designs (4 prospective cohort studies, 1 cross-sectional study); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention u. Heterogeneity (I^2) = 5.9% v. Mix of different observational designs (2 prospective cohort studies, 1 retrospective cohort study); high risk of selection bias, unblinded outcome assessment, lack of a comparison group w. Heterogeneity (I^2) not calculated; confidence intervals of each study are overlapping x. Mix of different observational designs (2 prospective single-arm cohort studies, 3 retrospective single-arm cohort studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention y. Mix of different observational designs (6 prospective cohort studies, 1 retrospective cohort study, 3 cross-sectional studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention z. Heterogeneity (I^2) = 69.25%; Vomiting alone I2 = 17.8%; Diarrhea alone: 69.5%												

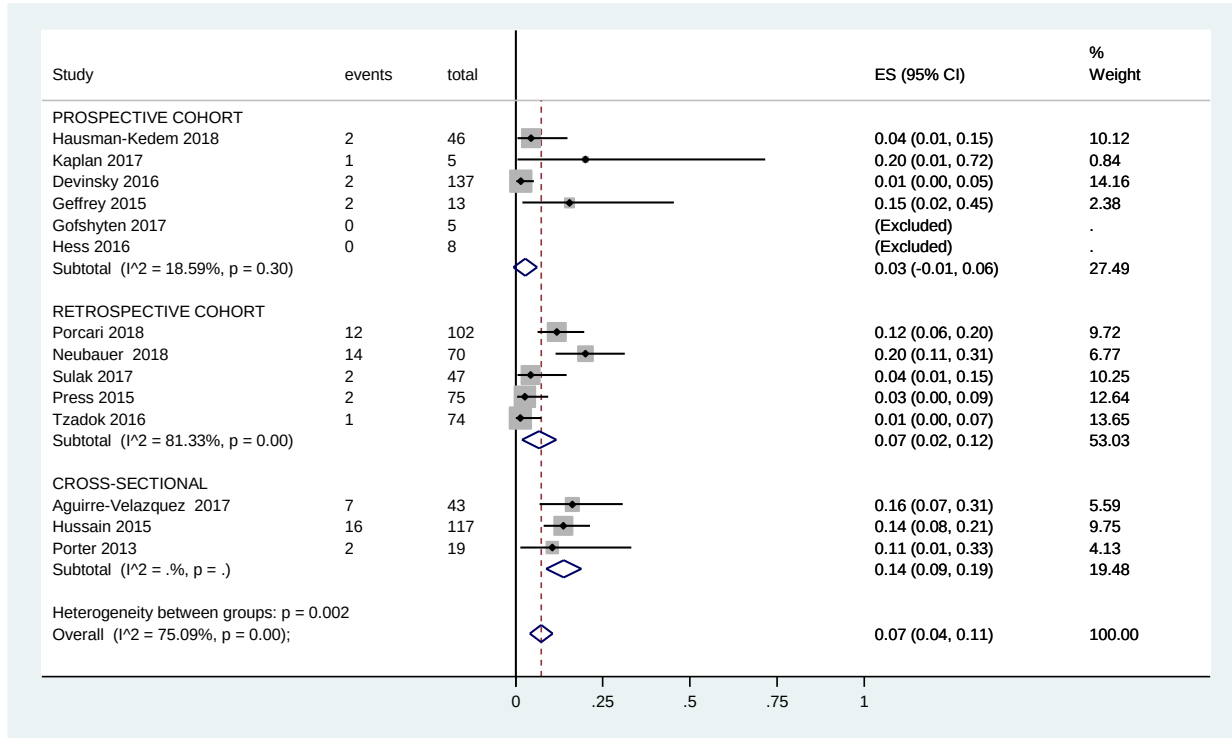
Appendix 9: Evidence summary — Seizure freedom (freedom from all seizure types)

A) All studies

Author, yr, page no.	Study design	Population	Treatments*	Duration	No. events/no. in group†	
					Cannabis-based treatment	Control
Devinsky 2017 ²²	RCT	Dravet syndrome	• Placebo • CBD	14 wk	3/61	0/59
Hausman-Kedem 2018 ²	Prospective single-group cohort	Drug-resistant epilepsy	• CBD¶	Median (range): 18 (3–33) mo	2/46	NA
Devinsky 2016 ⁸	Prospective single-group cohort	Drug-resistant epilepsy	• CBD	12 wk	2/137	NA
Geffrey 2015 ¹⁰	Prospective single-group cohort	Drug-resistant epilepsy taking CLO	• CBD	8 wk	2/13	NA
Hess 2016 ⁹	Prospective single-group cohort	TSC	• CBD	3 mo 12 mo	1/18 0/8	NA
Kaplan 2017 ⁶	Prospective single-group cohort	Sturge-Weber syndrome	• CBD	14 wk Most recent visit (6–82 wk)	0/5 1/5	NA
Gofshteyn 2017 ⁵	Prospective single-group cohort	FIRES (acute)	• CBD	4 wk	1/2	NA
		FIRES (chronic)		4 wk 48 wk	1/5 0/5	NA
Porcari 2018 ¹²	Retrospective comparative cohort	Drug-resistant epilepsy	• CBD • CBD + CLO • CLO	Mean (SD), yr 1.1 (0.8) 1.3 (1.0) 2.5 (1.9)	CBD: 7/48 CBD+CLO: 5/54	CLO: 8/74
Neubauer 2018 ¹¹	Retrospective single-group cohort	Drug-resistant epilepsy	• CBD	Median (range): 14.0 (6–29) mo	14/70	NA
Tzadok 2016 ¹⁶	Retrospective single-group cohort	Drug-resistant epilepsy	• CBD-enriched cannabis oil	≥ 3 mo	1/74	NA
Press 2015 ¹⁴	Retrospective single-group cohort	Drug-resistant epilepsy	• Mixed cannabis-based treatments	Mean (range): 5.59 (1–24) mo	2/75	NA
Sulak 2017 ¹⁵	Retrospective single-group cohort	Drug-resistant epilepsy‡	• Mixed cannabis-based treatments	NR	2/47	NA
Aguirre- Velazquez 2017 ¹⁷	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments	<1 to 12 mo	7/43	NA
Hussain 2015 ¹⁹	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments	Median (IQR): 6.8 (3.8–9.8) mo	16/117	NA
Porter 2013 ²⁰	Cross-sectional	Drug-resistant epilepsy	• CBD	> 1 yr	2/19	NA

Note: CBD = cannabidiol, CI = confidence interval, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, NA = not applicable, RCT = randomized controlled trial, SD = standard deviation, TSC = Tuberous sclerosis complex.
 *Treatments described in full in Table 1 and Appendix 5.
 †No. randomized for RCTs; otherwise, no. included in efficacy analysis.
 ‡Washington cohort
 ¶20:1 CBD:THC oil. 30% of participants were transferred to or added inhaled CBD-enriched cannabis during the treatment period.

B) Seizure freedom among non-randomized studies



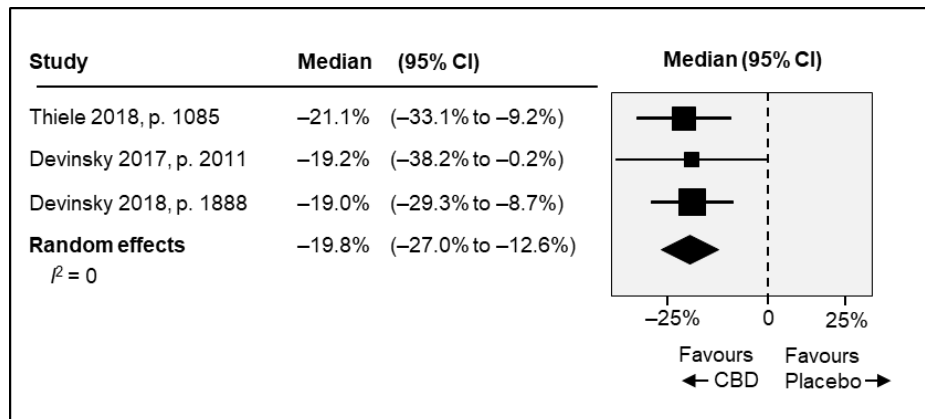
Appendix 10: Evidence summary — Seizure frequency

A) All studies

Author, yr	Study design	Population	Treatments* (no. in group)	Duration	Seizure frequency [†] ; median per month [‡]		Effect estimate
					Baseline	After treatment	
Devinsky 2018 ²³	RCT	Lennox-Gastaut syndrome	• Placebo (76) • CBD 10 mg/kg/d (73) • CBD 20 mg/kg/d (76)	14 wk	180.6 (IQR: 90.4–431.3) 165.0 (81.3–359.0) 174.3 (82.7–392.4)	NR	Change in median monthly seizure frequency: • Placebo: –18.5% • CBD 10 mg/kg/d: –36.4% • CBD 20 mg/kg/d: –38.4% Median difference v. placebo (95%CI): • CBD: 10 mg/kg/d: –19.5% (–30.4% to –7.5%) • CBD 20 mg/kg/d: –18.8% (–31.8% to –4.4%)
Thiele 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD 20 mg/kg/d (86)	14 wk	176.7 144.6	128.7 83.8	Change in median (IQR) monthly seizure frequency: • Placebo: –13.7% (–45.0% to 7.3%) • CBD 20 mg/kg/d: –41.2% (–62.9% to –13.0%) Median difference v. placebo (95%CI): –21.1% (–33.3% to –9.4%)
Devinsky 2017 ²²	RCT	Dravet syndrome	• Placebo (59) • CBD 20 mg/kg/d (61)	14 wk	41.5 24.0	31.1 13.7	Adjusted median change: • Placebo: –9% • CBD: –28.6% Median difference v. placebo (95%CI): –19.2% (95%CI –39.25% to –1.17%)
Devinsky 2016 ⁸	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD (137)	12 wk	60 (range: 22.0–131.8)	NR	Change in median (IQR) monthly seizure frequency from baseline: –34.6% (–66.7% to –9.8%)
Geffrey 2015 ¹⁰	Prospective single-arm cohort	Drug-resistant epilepsy taking CLO	• CBD (13)	8 wk	NR	NR	Mean (SD) change in monthly seizures from baseline: –51% (56%)
Hess 2016 ⁹	Prospective single-arm cohort	Tuberous sclerosis complex	• CBD (8)	3 mo	22.0 (IQR: 14.8–57.4) per wk	13.2 (IQR: 5.06–22.1) per wk	Change in median (IQR) weekly seizure frequency from baseline: –48.8% (–69.1% to –11.1%)
Gofshteyn 2017 ⁵	Prospective single-arm cohort	FIRES (chronic)	• CBD (5)	48 wk	NR	NR	Change in mean (SD) monthly seizures from baseline: 4 wk: –90.94% (19.9%)

Author, yr	Study design	Population	Treatments* (no. in group)	Duration	Seizure frequency†; median per month‡		Effect estimate
					Baseline	After treatment	
							48 wk: −63.3% (29.3%)
Porcari 2018 ¹²	Retrospective comparative cohort	Drug-resistant epilepsy	• CBD (48) • CBD + CLO (54) • CLO (74)	Mean (SD), yr 1.1 (0.8) 1.3 (1.0) 2.5 (1.9)	Mean (range): 89 (0–675) 372 (0.3–4680) 437 (0.2–10,800)	Mean (SE): 63 (21) 252 (88) 198 (58)	Change in seizures from baseline: • CBD alone: −30% • CBD + CLO: −33% • CLO: −55%
Suraev 2017 ¹⁸	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products (51) • No cannabis (340)	Mean (SD): 15.75 (15.65) mo	Mean (SD) 12.8 (16.7) 30.6 (196.4)	Mean (SD) 2.5 (73.2) NA	Change in seizures from baseline with cannabis-based product: −80%
Note: CBD = cannabidiol, CI = confidence interval, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, NR = not reported, RCT = randomized controlled trial, SD = standard deviation, SE = standard error. *Treatments described in full in Table 1 and Appendix 5. No. randomized for RCTs; otherwise, no. included in efficacy analysis. †Total seizures, includes convulsive and non-convulsive seizures. ‡Unless otherwise stated							

B) Pooled median difference in monthly frequency of total seizures — RCTs

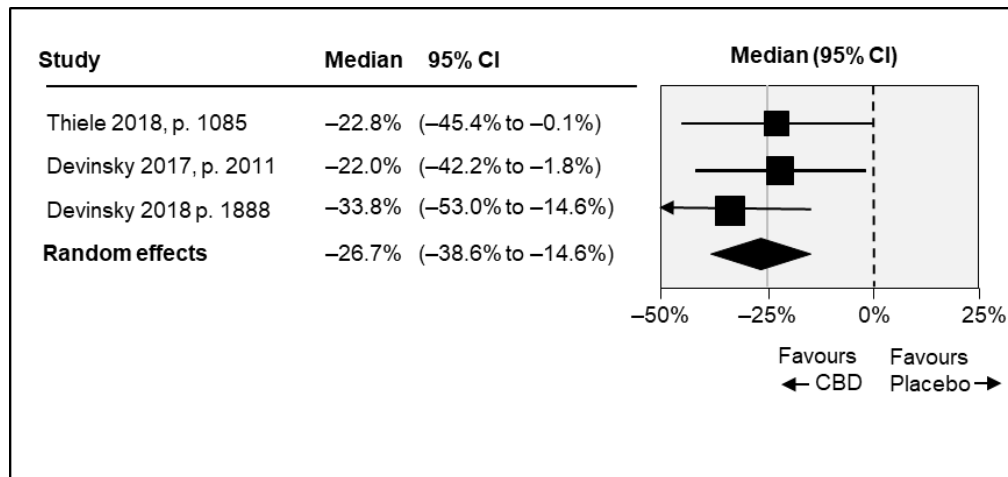


Appendix 11: Evidence summary — Tonic–clonic seizure frequency

A) All studies

Author, yr, page no.	Study design	Population	Treatments* (no. in group)	Duration	Seizure frequency; median per month		Effect estimate
					Baseline	After treatment	
Devinsky 2018, p. 1888 ²³	RCT	Lennox-Gastaut syndrome	• Placebo (34) • CBD 10 mg/kg/d (37) • CBD 20 mg/kg/d (41)	14 wk	NR	NR	Median difference (95% CI) v. placebo in monthly seizures • CBD 10 mg/kg/d: –39.92% (–64.55% to –19.66%) • CBD 20 mg/kg/d: –27.95% (–51.99% to –2.86%)
Devinsky 2017 ²²	RCT	Dravet syndrome	• Placebo (52) • CBD 20 mg/kg/d (55)	14 wk	NR	NR	Median difference (95% CI) v. placebo in monthly seizures –22.01% (–42.52% to –2.11%)
Thiele 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo (53) • CBD 20 mg/kg/d (49)	14 wk	NR	NR	Median difference (95% CI) v. placebo in monthly seizures –22.77 (–44.94% to 0.37%)
Devinsky 2016 ⁸	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD (89)	12 wk	10 (4–25) [†]	NR	Change in median (95% CI) monthly seizure frequency from baseline: –16.0% (–60.1% to 35.3%)
Hess 2016 ⁹	Prospective single-arm cohort	Tuberous sclerosis syndrome	• CBD (6)	12 mo	NR	NR	Change in median (95% CI) weekly seizure frequency from baseline: –91.4% (–100% to –13.9%)
Note: CBD = cannabidiol, CI= confidence interval, NR = not reported, RCT = randomized controlled trial. *Treatments described in full in Table 1 and Appendix 5. No. randomized for RCTs; otherwise, no. included in efficacy analysis. [†]Based on efficacy data set (n = 137); unclear if reported data are median (range) or median (IQR).							

B) Pooled median difference in monthly frequency of tonic-clonic seizures — RCTs



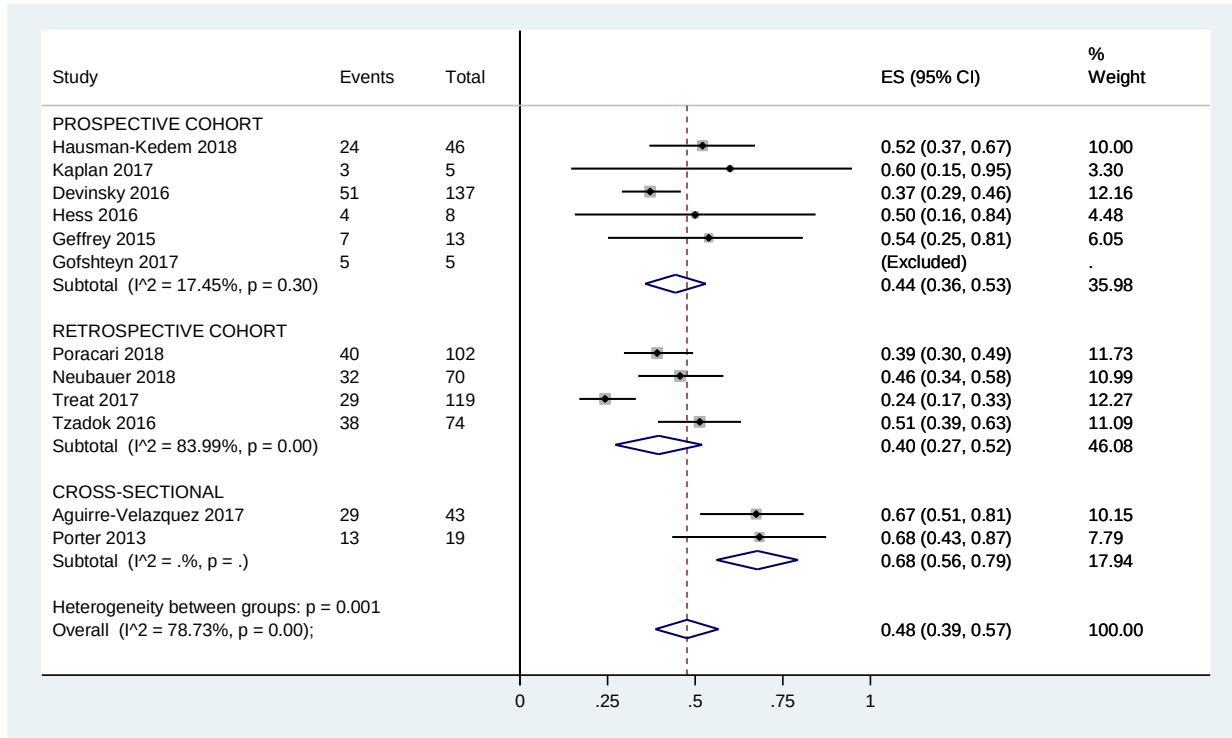
Appendix 12: Evidence summary — Treatment response

(≥ 50% reduction in total seizures from baseline period)

A. All studies

Author, yr, page no.	Study design	Population	Treatments*	Duration	No. events/no. randomized†	
					Cannabis-based treatment	Control
Thiele 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo • CBD	14 wk	32/86	18/85
Devinsky 2016 ⁸	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD	12 wk	51/137	NA
Geffrey 2015 ¹⁰	Prospective single-arm cohort	Drug-resistant epilepsy taking CLO	• CBD	8 wk	7/13	NA
Hess 2016 ⁹	Prospective single-arm cohort	Tuberous sclerosis complex	• CBD	3 mo 12 mo	9/18 4/8	NA
Kaplan 2017 ⁶	Prospective single-arm cohort	Sturge-Weber syndrome	• CBD	14 wk Last visit (6–82 wk)	2/4 3/5	NA
Gofshiteyn 2017 ⁵	Prospective single-arm cohort	FIRES (acute)	• CBD	4 wk 48 wk	1/2 NR	NA
		FIRES (chronic)		4 wk 48 wk	5/5 5/5	NA
Hausman-Kedem 2018 ²	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD‡	Mean 15.6 mo	24/46	NA
Porcari 2018 ¹²	Retrospective comparative cohort	Drug-resistant epilepsy	• CBD • CBD + CLO • CLO	Mean, yr: 1.1; 1.3; 2.5	CBD: 16/48 CBD+CLO: 24/54	CLO: 28/74
Neubauer 2018 ¹¹	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD	Median: 14.0 mo	32/70	NA
Tzadok 2016 ¹⁶	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD-enriched cannabis oil	≥ 3 mo	38/74	NA
Treat 2017 ¹³	Retrospective single-arm cohort	Drug-resistant epilepsy	• Mixed cannabis-based products	Mean (range): 11.7 (0.3–57) mo	29/119	NA
Aguirre-Velazquez 2017 ¹⁷	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products	<1 to 12 mo	29/43	NA
Porter 2013 ²⁰	Cross-sectional	Drug-resistant epilepsy	• CBD	> 1 yr	13/19	NA
Note: CBD = cannabidiol, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, NA = not applicable, NR = not reported, RCT = randomized controlled trial. *Treatments described in full in Table 1 and Appendix 5. †No. randomized for RCTs; otherwise, no. in efficacy analysis. ‡20:1 CBD:THC oil. 30% of participants were transferred to or added inhaled CBD-enriched cannabis during the study period.						

B. Treatment response reported in non-randomized studies



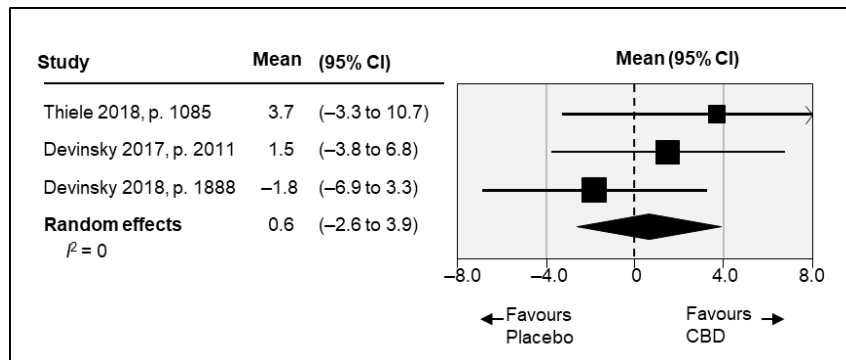
Appendix 13: Evidence summary — Quality of life (children)

A. All studies

Author, yr, page no.	Study design	Population	Treatments (no. in group)*	Duration	Quality of life; mean (SD)		Effect estimate
					Baseline	After treatment	
Thiele 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD (86)	14 wk	NR	NR	Adjusted [†] difference between groups after treatment: 3.7 (95% CI –3.3 to 10.7)¶
Devinsky 2018 ²³	RCT	Lennox-Gastaut syndrome	• Placebo (76)‡ • CBD 10 mg/kg/d (73) • CBD 20 mg/kg/d (76)	14 wk	NR	NR	Adjusted [†] mean difference (95%CI) between groups after treatment: • 10 mg/kg/d v. placebo: 1.6 (–4.5 to 7.8)¶ • 20 mg/kg/d v. placebo –5.1 (–11.4 to 1.2)¶
Devinsky 2017 ²²	RCT	Dravet syndrome	• Placebo (59) • CBD (61)	14 wk	NR	NR	Mean difference (95%CI) between groups after treatment: 1.5 (–3.8 to 6.8)¶
Rosenberg 2017 ⁷	Prospective single-group cohort	Drug-resistant epilepsy	• CBD (48)	12 wk	31.8 (7.8)	45.74 (8.50)	Mean (SD) difference before-after treatment: 8.12 (9.85); p < 0.001¶
Kaplan 2018 ⁶	Prospective single-group cohort	Sturge-Weber syndrome	• CBD (5)	Up to 82 wk	NR	NR	"All subjects reported improvements in QoL for most of their time on CBD. All three subjects who have continued on CBD reported their QoL at last visit being "a lot better" since starting CBD."***

Note: CBD = cannabidiol, CI = confidence interval, NR = not reported, QoL = quality of life, RCT = randomized controlled trial, SD = standard deviation.
 *Treatments described in full in Table 1 and Appendix 5. No. randomized for RCTs unless otherwise stated; otherwise, no. included in efficacy analysis.
 †Adjusted for baseline score and age group
 ‡Analysis included 38 participants in the placebo group, 36 in 10 mg/kg/d group, and 33 in 20 mg/kg/d group.
 ¶100-point Quality of Life in Childhood Epilepsy score; positive score favours CBD.
 ***Likert scale ranging from –3 to 3 ("A lot worse" to "A lot better"); no data reported.

B) Pooled mean difference in quality of life — RCTs



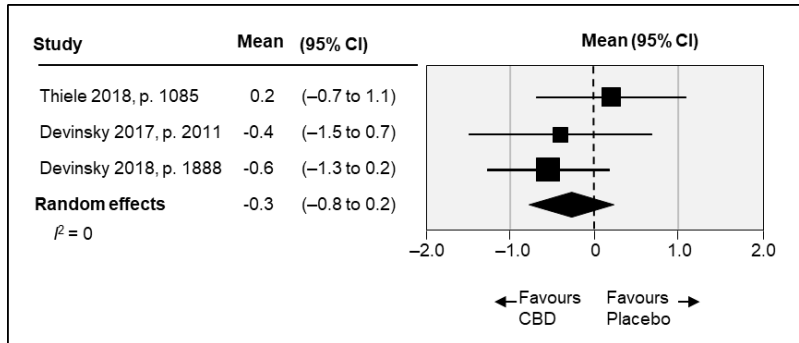
Appendix 14: Evidence summary — Sleep

A. Evidence summary — All studies

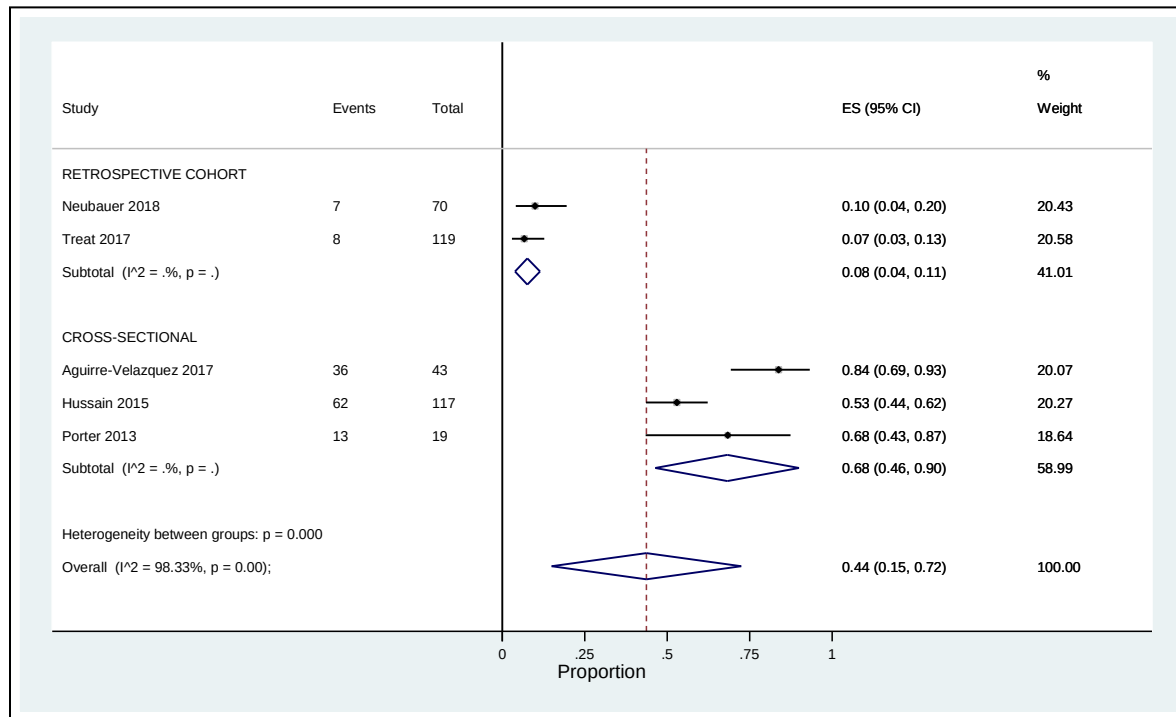
Author, yr	Study design	Population	Treatments* (no.)	Duration	Reported finding
Sleep Disruption Rating Scale score[†]					Mean difference (95%CI) between groups after treatment
Thiele 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD (86)	14 wk	−0.2 (−1.1 to 0.7)‡
Devinsky 2018 ²³	RCT	Lennox-Gastaut syndrome	• Placebo (76) • CBD 10 mg/kg/d (73) • CBD 20 mg/kg/d (76)	14 wk	• 10 mg/kg/d v. placebo: −0.8 (−1.7 to 0.1)‡ • 20 mg/kg/d v. placebo: −0.3 (−1.2 to 0.6)‡
Devinsky 2017 ²²	RCT	Dravet syndrome	• Placebo (59) • CBD (61)	14 wk	−0.4 (−1.5 to 0.7)¶¶
Impaired sleep					Reported finding
Thiele 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD (86)	14 wk	Sleep apnea: 1 participant (1.2%) in the cannabidiol group; none reported in placebo group
INYS 2017 ¹	Prospective comparative cohort	Drug-resistant epilepsy	• CBD 10 mg/kg/d (20) • CBD 20 mg/kg/d (20) • CBD 40 mg/kg/d (21)	10 d**	Sleep apnea: 1 participant (4.8%) in the CBD 40 mg/kg/d group; none in the other dosage groups
Geffrey 2015 ¹⁰	Prospective single-group cohort	Drug-resistant epilepsy taking CLO	• CBD (13)	8 wk	“Restless sleep” was reported for 1 participant (7.7%) who received CBD and CLO
Hess 2016 ⁹	Prospective single-group cohort	Tuberous sclerosis complex	• CBD (18)	Up to 12 mo	“Poor sleep” was reported for 2 participants (11.1%) who received CBD
Kaplan 2017 ⁶	Prospective single-group cohort	Sturge-Weber syndrome	• CBD (5)	Up to 82 wk	“Sleep difficulties” were reported for 1 participant (20%) who received CBD
Aguirre-Velazquez 2017 ¹⁷	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (43)	Range <1 to 12 mo	“Broken sleep” was reported for 3 participants (7.0%) who received mixed cannabis-based products
Improved sleep					Reported finding
Neubauer 2018 ¹¹	Single-arm retrospective cohort	Drug-resistant epilepsy	• CBD (70)	Median (range): 14.0 (6.0–29.3) mo	Better sleep was reported for 7 (10%) participants who received CBD

Author, yr	Study design	Population	Treatments* (no.)	Duration	Reported finding
Treat 2017 ¹³	Retrospective single-arm cohort	Drug-resistant epilepsy	• Mixed cannabis-based treatments (119)	Mean (range): 11.7 (0.3–57) mo	Better sleep was reported for 8 (6.7%) participants who received mixed cannabis-based products
Aguirre-Velazquez 2017 ¹⁷	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (43)	Range <1 to 12 mo	“Improvement in sleep” was reported for 83% of participants who received mixed cannabis-based products
Hussain 2015 ¹⁹	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (117)	Median (IQR): 6.8 (3.8–9.8) mo	“Improvement in sleep” was reported for 53% of participants who received mixed cannabis-based products
Porter 2013 ²⁰	Cross-sectional	Drug-resistant epilepsy	• CBD (19) • Stiripentol (22)	Range: 2 wk to > 1 yr	Better sleep was reported for 13 (68.4%) participants who received mixed cannabis-based products; better sleep was reported for 6 participants (27.3%) who received stiripentol
Note: CBD = cannabidiol, CI = confidence interval, CLO = clobazam, IQR = interquartile range, RCT = randomized controlled trial. *Treatments described in full in Table 1 and Appendix 5. No. randomized for RCTs; otherwise, no. included in analysis. †Sleep Disruption Rating Scale score, assessed on a numerical rating scale from 0 to 10, with higher scores indicating greater disruption. Negative mean difference favours cannabidiol. ‡Adjusted for baseline score and age group. ¶Adjusted; covariates not reported. **Treatment for 10 days, followed by withdrawal period for up to 7 days. Participants who enrolled into a subsequent rollover study may not have had adverse event data collected after day 11.					

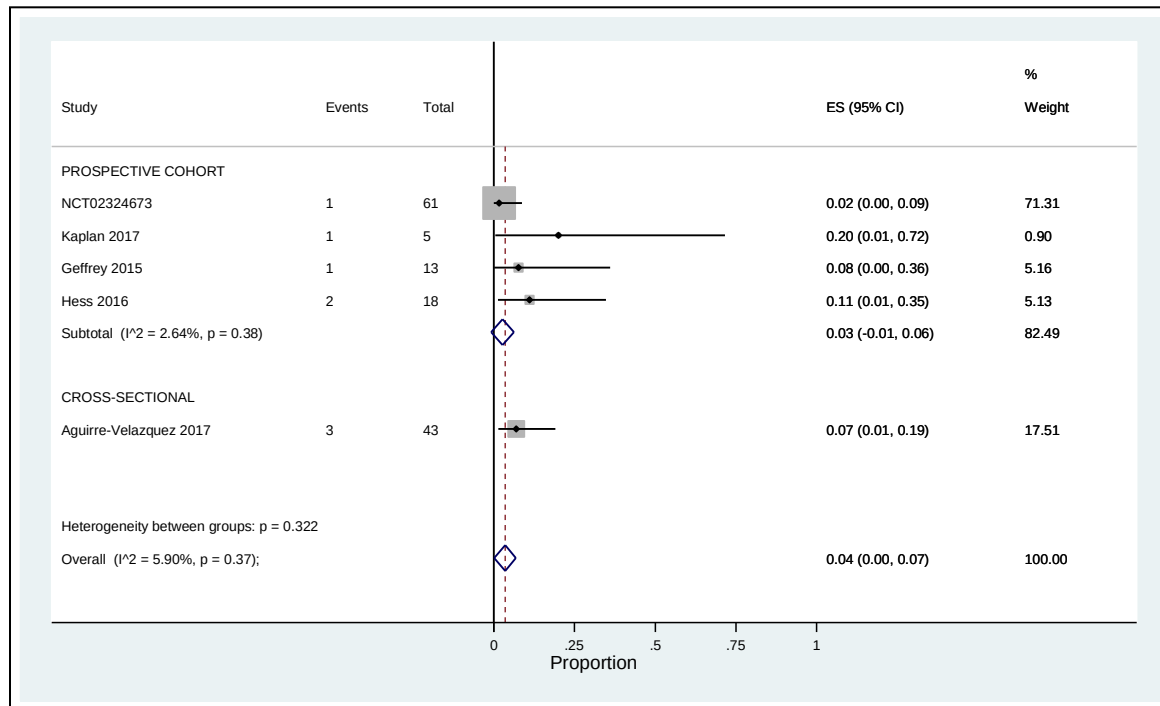
B. Sleep Disruption Rating Scale — RCTs



C. Improved sleep reported in non-randomized studies



D. Impaired sleep reported in non-randomized studies



Appendix 15: Evidence summary — Status epilepticus

A. All studies

Author, yr, page no.	Study design	Population	Duration	Treatment*	No. participants with status epilepticus /no. in group (%)
Thiele 2018 ²⁴	RCT	Lennox-Gastaut syndrome	14 wk	• Placebo • CBD	1/85 (1.2) 1/86 (1.2)
Devinsky 2018 ²³	RCT	Lennox-Gastaut syndrome	14 wk	• Placebo • CBD 10 mg/kg/d • CBD 20 mg/kg/d	3/76 (3.9) 7/67 (10.4) 4/82 (4.9)‡
Devinsky 2017 ²²	RCT	Dravet syndrome	14 wk	• Placebo • CBD	3/59 (5.1) 3/61 (4.9)
Devinsky 2016 ¹⁹	Prospective single-arm cohort	Drug-resistant epilepsy	12 wk	• CBD	13/162 (8.0)
Hausman-Kedem 2018 ²	Prospective single-arm cohort	Drug-resistant epilepsy	Median (range): 18 (3–33) mo	• CBD†	1/46 (2.2)
Press 2015 ¹⁴	Retrospective single-arm cohort	Drug-resistant epilepsy	Mean (range): 5.59 (1–24) mo	• CBD, CBD + other oral cannabis extract, THCA only, or "other"	1/75 (1.3)

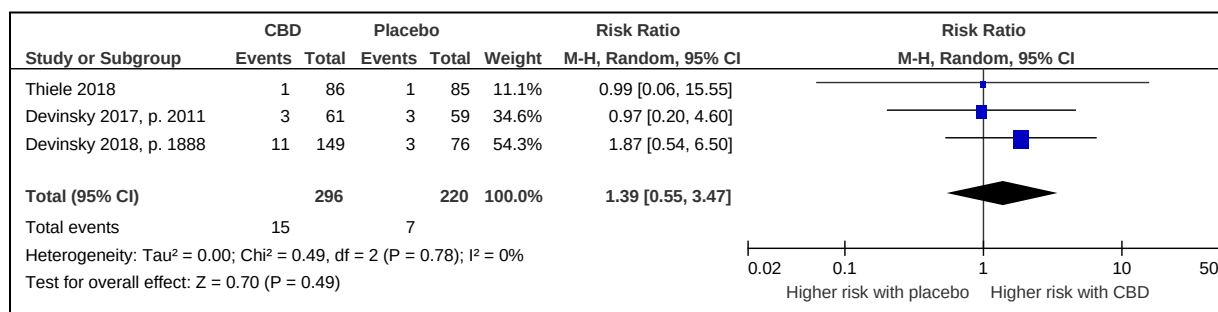
Note: CBD = cannabidiol, THCA = tetrahydrocannabinolic acid.

*Treatments described in full in Table 1 and Appendix 5. No. randomized for RCTs; otherwise, no. included in safety analysis.

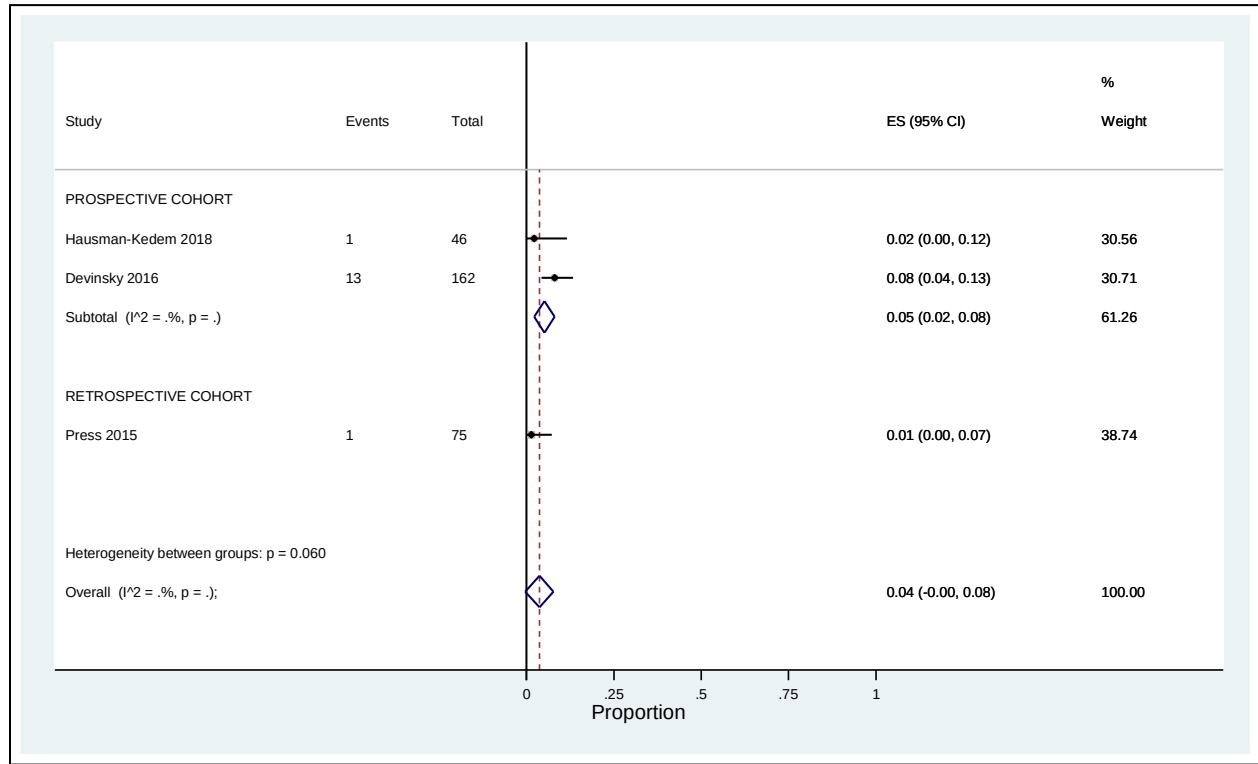
†20:1 CBD:THC oil. 30% of participants were transferred to or added inhaled CBD-enriched cannabis during the study period.

‡6 participants in the 10 mg/kg/d group received a dose above the target and were included in the 20 mg/kg/d group for the safety analysis.

B. Relative risk of status epilepticus reported in included RCTs



C. Pooled prevalence of status epilepticus among children administered CBD in non-randomized studies



Appendix 16: Evidence summary — Death

Author, yr*	Study design	Population	Duration	Treatment (no. in group)†	Deaths	Reported cause of death
Thiele 2018 ²⁴	RCT	Lennox-Gastaut syndrome	14 wk	• Placebo (85) • CBD (20 mg/kg/d) (86)	1 death reported in the CBD group; zero deaths in the placebo group	Respiratory failure (reported to be unrelated to study drug)
Devinsky 2016 ⁸	Prospective single-arm cohort	Drug-resistant epilepsy	12 wk	• CBD (50 mg/kg/d) (162)	1 death reported	SUDEP (reported to be unrelated to the study drug)
Gofshteyn 2017 ⁵	Prospective single-arm cohort	FIRES	48 wk	• CBD (up to 25 mg/kg/d) (acute: 2; chronic: 5)	1 death was reported in a child treated during the acute stage; no deaths in the chronic stage	Multi-organ failure (thought to be related to prolonged isoflurane exposure)
Press 2015 ¹⁴	Retrospective, single-arm cohort	Drug-resistant epilepsy	Mean (range): 5.59 (1–24) mo	• CBD, CBD + other oral cannabis extract, THCA only, or "other" (75)	1 death reported	NR
Neubauer 2018 ¹¹	Retrospective, single-arm cohort	Drug-resistant epilepsy	Median (range) 14.0 (6.0–29.3) mo	• CBD (up to 16 mg/kg/d) (70)	2 deaths reported	Multiple cavernomas (died suddenly during sleep; 1); bronchopneumonia (1)
Sulak 2017 ¹⁵	Case series‡	Drug-resistant epilepsy	NR	• THCA (2 mg/kg/d) (4‡)	1 death reported	SUDEP
Note: CBD = cannabidiol, FIRES = Febrile Infection-Related Epilepsy syndrome, NR = not reported, RCT = randomized controlled trial, SUDEP = sudden unexpected death in epilepsy, THCA = tetrahydrocannabinolic acid. *An additional three studies^{22,25,1} reported that no deaths occurred during the study period. †Treatments described in full in Table 1 and Appendix 5. No. randomized for RCTs; otherwise, no. included in safety analysis. ‡Case series of four children with epilepsy who received "herbal cannabinoid treatment."						

Appendix 17: Evidence summary — Gastrointestinal adverse events

A) All studies

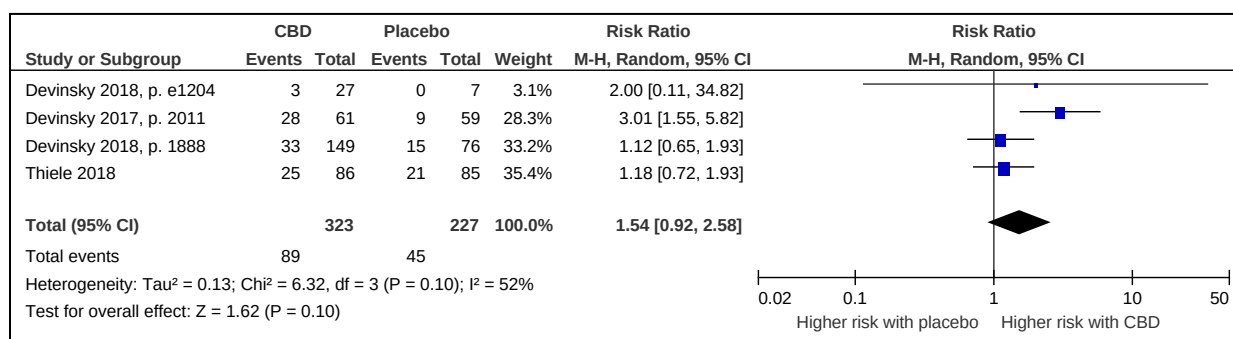
Author, yr, page no.	Study design	Population	Treatments (no. in group)*	Duration	No. events (%)	
					Vomiting	Diarrhea
Thiele 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD (86)	14 wk	14 (16) 9 (10)	7 (8) 16 (19)
Devinsky 2018 ²³	RCT	Lennox-Gastaut syndrome	• Placebo (76) • CBD 10 mg/kg/d (67) • CBD 20 mg/kg/d (82) [†]	14 wk	9 (12) 4 (6) 10 (12)	6 (8) 7 (10) 12 (15)
Devinsky 2018 ²⁵	RCT	Dravet syndrome	• Placebo (7) • CBD 5 mg/kg/d (10) • CBD 10 mg/kg/d (8) • CBD 20 mg/kg/d (9)	3 wk	0 1 1 1	NR
Devinsky 2017 ²²	RCT	Dravet syndrome	• Placebo (59) • CBD (61)	14 wk	3 (5) 9 (14.8)	6 (10.2) 19 (31.1)
Hausman-Kedem 2018 ²	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD (57) [‡]	Median (range): 18 (3–33) mo	5 (8.8)	1 (1.8)
INYS 2017 ¹	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD 10 mg/kg/d (20) • 20 mg/kg/d (20) • 40 mg/kg/d (21)	10 d¶	2 (10) 1 (5) 0 (0)	1 (5) 2 (10) 7 (33)
Kaplan 2017 ⁶	Prospective single-arm cohort	Sturge-Weber syndrome	• CBD (5)	Up to 82 wk	2 (40.0)	1 (20.0)
Gofshteyn 2017 ⁵	Prospective single-arm cohort	FIRES	• CBD (7)	48 wk	1 (14.3)	NR
Devinsky 2016 ⁸	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD (162)	12 wk	NR	13 (8.0)
Hess 2016 ⁹	Prospective single-arm cohort	Tuberous sclerosis complex	• CBD (18)	12 mo	1 (5.6)	4 (22.2)
Aguirre-Velazquez 2017 ¹⁷	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products (43)	Up to 12 mo	NR	1 (2.3)
Hussain 2015 ¹⁹	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products (117)	Median (IQR): 6.8 (3.8–9.8)	3 (2.6)	NR
Porter 2013 ²⁰	Cross-sectional	Drug-resistant epilepsy	• Stiripentol (22) • CBD (19)	> 1 yr	2 (9) 0 (0)	NR
Tzadok 2016 ¹⁶	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD-enriched cannabis oil, 1 to 20 mg/kg/d (20:1 CBD to THC ratio) (74)	≥ 3 mo	5 (7)	
Treat 2017 ¹³	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD, CBD + other oral cannabis extract, THCA only, or "other" (119)	Mean (range): 11.7 (0.3–57) mo	6 (5)	

Note: CBD = cannabidiol, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, NR = not reported, RCT = randomized controlled trial, THCA = tetrahydrocannabinolic acid, THC = tetrahydrocannabinol.

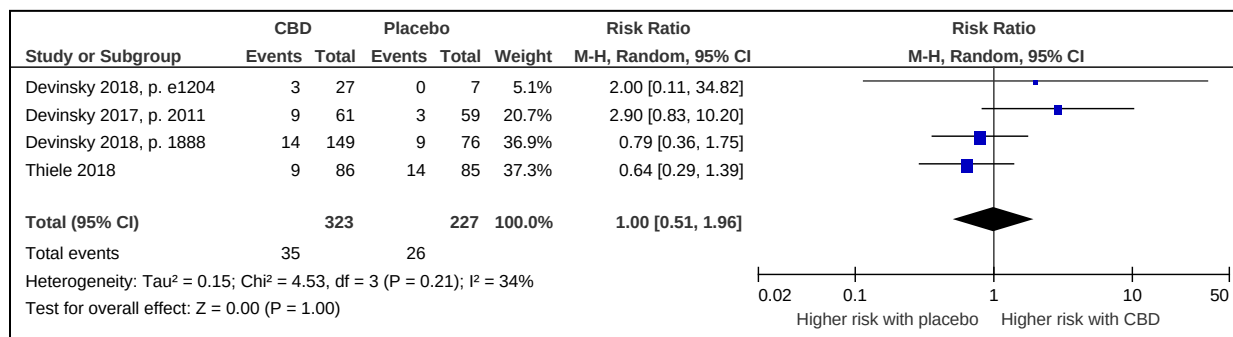
Author, yr, page no.	Study design	Population	Treatments (no. in group)*	Duration	No. events (%)	
					Vomiting	Diarrhea

* Treatments described in full in Table 1 and Appendix 5. No. randomized for RCTs; otherwise, no. included in safety analysis.
†6 participants in the 10 mg/kg/d group received a dose above the target and were included in the 20 mg/kg/d group for the safety analysis.
‡20:1 CBD:THC oil. 30% of participants were transferred to or added inhaled CBD-enriched cannabis during the treatment period.
¶Treatment for 10 days, followed by withdrawal period for up to 7 days. Participants who enrolled into a subsequent rollover study may not have had adverse event data collected after day 11.

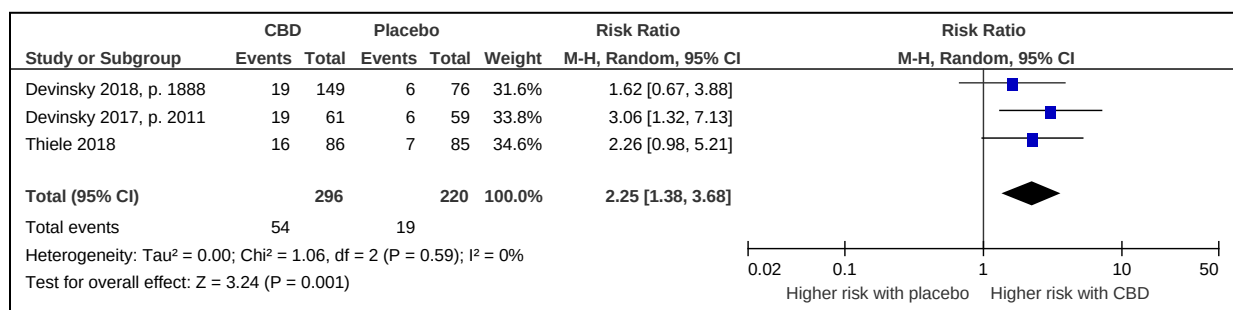
B) Relative risk of any gastrointestinal adverse event (vomiting and/or diarrhea) reported among the RCTs



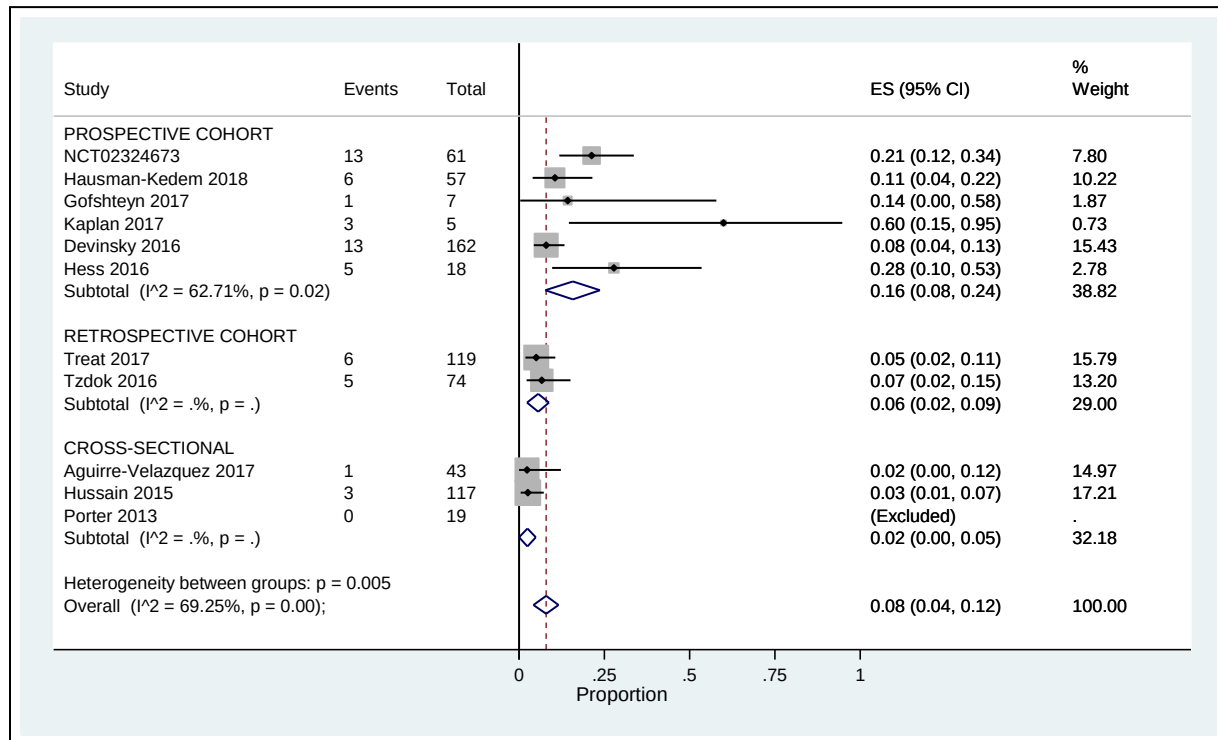
C) Relative risk of vomiting reported among the RCTs



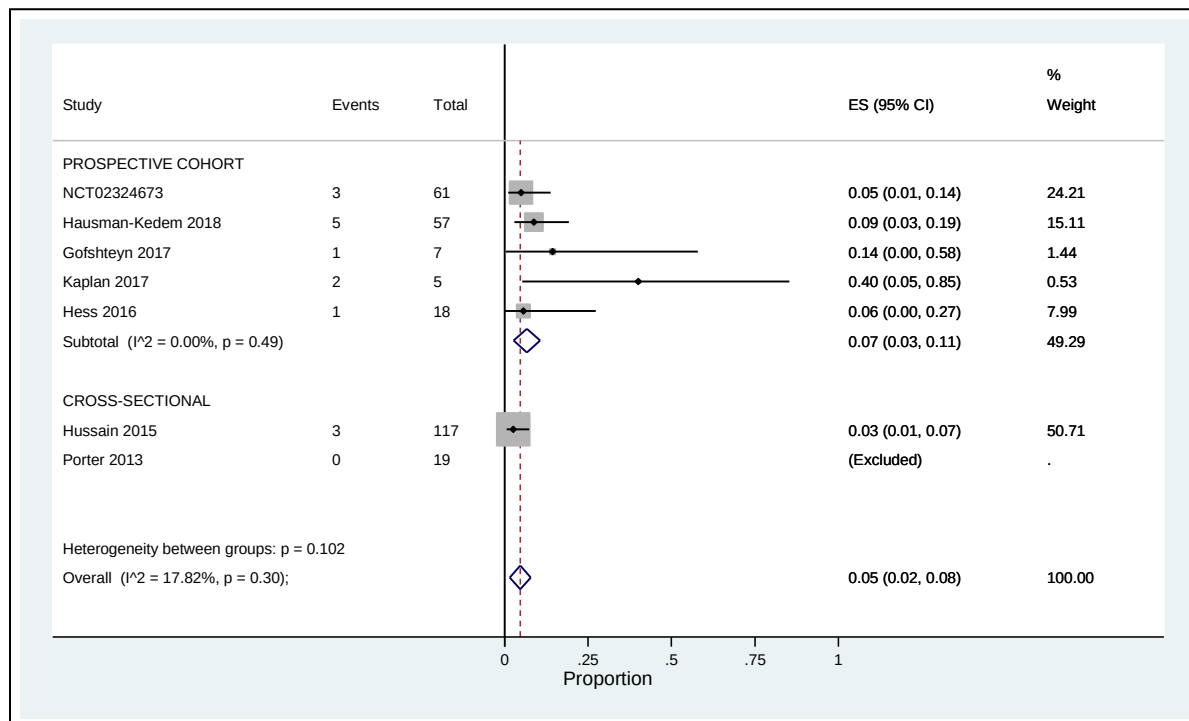
D) Relative risk of diarrhea reported among the RCTs



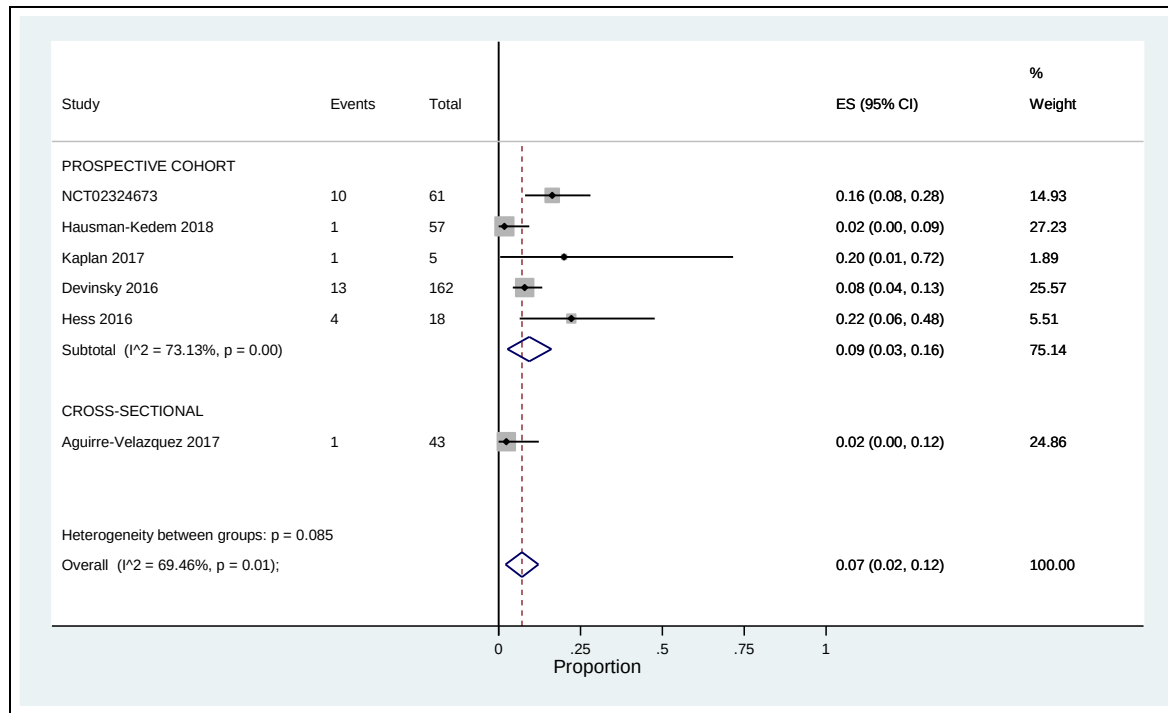
E) Pooled prevalence of any gastrointestinal adverse events (vomiting and/or diarrhea) reported among the non-randomized studies



F) Pooled prevalence of vomiting reported among the non-randomized studies



G) Pooled prevalence of diarrhea reported among the non-randomized studies



Appendix 18: Summary of outcomes by epilepsy syndrome

(a) Dravet syndrome

A total of seven studies (two RCTs,^{22,25} five NRS^{8,10,13,19,20}) reported outcomes among participants with Dravet syndrome as part of subgroup analysis or the entire study population. No outcome data were available for caregiver quality of life or visits to the emergency department.

Outcome	Total no. of studies	Study design (Author, yr); duration	Whole study population or subgroup (no. in group)	Finding
Seizure freedom	2 studies	RCT (Devinsky 2017 ²²); 14 wk	Whole study population (120)	5% (3/61) of children who received CBD (20 mg/kg/d) became seizure free (0/59 in the placebo group)
		Cross-sectional (Hussain 2015 ¹⁹); Median (IQR): 6.8 (3.8–9.8) mo	Subgroup (15)	13% of children became seizure free (type and dose of cannabis-based treatment NR)
Seizure frequency (all types)	3 studies	RCT (Devinsky 2017 ²²); 14 wk	Whole study population (120)	Adjusted median change in monthly seizure frequency: • Placebo: –9% • CBD: –28.6% Median difference v. placebo (95%CI): –19.2% (–39.25% to –1.17%)
		Prospective single-group cohort (Devinsky 2016 ⁸); 12 wk	Subgroup (32)	Change in median (IQR) monthly seizure frequency from baseline: –42.7% (–64.6% to –20.6%) among children administered CBD (up to 50 mg/kg/d)
		Prospective single-group cohort (Geffrey 2015 ¹⁰); 8 wk	Subgroup (3)	The 3 children with CBD (up to 25 mg/kg/d) and CLO use had reported reductions of 81%, 68% or 30% in seizures from baseline
Treatment response*	3 studies	Prospective single-group cohort (Geffrey 2015 ¹⁰); 8 wk	Subgroup (3)	Two children with CBD and CLO use (67%) experienced a ≥ 50% response to CBD (up to 25 mg/kg/d)
		Retrospective single-group cohort (Treat 2017 ¹³); mean (range): 11.7 (0.3–57) mo	Subgroup (17)	1 child (5.9%) had a ≥ 50% reduction in seizures (mixed cannabis-based products, dose NR)
		Cross-sectional study (Porter 2013 ²⁰); range: 2 wk to > 1 yr	Subgroup (13)	9 children (69%) had a ≥ 50% reduction in seizures (CBD 0.5 to 28.6 mg/kg/d)
Quality of life (child)	1 study	RCT (Devinsky 2017 ²²); 14 wk	Whole study population (120)	Mean difference between groups after treatment: 1.5 (95%CI –3.8 to 6.8) on the 100-point Quality of Life in Childhood Epilepsy score; positive score favours CBD (20 mg/kg/d) v. placebo
Quality of life (caregiver)	No studies	—	—	—
Sleep	1 study	RCT (Devinsky 2017 ²²); 14 wk	Whole study population (120)	No significant difference in sleep disturbances between the CBD (20 mg/kg/d) and placebo groups (adjusted mean difference –0.4 [95%CI –1.5 to 0.7]) [†]
Status epilepticus	1 study	RCT (Devinsky 2017 ²²); 14 wk	Whole study population (120)	Status epilepticus reported for 3 (n = 61) children who received CBD (20 mg/kg/d) and 3 (n = 59) children who received placebo

Outcome	Total no. of studies	Study design (Author, yr); duration	Whole study population or subgroup (no. in group)	Finding
Death	2 studies	RCT (Devinsky 2017 ²²); 14 wk	Whole study population	No deaths reported among children in either the CBD (n = 61) or placebo group (n = 59)
		RCT (Devinsky 2018 ²⁵); 3 wk	Whole study population (34)	No deaths reported among children who received CBD (5, 10, 20 mg/kg/d, n = 27) or placebo (n = 7)
Gastrointestinal adverse events	2 studies	RCT (Devinsky 2017 ²²); 14 wk	Whole study population (120)	Vomiting reported for 14.8% (6/61) of children who received CBD and 5% (3/59) of children in the placebo group; Diarrhea reported for 31.1% (19/61) and 10.2% (6/59) of children in each group, respectively
		RCT (Devinsky 2018 ²⁵); 3 wk	Whole study population (34)	Vomiting reported for 11% of children who received CBD (3/27) and zero children in the placebo group (n = 7); diarrhea NR
Visits to the ED	No studies	—	—	—
Note: CBD = cannabidiol, CI = confidence interval, CLO = clobazam, ER = emergency department, IQR = interquartile range, NR = not reported, RCT = randomized controlled trial *At least a 50% reduction in total seizures from baseline. †Sleep Disruption Rating Scale score, assessed on a numerical rating scale from 0 to 10, with higher scores indicating greater disruption. A negative mean difference favours cannabidiol.				

(b) Lennox–Gastaut syndrome

In total, two RCTs^{23,24} and five NRS^{8,12,13,19,20} studies have involved children with Lennox–Gastaut syndrome as part of subgroup analyses or the entire study population. No outcome data were available for quality of life of caregivers or visits to the emergency department.

Outcome	Total no. of studies	Study design (Author, yr); duration	Whole study population or subgroup (no. in group)	Finding
Seizure freedom	1 study	Cross-sectional (Hussain 2015 ¹⁹); median (IQR): 6.8 (3.8–9.8) mo	Subgroup (53)	Among children with Lennox–Gastaut syndrome or infantile spasms, 13% achieved seizure freedom (type and dose of cannabis-based treatment NR)
Seizure frequency (all seizures)	3 studies	RCT (Thiele 2018 ²⁴); 14 wk	Whole population (171)	Change in median (IQR) monthly seizure frequency: • Placebo: –13.7% (–45.0% to 7.3%) • CBD 20 mg/kg/d: –41.2% (–62.9% to –13.0%) Median difference v. placebo (95%CI): –21.1% (–33.3% to –9.4%)
		RCT (Devinsky 2018 ²³); 14 wk	Whole population (225)	Reduction in median monthly seizure frequency: • Placebo: –18.5% • CBD 10 mg/kg/d: –36.4% • CBD 20 mg/kg/d: –38.4% Median difference v. placebo (95%CI): • CBD: 10 mg/kg/d: –19.5% (–30.4% to –7.5%); • CBD 20 mg/kg/d: –18.8% (–31.8% to –4.4%)
		Prospective single-arm cohort (Devinsky 2016 ⁸); 12 wk	Subgroup (30)	Change in median (IQR) monthly seizure frequency from baseline: –35.5% (–55.1% to –16.4%) among children who received CBD (up to 50 mg/kg/d)
Seizure frequency (tonic–clonic seizures)	2 studies	RCT (Devinsky 2018 ²³); 14 wk	Whole population (225)	Median difference (95% CI) v. placebo in monthly seizures • CBD 10 mg/kg/d: –39.92% (–64.55% to –19.66%) • CBD 20 mg/kg/d: –27.95% (–51.99% to –2.86%)
		RCT (Thiele 2018 ²⁴); 14 wk	Whole population (171)	Median difference (95% CI) v. placebo in monthly seizures –22.77 (95%CI –44.94% to 0.37%)
Treatment response*	3 studies	RCT (Thiele 2018 ²⁴); 14 wk	Whole population (171)	37% of children in the CBD group (n = 86) had a ≥ 50% reduction in seizures; compared with 21% in the placebo group (n = 85). Odds ratio 2.21 (95%CI 1.12, 4.35) in favour of CBD
		Retrospective single-arm cohort (Treat 2017 ¹³); mean 11.7 (range 0.7–57) mo	Subgroup (19)	57.9% of children with LGS had a ≥ 50% reduction in seizures after treatment (mixed cannabis-based products, dose NR)
		Retrospective comparative cohort (Porcari 2018 ¹²); up to 2.5 yr	Subgroup (79)	58% (7/12) of children who received CBD alone had a ≥ 50% reduction from baseline, compared with 52% (14/27) who received CBD and concomitant CLO and 40% (16/40) who received CLO alone

Outcome	Total no. of studies	Study design (Author, yr); duration	Whole study population or subgroup (no. in group)	Finding
		Cross-sectional (Porter 2013 ²⁰); Range: 2 wk to > 1 yr	Subgroup (1)	The one child with LGS in this study had a more than 80% reduction in seizures with CBD
Quality of life (child)	2 studies	RCT (Thiele 2018 ²⁴); 14 wk	Whole population (171)	Adjusted [†] treatment difference: 3.7 (95% CI –3.3 to 10.7) on the 100-point Quality of Life in Childhood Epilepsy score; positive score indicates difference in favour of CBD
		RCT (Devinsky 2018 ²³); 14 wk	Whole population (225)	Adjusted [†] mean difference between groups after treatment [‡] : • 10 mg/kg/d v. placebo: 1.6 (–4.5 to 7.8) • 20 mg/kg/d v. placebo –5.1 (–11.4 to 1.2)
Quality of life (caregivers)	No studies	—	—	—
Sleep	2 studies	RCT (Thiele 2018 ²⁴); 14 wk	Whole population (171)	Adjusted [†] mean difference (95%CI) between groups after treatment: –0.2 (–1.1 to 0.7) on the Sleep Disruption Rating Scale (negative scores favour CBD); sleep apnea reported for 1 participant (1.2%) in the CBD group; none reported in placebo group
		RCT (Devinsky 2018 ²³); 14 wk	Whole population (225)	Adjusted [†] mean difference (95%CI) between groups after treatment on the Sleep Disruption Rating Scale (negative scores favour CBD) • 10 mg/kg/d v. placebo: –0.8 (–1.7 to 0.1) • 20 mg/kg/d v. placebo: –0.3 (–1.2 to 0.6)
Status epilepticus	2 studies	RCT (Thiele 2018 ²⁴); 14 wk	Whole population (171)	Status epilepticus reported for one child each in the placebo (n = 85; 1.2%) and CBD (n = 86; 1.2%) groups
		RCT (Devinsky 2018 ²³); 14 wk	Whole population (225)	Status epilepticus reported for 3 children in the placebo group (n=76; 3.9%), 7 in the CBD 10 mg/kg/d (n = 67; 10.4%), and 4 in the CBD 20 mg/kg/d (n = 82; 4.9%)¶
Death	1 study	RCT (Thiele 2018 ²⁴); 14 wk	Whole population (171)	1 death reported in the CBD group, attributed to respiratory failure and reported to be unrelated to treatment (n = 86; 1.2%); zero deaths in the placebo group (n = 85)
Gastrointestinal adverse events	2 studies	RCT (Thiele 2018 ²⁴); 14 wk	Whole population (171)	Vomiting reported for 9 children in the CBD group (10%; n = 86) and 14 (16%; n = 85) placebo group; diarrhea reported for 16 children in the CBD group (19%) and 7 (8%) in the placebo group
		RCT (Devinsky 2018 ²³); 14 wk	Whole population (225)	Vomiting reported for 9 children in the placebo group (n=76; 12%), 4 in the CBD 10 mg/kg/d (n = 67; 6%), and 10 in the CBD 20 mg/kg/d (n = 82; 12%); diarrhea reported for 6 children in the placebo group (8%), 7 in the CBD 10 mg/kg/d (10%), and 12 in the CBD 20 mg/kg/d (15%)¶
Visits to the ED	No studies	—	—	—
Note: CBD = cannabidiol, CI =confidence interval, CLO = clobazam, ED = emergency department, IQR = interquartile range, LGS = Lennox-Gastaut syndrome, NR = not reported, RCT = randomized controlled trial. *At least a 50% reduction in total seizures from baseline. †Adjusted for baseline score and age group; 100-point Quality of Life in Childhood Epilepsy score, positive score indicates difference in favour of CBD. ‡Analysis included 38 participants in the placebo group, 36 in 10 mg/kg/d group, and 33 in 20 mg/kg/d group. ¶6 participants in the 10 mg/kg/d group received a dose above the target and were included in the 20 mg/kg/d group for the safety analysis.				

(c) Doose syndrome

A total of three studies,^{10,14,20} involving between two and eight children with Doose syndrome, reported outcomes as part of subgroup analyses. No outcome data were available for quality of life (child or caregiver), sleep, status epilepticus, death, gastrointestinal adverse events, or visits to the emergency department.

Outcome	Total no. of studies	Study design (Author, yr); duration	Whole study population or subgroup (no. in group)	Finding
Seizure freedom	1 study	Prospective single-arm cohort (Geffrey 2015 ¹⁰); 8 wk	Subgroup (2)	1 child with CBD (up to 25 mg/kg/d) and CLO use achieved seizure freedom
Seizure frequency	1 study	Prospective single-arm cohort (Geffrey 2015 ¹⁰); 8 wk	Subgroup (2)	1 child experienced a 54% reduction in seizures from baseline; the other had a 100% reduction
Treatment response*	2 studies	Prospective single-arm cohort (Geffrey 2015 ¹⁰); 8 wk	Subgroup (2)	Both children with CBD and CLO use had a $\geq 50\%$ reduction in seizures
		Retrospective single-arm cohort (Treat 2017 ¹⁴); mean 11.7 (range 0.3–57) mo	Subgroup (8)	2 children (25%) had a $\geq 50\%$ reduction in seizures after treatment (mixed cannabis-based products, dose NR)
		Cross-sectional (Porter 2013 ²⁰); > 1yr	Subgroup (4)	3 children (75%) had a $\geq 50\%$ reduction in seizures after treatment with CBD
Quality of life (child)	No studies	—		
Quality of life (caregivers)	No studies	—	—	—
Sleep	No studies	—	—	—
Status epilepticus	No studies	—	—	—
Death	No studies	—	—	—
Gastrointestinal adverse events	No studies	—	—	—
Visits to the ED	No studies	—	—	—
Note: CBD = cannabidiol, CLO = clobazam, ED = emergency department, NR = not reported, RCT = randomized controlled trial. *At least a 50% reduction in total seizures from baseline.				

(d) Tuberous sclerosis complex

Two non-randomized studies^{9,10} have reported outcomes among participants with tuberous sclerosis complex, as either the entire study population or a subgroup of a larger cohort. No outcome data were available for quality of life (child or caregiver), status epilepticus, death, or visits to the emergency department.

Outcome	Total no. of studies	Study design (Author, yr); duration	Whole study population or subgroup (no. in group)	Finding
Seizure freedom	1 study	Prospective single-arm cohort (Hess 2016 ⁹); 12 mo	Whole population (18)	- After 3 months of CBD (up to 50 mg/kg/d), 1 participant experienced seizure freedom (6%); this participant remained seizure free until the 12 month, when seizures recurred (authors report that seizure recurrence was due to an attempted taper of lacosamide) - After 12 months of treatment, no patients experienced seizure freedom
Seizure frequency	1 study	Prospective single-arm cohort (Hess 2016 ⁹); 12 mo	Whole population (18)	- After 3 months of treatment with CBD, the median (IQR) reduction in total weekly seizures was 48.8% (–69.1% to –11.1%) per wk. - After 12 months of treatment, median (IQR) seizure frequency was 8.0 (3.7 to 47.7) per week (baseline 22.0 [14.8 to 57.4] per wk) - Tonic-clonic seizures were reduced by 91.4% (IQR –100% to –13.9%) after 3 months of treatment; data for 12 months NR
		Prospective single-arm cohort (Geffrey 2015 ¹⁰); 8 wk	Subgroup (2)	One child had a 58% reduction in seizures from baseline with CBD treatment (up to 25 mg/kg/d), the other had a 93% reduction
Treatment response*	2 studies	Prospective single-arm cohort (Hess 2016 ⁹); 12 mo	Whole population (18)	- After 3 months of CBD (up to 50 mg/kg/d), 50% (9/18) of participants had a ≥ 50% reduction in total seizures - After 12 months of treatment, 50% (4/8) of participants had ≥ 50% reduction in total seizures
		Prospective single-arm cohort (Geffrey 2015 ¹⁰); 8 wk	Subgroup (2)	Both children with CBD (up to 25 mg/kg/d) and CLO use experienced ≥ 50% reduction in seizures from baseline
Quality of life (child)	No studies	—	—	—
Quality of life (caregiver)	No studies	—	—	—
Sleep	1 study	Prospective single-arm cohort (Hess 2016 ⁹); 12 mo	Whole population (18)	Poor sleep was reported for 2 patients (11%) administered CBD (up to 50 mg/kg/d)
Status epilepticus	No studies	—	—	—
Death	No studies	—	—	—

Outcome	Total no. of studies	Study design (Author, yr); duration	Whole study population or subgroup (no. in group)	Finding
Gastrointestinal adverse events	1 study	Prospective single-arm cohort (Hess 2016 ⁹); 12 mo	Whole population (18)	Vomiting was reported for 1 (5.6%) patient and diarrhea was reported for 4 (22%) patients who received CBD (50 mg/kg/d)
Visits to the ED	No studies	—	—	—
Note: CBD = cannabidiol, CLO = clobazam, ED = emergency department, IQR = interquartile range, NR = not reported. *At least a 50% reduction in total seizures from baseline.				

(e) Sturge-Weber syndrome

One prospective single-group open-label cohort study (Kaplan 2017⁶) enrolled five children with Sturge-Weber syndrome with brain involvement; children received cannabidiol (up to 25 mg/kg/d) for up to 82 weeks. Mean participant age was 8 years and 10 months, and participants were taking between 1 and 4 concomitant antiepileptic drugs. Two participants withdrew because of a lack of efficacy, while a third participant withdrew because of an increase in seizures during dose-titration; this participant subsequently re-enrolled. No outcome data were available for caregiver quality of life, status epilepticus, death, or visits to the emergency department.

Outcome	Finding
Seizure freedom	• No participants were seizure free after 14 wk of treatment • One participant was seizure free at their last visit (82 wk)
Seizure frequency	• After 14 weeks of treatment, seizures were reduced by between 10% and 90%. • At the most recent visit on CBD (6 to 82 wk), seizures were reduced by 12% to 100%; increases in seizure frequency were reported for 2 children (100% to 133% increase); one of these children was removed from the study at wk 6 for lack of efficacy.
Treatment response*	Two of 4 children (50%) had $\geq 50\%$ reduction in seizures at 14 wk; at the last visit on CBD (5–82 wk), 3 of 5 children (60%) had a $\geq 50\%$ reduction
Quality of life (child)	• “All subjects reported improvements in QoL for most of their time on CBD. All three subjects who have continued on CBD reported their QoL at last visit being “a lot better” since starting CBD” as assessed by use of a Likert scale of –3 to +3 (“A lot worse” to “A lot better”) was used to evaluate QoL; no numerical data reported.
Quality of life (caregiver)	—
Sleep	• Sleep difficulties were reported for 1 child (20%)
Status epilepticus	—
Death	—
Gastrointestinal adverse events	• Vomiting was reported for two children (40%) • Diarrhea was reported for one child (20%)
Visits to the ED	—
Note: CBD = cannabidiol, ED = emergency department, QoL = quality of life. *At least a 50% reduction in total seizures from baseline.	

(f) Febrile Infection-Related Epilepsy syndrome (acute and chronic stage)

One prospective cohort study (Gofshteyn 2017⁵) involved seven children with FIRES in the acute (2) and chronic (5) phases from five centres in the US who received cannabidiol (up to 25 mg/kg/d). The average age was 7 years at the onset of status epilepticus (range 4 to 8.5 years), and participants had refractory seizures from 2.7 to 177.8 weeks (median 12.8 wk). Time of onset to cannabidiol administration was 19 and 33 days for the two children in the acute phase and 3–87 months for those in the chronic phase (median 3 months). Participants were taking between four and nine concomitant antiepileptic drugs. Data are reported for up to 48 weeks of cannabidiol treatment. No outcome data were available for quality of life (caregiver or child), sleep, or visits to the emergency department.

Outcome	Finding
Seizure freedom	• Of children in the chronic phase (n = 5), one had a 100% reduction in seizures after 4 wk of treatment. After 48 wk, this child had a 60% reduction in seizures • Of children treated in the acute phase (n = 2), one had a 100% reduction in all seizure types at 4 wk. This patient's seizures subsequently recurred; however, status epilepticus did not
Seizure frequency	• Of children treated in the acute phase (2), one had cessation of the status epilepticus • Among children treated in the chronic phase (5), the mean change from baseline after 4 wk of CBD treatment was -90.9% (+/- 18.9%). After 48 wk, the change as -65.3% (+/- 29.3%); tonic-clonic seizures were reduced by 75% +/- 35.3 at wk 4 and 73% (+/-38.1%) at wk 48
Treatment response*	• Of children who received treatment in the acute phase (2), one had ≥ 50% reduction in seizures at wk 4 • Of children who received treatment in the chronic phase (5), all had ≥ 50% reduction in seizures at wk 4 and 48
Quality of life (child)	—
Quality of life (caregivers)	—
Sleep	—
Status epilepticus	• Of the 2 patients treated in the acute phase, one had cessation of status epileptics. • No new status epilepticus events were reported for any participant (n = 7)
Death	• One child treated in the acute phase died of multi-organ failure, thought to be related to prolonged exposure to isoflurane; before death, this patient had a reduction in seizures, with all seizures after treatment reported as being stimulus induced
Gastrointestinal adverse events	• Nausea/vomiting was reported for one child; study authors deemed this likely unrelated to CBD treatment
Visits to the ED	—
Note: CBD = cannabidiol, ED = emergency department. *At least a 50% reduction in total seizures from baseline.	

Appendix 19: Trial registration records that met the eligibility criteria* (k = 33)

NCT number	Title	Sponsor	Population	Eligible ages, yr	Treatments	Design	Recruitment status	Primary completion date (estimated or actual)	Country
NCT02224573	GWPCARE5 - An open label extension study of cannabidiol (GWP42003-P) in children and young adults With Dravet or Lennox-Gastaut syndromes	GW Research Ltd	Dravet Syndrome, Lennox-Gastaut Syndrome	≥ 2 yr	CBD (GWP42003-P)	Single group interventional	Enrolling by invitation	June 2019	NR
NCT02224703	GWPCARE2 A study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome	GW Research Ltd	Dravet Syndrome	2–18 yr	CBD (GWP42003-P), high dose, low dose or placebo	Randomized	Recruiting	May 2017	Multi-national
NCT02229032	Genetic analysis between Charlotte's Web responders versus non-responders in a Dravet population	University of Colorado, Denver	Dravet Syndrome	1–50 yr	Charlotte's Web strain of medical marijuana	Cross-sectional	Completed	July 2017	US
NCT02286986	Cannabidiol (CBD) to 27 patients (Aged 2 Years - 19 Years) with drug resistant epilepsy	University of Utah	Treatment-resistant epilepsy	2–19 yr	CBD (GWP42003-P)	Single group interventional	Active, not recruiting	June 2018	US
NCT02318602	Cannabidiol oral solution as an adjunctive treatment for treatment-resistant seizure disorder	INSYS Therapeutics Inc	Treatment-resistant epilepsy, including Lennox-Gastaut and Dravet syndrome	1–30	CBD oral solution	Single group interventional	Completed	June 2017	US
NCT02332655	Cannabidiol expanded access study in medically refractory Sturge-Weber syndrome	GW Pharmaceutica ls Ltd.	Sturge-Weber Syndrome	1 mo–45 yr	CBD (Epidiolex)	Single group interventional	Active, not recruiting	June 2019	US
NCT02397863	Epidiolex and drug resistant epilepsy in children	Augusta University	Treatment-resistant epilepsy	1–18 yr	CBD (Epidiolex)	Single group interventional	Available	NR (last update Apr 2015)	US
NCT02447198	Cannabidiol (CBD) and pediatric epilepsy	University of Colorado, Denver	Epilepsy	1 mo–17 yr	CBD	Single group interventional	Recruiting	July 2018	US
NCT02461706	Treatment of drug resistant epilepsy	University of Florida	Treatment-resistant epilepsy	"children"	CBD 25 mg/kg/d	Single group interventional	Available	NR (last update March 2018)	US
NCT02523183	The use of medicinal cannabinoids as adjunctive treatment for medically refractory epilepsy	University of Colorado, Denver	Treatment-resistant epilepsy	1 mo–20 yr	Medical cannabis	Single group interventional	Recruiting	October 2018	US
NCT02544750	An open-label extension trial of cannabidiol (GWP42003-P, CBD) for seizures in Tuberous Sclerosis Complex	GW Research Ltd	Tuberous Sclerosis Complex	1–65 yr	CBD (GWP42003-P), up to 50 mg/kg/d	Open-label extension	Enrolling by invitation	September 2020	US

NCT number	Title	Sponsor	Population	Eligible ages, yr	Treatments	Design	Recruitment status	Primary completion date (estimated or actual)	Country
	(GWPCARE6)								
NCT02544763	A randomized controlled trial of cannabidiol (GWP42003-P, CBD) for seizures in Tuberous Sclerosis Complex (GWPCARE6)	GW Research Ltd	Tuberous Sclerosis Complex	1–65 yr	CBD (GWP42003-P) 25 mg/kg/d, 50 mg/kg/d or placebo	Randomized	Recruiting	September 2018	US
NCT02551731	Cannabidiol oral solution for treatment of refractory Infantile Spasms	INSYS Therapeutics Inc	Treatment-resistant Spasms, Infantile	6–36 mo	CBD oral solution, 20-40 mg/kg/d	Single group interventional	Terminated	September 2016	US
NCT02556008	Cannabidiol for pediatric epilepsy (compassionate use)	University of California, Los Angeles	Refractory Childhood Epilepsy	NR	Epidiolex, up to 25 mg/kg/d	Single group interventional	No longer available	NR (last updated May 2017)	US
NCT02607891	A study to investigate possible drug-drug interactions between stiripentol or valproate and cannabidiol in patients with epilepsy	GW Research Ltd	Epilepsy	16–55 yr	CBD (Epidiolex; GWP42003-P), up to 20 mg/kg/d, v. placebo	Randomized	Recruiting	August 2018	Multi-national
NCT02607904	An open-label extension trial to investigate possible drug-drug interactions between stiripentol or valproate and cannabidiol in patients with epilepsy	GW Research Ltd	Epilepsy	16–55 yr	CBD (GWP42003-P), up to 20 mg/kg/d	Open-label extension	Enrolling by invitation	August 2019	NR
NCT02660255	Safety and tolerability of cannabidiol in subjects with drug resistant epilepsy	GW Pharmaceutica ls Ltd.	Treatment-resistant epilepsy	1–60 yr	CBD (Epidiolex)	Single group interventional	Available	NR (last updated May 2017)	NR
NCT02700412	University of Alabama at Birmingham (UAB) adult CBD program	University of Alabama at Birmingham	Treatment-resistant epilepsy	15–99	CBD (Epidiolex), up to 50 mg/kg/day	Single group interventional	Recruiting	April 2019	US
NCT02783092	A double-blind trial to evaluate efficacy and safety of cannabidiol as an add-on therapy for treatment in refractory epilepsy	Prati Donaduzzi & Cia Ltda	Treatment-resistant epilepsy	2–18	Oral CBD solution, up to 25 mg/kg/d, v. placebo	Randomized	Not yet recruiting	August 2019	Brazil
NCT02815540	The effects of cannabidiol (CBD) on electrical and autonomic cardiac function in children with severe epilepsy	Gillette Children's Specialty Healthcare	Lennox-Gastaut, Dravet Syndrome	2–30 yr	CBD	Single group interventional	Not yet recruiting	June 2017	US
NCT02910297	The pharmacokinetics of cannabidiol (CBD) and its effects in children with severe epilepsy	Gillette Children's Specialty Healthcare	Lennox-Gastaut, Dravet Syndrome	2–30 yr	CBD	Single group interventional	Withdrawn	December 2017	US
NCT02953548	Trial of cannabidiol (CBD; GWP42003-P)	GW Research	Infantile Spasms	1–24 mo	CBD (GWP42003-P), up to 40	Single group	Recruiting	December 2017	Multi-

NCT number	Title	Sponsor	Population	Eligible ages, yr	Treatments	Design	Recruitment status	Primary completion date (estimated or actual)	Country
	for Infantile Spasms (GWPCARE7)	Ltd			mg/kg/d	interventional			national
NCT02954887	Phase 3 trial of cannabidiol (CBD; GWP42003-P) for Infantile Spasms: Open-label extension phase (GWPCARE7)	GW Research Ltd	Infantile Spasms	1–24 mo	CBD (GWP42003-P)	Single group interventional	Enrolling by invitation	December 2018	Multi-national
NCT02983695	Cannabinoid therapy for pediatric epilepsy	Tilray	Dravet syndrome	1–18 yr	CBD-rich whole plant extract (TIL-TC150; contains THC and CBD)	Single group interventional	Active, not recruiting	September 2018	Canada
NCT02987114	A study to evaluate the safety, tolerability and efficacy of oral administration of PTL101 (cannabidiol) as an adjunctive treatment for pediatric intractable epilepsy	PhytoTech Therapeutics, Ltd.	Treatment-resistant epilepsy	2–15 yr	CBD (PLT101), up to 25 mg/kg/d	Single group interventional	Recruiting	December 2017	Israel
NCT03014440	Study of cannabidiol for drug-resistant epilepsies	University of Pittsburgh	Treatment-resistant epilepsy	1–20 yr	CBD (Epidiolex)	Single group interventional	No longer available	NR (last updated April 2017)	NR
NCT03024827	Cannabidiol in children with refractory epileptic encephalopathy	University of Saskatchewan	Treatment-resistant epilepsy	1–10 yr	CanniMed (CBD 1:THC 20)	Single group interventional	Recruiting	September 2018	Canada
NCT03196934	Expanded use of cannabidiol oral solution	MultiCare Health System Research Institute	Treatment-resistant epilepsy	1–18 yr	CBD oral solution	Single group interventional	Available	NR (last updated June 2017)	NR
NCT03336242	Cannabidiol oral solution in pediatric participants with treatment-resistant childhood absence seizures	INSYS Therapeutics Inc	Childhood Absence Epilepsy	3–17 yr	CBD oral solution: • 20 mg/kg/d • 30 mg/kg/d • 40 mg/kg/d	Non-randomized, parallel group interventional	Recruiting	November 2018	US
NCT03355300	Long-term safety of pharmaceutical grade synthetic cannabidiol oral solution in pediatric participants with treatment-resistant childhood absence seizures	INSYS Therapeutics Inc	Childhood Absence epilepsy	3–17 yr	CBD oral Solution	Single group interventional	Recruiting	November 2019	US
NCT03467113	A study to assess the safety and tolerability of ZX008 in children and young adults with DS or LGS currently taking CBD	Zogenix Inc	LGS, DS	2–18 yr	CBD + fenfluramine	Single group interventional	Enrolling by invitation	February 2019	US
NCT03421496	A study to assess the efficacy, safety, and tolerability of cannabidiol oral solution with vigabatrin as initial therapy in participants with infantile spasms	INSYS Therapeutics Inc	Infantile spasms	1–24 mo	Oral CBD (40 mg/kg/d) + vigabatrin v. placebo + vigabatrin	Randomized	Recruiting	October 2018	US
ACTRN1261800516280	Open label study to assess the safety and efficacy of ZYN002 administered as a transdermal gel to children and	Zynerba Pharmaceutica Is Pty Ltd	Developmental and epileptic encephalopathy	3–18 yr	Transdermal CBD gel, 250 mg/d (weight < 25 kg) or 500 mg/d (>25 kg)	Single group interventional	Not yet recruiting	May 2019	New Zealand

NCT number	Title	Sponsor	Population	Eligible ages, yr	Treatments	Design	Recruitment status	Primary completion date (estimated or actual)	Country
	adolescents (3 to <18 years) with developmental and epileptic encephalopathy (BELIEVE 1).								
Note: CBD = cannabidiol, NR = not reported, THC = tetrahydrocannabinol *ClinicalTrials.gov registration records that did not correspond to published eligible studies and that did not report study results as of April 28, 2018.									

Appendix 20: Conference abstracts that met the eligibility criteria (not matched to an included published study, $k = 14$)

Author, year	Population; study design	Treatment (no. in group)	Finding
Devinsky 2017 ²⁶	Drug-resistant epilepsy, aged 13–19 yr, mean 10 yr, 50% male; open-label extension of NCT02091375 or NCT02224703	CBD, 100 ng/ml, mean dose 21 mg/kg/d (264) Duration: mean 36 wk (range 1d–73 wk)	• “There were 2 deaths; neither were deemed treatment related” • “In patients with baseline data, median monthly convulsive seizures and total seizures assessed over five 12-week periods decreased by (min-max) 38%-57% and 40%-60% respectively.”
Garza 2017 ²⁷	Lennox-Gastaut syndrome taking at least 3 AEDs, age 10.9 (+/- 6) yr; single group, prospective cohort	CBD (RSHO 5000), up to 5–7 mg/kg Duration: at least 6 mo	• “A significant reduction in the frequency of seizures ($\geq 50\%$) was obtained in 86% of the cases (33/38) and 55% of the cases achieved an overall reduction of over 75% (21/38).” • “A complete control of the events for at least 4 months was achieved in 5 cases (13%)...”
Preto 2017 ²⁸	Drug-resistant epilepsy, mean age 12.3 yr (range 4–23 yr); design unclear	CBD, 1.2 mg to 10 mg/kg/d (10) Duration: 2–24 mo (mean 13.4)	• “Nine of the 10 patients showed an average decrease of 63% in the number of seizures (ranging from a 30% to a 90% decrease).” • “No significant adverse effects were observed, except for sleepiness and fatigability.”
Szaflarski 2017 ²⁹	Drug-resistant epilepsy, failure of at least 4 AEDs; open-label, single-group prospective cohort	CBD up to 50 mg/kg/d (115, inc. 59 children)	• Seizure frequency: “For all patients, the estimated coefficient of CBD dose is significant (t value=-2.44, $p < 0.05$); this was not significant for adults (t value=-1.82, $p > 0.05$) or children (t value=-1.68, $p > 0.05$), separately.” • “For every unit increase in CBD dose there is a decrease of seizure severity and frequency. There is consistency in subgroups though seizure frequency decreases are significant only when data from children and adults are combined. Decreases in seizure frequency and severity occur in parallel”
Vezyroglou 2017 ³⁰	Drug-resistant epilepsy, aged 2–19 yr (mean 10 yr); single-arm, prospective cohort†	CBD oil, 2 mg/kg/day in 2 divided doses, increased to 16 mg/kg/day by 2 mg/kg/wk, further up-titration as tolerated individually (24; 23 included in analysis) Duration: NR (at least 8 wk)	• >50% seizure reduction reported in 11 participants (47.8%) • Diarrhea (n = 5, 21.7%) • Improved sleep (n = 2, 9.5%) • “One patient died of pneumonia unrelated to the drug.” • “One patient was excluded, who only received 5 days of CBD add-on treatment as part of his acute treatment for ultimately fatal refractory status epilepticus (presumed FIRES).”
Vezyroglou 2017 ³¹	Drug-resistant epilepsy, aged 2–19 yr, mean 10 yr; open-label, single-arm, prospective cohort†	CBD, target dose 16 mg/kg/d, further up-titration as tolerated, mean dose 20 (range 6–45) mg/kg/d (24; 20 included in analysis)	• “One received only 5 days of CBD treatment as part of acute treatment for ultimately fatal status epilepticus (presumed FIRES)” • “One patient died of pneumonia during the trial unrelated to CBD.” • “Eight (40%) reported >50% seizure reduction, while 12 (60%) showed little change.” • “Diarrhea (n = 4, 20%)”

Kuester 2016 ³²	Drug-resistant epilepsy (mean 11.5 yr (range: 1–37 yr; 9 children); retrospective chart review	Oral cannabis extracts, dose NR (9) Duration: mean 14 mo	• “Most patients had significant improvement in seizure frequency and one evolved seizure-free.” • “Most parents/patients reported improvement in ... sleep... as well as in QOL with cannabis.”
Linder 2016 ³³	Pediatric patients with intractable epilepsy; prospective cohort	Vaporized medical cannabis, dose NR (24) Duration NR	• “Sixteen responded (two substantially, eight mildly and six shortened seizure clusters) while six had no response whatsoever”
Abati 2015 ³⁴	Drug-resistant epilepsy and infantile or epileptic spasms, 2–16 years (average 9 years); prospective cohort	Oral CBD, up to 25 mg/kg/day (9) Duration: 12 mo	• “Overall there was a response rate [$\geq$ 50% reduction from baseline] to CBD of 37.5, 43, 50 and 30% at 3, 6, 9, 12 months.” • “Three patients were seizure free after two months of treatment.”
Morgan 2015 ³⁵	Drug-resistant epilepsy (mean age 12.3 yr); prospective cohort	Oral CBD, dose NR (15) Duration: 3 mo	• “School-related quality of life at interim evaluation had improved (... p < 0.05).”
Schimpfoss 2015 ³⁶	Drug-resistant epilepsy (28 of 31 patients), aged 0.5–21 yr (mean 9 yr); retrospective chart review	In-patient THC treatment, dose NR (31) Duration: NR	• “An effect on epileptic seizures could not be noticed.” • Improvements in sleep disorders were noted for 2 participants (n = 4)
Wilson 2015 ³⁷	Children and young adults with drug-resistant epilepsy; open-label, prospective cohort	Oral CBD, 2–25 mg/kg/d (25) Duration: 3 mo	• “Total number of seizures were reduced by a median of 38% at 3 months. Eighteen patients (72% of participants) experienced fewer seizures with an average frequency reduction of 50%.” • “Seven patients reduced dose due to side effects; one discontinued due to diarrhea and lack of efficacy, another for persistent nausea/vomiting.”
Gedde 2014 ³⁸	Children with drug-resistant epilepsy; cross-sectional	Charlotte's Web (CW Realm Oil, or Realm Oil), >16:1 ratio of CBD to other cannabinoids, average therapeutic dose of CBD 4–12 mg/kg/d, in 2 or 3 divided doses (11) Duration: at least 3 mo	• “Eleven of 11 patients (100%) reported reduction in weekly frequency of motor type seizures (generalized tonic-clonic plus tonic, myoclonic and atonic seizures). Of the 11, 8 reported 98-100% reduction, 1 reported 75% reduction, and 2 reported 20-45% reduction in weekly seizures at the end of three months.” • “At three months, 5 of the 11 patients (50%) were seizure-free. Of the 2 patients who have received Realm Oil for more than one year, both have continued to enjoy the seizure reduction attained after 3 months of Realm Oil treatment.
Lodi 2013 ³⁹	Drug-resistant epilepsy; design unclear	“High levels of essential fatty acid (omega 3 and 6) Hemp oil, without significant levels of TCH (0.049y/ml), at a medium dose of 10 ml and 20 ml” (16) Duration: NR	• “One patient became seizure free; seizure frequency was reduced of 50% in two patients.”
Note: AED = antiepileptic drug, CBD = cannabidiol, FIRES = Febrile Infection-Related Epilepsy syndrome, NR = not reported, QOL = quality of life, THC = tetrahydrocannabinol. *Records were matched to included published studies by study name, ClinicalTrials.gov record number, study authors, or description of the study population and results. †Abstracts likely correspond to the same study.			

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Section 3.3

Cannabis-based products for pediatric epilepsy:

An updated systematic review

SECTION OVERVIEW

This section presents a manuscript describing the findings of the updated living systematic review, which incorporates evidence available up to May 2019. Following the protocol described in **Section 3.1**, evidence from studies identified in the first and second review updates (October 2018, May 2019, respectively) was combined with that from the baseline review (**Section 3.2**), in order to produce an up-to-date comprehensive overview of the literature. Note: a summary of the findings of the first review update (October 2018) is available in Appendix D.

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Supporting material

Supporting file: PRISMA checklist

Appendix 1: Literature search

Appendix 2: Included and excluded records

Appendix 3: Characteristics of the included studies

Appendix 4: Characteristics of participant in the included studies

Appendix 5: Risk of bias assessment

Appendix 6: GRADE assessment, by outcome

Appendix 7: Summary of outcomes by epilepsy syndrome

Appendix 8: Evidence summary — Seizure freedom

Appendix 9: Evidence summary — Seizure frequency

Appendix 10: Evidence summary — Quality of life (children)

Appendix 11: Evidence summary — Sleep

Appendix 12: Evidence summary — Status epilepticus

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Appendix 14: Evidence summary — Gastrointestinal adverse events

Appendix 15: Evidence summary — Visits to the emergency room

Appendix 16: Trial registration records that met the eligibility criteria

Author roles and contributions

JE, TC, DC, BP, CA, AR, BM and GW designed the study; CA and AR provided patient and family perspectives; BM provided clinical input. BS developed and executed the search strategy. JE and DD selected studies for inclusion and assessed risk of bias. JE extracted study data, which were checked by DD. JE and VS assessed the certainty of the evidence using GRADE criteria. JE analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors provided comments on the draft and approved the version of the manuscript submitted for publication.

RELATED THESIS APPENDICES

Appendix B: Abstracts accepted for poster presentation. Findings from this study were presented at the Canadian League Against Epilepsy 2019 Annual Scientific Meeting.

Elliott J, DeJean D, Clifford T, Coyle C, Potter B, Skidmore S, Alexander C, Repetski A, McCoy B, Wells GA. Cannabis-based products for the treatment of pediatric epilepsy: A systematic review. Canadian League Against Epilepsy 2019 Annual Scientific Meeting, Winnipeg, Manitoba (September 2019).

Appendix D: Living systematic review— Update 1: Cannabis-based products for pediatric epilepsy.

Appendix D presents the results of the first update of the living systematic review described in

Section 3.2. The update was performed in October 2018, six months after the baseline review. The data contained in this appendix were subsequently included in the manuscript presented in **Section 3.3**.

Appendix G: Published manuscripts. The PDF of the published manuscript is presented in Appendix G.

Cannabis-based products for pediatric epilepsy: An updated systematic review

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Keywords: paediatric drug-resistant epilepsy, cannabidiol, seizure, efficacy, safety, living systematic review

Abbreviations: CBD = cannabidiol, LSR = living systematic review; NRS = non-randomized study; RCT = randomized controlled trial; QoL = quality of life, SUDEP = sudden unexpected death in epilepsy; ER = emergency room; ROB = risk of bias; RR = relative risk; RD = risk difference, MD = mean difference, CI = confidence interval

ABSTRACT

Purpose: To provide an up-to-date summary of the benefits and harms of cannabis-based products for epilepsy in children.

Methods: We updated our earlier systematic review, by searching for studies published up to May 2019. We included randomized controlled trials (RCTs) and non-randomized studies (NRS) involving cannabis-based products administered to children with epilepsy. Outcomes were seizure freedom, seizure frequency, quality of life, sleep, status epilepticus, death, gastrointestinal adverse events, and emergency room visits.

Results: Thirty-five studies, including four RCTs, have assessed the benefits and harms of cannabis-based products in pediatric epilepsy (12 since April 2018). All involved cannabis-based products as adjunctive treatment, and most involved cannabidiol. In the RCTs, there was no statistically significant difference between cannabidiol and placebo for seizure freedom (relative risk 6.77, 95% confidence interval [CI] 0.36 to 128.38), quality of life (mean difference [MD] 0.6, 95%CI –2.6 to 3.9), or sleep disruption (MD –0.3, 95%CI –0.8 to 0.2). Data from both RCTs and NRS suggest that cannabidiol reduces seizure frequency and increases treatment response; however, there is an increased risk of gastrointestinal adverse events.

Conclusion: Newly available evidence supports earlier findings that cannabidiol probably reduces the frequency of seizures among children with drug-resistant epilepsy.

PROSPERO: CRD42018084755

Competing interests: Bláthnaid McCoy is principal investigator in a study of cannabinoids for Dravet syndrome. Alexander Repetski is director of communications at a licensed cannabis producer. Deirdre DeJean is an employee of CADTH; this work was unrelated to her employment and was not funded by CADTH. The remaining authors have no conflicts of interest.

INTRODUCTION

Interest in cannabis for treatment of pediatric epilepsy has grown over the last decade,¹ and the number of studies assessing its benefits and harms has grown in parallel. In 2018, we initiated a living systematic review (LSR) of cannabis-based products for pediatric epilepsy.² LSRs search for newly available studies at *a priori*-defined intervals, allowing evidence to be incorporated into the review shortly after it becomes available.³ In the first iteration (“baseline review”),² we identified 23 studies, the findings of which supported a beneficial role for cannabis-based products, particularly cannabidiol (CBD), in reducing seizures among children with drug-resistant epilepsy. At that time, we also identified 33 ongoing studies, signalling that the evidence base would continue to evolve.

In this updated review, we incorporated studies published in the year following the baseline review, thus providing an up-to-date overview of the evidence base.

METHODS

The protocol⁴ and baseline review² have been published and PRISMA guidelines were followed.⁵ The baseline review encompassed studies published up to April 2018; the present update is current to May 9, 2019. Briefly, we searched Ovid MEDLINE, Embase, PsycINFO, and the Cochrane Library (Appendix 1), as well as ClinicalTrials.gov and ICTRP Search Portal. Two independent reviewers (J.E., D.D.) selected randomized controlled trials (RCTs) and non-randomized studies (NRS) involving children with epilepsy who were administered a cannabis-based product, compared to pharmacologic treatment (i.e., antiepileptic drugs), non-pharmacologic treatment (e.g., diet therapy, vagus nerve stimulation), placebo, usual care, or no treatment. The primary outcome was seizure freedom; secondary outcomes were seizure frequency (total, tonic-clonic, $\geq 50\%$ reduction from baseline), quality of life (QoL), sleep, status epilepticus, death, gastrointestinal adverse events (vomiting, diarrhea), and emergency room (ER) visits. Risk of bias (RoB) and certainty of the evidence was assessed (GRADE criteria)⁶ Data from RCTs were pooled by random-effects meta-analyses and are reported as relative risk (RR), risk difference (RD), mean

difference (MDs), or median difference with 95% confidence intervals (CIs). Data from NRS are reported as the percentage of participants who experienced an outcome. Data were not pooled if there was substantial clinical or statistical heterogeneity (i.e., $I^2 > 75\%$). Data from the longest duration of follow-up were analyzed.

RESULTS

Thirty-five studies have assessed the benefits and harms of cannabis-based treatments in children with epilepsy (4 RCTs^{7–10}; 31 NRS^{11,12,21–30,13,31–40,14,41–46,15–20}; Figure 1, Appendix 2). This reflects a 52% increase since April 2018. Most studies involved purified CBD products (63%); of those, 77% involved Epidiolex (Greenwich Biosciences; Appendix 3). Few studies involved products containing both CBD and delta-9-tetrahydrocannabinol (THC) (e.g., CBD:THC cannabis oil),^{11,28,37} while others involved products from illicit cannabis suppliers,¹⁹ home-made extracts,⁴⁶ or “artisanal” products.²⁰ All studies involved cannabis added to an established regimen of antiepileptic therapies; no studies involved first-line treatment. Treatment duration ranged from 10 days to 146 weeks (RCTs up to 14 wk). All RCTs involved children with Dravet or Lennox-Gastaut syndrome (LGS), while NRS enrolled a wider range of drug-resistant epilepsy syndromes and participant characteristics (Appendix 4). All RCTs were considered low RoB; NRS were at high RoB, owing primarily to lack of a control group and unblinded outcome assessment (Appendix 6). In the following sections, data are summarized for all participants; data pertaining specifically to Dravet and LGS are presented in Appendix 7.

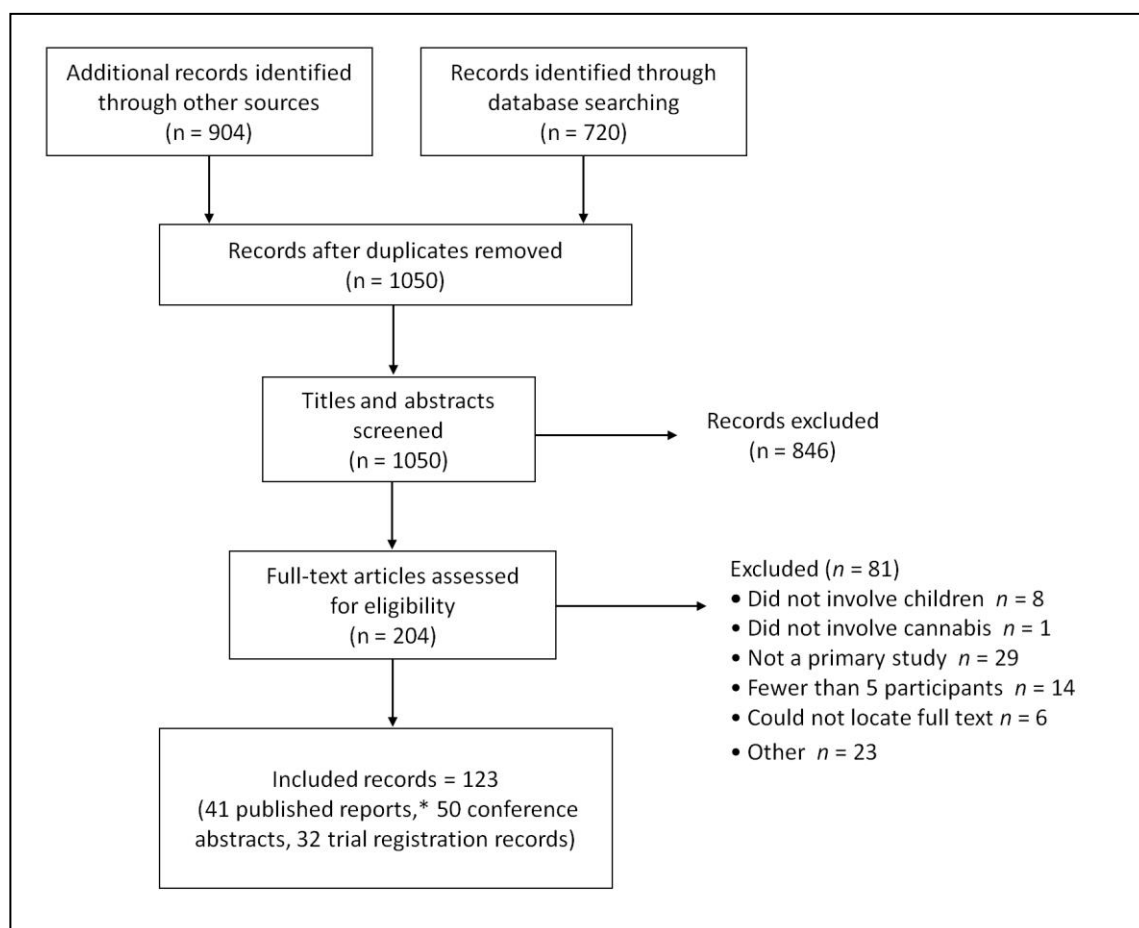


Figure 1: PRISMA flow diagram showing selection of studies. *Includes 35 unique studies (4 randomized controlled trials, 31 non-randomized studies) available as published studies or as clinical trial records with available data.

Seizure freedom

Twenty-three studies (one RCT,⁷ 22 NRS^{11,13,28,31,33,35–39,43,44,15,45,46,17,20,21,24–27}) have reported seizure freedom with cannabis treatment; an additional 3 studies reported that no children became seizure free (Table 1, Appendix 8). Among children with Dravet syndrome (61) who received CBD in one 14-wk RCT,⁷ 5% became seizure free, compared with none in the placebo group (n = 59; RD 5%, 95%CI –1% to 11%; low certainty). Among NRS, 8% (95%CI 5% to 10%) became seizure free with cannabis treatment (duration: 14 d to 53 mo; very low certainty).

Table 1: Evidence summary*

Outcome	Randomized controlled trials					Non-randomized studies				
	No. of studies	No. of participants	Effect estimate (95%CI), cannabidiol v. placebo	I ²	GRADE assessment	No. of studies	No. of participants	Proportion of those exposed to a cannabis-based product (95%CI) [†]	I ²	GRADE assessment
Primary outcome										
Seizure freedom	1	120	RR 6.77 (0.36 to 128.38) RD 0.05 (−0.01 to 0.11)	NA	Low	23	1488	8% (5% to 10%)	70%	Very low
Secondary outcomes										
Total seizure frequency	3	516	Median reduction in monthly seizures v. placebo: −19.8% (−27.0% to −12.6%)	0%	Moderate	11	1914	NA**	NA	Very low
Tonic-clonic seizure frequency	3	321	Median reduction in monthly seizures v. placebo: −27.5% (−38.7% to −16.3%)	0%	Moderate	2	95	NA**	NA	Very low
Treatment response‡	1	171	RR 1.76 (1.07 to 2.88) RD 0.16 (0.03 to 0.29)	NA	Moderate	18	1164	Prospective cohorts: 48% (41% to 56%)	71%	Very low
Quality of life: Child	3	516	Pooled mean difference 0.6 (−2.6 to 3.9)¶	0%	Moderate	3	72	NA** (each study reported QoL improvement after treatment)	NA	Very low
Sleep disruption	3	516	Pooled mean difference: −0.3 (−0.8 to 0.2)§	0%	Moderate	0	NA	NA	NA	NA
Improved sleep	0	NA	NA	NA	NA	6	381	NA††	NA	Very low
Impaired sleep	1	171	Sleep apnea reported for 1 participant (1.2%) in the CBD group; none in the placebo group	NA	NA	6	166	3% (1% to 6%)	0%	Very low
Status epilepticus	3	516	RR 1.39 (0.55 to 3.47) RD 0.01 (−0.02 to 0.03)	0%	Low	8	1601	7% (4% to 9%)	74%	Very low
Death	1	171	1 death reported in the CBD group (n = 86); zero deaths in the placebo group (n= 85)	NA	Low	9	1623	1% (1% to 2%)	0%	Very low
Gastrointestinal AEs	4	550	RR 1.54 (0.92 to 2.58)	52%	Low	19	2079	NA††	NA	Very low
Vomiting	4	550	RR 1.00 (0.51 to 1.96)	34%		14	1662	NA††	NA	
Diarrhea	3	516	RR 2.25 (1.38 to 3.68)	0%		14	1743	NA††	NA	
ER visits	0	NA	NA	NA	NA	2	64	NA**	NA	Very low

Note: AE = adverse event, CBD = cannabidiol, CI = confidence interval, ER = emergency room, NA = not applicable, QoL = quality of life, RD = risk difference, RR = relative risk.

*Adapted from Elliott et al. 2019.

†Unless otherwise stated.

‡≥50% reduction in seizure frequency relative to baseline period.

¶Quality of Life in Childhood Epilepsy scale.

§Assessed by use of the Sleep Disruption Rating Scale (negative value favours CBD).

**Data reported in a variety of ways precluded pooling; see Appendices for full details.

††High heterogeneity precluded pooling.

Seizure frequency

Fourteen studies (three RCTs,^{7,9,10} 11 NRS^{13,15,44,17,19,26,32,36,38,39,43}) assessed seizure frequency (Appendix 9). Total monthly seizures were reduced by CBD compared to placebo in the RCTs (median reduction 19.8%, 95%CI 27.0% to 12.6%; duration: 14 wk; moderate certainty), as well as by cannabis-based products in the NRS (30% to 90%; duration: 11 d to 96 wk duration; very low certainty). Data from NRS suggest that the effects are maintained through at least 48 weeks of treatment in some children.^{13,15,17,43}

Quality of life

Six studies (three RCTs,^{7,9,10} three NRS^{23,28,31}) assessed the impact of cannabis-based products on childhood QoL (Appendix 10); no studies have assessed the effect on caregivers. Evidence from three 14-wk RCTs involving children with Dravet and LGS,^{7,9,10} suggests no statistically significant effect of CBD on QoL (MD 0.6, 95%CI –2.6 to 3.9; moderate certainty); however, data from NRS^{23,28,31} suggest an improvement relative to before cannabis treatment (very low certainty).

Sleep

Fourteen studies (three RCTs,^{7,9,10} 11 NRS^{12,21,46,22,25,27,31,32,35,36,39}) reported changes in sleep with cannabis-based products (Appendix 11). Among children with Dravet or LGS in three 14-wk RCTs,^{7,9,10} there was no statistically significant difference in sleep between CBD and placebo (MD –0.3, 95%CI –0.8 to 0.2; moderate certainty). Improved sleep was reported in six NRS,^{12,22,25,27,35,46} with a higher proportion reported in cross-sectional studies^{22,25,35,46} (74%, 95%CI 54% to 94%) compared with retrospective cohort studies (8%, 95%CI 4% to 11%) (duration: 2 wk to 57 mo; very low certainty). Impaired sleep was reported in six NRS,^{21,31,32,36,39,46} affecting 3% (95%CI 1% to 6%) of children who received a cannabis-based product (duration: 10 d to 53 mo; very low certainty).

Status epilepticus

Status epilepticus was reported in eleven studies (three RCTs,^{7,9,10} eight NRS^{13,17,21,24,37,42–44}) among children who received a cannabis-based product (Appendix 12). In the RCTs, there was no

statistically significant difference in the frequency of status epilepticus among children with Dravet or LGS who received CBD or placebo for 14 weeks^{7,9,10} (RR 1.39, 95%CI 0.55 to 3.47; low certainty). Among NRS, 7% (95%CI 4% to 9%) of children who received a cannabis-based product experienced status epilepticus, with higher rates reported among children with Dravet⁴³ or LGS¹³ who received more than 20 mg/kg/d of CBD compared to 20 mg/kg/d (median duration: 263, 274 d).

Death

Twenty-six deaths, including seven owing to sudden unexpected death in epilepsy, have been reported among 1713 children who received a cannabis-based treatment (Appendix 12) in 10 studies (one RCT,¹⁰ nine NRS^{13,17,20,24,27,28,38,43,44}). Most deaths were reported as having been unrelated to treatment.

Gastrointestinal adverse events

Gastrointestinal adverse events were commonly reported among children who received a cannabis-based product (four RCTs,^{7–10} 19 NRS^{11,12,36–38,41–46,13,17,21,25,28,31,32,35}; Appendix 14). Risk of diarrhea was higher among those who received CBD compared to placebo (RR 2.25, 95%CI 1.38 to 3.68; low certainty) despite no overall significant difference in gastrointestinal adverse events. In the NRS, gastrointestinal adverse events have been reported for 2%–60% of participants who received a cannabis-based product (vomiting: 3%–40%; diarrhea: 2%–35%), with high heterogeneity between studies.

ER visits

Two NRS have assessed ER visits (Appendix 15).^{21,45} Chen and colleagues⁴⁵ reported no statistically significant difference in the monthly rate of visits per child before or during cannabis treatment (12-wk treatment). Sands and colleagues²¹ reported that, of children who had an ER visit during the 6-month baseline period, all had fewer visits during the treatment period (4–53 mo).

DISCUSSION

This updated review incorporating studies published up to May 2019, reflecting a 52% increase in the evidence base in the previous year. This is an active area of research, and clinicians require up-to-date evidence summaries on which to base treatment decisions. The findings of newly available studies were consistent with earlier studies, although the certainty of evidence did not change for any outcome, and no new RCTs were published during the update period. We identified an additional 32 clinical studies that have yet to report results (Appendix 16), including six RCTs, suggesting that further evidence will be available for future updates of this LSR. Because the certainty of the evidence is currently low for most outcomes, additional evidence may change the effect estimates and give clinicians more confidence in the effects of cannabis-based treatments in this population. Importantly, ongoing studies may provide data for longer treatment durations, helping us to better understand the long-term effects of cannabis-based products.

Limitations

First, most available evidence is from NRS, all of which are at risk of important sources of bias, primarily related to study design (e.g., lack of a comparison group, unblinded outcome assessment), and the certainty of the evidence from such studies is very low. Second, most studies have involved Epidiolex (purified pharmaceutical-grade CBD), and may not be generalizable to other cannabis-based products (e.g. CBD-THC cannabis oil). Third, most studies have involved participants with Dravet or LGS, and less is known about the effects on other epilepsy syndromes. Fourth, the treatment duration of the included studies was variable, ranging from 10 days to 146 weeks, with evidence from RCTs available only up to 14 weeks of treatment. The long-term effects of these products have not been evaluated in long-term randomized studies.

Conclusion

Newly available studies support CBD as an effective treatment option for reducing the frequency of seizures among children with drug-resistant epilepsy. Products containing both CBD and THC may

also be effective; however, most available evidence pertains to pharmaceutical-grade CBD alone. This is an active area of research, and future updates will include additional evidence as it becomes available.

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SUPPORTING INFORMATION

Supplemental File: Elliott et al (2019). Cannabis-based products for pediatric epilepsy: An updated systematic review. Contains Appendices 1–16.

PRISMA Guideline – For Elliott et al. 2019 Cannabis-based products for pediatric epilepsy: An updated systematic review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4 [*Full details available in published protocol]
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3*
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3*
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	*
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	*

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	*
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	*
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	*
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4, Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	4-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendix
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

Appendix 1: Literature search

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2017 December 13>, Ovid MEDLINE(R) ALL <1946 to December 14, 2017>, PsycINFO <1806 to December Week 2 2017> Note: The numbers below pertain to an initial search run December 15, 2017; the search was subsequently updated April 25, 2018; October 25 2018; and May 9, 2019

Search Strategy:

- 1 exp Epilepsy/ (413158)
- 2 (epileps* or epilept*).tw,kf. (354209)
- 3 seizure*.tw,kf. (308442)
- 4 convulsi*.tw,kf. (73122)
- 5 falling sickness*.tw,kf. (61)
- 6 comitial disease*.tw,kf. (3)
- 7 (petit mal or grand mal or absence status).tw,kf. (8405)
- 8 Landau-Kleffner Syndrome*.tw,kf. (1213)
- 9 Lennox Gastaut Syndrome*.tw,kf. (3397)
- 10 Dravet Syndrome*.tw,kf. (2044)
- 11 West syndrome*.tw,kf. (2852)
- 12 Doose syndrome*.tw,kf. (167)
- 13 Ohtahara syndrome*.tw,kf. (499)
- 14 Sturge-Weber Syndrome/ (3596)
- 15 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kf. (8090)
- 16 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw,kf. (776)
- 17 SMEI.tw,kf. (461)
- 18 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw,kf. (1137)
- 19 Lafora.tw,kf. (1430)
- 20 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kf. (735)
- 21 ((infantile or nodding) adj2 spasm?).tw,kf. (6276)
- 22 ((flexor or "in flexion") adj2 spasm?).tw,kf. (332)
- 23 ((lightning or salaam) adj2 attack?).tw,kf. (16)
- 24 hypsarrhythmi*.tw,kf. (2063)
- 25 or/1-24 [EPILEPSY] (627889)
- 26 Adolescent/ (3482184)
- 27 exp Child/ (4584752)
- 28 exp Infant/ (2191998)
- 29 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kf. (5312514)
- 30 (newborn* or neonat*).tw,kf. (874968)
- 31 (pediatric* or paediatric*).tw,kf. (811013)
- 32 or/26-31 (9306058)
- 33 25 and 32 [PEDIATRIC EPILEPSY] (223050)
- 34 Cannabis/ (43738)
- 35 exp Cannabinoids/ (76752)
- 36 Medical Marijuana/ (1233)
- 37 Marijuana Smoking/ (6987)
- 38 ("c.indica" or cannabi* or bhang or cannador or charas or eucannabinolide* or ganja or ganjah or hash or hashish or hemp or marihuana* or marijuana*).tw,kf. (112741)
- 39 (epidioxol or gwp 42003p or gwp42003p or nabidioxol).tw,kf. (79)
- 40 (dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetranabinex).tw,kf. (23589)
- 41 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kf. (22)
- 42 or/34-41 (144274)
- 43 33 and 42 [CANNABIS - PEDIATRIC EPILEPSY] (670)
- 44 exp Animals/ not (exp Animals/ and Humans/) (16160986)
- 45 43 not 44 [ANIMAL-ONLY REMOVED] (453)
- 46 45 use medall (185)

47 exp epilepsy/ (413158)
 48 (epileps* or epilept*).tw,kw. (359359)
 49 seizure*.tw,kw. (310739)
 50 convulsi*.tw,kw. (74278)
 51 falling sickness*.tw,kw. (64)
 52 comitial disease*.tw,kw. (3)
 53 (petit mal or grand mal or absence status).tw,kw. (8283)
 54 Landau-Kleffner Syndrome*.tw,kw. (1248)
 55 Lennox Gastaut Syndrome*.tw,kw. (3450)
 56 Dravet Syndrome*.tw,kw. (2094)
 57 West syndrome*.tw,kw. (2980)
 58 Doose syndrome*.tw,kw. (181)
 59 Ohtahara syndrome*.tw,kw. (513)
 60 sturge-weber syndrome/ (3596)
 61 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kw. (8213)
 62 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or
 biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy
 syndrome* or naito oyanagi disease*).tw,kw. (785)
 63 SMEI.tw,kw. (485)
 64 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or
 myoencephalopathy ragged-red fibre disease*).tw,kw. (1167)
 65 Lafora.tw,kw. (1443)
 66 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kw. (740)
 67 ((infantile or nodding) adj2 spasm?).tw,kw. (6422)
 68 ((flexor or "in flexion") adj2 spasm?).tw,kw. (332)
 69 ((lightning or salaam) adj2 attack?).tw,kw. (16)
 70 hypsarrhythmi*.tw,kw. (2094)
 71 or/47-70 [EPILEPSY] (630155)
 72 juvenile/ (38711)
 73 exp adolescent/ (3482352)
 74 exp child/ (4584752)
 75 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school*
 or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kw.
 (5321220)
 76 (newborn* or neonat*).tw,kw. (870009)
 77 (pediatric* or paediatric*).tw,kw. (831059)
 78 or/72-77 (9154566)
 79 71 and 78 [PEDIATRIC EPILEPSY] (221973)
 80 cannabis/ (43738)
 81 exp cannabinoid/ (63688)
 82 medical cannabis/ (1625)
 83 exp "cannabis use"/ (7317)
 84 ("c.indica" or cannabi* or bhang or cannador or charas or eucannabinolide* or ganja or ganjah or hash or hashish or
 hemp or marihuana* or marijuana*).tw,kw. (113719)
 85 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw,kw. (79)
 86 (dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or
 tetranabinex).tw,kw. (23862)
 87 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kw. (22)
 88 or/80-87 (143934)
 89 79 and 88 [CANNABIS - PEDIATRIC EPILEPSY] (678)
 90 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
 (48509001)
 91 exp human/ or exp human experimentation/ or exp human experiment/ (37777771)
 92 90 not 91 (10732950)
 93 89 not 92 [ANIMAL-ONLY REMOVED] (631)
 94 93 use emcxd [EMBASE RECORDS] (399)
 95 exp Epilepsy/ (413158)
 96 Status Epilepticus/ (17946)
 97 (epileps* or epilept*).tw. (350570)
 98 seizure*.tw. (307670)
 99 convulsi*.tw. (71469)
 100 falling sickness*.tw. (59)

101 comitial disease*.tw. (3)
 102 Grand Mal Seizures/ (196)
 103 Petit Mal Seizures/ (127)
 104 (petit mal or grand mal or absence status).tw. (8218)
 105 Landau-Kleffner Syndrome*.tw. (1210)
 106 Lennox Gastaut Syndrome*.tw. (3379)
 107 Dravet Syndrome*.tw. (2019)
 108 West syndrome*.tw. (2812)
 109 Doose syndrome*.tw. (160)
 110 Ohtahara syndrome*.tw. (494)
 111 ((sturge* or weber) adj2 (disease* or syndrome*)).tw. (8041)
 112 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or
 biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy
 syndrome* or naito oyanagi disease*).tw. (775)
 113 SMEI.tw. (456)
 114 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or
 myoencephalopathy ragged-red fibre disease*).tw. (1127)
 115 Lafora.tw. (1421)
 116 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw. (730)
 117 ((infantile or nodding) adj2 spasm?).tw. (6224)
 118 ((flexor or "in flexion") adj2 spasm?).tw. (332)
 119 ((lightning or salaam) adj2 attack?).tw. (15)
 120 hypsarrhythmi*.tw. (2024)
 121 or/95-120 [EPILEPSY] (626451)
 122 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school*
 or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw.
 (5256005)
 123 (newborn* or neonat*).tw. (860199)
 124 (pediatric* or paediatric*).tw. (800591)
 125 or/122-124 (6005033)
 126 121 and 125 [PEDIATRIC EPILEPSY] (158962)
 127 exp Cannabis/ (46269)
 128 exp Cannabinoids/ (76752)
 129 Marijuana Usage/ (2514)
 130 ("c.indica" or cannabi* or bhang or cannador or charas or eucannabinolide* or ganja or ganjah or hash or hashish or
 hemp or marihuana* or marijuana*).tw. (112358)
 131 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw. (79)
 132 (dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or
 tetranabinex).tw. (23463)
 133 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw. (22)
 134 or/127-133 (143233)
 135 126 and 134 [CANNABIS - PEDIATRIC EPILEPSY] (510)
 136 exp Animals/ not (exp Animals/ and Humans/) (16160986)
 137 135 not 136 [ANIMAL-ONLY REMOVED] (333)
 138 137 use medall,emcxd (279)
 139 137 not 138 [PSYCINFO RECORDS] (54)
 140 46 or 94 or 139 [ALL DATABASES] (638)
 141 remove duplicates from 140 (441) [TOTAL UNIQUE RECORDS]
 142 141 use medall [MEDLINE UNIQUE RECORDS] (138)
 143 141 use emcxd [EMBASE UNIQUE RECORDS] (270)
 144 141 not (142 or 143) [PSYCINFO UNIQUE RECORDS] (33)

Appendix 2: Included and excluded records

Note: Because of multiple publications from a single study, the number of records exceeds the number of studies.

Included records (k = 123)

Studies with available data (published reports and clinical trial records with study results) (k = 41)

1. Aguirre-Velazquez CG. Report from a survey of parents regarding the use of cannabidiol (medicinal cannabis) in Mexican children with refractory epilepsy. *Neurol Res Int.* 2017;2017; 2985729
2. Cannabidiol oral solution as an adjunctive treatment for treatment-resistant seizure disorder. <http://ClinicalTrials.gov> identifier: NCT02318602. <https://clinicaltrials.gov/ct2/show/NCT02318602>. Updated February 5, 2018. Accessed April 24, 2018.
3. Cannabidiol oral solution for treatment of refractory Infantile Spasms. <http://ClinicalTrials.gov> identifier: NCT02551731. <https://clinicaltrials.gov/ct2/show/NCT02551731>. Updated February 5, 2018. Accessed April 24, 2018.
4. Cannabidiol oral solution in pediatric participants with treatment-resistant seizure disorders. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT02324673) identifier: NCT02324673. <https://clinicaltrials.gov/ct2/show/NCT02324673>. Updated June 23, 2017. Accessed May 10, 2018.
5. Chen KA, Farrar M, Cardamone M, et al. Cannabidiol for treating drug-resistant epilepsy in children: The New South Wales experience. *Med J Aust.* 2018;209:217.
6. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *NEJM.* 2017;376:2011.
7. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: An open-label interventional trial. *Lancet Neurol.* 2016;15:270.
8. Devinsky O, Nabbout R, Miller I, et al. Long-term cannabidiol treatment in patients with Dravet syndrome: An open-label extension trial. *Epilepsia.* 2019;60:294.
9. Devinsky O, Patel AD, Cross H, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *NEJM.* 2018;378:1888.
10. Devinsky O, Patel AD, Thiele EA, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology.* 2018; 90:e1204.
11. Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy Behav.* 2018;86:131.
12. Freeman JL. Safety of cannabidiol prescribed for children with refractory epilepsy. *Med J Aust.* 2018;209:228.
13. Gaston TE, Bebin EM, Cutter GR, et al. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia.* 2017;58:1586.
14. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia.* 2015;56:1246.
15. Gofshteyn JS, Wilfong A, Devinsky O, et al. Cannabidiol as a potential treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES) in the acute and chronic phases. *J Child Neurol.* 2017;32:35.
16. Hausman-Kedem M, Menascu S, Kramer U. Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents – An observational, longitudinal study. *Brain Dev.* 2018;40(7):544-551.

17. Hess EJ, Moody KA, Geoffrey AL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. *Epilepsia*. 2016;57:1617.
18. Hussain SA, Zhou R, Jacobson C, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome. *Epilepsy Behav*. 2015;47:138.
19. Kaplan EH, Offermann EA, Sievers JW, et al. Cannabidiol treatment for refractory seizures in Sturge-Weber syndrome. *Pediatr Neurol*. 2017;71:18.
20. Laux LC, Bebin EM, Checketts D, et al. Long-term safety and efficacy of cannabidiol in children and adults with treatment-resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results. *Epilepsy Res*. 2019;154:13.
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24. Porcari GS, Fu C, Doll ED, et al. Efficacy of artisanal preparations of cannabidiol for the treatment of epilepsy: Practical experiences in a tertiary medical center. *Epilepsy Behav*. 2018;80:240.
25. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav*. 2013; 29:574.
26. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy Behav*. 2015;45:49.
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29. Ryan J. Parents' experiences using medical marijuana for their children (thesis). Villanova University; ProQuest. 2018; 1-148.
30. Sands TT, Rahdari S, Oldham MS, et al. Long-term safety, tolerability, and efficacy of cannabidiol in children with refractory epilepsy: Results from an expanded access program in the US. *CNS Drugs*. 2019;33:47.
31. Sulak D, Saneto R, Goldstein B. The current status of artisanal cannabis for the treatment of epilepsy in the United States. *Epilepsy Behav*. 2017;70:328.
32. Suraev A, Lintzeris N, Stuart J, et al. Composition and use of cannabis extracts for childhood epilepsy in the Australian community. *Sci Rep*. 2018;8:10154.
33. Suraev AS, Todd L, Bowen MT, et al. An Australian nationwide survey on medicinal cannabis use for epilepsy: History of antiepileptic drug treatment predicts medicinal cannabis use. *Epilepsy Behav*. 2017;70:334.
34. Szaflarski JP, Bebin EM, Comi AM, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results. *Epilepsia*. 2018;59:1540.
35. Szaflarski JP, Bebin EM, Cutter G, et al. Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. *Epilepsy Behav*. 2018;87:131.
36. Szaflarski JP, Hernando K, Bebin EM, et al. Higher cannabidiol plasma levels are associated with better seizure response following treatment with a pharmaceutical grade cannabidiol. *Epilepsy Behav*. 2019;95:131.

37. Szaflarski M, Hansen B, Bebin EM, et al. Social correlates of health status, quality of life, and mood states in patients treated with cannabidiol for epilepsy. *Epilepsy Behav.* 2017;70:364.
38. Thiele E, Marsh E, Mazurkiewicz-Beldzinska M, et al. Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. *Epilepsia.* 2019;60:419.
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40. Treat L, Chapman KE, Colborn KL, et al. Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients. *Epilepsia.* 2017;58:123.
41. Tzadok M, Uliel-Siboni S, Linder I, et al. CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience. *Seizure.* 2016;35:41.

Conference abstracts (k = 50)

1. Abati E, Hess E, Morgan A, et al. Cannabidiol treatment of refractory epileptic spasms: An open-label study. *American Epilepsy Society*;2015.
2. Bruno PL, Geffrey AL, Pollack SF, et al. Effect of cannabidiol on the antiepileptic drug clobazam. *Epilepsy Curr* 2015;15:383.
3. Cross JH, Devinsky O, Laux L, et al. Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet syndrome: Results of a multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE1). International Epilepsy Congress, Barcelona Spain, 2-6 September 2017; *Epilepsia.* Supplement 5;S12
4. Cross JH, Devinsky O, Marsh E, et al. Cannabidiol(CBD) reduces convulsive seizure frequency in Dravet syndrome: results of a multi-center, randomized, controlled trial (GWPCARE1). *Neurology* 2017; (16 Suppl 1).
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6. Devinsky O, Nabbout R, Miller I, et al. Maintenance of long-term safety and efficacy of cannabidiol (CBD) treatment in dravet syndrome (DS): Results of the open-label extension (OLE) trial (GWPCARE 5). *Developmental Medicine and Child Neurology.* 2017; American Epilepsy Society: December 1-5, Washington DC, USA.S4:126.
7. Devinsky O, Nabbout R, Miller I, et al. Maintenance of long-term safety and efficacy of cannabidiol treatment in Dravet syndrome: Results of the open-label extension trial (GWPCARE5). *Epilepsia.* 2018;59:S73.
8. Devinsky O, Sullivan J, Friedman D, et al. Efficacy and safety of Epidiolex (cannabidiol) in children and young adults with treatment-resistant epilepsy: Initial data from an expanded access program. *Epilepsy Curr* 2015;15:532.
9. French J, Thiele E, Mazurkiewicz-Beldzinska M, et al. Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a multi-center, randomized, double-blind, placebo controlled trial (GWPCARE4). *Neurology* 2017;(16 Suppl 1).
10. Friedman D, Cilio MR, Tilton N, et al. The effect of Epidiolex (cannabidiol) on serum levels of concomitant anti-epileptic drugs in children and young adults with treatment-resistant epilepsy in an expanded access program. *Epilepsy Curr* 2015;15:332.
11. Gedde MM, Maa E. Whole cannabis extract of high concentration cannabidiol may calm seizures in highly refractory pediatric epilepsies. *Epilepsy Curr* 2014;14:449.
12. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* 2015;56:1246-1251.
13. Gofshteyn J, Wilfong A, Devinsky O, et al. The use of cannabidiol for the treatment of febrile infection related epilepsy syndrome (FIRES). *Ann Neurol* 2016;S323.

14. Halford H, Marsh E, Mazurkiewicz-Beldzinska M, et al. Long-term safety and efficacy of cannabidiol (CBD) in patients with Lennox-Gastaut syndrome (LGS): Results from open-label extension trial (GWPCARE5). *Neurology*. 2018.
15. Joshi C, Thiele E, Marsh E, et al. Treatment with cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a multicenter, randomized, double-blind, placebo controlled trial (GWPCARE4). *Annals of Neurology*. 2017;S293.
16. Kaplan E, Sievers J, Comi A. Investigator IND trial of cannabidiol in Sturge-weber syndrome. *Ann Neurol* 2016;S320.
17. Kuester G, Gazmuri AM, Ahumada A, et al. Clinical response to oral cannabis extracts in severe refractory epilepsy: Preliminary experience in Chilean patients. *Epilepsia* 2016;147.
18. Laux L, Devinsky O, Miller I, et al. Maintenance of long-term safety and efficacy of cannabidiol (CBD) treatment in Dravet syndrome (DS): Results of the open-label extension (OLE) trial (GWPCARE5). *Ann Neurol*. 2018;S344
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21. Mazurkiewicz-Beldzinska M, Thiele EA, Benbadis S, et al. Treatment with cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a multi-centre, randomised, double-blind, placebocontrolled trial (GWPCARE4). *Epilepsia*. 2017;S55
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23. Mimura PM, Lima MTAD, Picoli RL, et al. Seguti. Follow-up of patients with refractory epilepsy treated with cannabidiol. *J Neurologic Sci*. 2017;683
24. Morales SJG, Benavides AO, Bastida ME. Use of cannabidiol (RSHO) in the treatment of refractory epilepsy (Lennox-Gastaut Syndrome), experience of 38 cases. *Epilepsia*. 2017;S53.
25. Moreno M, Vaillancourt R, Pouliot A, et al. A survey of the use of cannabis in children at a tertiary teaching hospital. *Can J Hospital Pharm*. 2018.
26. Morgan AK, Pan J, Bruno P, et al. Impact of cannabidiol on quality of life in pediatric drug resistant epilepsy. *Epilepsy Curr* 2015;15:370.
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28. Morrison G, Sardu ML, Rasmussen CH, et al. Exposure-response analysis of cannabidiol for the treatment of Lennox-Gastaut syndrome. *Epilepsia*. 2018;59;S11-S12.
29. Patel A, Devinsky O, Cross JH, et al. Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): results of a dose-ranging, multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE3). *Neurology*. 2017;e100.
30. Patel A, Devinsky O, Thiele E, et al. A dose ranging safety and pharmacokinetic study of cannabidiol (CBD) in children with Dravet syndrome (GWPCARE1). *Neurology* 2017;(16 Suppl 1).
31. Patel A, Gil-Nagel A, Chin R, et al. Long-term safety and efficacy of add-on cannabidiol treatment in patients with Lennox Gastaut syndrome in an open-label extension trial (GWPCARE5). *Dev Med Child Neurol* 2019.
32. Press C, Knupp K, Chapman K. Parental reporting of response to oral cannabis extracts as adjunctive treatment for medically refractory epilepsy. *Epilepsy Curr* 2015;15:153.

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34. Scheffer IE, Halford J, Nabbout R, et al. Long-term safety and efficacy of add-on cannabidiol (CBD) treatment in patients with Dravet syndrome (DS) in an open-label extension (OLE) trial. *Dev Med Child Neurol* 2019.
35. Schimpfoss M, Berweck S, Betzler C, et al. Retrospective analysis of tetrahydrocannabinol based on 31 neurologically critically ill children. *Neuropediatrics* 2015.
36. Szaflarski J, Bebin E, Gaston T, et al. Response to pharmaceutical formulation of purified cannabidiol (CBD) in pediatric and adult patients with treatment-refractory epilepsy. *Neurol.* 2018.
37. Szaflarski JP, Bebin EM, Gaston G, et al. Improvements in seizure frequency parallel improvements in seizure severity in an open label study of cannabidiol. *Epilepsia.* 2017;S158.
38. Thiele E, Marsh E, Halford J, et al. Long-term safety and efficacy of cannabidiol (CBD) in patients with Lennox-Gastaut syndrome (LGS): Results of the open-label extension (OLE) trial (GWPCARE5). *Ann Neurol.* 2018;S336.
39. Thiele EA, Mazurkiewicz-Beldzinska M, Benbadis S, et al. Treatment with cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox Gastaut Syndrome (LGS): Results of a multi - Center, randomized, double-blind, Placebo-controlled trial (GWPCARE4). *Neurotherapeutics* 2017;(3):824.
40. Tzadok M, Linder I, Kramer U, et al. CBD-Enriched medical cannabis for intractable pediatric epilepsy. *Epilepsia* 2016;169.
41. Vezyroglou K, Eltze C, Varadkar S, et al. Cannabidiol as add on therapy in children with complex epilepsy. *Dev Med Child Neurol* 2017;17.
42. Vezyroglou K, Eltze C, Varadkar S, et al. Efficacy and safety of cannabidiol as add-on therapy in drugresistant epilepsy, a single center experience. *Eur J Paediatr Neurol* 2017;(Supplement 1):e87.
43. Wilson CA, Spigarelli M, Sweney M, et al. Efficacy, adverse effects, and additional benefits of epidiolex[®] in children and young adults with treatment resistant epilepsy. *Ann Neurol* 2015;78:S180.
44. Wirrell E, Devinsky O, Patel A, et al. Cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a dose ranging, multicenter, randomized, double blind, placebo controlled trial (GWPCARE3). *Ann Neurol.* 2017;S279.
45. Wirrell E, Privitera M, Bhathal H, et al. Cannabidiol (CBD) treatment effect and adverse events (AES) by time in patients with Lennox-Gastaut syndrome (LGS): Pooled results from 2 trials. *Ann Neurol.* 2018;S341.
46. Wirrell EC, Privitera M, Bhathal H, et al. Cannabidiol (CBD) treatment effect and adverse events (AES) by time in patients with Lennox-Gastaut syndrome (LGS): Pooled results from 2 trials. *Neurology.* 2018.
47. Wright S, Devinsky O, Thiele EA, et al. Cannabidiol (CBD) in Dravet syndrome: A randomised, dose-ranging pharmacokinetics and safety trial (GWPCARE1). *Epilepsia.* 2017;S56.
48. Zhou R, Jacobson C, Weng J, et al. Potential efficacy of cannabidiol for treatment of refractory infantile spasms and Lennox-Gastaut syndrome. *Epilepsy Curr* 2015;15:360.
49. Zuberi S, Patel AD, Wilfong A, et al. Cannabidiol (CBD) significantly reduces drop-seizure frequency in Lennox-Gastaut syndrome (LGS): Pooled efficacy and safety results from two randomized controlled trials. *Dev Med Child Neurol.* 2017;18.
50. Zuberi S, Devinsky O, Patel A, et al. Cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a dose-ranging, multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE3). *Epilepsia.* 2017;S13.

Clinical trial registration records (k = 32)

Note: Registration records with posted results are included under the published reports heading

1. A double-blind placebo-controlled study investigating the safety, tolerability, efficacy and pharmacokinetics of EP1, and enriched cannabidiol oil in children and adolescents with medication resistant refractory epilepsy. ANZCTR identifier: ACTRN12618001706268.
www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376037
2. A double-blind trial to evaluate efficacy and safety of cannabidiol as an add-on therapy for treatment in refractory epilepsy. <http://ClinicalTrials.gov> identifier: NCT02783092.
<https://clinicaltrials.gov/ct2/show/NCT02783092>. Updated April 18, 2018. Accessed April 24, 2018.
3. A randomized controlled trial of cannabidiol (GWP42003-P, CBD) for seizures in Tuberous Sclerosis Complex (GWPCARE6). <http://ClinicalTrials.gov> identifier: NCT02544763.
<https://clinicaltrials.gov/ct2/show/NCT02544763>. Updated October 24, 2017. Accessed April 24, 2018.
4. A study to assess the efficacy, safety, and tolerability of cannabidiol oral solution with vigabatrin as initial therapy in participants with infantile spasms. <http://ClinicalTrials.gov> identifier: NCT03421496.
<https://clinicaltrials.gov/ct2/show/NCT03421496>. Updated April 3, 2018. Accessed April 24, 2018.
5. A study to assess the safety and tolerability of ZX008 in children and young adults with DS or LGS currently taking CBD. <http://ClinicalTrials.gov> identifier: NCT03467113.
<https://clinicaltrials.gov/ct2/show/NCT03467113>. Updated March 15, 2018. Accessed April 24, 2018.
6. A study to evaluate the safety, tolerability and efficacy of oral administration of PTL101 (cannabidiol) as an adjunctive treatment for pediatric intractable epilepsy. <http://ClinicalTrials.gov> identifier: NCT02987114. <https://clinicaltrials.gov/ct2/show/NCT02987114>. Updated September 15, 2017. Accessed April 24, 2018.
7. A study to investigate possible drug-drug interactions between stiripentol or valproate and cannabidiol in patients with epilepsy. <http://ClinicalTrials.gov> identifier: NCT02607891.
<https://clinicaltrials.gov/ct2/show/NCT02607891>. Updated November 1, 2017. Accessed April 24, 2018.
8. An open-label extension trial of cannabidiol (GWP42003-P, CBD) for seizures in Tuberous Sclerosis Complex (GWPCARE6). <http://ClinicalTrials.gov> identifier: NCT02544750.
<https://clinicaltrials.gov/ct2/show/NCT02544750>. Updated October 24, 2017. Accessed April 24, 2018.
9. An open-label extension trial to investigate possible drug-drug interactions between stiripentol or valproate and cannabidiol in patients with epilepsy. <http://ClinicalTrials.gov> identifier: NCT02607904.
<https://clinicaltrials.gov/ct2/show/NCT02607904>. Updated November 1, 2017. Accessed April 24, 2018.
10. Cannabidiol (CBD) and pediatric epilepsy. <http://ClinicalTrials.gov> identifier: NCT02447198.
<https://clinicaltrials.gov/ct2/show/NCT02447198>. Updated September 20, 2017. Accessed April 24, 2018.
11. Cannabidiol (CBD) to 27 patients (Aged 2 Years - 19 Years) with drug resistant epilepsy. <http://ClinicalTrials.gov> identifier: NCT02286986. <https://clinicaltrials.gov/ct2/show/NCT02286986>. Updated April 12, 2017. Accessed April 24, 2018.
12. Cannabidiol expanded access study in medically refractory Sturge-Weber syndrome. <http://ClinicalTrials.gov> identifier: NCT02332655. <https://clinicaltrials.gov/ct2/show/NCT02332655>. Updated March 1, 2018. Accessed April 24, 2018.
13. Cannabidiol for drug resistant pediatric epilepsy. <http://ClinicalTrials.gov> identifier: NCT03676049. <https://clinicaltrials.gov/ct2/show/NCT03676049>. Updated September 18, 2018. Accessed May 12, 2019.
14. Cannabidiol for pediatric epilepsy (compassionate use). <http://ClinicalTrials.gov> identifier: NCT02556008. <https://clinicaltrials.gov/ct2/show/NCT02556008>. Updated May 3, 2017. Accessed April 24, 2018.
15. Cannabidiol in children with refractory epileptic encephalopathy. <http://ClinicalTrials.gov> identifier: NCT03024827. <https://clinicaltrials.gov/ct2/show/NCT03024827>. Updated February 5, 2018. Accessed April 24, 2018.

16. Cannabidiol oral solution in pediatric participants with treatment-resistant childhood absence seizures. <http://ClinicalTrials.gov> identifier: NCT03336242. <https://clinicaltrials.gov/ct2/show/NCT03336242>. Updated April 24, 2018. Accessed April 24, 2018.
17. Epidiolex and drug resistant epilepsy in children. <http://ClinicalTrials.gov> identifier: NCT02397863. <https://clinicaltrials.gov/ct2/show/NCT02397863>. Updated April 24, 2015. Accessed April 24, 2018.
18. Expanded use of cannabidiol oral solution. <http://ClinicalTrials.gov> identifier: NCT03196934. <https://clinicaltrials.gov/ct2/show/NCT03196934>. Updated June 23, 2017. Accessed April 24, 2018.
19. Genetic analysis between Charlotte's Web responders versus non-responders in a Dravet population. <http://ClinicalTrials.gov> identifier: NCT02229032. <https://clinicaltrials.gov/ct2/show/NCT02229032>. Updated December 15, 2017. Accessed April 24, 2018.
20. GWPCARE2 A study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome. <http://ClinicalTrials.gov> identifier: NCT02224703. <https://clinicaltrials.gov/ct2/show/NCT02224703>. Updated October 12, 2016. Accessed April 24, 2018.
21. Long-term safety of pharmaceutical grade synthetic cannabidiol oral solution in pediatric participants with treatment-resistant childhood absence seizures. <http://ClinicalTrials.gov> identifier: NCT03355300. <https://clinicaltrials.gov/ct2/show/NCT03355300>. Updated April 24, 2018. Accessed April 24, 2018.
22. Open label study to assess the safety and efficacy of ZYN002 administered as a transdermal gel to children and adolescents (3 to <18 years) with developmental and epileptic encephalopathy (BELIEVE 1). ANZCTR register identifier: ACTRN1261800051620. <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12618000516280>. Updated April 9, 2018. Accessed April 24, 2018.
23. Outcomes Mandate National Integration with cannabis as medicine (OMNI-Can). <http://ClinicalTrials.gov> identifier: NCT0394447. <https://clinicaltrials.gov/ct2/show/NCT0394447>. Updated May 9, 2019. Accessed May 15, 2019.
24. Phase 3 trial of cannabidiol (CBD; GWP42003-P) for Infantile Spasms: Open-label extension phase (GWPCARE7). <http://ClinicalTrials.gov> identifier: NCT02954887. <https://clinicaltrials.gov/ct2/show/NCT02954887>. Updated October 24, 2017. Accessed April 24, 2018.
25. Safety and tolerability of cannabidiol in subjects with drug resistant epilepsy. <http://ClinicalTrials.gov> identifier: NCT02660255. <https://clinicaltrials.gov/ct2/show/NCT02660255>. Updated May 3, 2017. Accessed April 24, 2018.
26. Study of cannabidiol for drug-resistant epilepsies. <http://ClinicalTrials.gov> identifier: NCT03014440. <https://clinicaltrials.gov/ct2/show/NCT03014440>. Updated April 4, 2017. Accessed April 24, 2018.
27. The effects of cannabidiol (CBD) on electrical and autonomic cardiac function in children with severe epilepsy. <http://ClinicalTrials.gov> identifier: NCT02815540. <https://clinicaltrials.gov/ct2/show/NCT02815540>. Updated June 28, 2016. Accessed April 24, 2018.
28. The pharmacokinetics of cannabidiol (CBD) and its effects in children with severe epilepsy. <http://ClinicalTrials.gov> identifier: NCT02910297. <https://clinicaltrials.gov/ct2/show/NCT02910297>. Updated February 21, 2018. Accessed April 24, 2018.
29. The use of medicinal cannabinoids as adjunctive treatment for medically refractory epilepsy. <http://ClinicalTrials.gov> identifier: NCT02523183. <https://clinicaltrials.gov/ct2/show/NCT02523183>. Updated January 17, 2018. Accessed April 24, 2018.
30. Treatment of drug resistant epilepsy. <http://ClinicalTrials.gov> identifier: NCT02461706. <https://clinicaltrials.gov/ct2/show/NCT02461706>. Updated March 2, 2018. Accessed April 24, 2018.
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Excluded studies (k = 81)

Wrong population (k = 8)

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Fewer than 5 participants (k = 14)

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Not a primary study (k = 29)

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Other (k = 23)

Note: records pertaining to studies included in previous review updates were excluded from the current review (as duplicates)

1. GWPCARE5 - An open label extension study of cannabidiol (GWP42003-P) in children and young adults with Dravet or Lennox-Gastaut syndromes. <http://ClinicalTrials.gov> identifier: NCT02224573. <https://clinicaltrials.gov/ct2/show/NCT02224573>. Updated October 24, 2017. Accessed April 24, 2018.
2. A dose-ranging pharmacokinetics and safety study of GWP42003-P in children with Dravet syndrome (GWPCARE1). <http://ClinicalTrials.gov> identifier: NCT02091206; <https://clinicaltrials.gov/show/nct02091206>
3. A dose-ranging pharmacokinetics and safety study of GWP42003-P in children with Dravet syndrome (GWPCARE1). <http://ClinicalTrials.gov> identifier: NCT02091206; <https://clinicaltrials.gov/show/nct02091206>
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5. A study to assess the efficacy, safety, and tolerability of cannabidiol oral solution with vigabatrin as initial therapy in participants with infantile spasms. <http://ClinicalTrials.gov> identifier: NCT03421496. <https://clinicaltrials.gov/show/nct03421496>.
6. A study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults. <http://ClinicalTrials.gov> identifier: NCT02224690. <https://clinicaltrials.gov/show/nct02224690>
7. A study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults. <http://ClinicalTrials.gov> identifier: NCT02224560. <https://clinicaltrials.gov/show/nct02224560>
8. A study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults (GWPCARE4). <http://ClinicalTrials.gov> identifier: NCT02224690. <https://clinicaltrials.gov/ct2/show/NCT02224690>
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10. Cannabidiol (CBD) to 27 patients (aged 2 years – 19 years) with drug resistant epilepsy. <http://ClinicalTrials.gov> identifier: NCT02286986. <https://clinicaltrials.gov/ct2/show/NCT02286986>
11. Cannabidiol for pediatric epilepsy (compassionate use). <http://ClinicalTrials.gov> identifier: NCT02556008. <https://clinicaltrials.gov/ct2/show/NCT02556008>
12. Cannabidiol oral solution in pediatric participants with treatment-resistant seizure disorders. <http://ClinicalTrials.gov> identifier: NCT02324673. <https://clinicaltrials.gov/ct2/show/NCT02324673>
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14. Efficacy and safety of GWP42003-P for seizures associated with Lennox-Gastaut syndrome in children and adults (GWPCARE3). <http://ClinicalTrials.gov> identifier: NCT02224560. <https://clinicaltrials.gov/ct2/show/NCT02224560>
15. EUCTR2014-000995-24-PL. A study of the safety, pharmacokinetics and efficacy of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome.
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23. Trial of cannabidiol (CBD; GWP42003-P) for infantile spasms (GWPCARE7). <http://ClinicalTrials.gov> identifier: NCT02953548. <https://clinicaltrials.gov/show/nct02953548>.

Appendix 3: Characteristics of the included studies^a

Author, yr, page no. (NCT number)	Design features	Population	Inclusion criteria	Treatments (no. randomized) ^b	Duration	No. centres; country	Funding source
Studies identified as part of the review update (published April 2018 to May 2019)							
RANDOMIZED CONTROLLED TRIALS							
No new studies							
NON-RANDOMIZED STUDIES							
Thiele 2019, p. 419 (NCT02224573; GWPCARE5) ¹	Prospective, open-label extension, single-group cohort	Lennox-Gastaut syndrome	Participants who completed GWPCARE3 (NCT02224560) or GWPCARE4 (NCT02224690); LGS: 2–55 yr; DS: 2–18 yr	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 30 mg/kg/d, given in 2 divided doses. LGS (366); DS (264)	Median (range) 263 (3–430) d ^c	53 centres; US, Europe	GW Research Ltd
Devinsky 2018, p. 294 (NCT02224573; GWPCARE5) ²		Dravet syndrome			Median (range) 274 (1–512) d ^c	49 centres; US, Europe, Israel	
Ryan 2019, p. 1 ³	Cross- sectional	Epilepsy	Epilepsy Respondent: Parent Online survey link distributed via social media	Mixed cannabis-based treatments (THC+CBD, CBD alone, THCA +CBD) (14)	NA	US	Alpha Nu Chapter of Sigma Theta Tau International (Villanova University); Delaware Valley Chapter of the National Association of Pediatric Nurse Practitioners
Sands 2019, p. 47 ⁴	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	1–17 yr	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 25 mg/kg/d (26)	Mean (range) 21 (4–53) mo	1 centre; US	None declared ^d
Chen 2018, p. 217 ⁵	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	<18 years, DRE, ≥ 1 seizure/d for ≥ 6 mo, ≥ 1 epilepsy- related hospital admissions, failure of ≥ 5 AEDs including a trial of a combination of 2 drugs	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 25 mg/kg/d, given in 2 divided doses (40)	12 wk	3 centres; Australia	NSW Government, GW Pharmaceuticals ^e
Devinsky 2018, p. 131 ⁶	Prospective, single-group, open-label cohort¶	CDKL deficiency, Aicardi, Dup15Q, Doose syndrome	Severe childhood-onset epilepsy (CDKL deficiency, Aicardi, Dup15Q, or Doose syndrome)	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 25 mg/kg/d or 50 mg/kg/d	48 wk (efficacy); up to 144 wk (safety)	8 centres; US	GW Pharmaceuticals ^e

Author, yr, page no. (NCT number)	Design features	Population	Inclusion criteria	Treatments (no. randomized) ^b	Duration	No. centres; country	Funding source
				(depending on study centre), given in 2 divided doses (55)			
Freeman 2018, p. 228 ⁷	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	Children with severe refractory epilepsy	CBD oral solution (CBD MAX, Tilray), up to 20 mg/kg/d, given in 2 divided doses (20)	Up to 40 weeks; median 23 weeks	1 centre; Australia	NR
INSYS 2018 (NCT02318602) ⁸	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	1–18 yr; participants who completed NCT02324673 or NCT02551731	CBD oral solution, up to 40 mg/kg/d, given in 2 divided doses (52)	Up to 50 wk	11 centres; US	INSYS Therapeutics
INSYS 2018 (NCT02551731) ⁹	Prospective, single-group, open-label cohort	Infantile spasms	6–36 mo, with infantile spasms	CBD oral solution, 20 or 40 mg/kg/d, given in 2 divided doses (9)	14 d	4 centres; US	INSYS Therapeutics
McCoy 2018, p. 1077 ¹⁰ (NCT02983695)	Prospective, single-group, open-label cohort	Dravet syndrome	1–18 yr, Dravet syndrome with DRE, frequent motor seizures, stable AED therapy for 4 wk and stable KD/VNS settings for ≥ 3 mo	Oral solution (50:1 CBD:THC; TIL-150; TILRAY), up to 16 mg/kg/d CBD (0.32 mg/kg/d THC) (20)	20 wk	1 centre; Canada	Tilray, The Little Rocky Project
Suraev 2018, p. 10154 ¹¹	Cross- sectional	Children with epilepsy (72% with DRE)	Epilepsy, with or without current or prior use of medical cannabis Respondent: Parent or guardian Control: no cannabis use Online survey link distributed by Epilepsy Action Australia	41 families provided 61 cannabis samples; of these, 62% extracts were from medicinal suppliers, 15% were from a recreational “dealer”, 13% were made by the family, 9% were from online suppliers, 3% were from federal/state government schemes	NR	NA	The Lambert Initiative for Cannabinoid Therapeutics
Szaflarski 2018, p. 1540 ¹² (Laux 2019, p. 13 ¹³)	Prospective, single-group, open-label cohort	Drug-resistant epilepsy ¹²	DRE, receiving stable doses of AEDs for ≥ 4 weeks before enrollment	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 50 mg/kg/d, given in 2 divided doses (607)	Median (range) 48 (2–146) wk	25 centres; US	Alabama General Funds; GW Research; New York State Department of Health; Epilepsy Foundation
		Dravet syndrome or	Receiving stable doses of	CBD oral solution	Median (range)		

Author, yr, page no. (NCT number)	Design features	Population	Inclusion criteria	Treatments (no. randomized) ^b	Duration	No. centres; country	Funding source
		Lennox-Gastaut syndrome	AEDs for ≥ 4 weeks before enrollment	(Epidiolex, GW Pharmaceuticals), up to 50 mg/kg/d, given in 2 divided doses (152)	78.3 (4.1–146.4) wk		
Szaflarski 2018, p. 131 ¹⁴ , Szaflarski 2019, p. 131 ¹⁵ (companions to Gaston 2017, p. 1586 ¹⁶ , Szaflarski 2017, p. 364 ¹⁷) (NCT02695537)	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	>1 yr to 19 yr, failure of ≥ 4 AEDs at an adequate dose, including ≥ 1 trial of 2 concomitant AEDs, stable VNS settings and KD for ≥ 3 mo	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 50 mg/kg/d, given in 2 divided doses (77)	12 mo	1 centre; US	State of Alabama, UAB Epilepsy Center, Greenwich Biosciences ^e
PROTOCOL							
Reithmeier 2018, p. 221 ¹⁸ (NCT03024827)	Protocol: open-label, dose-escalation phase 1 trial	Drug-resistant epilepsy	1–10 years with drug-resistant* epileptic encephalopathy	Oil-based extract of Cannabis sativa (CanniMed Therapeutics Inc.), 20:1 CBD:THC ratio (NR)	6 months	1; Canada	Non-industry
Studies identified as part of the baseline review (published up to April 2018)							
RANDOMIZED CONTROLLED TRIALS							
Devinsky 2018, p. e1204 (NCT02091206; GWPCARE1 Part A) ¹⁹	Double-blind, placebo controlled RCT	Dravet syndrome	4–10 yr, taking ≥ 1 AED and experiencing < 4 convulsive seizures during a 4-wk baseline period, stable medications or interventions (inc. KD and VNS) for 4 wk	- CBD oral solution (Epidiolex, GW Pharmaceuticals): 5 mg/kg/d (10), 10 mg/kg/d (8), 20 mg/kg/d (9); given in 2 divided doses - Placebo (7)	3-wk treatment, 10-d taper, 4-wk follow-up	12 centres; US, UK	GW Research Limited
Devinsky 2017, p. 2011 (NCT02091375; GWPCARE1 Part B) ²⁰	Double-blind, placebo controlled RCT	Dravet syndrome	2–18 yr, taking ≥ 1 AED, ≥ 4 convulsive seizures during the 28-d baseline period, stable medications or interventions (inc. KD and VNS) for 4 wk	- CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 20 mg/kg/d (61); given in 2 divided doses - Placebo (59)	14-week treatment period (2 wk escalation, 12 wk maintenance), 10-d taper, 4-wk follow-up	23 centres; US and Europe	GW Pharmaceuticals
Devinsky 2018, p. 1888 (NCT02224560; GWPCARE3) ²¹	Double-blind, placebo controlled RCT	Lennox-Gastaut syndrome	2–55 yr, with an electroencephalogram that showed a pattern of slow	• CBD oral solution (Epidiolex, GW Pharmaceuticals),	14 wk (2 wk escalation, 12 wk treatment), 4-wk	30 centres; US, Spain, UK, France	GW Pharmaceuticals

Author, yr, page no. (NCT number)	Design features	Population	Inclusion criteria	Treatments (no. randomized) ^b	Duration	No. centres; country	Funding source
			spike-and-wave complexes and ≥ 2 types of generalized seizures, inc. drop seizures, for ≥ 6 mo, with use of 1–4 AEDs and ≥ 2 drop seizures per wk during the 28-d baseline period	10 mg/kg/d (73), 20 mg/kg/d (76); given in 2 divided doses • Placebo (76)	follow-up		
Thiele 2018, p. 1085 (NCT02224690; GWPCARE4) ²²	Double-blind, placebo controlled RCT	Lennox-Gastaut syndrome	2–55 yr, >1 type of generalized seizure, inc. drop seizures, for at least 6 mo; taking 1–4 AEDs, and ≥ 2 drop seizures per wk during the 4-wk baseline period; stable medications or interventions (inc. KD and VNS) for 4 wk	• CBD oral solution, (Epidiolex, GW Pharmaceuticals), 20 mg/kg/d (86); given in 2 divided doses • Placebo (85)	14 wk (2 wk escalation, 12 wk treatment), taper period, 4-wk follow-up	24 centres; US, Netherlands, Poland	GW Pharmaceuticals
NON-RANDOMIZED STUDIES							
Hausman-Kedem 2018, p.544 ²³	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	1–20 yr with refractory epilepsy (failure of ≥ 4 AEDs, including KD or VNS) with stable doses of AEDs for at least 4 wk	CBD-enriched cannabis oil from whole plant mixture with 20:1 CBD:THC ratio, up to 50 mg/kg/d of CBD (57 ^f); 30% of patients were transferred to or added inhaled CBD-enriched cannabis during the observation period	Median (range) 18 (3–33) mo; mean (SD): 15.6 (7.23) mo	1 centre; Israel	No funding
Neubauer 2018, p. 79 ²⁴	Retrospective, single-group cohort	Drug-resistant epilepsy	Children, adolescents, young adults who were given CBD for treatment of refractory epilepsy	CBD (Bionorica), up to 16 mg/kg/d (70)	Median (range) 14.0 mo (6.0–29.3)	1 centre; Slovenia	NR
Porcari 2018, p. 240 ²⁵	Retrospective comparative cohort	Drug-resistant epilepsy	< 19 yr with epilepsy	• CBD up to 50 mg/kg/d (48) • CBD + CLO (54) • CLO 1.5 (1.4) mg/kg/d (74) Artisanal CBD: 10 different products with varying CBD content	Mean (SD), yr CBD: 1.1 (0.8) CBD + CLO: 1.3 (1.0) CLO treatment: 2.5 (1.9)	1 centre; US	None

Author, yr, page no. (NCT number)	Design features	Population	Inclusion criteria	Treatments (no. randomized) ^b	Duration	No. centres; country	Funding source
Aguirre- Velazquez 2017, p. 1 ²⁶	Cross- sectional	Drug-resistant epilepsy	Children with a diagnosis of treatment-resistant epilepsy without controlled symptoms and current use of medical cannabis (CBD alone or in combination) Respondent: Parent, Online survey, invitations via email or Facebook group about the use of medical cannabis in children	RSHO-X; CBD (<0.1% THC); combination of CBD + THC (e.g., Charlotte's web); home-made cannabis extracts (43)	Range <1 to 12 mo	NA; Mexico	NR
Gaston 2017, p. 1586 ¹⁶ (Szaflarski 2017, p. 364 ¹⁷ ; NCT02695537)	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	>1 yr to 19 yr, failure of ≥ 4 AEDs at an adequate dose, including ≥1 trial of 2 concomitant AEDs, stable VNS settings and KD for ≥ 3 mo	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 50 mg/kg/d, given in 2 divided doses (77)	12 mo	1 centre; US	State of Alabama, UAB Epilepsy Center, Greenwich Biosciences ^e
Gofshteyn 2017, p. 35 ²⁷	Prospective, single-group, open-label cohort	FIRES (acute or chronic)	Children with prior failed treatment response	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 25 mg/kg/d (7) ^g	48 wk	5 centres; US	GW Pharmaceuticals ^e
INSYS 2017 ²⁸ (NCT02324673)	Non- randomized, open-label comparative prospective cohort	Drug-resistant epilepsy	1–17 yr with treatment- resistant seizure disorder	CBD oral solution • 10 mg/kg/d (20) • 20 mg/kg/d (20) • 40 mg/kg/d (21)	10 d	10 centres; US	INSYS Therapeutics
Kaplan 2017, p.18 ²⁹	Prospective, single-group, open-label cohort	Sturge-Weber syndrome with brain involvement	1 mo to 45 yr, diagnosis of drug-resistant epilepsy (failure of ≥2 AEDs), ≥1 quantifiable defined seizure with motor signs per mo for ≥3 mo, use of 1–5 AEDs at a stable dose for ≥ 4 wk before enrollment, stable VNS and KD or Atkins diet for ≥ 3 mo	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 25 mg/kg/d, given in 2 divided doses (5)	Up to 82 wk	NR; US	Faneca 66 Foundation and Celebrate Hope Foundation; GW Pharmaceuticals ^e

Author, yr, page no. (NCT number)	Design features	Population	Inclusion criteria	Treatments (no. randomized) ^b	Duration	No. centres; country	Funding source
Rosenberg 2017, p.e96 ³⁰	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	1–30 yr, ≥4 countable seizures with a motor component per 4 wk period; receiving stable doses of AEDs, diet therapy or VNS settings for ≥4 wk before enrolment	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 50 mg/kg/d, given in 2 divided doses (48 ^h)	12 wk	1 centre, US	GW Pharmaceuticals ^e
Sulak 2017, p. 328 ³¹	Retrospective, single-group cohort; case- series	Drug-resistant epilepsy	NR	Artisanal or hemp-based CBD and/or other related products (CBD, THC, THCA) (cohort: 47; case series: 4) ⁱ	NR	1 centre; US	No funding
Suraev 2017, p. 334 ³²	Cross- sectional	Children with epilepsy	Epilepsy, with or without current or prior use of medical cannabis Respondent: Parent or guardian Control: no cannabis use Online survey link distributed by Epilepsy Action Australia	• Cannabis products obtained from illegal suppliers with unknown composition (51); • No cannabis use (340)	Mean (SD) 15.75 (15.65) mo	NA; Australia	The Lambert Initiative for Cannabinoid Therapeutics, The University of Sydney, Epilepsy Action Australia
Treat 2017, p. 123 ³³ (Press 2015, p. 49 ³⁴)	Retrospective, single-group cohort	Drug-resistant epilepsy	30 d to 18 yr, diagnosed epilepsy and documented seizure frequency before initiation of cannabis, daily use of an oral cannabis extract	CBD, CBD + other oral cannabis extract, THCA only, or "other" (119)	Mean (range) 11.7 (0.3–57) mo	1 centre; US	NR
Devinsky 2016, p. 270 ³⁵	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	1–30 yr, ≥4 countable seizures with a motor component per 4 wk period; receiving stable doses of AEDs, diet therapy or VNS settings for ≥ 4 wk before enrolment	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 50 mg/kg/d, given in 2 divided doses (214)	12 wk	11 centres; US	GW Pharmaceuticals; Epilepsy Therapy Project of the Epilepsy Foundation; Finding a Cure for Epilepsy and Seizures
Hess 2016, p. 1617 ³⁶	Prospective, single-group, open-label cohort	TSC and drug- resistant epilepsy	Taking 1–7 AEDs at stable doses for ≥2 wk, and stable VNS settings and KD ratios for ≥4 wk	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 50 mg/kg/d, given in 2 divided	Up to 12 mo	1 centre; US	Herscot Center for Tuberous Sclerosis Complex, GW Pharmaceuticals ^e

Author, yr, page no. (NCT number)	Design features	Population	Inclusion criteria	Treatments (no. randomized) ^b	Duration	No. centres; country	Funding source
				doses (18) ^j			
Tzadok 2016, p. 41 ³⁷	Retrospective, single-group cohort	Drug-resistant epilepsy	1–18 yr, daily seizures refractory to > 7 “appropriate” AEDs and other treatment modes (VNS, surgery, KD)	CBD-enriched cannabis oil, 1 to 20 mg/kg/d (20:1 CBD to THC ratio) (74)	Median (range) 5.5 (3–12) mo	4 centres; Israel	NR
Geffrey 2015, p. 1246 ³⁸	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	4–19 yr, with concomitant use of CLO and CBD	CBD oral solution (Epidiolex, GW Pharmaceuticals), up to 25 mg/kg/d (13)	8 wk	1 centre; US	Pediatric Epilepsy Program at Massachusetts General Hospital, GW Pharmaceuticals ^e
Hussain 2015, p. 138 ³⁹	Cross- sectional	Drug-resistant epilepsy	Child with epilepsy and use of a cannabinoid product Respondent: Parent or guardian Online survey advertised online, including via the Infantile Spasms Community and the Lennox-Gastaut Foundation	CBD-enriched oil-based extracts 2–3 times/d; of parents who knew the CBC:THC ratio, 83.5% reported ratios of at least 15:1; few parents were able to provide specific CBD dosages (median 4.3 mg/kg/d; IQR 2.9–7.5) (117)	Median (IQR) 6.8 (3.8–9.8) mo	NA; US ^k	Epilepsy Therapy Project, the Milken Family Foundation, the Hughes Family Foundation, UCLA Children's Discovery and Innovation Institute
Porter 2013, p. 574 ⁴⁰	Cross- sectional	Drug-resistant epilepsy	Children with a diagnosis of treatment-resistant epilepsy and CBD-enriched cannabis use Respondent: Parent Control: children with stiripentol use Survey administered in a Facebook group composed of parents supporting the use of CBD	• CBD, ranging from less than 0.5 mg/kg/d to 28.6 mg/kg/d, with reported THC dose in the products between 0 and 0.8 mg/kg/d (19) • Stiripentol, dose NR (22)	Range: 2 wk to > 1 yr	NA; US ^k	Stanford University Institutional Epilepsy Training grant, National Center for Research Resources, National Center for Advancing Translational Sciences, National Institutes of Health
Lorenz 2004, p. 40 ⁴¹	Case series	Neurodegenerative disease, mitochondrio- pathy, posthypoxic- state, epilepsy, posttraumatic	NR	THC (Dronabinol, Marinol), 0.04 to 0.12 mg/kg/d, administered orally (7 patients) or via percutaneous gastroenterostomy tube (1	NR	NR; Germany ^m	NR

Author, yr, page no. (NCT number)	Design features	Population	Inclusion criteria	Treatments (no. randomized) ^b	Duration	No. centres; country	Funding source
		reaction		patient) (8) ^l			
Note: AED = antiepileptic drugs, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, KD = ketogenic diet, RCT = randomized controlled trial, THC = tetrahydrocannabinol, THCA = tetrahydrocannabinolic acid, TSC = tuberous sclerosis complex, VNS = vagus nerve stimulation. a. Adapted from Elliott et al. 2019.⁴² b. Number randomized for RCTs; otherwise, number of participants assigned to group at baseline. c. Interim analysis (up to November 2016). d. No funding declared by Sands et al. in the current publication. This study reports on a subgroup of patients enrolled in an Expanded Access Program in the US and previously included in Devinsky 2016³⁵, which reported funding by GW Pharmaceuticals. e. Provided Epidiolex. f. 18 participants were also included in Tzadok 2016.³⁷ g. 1 patient was also included in Devinsky 2016.³⁵ h. 24 of 48 patients in this cohort were included in Devinsky 2016.³⁵ i. Washington cohort only. j. 5 patients were also included in Devinsky 2016.³⁵ k. Obtained REB approval at a US institution. l. Six of eight included children had epilepsy. m. Based on author affiliation.							

Appendix 4: Characteristics of participants in the included studies^a

Author, yr, page no.	Treatments (no. randomized) ^b	Baseline total seizure frequency, median (IQR), mo	Age, yr, mean (SD)	Male, %	BMI, mean (SD)	No. of concomitant AEDs, mean (SD) ^c	No. previous AEDs, mean (SD) ^c	Ketogenic diet, no. (%)	VNS, no. (%)
RANDOMIZED CONTROLLED TRIALS									
Devinsky 2018, p. e1204 ¹⁹	• Placebo (7) • CBD 5 mg/kg/d (10) • CBD 10 mg/kg/d (8) • CBD 20 mg/kg/d (9)	NR	7.0 (0.9) 7.2 (1.9) 7.4 (2.1) 8.7 (1.8)	71 50 38 33	18.7 (4.0) 18.9 (4.4) 16.1 (1.5) 16.1 (2.3)	2.1 (0.9) 2.6 (1.1) 2.8 (0.5) 2.8 (0.8)	NR	0 1 (10) 2 (25) 3 (33)	0 1 (10) 0 1 (11)
Devinsky 2017, p. 2011 ²⁰	• Placebo (59) • CBD 20 mg/kg/d (61)	41.5 (NR) 24.0 (NR)	9.8 (4.8) 9.7 (4.7)	46 47	19.1 (4.7) 18.3 (4.5)	2.9 (1.0) 3.0 (1.1)	4.6 (3.3) 4.6 (4.3)	4 (7) 6 (10)	9 (15) 6 (10)
Devinsky 2018, p. 1888 ²¹	• Placebo (76) • CBD 10 mg/kg/d (73) • CBD 20 mg/kg/d (76)	180.6 (90.4–431.3) 165.0 (81.3–359.0) 174.3 (82.7–392.4)	15.3 (9.3) 15.4 (9.5) 16.0 (10.8)	58 55 59	NR	Median (range) 3 (1–5) 3 (1–5) 3 (0–5)	Median (range) 6 (1–22) 6 (0–21) 6 (1–18)	6 (8) 6 (8) 6 (8)	21 (28) 15 (21) 17 (22)
Thiele 2018, p. 1085 ²²	• Placebo (85) • CBD 20 mg/kg/d (86)	176.7 (68.6–359.5) 144.6 (72.0–385.7)	15.3 (9.8) 15.5 (8.7)	51 52	NR	Median (IQR) 3 (1–4) 3 (1–5)	Median (IQR) 6 (0–28) 6 (1–18)	10 (12) 4 (5)	25 (29) 26 (30)
NON-RANDOMIZED STUDIES									
Thiele 2019, p. 419 ¹	• CBD, up to 30 mg/kg/d (366)	NR ^d	15.9 (9.5)	54	20.2 (6.3)	Median (range) 3.0 (0–9.0)	NR	NR	NR
Devinsky 2019, p. 294 ²	• CBD, up to 30 mg/kg/d (264)	NR ^d	9.4 (4.4)	50	18.3 (4.2)	Median (range) 3.0 (1–6)	Median 4 (NR)	NR	NR
Sands 2019, p. 47 ⁴	• CBD, up to 25 mg/kg/d (26)	Range 1/mo to 150/d	9 (range 1–17)	50	NR	Mean (range) 2 (0–3)	Mean (range) 7 (4–11)	4 (15)	5 (19)
Chen 2018, p. 217 ⁵	• CBD, up to 25 mg/kg/d (40)	NR	Median 8.5 (1.6–16.6)	55	NR	Median 3 (range 1–5)	Median 9 (range 3–14)	19 (48)	2 (5)
Devinsky 2018, p. 131 ⁶	• CBD, up to 50 mg/kg/d (55)	59.4 (25–126)	32% <5 yr; 60% 6–17 yr; 8% ≥18	20	NR	Range 0 to >4; 70% taking 2 or 3 AEDs	NR	NR	NR
Freeman 2018, p. 228 ⁷	• CBD, up to 20 mg/kg/d (20)	NR	Median 10 (2–17)	25	NR	NR	NR	NR	NR
Hausman-Kedem 2018, p. 544 ²³	• CBD:THC 20:1, up to 50 mg/kg/d CBD (57)	NR	9.6 (4.9)	NR	NR	Up to 4	Range 3–17	19 (33)	18 (31)
INSYS 2018	• CBD, up to 40	NR	8.1 (5.07)	54	NR	NR	NR	NR	NR

(NCT02318602) ⁸	mg/kg/d (52)								
INSYS 2018 (NCT02551731) ⁹	• CBD, 20 or 40 mg/kg/d (9)	NR	23.0 (7.11)	33	NR	NR	NR	NR	NR
McCoy 2018, p. 1077 ¹⁰	• CBD:THC 50:1, up to 16 mg/kg/d CBD (20)	Motor seizures 17.0 (31)	10.2 (2.1–17.8)	50	Mean (range) 19.2 (15.8–30.7)	2.9 (range 1–4)	NR	2 (10)	4 (20)
Neubauer 2018, p. 79 ²⁴	• CBD, up to 16 mg/kg/d (70)	NR	Median (range) 8.0 (0.5–23.0)	57	NR	Median (range) 2 (1–4)	Median (range) 3 (1–14) ^f	0 (0)	4 (6)
Porcari 2018, p. 240 ²⁵	• CBD, up to 50 mg/kg/d (48) • CBD + CLO (54) • CLO (74)	Mean (range) 89 (0–675) 372 (0.33–4680) 437 (0.25–10800)	Mean (range) 10.4 (1.1–18) 7.8 (1.4–16) 8.5(1.4–18)	52 56 54	NR	4.5 (2.7) ^e 6.5 (2.3) 6.1 (2.1)		4 (8) 10 (19) 9 (12)	4 (8) 7 (13) 16 (21)
Ryan 2018, p. 1 ³	• Mixed cannabis- based treatments (14)	<1 to >100 per d	NR	NR	NR	NR	Range <1 to >10	NR	NR
Szaflarski 2018, p. 131 ¹⁴	• CBD, up to 50 mg/kg/d (77)	2 wk: 44.8 (10.2,232.2)	10.1 (SD 4.9)	47	NR	2.7 (1.0)	8.2 (2.8)	NR	NR
Szaflarski 2018, p. 1540 ¹²	• CBD, up to 50 mg/kg/d (607)	72 (22–196)	13.2 (0.4–62.1)	52	NR	Median (range) 3 (0–10)	NR	NR	NR
Aguirre-Velazquez 2017, p. 1 ²⁶	• Mixed cannabis- based treatments (43)	NR	7.6 (SD 4.3)	63	NR	Range 1 to > 10	Range 1–10	NR	NR
Gofshteyn 2017, p. 35 ²⁷	• CBD, up to 25 mg/kg/d (7)	Range: 4–5600	NR	71	NR	Range 4–9	Median (range) 7 (4–9)	6 (86)	2 (29)
INSYS 2017 ²⁸ (NCT02324673)	• CBD 10 mg/kg/d (20) • CBD 20 mg/kg/d (20) • CBD 40 mg/kg/d (21)	NR	7.5 (5.3) 7.7 (5.2) 7.8 (5.4)	50 65 48	NR	NR	NR	NR	NR
Kaplan 2017, p.18 ²⁹	• CBD, up to 25 mg/kg/d (5)	Range 1.5 to 33	8 yr 10 mo (6 yr, 4 mo)	20	NR	Range 1–4	Range 2–7	NR	NR
Rosenberg 2017, p.e96 ³⁰	• CBD, up to 50 mg/kg/d (48)	33.0 (16.4–108.7)	Median (range) 11.7 (3.1–27.2)	48	NR	Median (range) 3 (1–5)	NR	NR	NR
Treat 2017 ³³	• Mixed cannabis- based treatments (119)	NR	7.5 (range 0.6– 18)	NR	NR	NR	NR	NR	NR
Sulak 2017, p. 328 ³¹	• Mixed cannabis- based treatments (47)	NR	Range 2–18	43	NR	2.5 (NR)	2.5 (NR)	NR	NR
Suraev 2017, p. 334 ³²	• Mixed cannabis- based treatments (51)	12.8 (16.7) 30.6 (196.4)	Range 0–17	NR	NR	NR	CBD use: 7.64 (5.9) No CBD use: 4.65	CBD use: 12 (24) No CBD use: 31	NR

	No CBD (340)						(4.3)	(9)	
Devinsky 2016, p. 270 ³⁵	• CBD, up to 50 mg/kg/d (214)	60.5 (19.6–151)	Median (range) 10.5 (0.9–26.2)	49	NR	Median (range) 3 (0–7)	NR	13 (8)	17 (10)
Hess 2016, p. 1617 ³⁶	• CBD, up to 50 mg/kg/d (18)	Per week: 22.0 (14.8–57.4)	14 (range 2–31)	50	NR	Median (range) 3 (1–7)	Median (range) 7 (4–11)	11 (61)	11 (61)
Tzadok 2016, p. 41 ³⁷	• CBD, up to 20 mg/kg/d (74)	NR	NR	NR	NR	NR	NR	29 (39)	35 (47)
Geffrey 2015, p. 1246 ³⁸	• CBD, up to 25 mg/kg/d (13)	NR	Mean (range) 10.7 (4–19)	54	NR	Range: 1–3	NR	NR	NR
Hussain 2015, p. 138 ³⁹	• Mixed cannabis-based treatments (117)	NR	Median (IQR) 6.0 (3.0–10.0)	NR	NR	NR	Median (IQR) 8 (4.0–12.0)	53 (45)	21 (18)
Porter 2013, p. 574 ⁴⁰	• CBD, up to 28.6 mg/kg/d (19) • Stiripentol (22)	Range: 3 per wk to >100 per d	Range 2–16	33	NR	NR	Mean (range) 12 (4–17)	NR	NR
Note: AED = antiepileptic drug, CBD = cannabidiol, IQR = interquartile range, NR = not reported, SD = standard deviation, THC = tetrahydrocannabinol, VNS = vagus nerve stimulation. a. Adapted from Elliott et al. 2018.⁴² b. Number randomized for RCTs; otherwise, number of participants assigned to group at baseline. c. Unless otherwise stated. d. Baseline seizure frequency was based pre-treatment baseline from the original randomized controlled trials. e. Reported as “total AED exposure”: unclear if concomitant or previous use. f. AEDs and/or VNS.									

Appendix 5: Risk of bias assessment

Note: risk of bias assessment was conducted for studies that reported at least one outcome of interest

Author, yr, page no. (NCT record)	Risk of bias	Design features	Considerations
RANDOMIZED CONTROLLED TRIALS			
Devinsky 2018, p. e1204 (NCT02091206; GWPCARE1 Part A) ¹⁹	Low	Double-blind, placebo controlled	Low risk of bias related to allocation concealment, blinding, and outcome data
Devinsky 2017, p. 2011 (NCT02091375; GWPCARE1 Part B) ²⁰	Low	Double-blind, placebo controlled	Low risk of bias related to allocation concealment, blinding, and outcome data; potential publication bias (data not reported for some outcomes listed in protocol)
Devinsky 2018, p. 1888 (NCT02224560; GWPCARE3) ²¹	Low	Double-blind, placebo controlled	Low risk of bias related to allocation concealment, blinding, and outcome data
Thiele 2018, p. 1085 (NCT02224690; GWPCARE4) ²²	Low	Double-blind, placebo controlled	Low risk of bias related to allocation concealment, blinding, and outcome data; potential publication bias (data not reported for some outcomes listed in protocol)
NON-RANDOMIZED STUDIES			
Thiele 2019, p. 419 (NCT02224573) ¹	High	Prospective, open-label extension, single-group cohort	Potential selection bias (enrolled those who completed prior RCT); unblinded outcome assessment; lack of a comparison group; no statistical analysis
Devinsky 2019, p. 294 (NCT02224573) ²	High	Prospective, open-label extension, single-group cohort	Potential selection bias (enrolled those who completed prior RCT); unblinded outcome assessment; lack of a comparison group; no statistical analysis
Sands 2019, p. 47 ⁴	High	Prospective, single-group, open-label cohort	Potential selection bias (eligibility criteria not stated); open-label; small sample size; unblinded outcome assessment; lack of a comparison group; no statistical analysis; single centre. No funding declared; however, study reports on a subgroup of patients enrolled in an Expanded Access Program in the US and previously included in Devinsky 2016 ³⁵ , which reported funding by GW Pharmaceuticals.
Chen 2018, p. 217 ⁵	High	Prospective, single-group, open-label cohort	Small sample size; unblinded outcome assessment; lack of a comparison group; potential publication bias (data for total seizures collected but not reported)
Devinsky 2018, p. 131 ⁶	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; potential publication bias (data for total seizures collected but not reported); data collected by study funder and provided to Devinsky for analysis
Freeman 2018, p. 228 ⁷	High	Prospective, single-group, open-label cohort	Eligibility criteria not stated; limited information provided about participants; outcomes not stated in methods; unblinded outcome assessment; lack of a comparison group; no statistical analysis; time frame for outcome assessment not clear; funding source not stated; single centre
Hausman-Kedem 2018 ²³	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; important variation in the intervention; unclear time of outcome assessment; unclear analysis population; single centre

Author, yr, page no. (NCT record)	Risk of bias	Design features	Considerations
INSYS 2018 (NCT02318602) ⁸	High	Prospective, single-group, open-label cohort	Insufficient information to judge most of the criteria; unblinded outcome assessment; lack of a control group, small sample size
INSYS 2018 (NCT02551731) ⁹	High	Prospective, single-group, open-label cohort	Insufficient information to judge most of the criteria at this time; unblinded outcome assessment; lack of a control group; small sample size; study was terminated by sponsor (reason NR)
McCoy 2018, p. 1077 ¹⁰ (NCT02983695)	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment (most outcomes; EEGs assessed by blinded assessors); lack of a comparison group; small sample size; single centre
Neubauer 2018 ²⁴	High	Retrospective, single-group cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; single centre; funding source not reported; unclear timing of outcome assessment
Porcari 2018 ²⁵	High	Retrospective comparative cohort	Unblinded outcome assessment; unclear time of outcome assessment relative to treatment duration; unclear if the outcome was assessed only once; important differences in the intervention; single centre
Ryan 2018, p. 1 ³	High	Cross-sectional	Possible selection bias; unblinded outcome assessment based on parent recall; differences in exposure (cannabis) and duration of treatment; unclear time of outcome assessment relative to treatment duration; no comparison group
Szaflarski 2018, p. 1540 ¹² (Laux 2019, p. 13 ¹³)	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; subgroup data (Dravet syndrome, Lennox-Gastaut syndrome) provided in Laux 2019, p. 13 ¹³
Aguirre- Velazquez 2017 ²⁶	High	Cross-sectional	Possible selection bias; unblinded outcome assessment based on parent recall; differences in exposure (cannabis) and duration of treatment; unclear time of outcome assessment relative to treatment duration; no comparison group
Gaston 2017 ¹⁶ (NCT02695537) (Szaflarski 2017 ¹⁷ ; Szaflarski 2018, p. 131 ¹⁴ , Szaflarski 2019, p. 131) ¹⁵	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; single centre
Gofshteyn 2017 ²⁷	High	Prospective, single-group, open-label cohort	Potential selection bias; eligibility criteria not described; unblinded outcome assessment; lack of a comparison group; small sample size
INSYS 2017 ²⁸ (NCT02324673)	High	Prospective, comparative, open-label cohort	Insufficient information to judge most of the criteria; outcome assessment was unblinded, lack of a control group
Kaplan 2017 ²⁹	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; small sample size; number of centres not stated
Rosenberg 2017 ³⁰	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; small sample size; single centre; outcome assessed at a single time point
Sulak 2017 ³¹	High	Retrospective, single-group cohort; case-	Limited methods provided with insufficient detail; high potential for selection bias; likely unblinded outcome

Author, yr, page no. (NCT record)	Risk of bias	Design features	Considerations
		series	assessment; variation in treatment and duration; single centre
Suraev 2017 ³²	High	Cross-sectional	Possible selection bias; unblinded outcome assessment based on parent recall; differences in exposure (cannabis) and duration of treatment; unclear time of outcome assessment relative to treatment duration
Treat 2017 ³³ (Press 2015 ³⁴)	High	Retrospective, single-group cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; single centre; funding source not reported; unclear timing of outcome assessment. Participants in the cohort described by Press 2015 ³⁴ were all included in the Treat 2017 ³³ cohort.
Devinsky 2016 ³⁵	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group
Hess 2016 ³⁶	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; small sample size; single centre
Tzadok 2016 ³⁷	High	Retrospective, single-group cohort	Possible selection bias; unblinded outcome assessment; lack of a comparison group; funding source not reported; unclear timing of outcome assessment
Geffrey 2015 ³⁸	High	Prospective, single-group, open-label cohort	Potential selection bias; unblinded outcome assessment; lack of a comparison group; small sample size; single centre
Hussain 2015 ³⁹	High	Cross-sectional	Possible selection bias; unblinded outcome assessment based on parent recall; lack of a control group; differences in exposure (cannabis) and duration of treatment; unclear time of outcome assessment relative to treatment duration
Porter 2013 ⁴⁰	High	Cross-sectional	Possible selection bias; unblinded outcome assessment based on parent recall; control group selected from a different source population, demographic information not reported for comparison group; differences in exposure and duration of treatment; unclear time of outcome assessment relative to treatment duration.

Appendix 6: GRADE assessment, by outcome*

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	Standard care	Relative (95% CI)	Absolute (95% CI)		
Randomized controlled trials												
Seizure freedom (total seizures) (treatment duration: 14 weeks; number of patients with zero seizures during treatment)												
1	randomised trials	not serious	not serious	not serious	very serious ^{a,b,c}	none	3/61 (4.9%)	0/59 (0.0%)	RR 6.77 (0.36 to 128.38) ^d	—	⊕⊕○○ LOW	CRITICAL
Total seizure frequency (treatment duration: 14 weeks; median % reduction in monthly seizures from baseline)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	296	220	-	-19.8% (-27.0% to -12.6%)	⊕⊕⊕○ MODERATE	
Tonic-clonic seizure frequency (treatment duration: 14 weeks; median % reduction in monthly seizures from baseline)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	219	171	-	-26.7% (-38.6% to -14.6%)	⊕⊕⊕○ MODERATE	
Treatment response (treatment duration: 14 weeks; number of participants with at least a 50% reduction in total seizures from baseline)												
1	randomised trials	not serious	not serious	not serious	serious ^a	none	32/86 (37.2%)	18/85 (21.2%)	RR 1.76 (1.07 to 2.88)	161 more per 1,000 (from 15 more to 398 more)	⊕⊕⊕○ MODERATE	CRITICAL
Quality of life (child) (treatment duration: 14 weeks; Quality of Life in Childhood Epilepsy Scale, range: 0 to 100)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	296	220	-	MD 0.6 higher (2.6 lower to 3.9 higher)	⊕⊕⊕○ MODERATE	
Sleep disruption (treatment duration: 14 weeks; Sleep Disruption Rating Scale; range: 0 to 10)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	296	220	-	MD 0.3 lower (0.8 lower to 0.2 higher)	⊕⊕⊕○ MODERATE	
Status epilepticus (treatment duration: 12 weeks; number of children with status epilepticus during the treatment period)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	Standard care	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	15/296 (5.1%)	7/220 (3.2%)	RR 1.39 (0.55 to 3.47)	12 more per 1,000 (from 14 fewer to 79 more)	⊕⊕○○ LOW	
Death (treatment duration: 14 weeks; number of deaths during the treatment period)												
1	randomised trials	not serious	not serious	not serious	very serious ^{c,e}	none	1/86 (1.2%)	0/85 (0.0%)	not estimable		⊕⊕○○ LOW	
Gastrointestinal adverse events (treatment duration: 3 to 14 weeks; number of children with vomiting or diarrhea or both)												
4	randomised trials	not serious	serious ^f	not serious	serious ^{a,b}	none	89/323 (27.6%)	45/227 (19.8%)	RR 1.54 (0.92 to 2.58)	107 more per 1,000 (from 16 fewer to 313 more)	⊕⊕○○ LOW	CRITICAL
Observational (non-randomized) studies												
Seizure freedom (total seizures) (treatment duration: 1 day to 53 months; number of patients with zero seizures during treatment)												
22	observational studies	very serious ^g	serious ^h	serious ⁱ	not serious	none	The estimate of seizures freedom ranged from 0% to 20% (pooled proportion 8%, 95%CI 5% to 10%)				⊕○○○ VERY LOW	CRITICAL
Total seizure frequency (treatment duration: 11 days to 96 weeks; % reduction in seizures from baseline)												
11	observational studies	very serious ^j	very serious ^k	serious ⁱ	not serious	none	The reduction in total seizures among NRS with use of cannabis products between 30% and 90%; difference in reporting precluded pooling of effect estimates				⊕○○○ VERY LOW	
Tonic-clonic seizure frequency (treatment duration: 12 weeks to 12 months; % reduction in seizures from baseline)												
2	observational studies	very serious ^l	serious ^{k,m}	very serious ^{m,n}	serious ^e	none	Devinsky et al (2016) reported median frequency of monthly tonic-clonic seizures with any type of drug resistant epilepsy (−16%, 95%CI −60.1% to 35.3%, n=89) while Hess et al (2016) reported weekly reduction of tonic–clonic seizures: −91.4%, 95%CI −100 to −13.9%, n=6) in participants with tuberous sclerosis complex				-	
Treatment response (treatment duration: 4 weeks to 57 months; at least a 50% reduction in total seizures from baseline)												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	Standard care	Relative (95% CI)	Absolute (95% CI)		
18	observational studies	very serious ^o	very serious ^p	serious ⁱ	not serious	none	Range of reported treatment response: 24%–100%, with high heterogeneity precluding pooling. Among prospective cohort studies: 48% (95%CI 41% to 56%; 11 studies)				⊕○○○ VERY LOW	
Quality of life (child) (treatment duration: 12 to 82 weeks; assessed with: score from 0 to 100)												
3	observational studies	very serious ^q	serious ⁿ	serious ⁿ	very serious ^r	none	McCoy et al (2018) reported a statistically significant improvement in quality of life after treatment with a cannabis-based extract) Rosenberg et al (2017) reported a mean improvement of 8.12 points (SD 9.5; p<0.001) on the Quality of Life in Childhood Epilepsy scale after treatment with cannabidiol. Kaplan et al (2018) reported improved QoL for all participants, with no numerical data reported.				⊕○○○ VERY LOW	
Improved sleep (treatment duration: 2 weeks to 57 months; number of children with improved sleep)												
6	observational studies	very serious ^s	very serious	serious ⁱ	not serious	none	Pooled proportion of children who experienced an improvement in sleep (a) 8% (95%CI 4% to 11%) based on pooled analysis of 2 retrospective cohort studies; high heterogeneity among cross-sectional studies precludes pooling stud				⊕○○○ VERY LOW	
Impaired sleep (treatment duration: 10 days to 53 months; number of children with impaired sleep)												
6	observational studies	very serious ^t	not serious ^u	serious ⁱ	serious	none	Pooled proportion of children with impaired sleep: 3% (95%CI 1% to 6%)				⊕○○○ VERY LOW	
Status epilepticus (treatment duration: 1 day to 53 months; number of children with status epilepticus)												
8	observational studies	very serious ^v	not serious ^w	serious ⁱ	serious ^c	none	Pooled prevalence of status epilepticus: 7% (95% 4% to 9%)				⊕○○○ VERY LOW	
Death (treatment duration: range 1 day to 146 weeks; number of deaths)												
9	observational studies	very serious ^x	not serious ^k	serious ⁱ	very serious ^c	none	26 deaths from various causes (including 7 reports of SUDEP) were reported in 9 non-randomized studies (n = 1713)				⊕○○○ VERY LOW	
Gastrointestinal adverse events (treatment duration: 1 day to 53 months; number of children with vomiting and/or diarrhea)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	Standard care	Relative (95% CI)	Absolute (95% CI)		
19	observational studies	very serious ^y	serious ^z	serious ⁱ	not serious	none	Gastrointestinal AEs (vomiting and/or diarrhea) reported for between 2% and 60% of participants; high heterogeneity between studies precluded pooling. Important differences in estimates between study designs were noted				⊕○○○ VERY LOW	
Quality of life (caregiver)												
0									not estimable		-	
Visits to the emergency department (treatment duration: 12 weeks to 53 months; number of ER visits and/or hospital admissions per patient)												
2	Observational studies	serious ^{aa}	not serious	not serious	serious ^e	none	Chen 2018 ⁵ reported no statistically significant difference in the monthly rate of ER visits or hospital admissions in the year before treatment compared with 12 weeks of cannabidiol treatment. Sands 2019 ⁴ reported that of the children who had an ER visit during the 6-month baseline period, all had fewer visits during the treatment period.				⊕○○○ VERY LOW	
Note: footnotes appear on next page												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	Standard care	Relative (95% CI)	Absolute (95% CI)		
Note: CI = confidence interval, RR = relative risk, MD = mean difference												
*Adapted from Elliott et al. 2019. ⁴²												
a. Number of participants is less than the optimal information size. 95%CI includes important benefits and harms												
c. Rare event; confidence intervals may be misleading because of fragility												
d. Risk difference: 5% (95% –1% to 11%)												
e. Small sample size												
f. Heterogeneity (<i>I</i> ²): 52%												
g. Mix of different observational study designs (14 prospective cohort studies, 5 retrospective cohort studies, 3 cross-sectional surveys); risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in intervention												
h. Heterogeneity (<i>I</i> ²): 70%												
i. Differences in patient populations, differences in exposure (type, dose of cannabis-based products), and differences in the duration of treatment across studies												
j. Mix of different observational study designs (1 comparative retrospective cohort, 9 single-group prospective cohorts, and 1 cross sectional study); risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in intervention												
k. Not pooled												
l. Two single-arm prospective cohort studies; risk of selection bias, unblinded outcome assessment, lack of a comparison group												
m. Considerable differences in point estimates and confidence intervals between the two studies, which involved different study populations												
n. Different patient populations, different duration of treatment across studies												
o. Mix of different observational designs (12 prospective cohort studies, 4 retrospective cohort studies, 2 cross-sectional studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention												
p. Heterogeneity (<i>I</i> ²) = 80%, with differences in effect estimates between study designs												
q. Three prospective single-group cohort studies; high risk of selection bias, unblinded outcome assessment, lack of a comparison group												
r. Numerical data only reported for two of three studies; small sample size; differences in intervention across studies.												
s. Mix of different observational designs (2 retrospective cohort studies, 4 cross-sectional studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention												
t. Mix of different observational designs (5 prospective cohort studies, 1 cross-sectional study); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention												
u. Heterogeneity (<i>I</i> ²) = 0%												
v. Mix of different observational designs (7 prospective cohort studies, 1 retrospective cohort study); high risk of selection bias, unblinded outcome assessment, lack of a comparison group												
w. Heterogeneity (<i>I</i> ²) = 74%												
x. Mix of different observational designs (6 prospective single-arm cohort studies, 2 retrospective single-arm cohort studies, 1 case series); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention												
y. Mix of different observational designs (14 prospective cohort studies, 2 retrospective cohort study, 3 cross-sectional studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention												
z. Heterogeneity (<i>I</i> ²) = 95%; Vomiting alone <i>I</i> ² = 87%; Diarrhea alone: <i>I</i> ² = 95%												
aa. Both studies at high risk of bias owing to small sample size; unblinded outcome assessment; lack of a comparison group												

Appendix 7: Summary of outcomes by epilepsy syndrome

A. Dravet syndrome^a

A total of nine studies (two RCTs,^{19,20} seven NRS^{2,10,33,35,38–40}) have reported outcomes among participants with Dravet syndrome as part of subgroup analysis or the entire study population. No outcome data were available for caregiver quality of life or visits to the emergency department.

Outcome (no. of studies)	Author, yr	Study design; duration	No. with DS	Treatment	Finding
Seizure freedom (4 studies)	Devinsky 2019 ²	Prospective single-group cohort; Median (range) 274 (1–512) d	Whole population (104)	• CBD, up to 20 mg/kg/d	No participants were seizure free over the entire treatment period; however, 3 (3%) were seizure free for the final 12 weeks of treatment.
	McCoy 2018 ¹⁰	Prospective single-group cohort; 20 wk	Whole population (20)	• CBD:THC, up to 16 mg/kg/d CBD	11% of children (2/19) who received treatment became seizure free
	Devinsky 2017 ²⁰	RCT; 14 wk	Whole population (120)	• CBD, 20 mg/kg/d • Placebo	5% (3/61) of children who received CBD became seizure free (0/59 in the placebo group)
	Hussain 2015 ³⁹	Cross-sectional; Median (IQR): 6.8 (3.8–9.8) mo	Subgroup (15)	• Mixed cannabis-based treatments; type and dose NR	13% of children became seizure free
Seizure frequency (all types) (4 studies)	Devinsky 2019 ²	Prospective single-group cohort; up to 48 wk	Whole population (104)	• CBD, up to 30 mg/kg/d	Change in median monthly seizure frequency (IQR) from baseline ^b : • 12 wk: –40% (–82%, 3%) • 24 wk: –49% (–84%, –5%) • 36 wk: –39% (–82%, 17%) • 48 wk: –51% (–86%, 7%)
	Devinsky 2017 ²⁰	RCT; 14 wk	Whole population (120)	• CBD 20 mg/kg/d • Placebo	Adjusted median change in monthly seizure frequency: • Placebo: –9% • CBD: –28.6% Median difference v. placebo (95%CI): –19.2% (–39.25% to –1.17%)
	Devinsky	Prospective single-group cohort;	Subgroup (32)	• CBD, up to 50 mg/kg/d	Change in median (IQR) monthly seizure frequency from

	2016 ³⁵	12 wk			baseline: -42.7% (-64.6% to -20.6%) among children administered CBD (up to 50 mg/kg/d)
	Geffrey 2015 ³⁸	Prospective single-group cohort; 8 wk	Subgroup (3)	• CBD, up to 25 mg/kg/d	The 3 children with CBD (up to 25 mg/kg/d) and CLO use had reported reductions of 81%, 68% or 30% in seizures from baseline
Treatment response^c (5 studies)	Devinsky 2019, p. 294 ²	Prospective single-group cohort; up to 48 wk	Whole population (104)	• CBD, up to 30 mg/kg/d	12 wk 47/102 (46) 24 wk: 45/93 (48) 36 wk: 38/87 (44) 48 wk: 38/75 (51)
	McCoy 2018 ¹⁰	Prospective single-group cohort; 20 wk	Whole population (20)	• CBD:THC, up to 16 mg/kg/d CBD	12/19 (63)
	Geffrey 2015 ³⁸	Prospective single-group cohort; 8 wk	Subgroup (3)	• CBD, up to 25 mg/kg/d	Two children with CBD and CLO use (67%) experienced a ≥ 50% response to CBD (up to 25 mg/kg/d)
	Treat 2017 ³³	Retrospective single-group cohort; mean (range): 11.7 (0.3–57) mo	Subgroup (17)	• Mixed cannabis-based products	1 child (5.9%) had a ≥ 50% reduction in seizures (mixed cannabis-based products, dose NR)
	Porter 2013 ⁴⁰	Cross-sectional study; range: 2 wk to > 1 yr	Subgroup (13)	• CBD, up to 28.6 mg/kg/d	9 children (69%) had a ≥ 50% reduction in seizures (CBD 0.5 to 28.6 mg/kg/d)
Quality of life; child (2 studies)	McCoy 2018 ¹⁰	Prospective single-group cohort; 20 wk	Whole population (20)	• CBD:THC, up to 16 mg/kg/d CBD	Statistically significant difference between groups after treatment in favour of CBD on the 100-point Quality of Life in Childhood Epilepsy score; Baseline: mean (SD) 39.60 (11.1); after treatment: 46.02 (14.2)
	Devinsky 2017 ²⁰	RCT; 14 wk	Whole population (120)	• CBD 20 mg/kg/d • Placebo	Mean difference between groups after treatment: 1.5 (95%CI -3.8 to 6.8) on the 100-point Quality of Life in Childhood Epilepsy score; positive score favours CBD
Quality of life; caregiver (No studies)		—	—	—	—
Sleep (1 study)	Devinsky 2017 ²⁰	RCT; 14 wk	Whole population (120)	• CBD 20 mg/kg/d • Placebo	No significant difference in sleep disturbances between the CBD and placebo groups (adjusted mean difference -0.4 [95%CI -1.5 to 0.7] ^d)
Status epilepticus (2 studies)	Devinsky 2019 ²	Prospective single-group cohort; Median (range) 274 (1–512) d	Whole population (264)	• CBD, up to 30 mg/kg/d	• CBD (total): 29/264 (11%) • CBD ≤ 20 mg/kg/d: 17/190 (8.9%) • CBD > 20 mg/kg/d: 12/74 (16.2%)
	Devinsky 2017 ²⁰	RCT; 14 wk	Whole study population (120)	• CBD 20 mg/kg/d • Placebo	Status epilepticus reported for 3 (n = 61) children who received CBD and 3 (n = 59) children who received placebo
Death (4 studies)	Devinsky 2019 ²	Prospective single-group cohort; Median (range) 274 (1–512) d	Whole population (264)	• CBD, up to 30 mg/kg/d	2 deaths reported, both owing to SUDEP and reported to be unrelated to study drug

	McCoy 2018 ¹⁰	Prospective single-group cohort; 20 wk	Whole population (20)	• CBD:THC, up to 16 mg/kg/d CBD	1 death reported, due to SUDEP (reported to be unrelated to study drug)
	Devinsky 2017 ²⁰	RCT; 14 wk	Whole population	• CBD 20 mg/kg/d • Placebo	No deaths reported among children in either the CBD (n = 61) or placebo group (n = 59)
	Devinsky 2018 ¹⁹	RCT; 3 wk	Whole population (34)	• CBD 5, 10 or 20 mg/kg/d • Placebo	No deaths reported among children who received CBD (n = 27) or placebo (n = 7)
Gastrointestinal AEs (4 studies)	Devinsky 2019 ²	Prospective single-group cohort; Median (range) 274 (1–512) d	Whole population (264)	• CBD, up to 30 mg/kg/d	Vomiting reported for 14% (37/264) of children who received CBD (12.6% for doses ≤ 20 mg/kg/d; 17.6% for doses > 20 mg/kg/d. Diarrhea reported for 35% (91/264) of children who received CBD (31.6% for doses ≤ 20 mg/kg/d; 41.9% for doses > 20 mg/kg/d.
	McCoy 2018 ¹⁰	Prospective single-group cohort; 20 wk	Whole population (20)	• CBD:THC, up to 16 mg/kg/d CBD	Diarrhea reported for 31.6% of children who received CBD (6/20); vomiting NR
	Devinsky 2017 ²⁰	RCT; 14 wk	Whole population (120)	• CBD 20 mg/kg/d • Placebo	Vomiting reported for 14.8% (6/61) of children who received CBD and 5% (3/59) of children in the placebo group; Diarrhea reported for 31.1% (19/61) and 10.2% (6/59) of children in each group, respectively
	Devinsky 2018 ¹⁹	RCT; 3 wk	Whole study population (34)	• CBD 5, 10 or 20 mg/kg/d • Placebo	Vomiting reported for 11% of children who received CBD (3/27) and zero children in the placebo group (n = 7); diarrhea NR
Visits to the ER (No studies)		—	—	—	—
Note: AE = adverse event, CBD = cannabidiol, CI = confidence interval, CLO = clobazam, ER = emergency room, IQR = interquartile range, NR = not reported, RCT = randomized controlled trial, SD = standard deviation, THC = tetrahydrocannabinol. a. Updated from Elliott et al. 2019.⁴² b. Change from baseline of prior RCT. c. At least a 50% reduction in total seizures from baseline. d. Sleep Disruption Rating Scale score, assessed on a numerical rating scale from 0 to 10, with higher scores indicating greater disruption. A negative mean difference favours cannabidiol.					

B. Lennox–Gastaut syndrome^a

In total, two RCTs^{21,22} and six NRS^{1,25,33,35,39,40} studies have involved children with Lennox-Gastaut syndrome as part of subgroup analyses or the entire study population. No outcome data were available for quality of life of caregivers or visits to the emergency department.

Outcome (no. of studies)	Author, yr	Study design; duration	No. with LGS	Treatment	Finding
Seizure freedom (2 studies)	Thiele 2019 ¹	Prospective single-group cohort; median (range) 263 (3–430) d	Whole population (366)	• CBD, up to 30 mg/kg/d	No participants were seizure free over the entire treatment period; however, 6 (1.6%) were seizure free for the final 12 weeks of treatment.
	Hussain 2015 ³⁹	Cross-sectional; median (IQR): 6.8 (3.8–9.8) mo	Subgroup (53)	• Mixed cannabis-based treatments	Among children with Lennox-Gastaut syndrome or infantile spasms, 13% achieved seizure freedom (type and dose of cannabis-based treatment NR)
Seizure frequency (all seizures) (4 studies)	Thiele 2018 ²²	RCT; 14 wk	Whole population (171)	• Placebo • CBD, 20 mg/kg/d	Change in median (IQR) monthly seizure frequency: • Placebo: –13.7% (–45.0% to 7.3%) • CBD 20 mg/kg/d: –41.2% (–62.9% to –13.0%) Median difference v. placebo (95%CI): –21.1% (–33.3% to –9.4%)
	Devinsky 2018 ²¹	RCT; 14 wk	Whole population (225)	• Placebo • CBD, 10 mg/kg/d • CBD, 20 mg/kg/d	Reduction in median monthly seizure frequency: • Placebo: –18.5% • CBD 10 mg/kg/d: –36.4% • CBD 20 mg/kg/d: –38.4% Median difference v. placebo (95%CI): • CBD: 10 mg/kg/d: –19.5% (–30.4% to –7.5%); • CBD 20 mg/kg/d: –18.8% (–31.8% to –4.4%)
	Thiele 2019 ¹	Prospective single-group cohort; median (range) 263 (3–430) d	Whole population (366)	• CBD, up to 30 mg/kg/d	Change in median monthly seizure frequency (IQR) from baseline ^b : • 12 wk: –48% (–75%, 12%) • 24 wk: –55% (–81%, –25%) • 36 wk: –58% (–81%, –24%) • 48 wk: –57% (–82%, –22%)
	Devinsky 2016 ³⁵	Prospective single-arm cohort; 12 wk	Subgroup (30)	• CBD, up to 50 mg/kg/d	Change in median (IQR) monthly seizure frequency from baseline: –35.5% (–55.1% to –16.4%) among children who received CBD (up to 50 mg/kg/d)

Seizure frequency (tonic-clonic seizures) (2 studies)	Devinsky 2018 ²¹	RCT; 14 wk	Whole population (225)	• Placebo • CBD, 10 mg/kg/d • CBD, 20 mg/kg/d	Median difference (95% CI) v. placebo in monthly seizures • CBD 10 mg/kg/d: -39.92% (-64.55% to -19.66%) • CBD 20 mg/kg/d: -27.95% (-51.99% to -2.86%)
	Thiele 2018 ²²	RCT; 14 wk	Whole population (171)	• Placebo • CBD, 20 mg/kg/d	Median difference (95% CI) v. placebo in monthly seizures -22.77 (95%CI -44.94% to 0.37%)
Treatment response^c (5 studies)	Thiele 2018 ²²	RCT; 14 wk	Whole population (171)	• Placebo • CBD, 20 mg/kg/d	37% of children in the CBD group (n = 86) had a ≥ 50% reduction in seizures; compared with 21% in the placebo group (n = 85). Odds ratio 2.21 (95%CI 1.12, 4.35) in favour of CBD
	Thiele 2019 ¹	Prospective single-group cohort; median (range) 263 (3–430) d	Whole population (366)	• CBD, up to 30 mg/kg/d	After 12 weeks of treatment, 48% of children had ≥ 50% reduction in seizures (175/364); 24 wks: 184/334 (55%); 36 wk: 182/314 (58%); 48 wk: 123/209 (59%)
	Porcari 2018 ²⁵	Retrospective comparative cohort; up to 2.5 yr	Subgroup (79)	• CBD, up to 50 mg/kg/d • CBD + CLO • CLO	58% (7/12) of children who received CBD alone had a ≥ 50% reduction from baseline, compared with 52% (14/27) who received CBD and concomitant CLO and 40% (16/40) who received CLO alone
	Treat 2017 ³³	Retrospective single-arm cohort; mean 11.7 (range 0.7–57) mo	Subgroup (19)	• Mixed cannabis-based products	57.9% of children with LGS had a ≥ 50% reduction in seizures after treatment (mixed cannabis-based products, dose NR)
	Porter 2013 ⁴⁰	Cross-sectional; Range: 2 wk to > 1 yr	Subgroup (1)	• CBD, up to 28.6 mg/kg/d	The one child with LGS in this study had a more than 80% reduction in seizures with CBD
Quality of life: child (2 studies)	Thiele 2018 ²²	RCT; 14 wk	Whole population (171)	• Placebo • CBD, 20 mg/kg/d	Adjusted ^d treatment difference: 3.7 (95% CI -3.3 to 10.7) on the 100-point Quality of Life in Childhood Epilepsy score; positive score indicates difference in favour of CBD
	Devinsky 2018 ²¹	RCT; 14 wk	Whole population (225)	• Placebo • CBD, 10 mg/kg/d • CBD, 20 mg/kg/d	Adjusted ^d mean difference between groups after treatment ^e : • 10 mg/kg/d v. placebo: 1.6 (-4.5 to 7.8) • 20 mg/kg/d v. placebo -5.1 (-11.4 to 1.2)
Quality of life: caregiver (No studies)	—	—	—	—	—
Sleep (2 studies)	Thiele 2018 ²²	RCT; 14 wk	Whole population (171)	• Placebo • CBD, 20 mg/kg/d	Adjusted ⁺ mean difference (95%CI) between groups after treatment: -0.2 (-1.1 to 0.7) on the Sleep Disruption Rating Scale (negative scores favour CBD); sleep apnea reported for 1 participant (1.2%) in the CBD group; none reported in placebo group
	Devinsky 2018 ²¹	RCT; 14 wk	Whole population (225)	• Placebo • CBD, 10 mg/kg/d • CBD, 20 mg/kg/d	Adjusted ⁺ mean difference (95%CI) between groups after treatment on the Sleep Disruption Rating Scale (negative scores favour CBD) • 10 mg/kg/d v. placebo: -0.8 (-1.7 to 0.1)

					• 20 mg/kg/d v. placebo: -0.3 (-1.2 to 0.6)
Status epilepticus (2 studies)	Thiele 2018 ²²	RCT; 14 wk	Whole population (171)	• Placebo • CBD, 20 mg/kg/d	Status epilepticus reported for one child each in the placebo (n = 85; 1.2%) and CBD (n = 86; 1.2%) groups
	Devinsky 2018 ²¹	RCT; 14 wk	Whole population (225)	• Placebo • CBD, 10 mg/kg/d • CBD, 20 mg/kg/d	Status epilepticus reported for 3 children in the placebo group (n=76; 3.9%), 7 in the CBD 10 mg/kg/d (n = 67; 10.4%), and 4 in the CBD 20 mg/kg/d (n = 82; 4.9%) ^f
	Thiele 2019 ¹	Prospective single-group cohort; median (range) 263 (3–430) d	Whole population (366)	• CBD, up to 30 mg/kg/d	Status epilepticus was reported for 7.1% (26/366) of children who received CBD; with 5.7% (11/192) among those who received a dose ≤ 20 mg/kg/d and 8.6% (15/174) among those who received > 20 mg/kg/d
Death (1 study)	Thiele 2018 ²²	RCT; 14 wk	Whole population (171)	• Placebo • CBD, 20 mg/kg/d	1 death reported in the CBD group, attributed to respiratory failure and reported to be unrelated to treatment (n = 86; 1.2%); zero deaths in the placebo group (n = 85)
	Thiele 2019 ¹	Prospective single-group cohort; median (range) 263 (3–430) d	Whole population (366)	• CBD, up to 30 mg/kg/d	4 deaths reported: Respiratory failure as a complication of aspiration pneumonia (1), bowel obstruction with necrotic bowel and severe septic shock (1), seizure disorder as primary cause with severe cerebral and pulmonary edema as secondary causes (1), and complications of seizure disorder due to perinatal hypoxic ischemic encephalopathy (1); All deaths were reported to be unrelated to study drug
Gastrointestinal AEs (3 studies)	Thiele 2018 ²²	RCT; 14 wk	Whole population (171)	• Placebo • CBD, 20 mg/kg/d	Vomiting reported for 9 children in the CBD group (10%; n = 86) and 14 (16%; n = 85) placebo group; diarrhea reported for 16 children in the CBD group (19%) and 7 (8%) in the placebo group
	Devinsky 2018 ²¹	RCT; 14 wk	Whole population (225)	• Placebo • CBD, 10 mg/kg/d • CBD, 20 mg/kg/d	Vomiting reported for 9 children in the placebo group (n=76; 12%), 4 in the CBD 10 mg/kg/d (n = 67; 6%), and 10 in the CBD 20 mg/kg/d (n = 82; 12%); diarrhea reported for 6 children in the placebo group (8%), 7 in the CBD 10 mg/kg/d (10%), and 12 in the CBD 20 mg/kg/d (15%) ^f
	Thiele 2019 ¹	Prospective single-group cohort; median (range) 263 (3–430) d	Whole population (366)	• CBD, up to 30 mg/kg/d	Vomiting reported for 18% (65/366) of children who received CBD (15.6% for doses ≤ 20 mg/kg/d; 20.1% for doses > 20 mg/kg/d). Diarrhea reported for 26.8% (98/366) of children who received CBD (22.4% for doses ≤ 20 mg/kg/d; 31.6% for doses > 20 mg/kg/d).
Visits to the ER (No studies)	—	—	—	—	—
Note: AE = adverse events, CBD = cannabidiol, CI =confidence interval, CLO = clobazam, ER = emergency room, IQR = interquartile range, LGS = Lennox-Gastaut syndrome, NR = not reported, RCT = randomized controlled trial.					

- a. Updated from Elliott et al. 2019.⁴²
- b. Reduction from baseline in prior RCT.
- c. At least a 50% reduction in total seizures from baseline.
- d. Adjusted for baseline score and age group; 100-point Quality of Life in Childhood Epilepsy score, positive score indicates difference in favour of CBD.
- e. Analysis included 38 participants in the placebo group, 36 in 10 mg/kg/d group, and 33 in 20 mg/kg/d group.
- f. 6 participants in the 10 mg/kg/d group received a dose above the target and were included in the 20 mg/kg/d group for the safety analysis.

(c) Doose syndrome, Tuberous sclerosis complex, Sturge-Weber syndrome, Febrile Infection-Related Epilepsy syndrome (FIREs)

For a summary of the evidence related to these conditions, see Elliott et al. Cannabis-based products for pediatric epilepsy: A systematic review. *Epilepsia* 2019;60:6-19.⁴² No additional studies related to the use of cannabis for these conditions were published between April 2018 and May 2019.

Appendix 8: Evidence summary — Seizure freedom

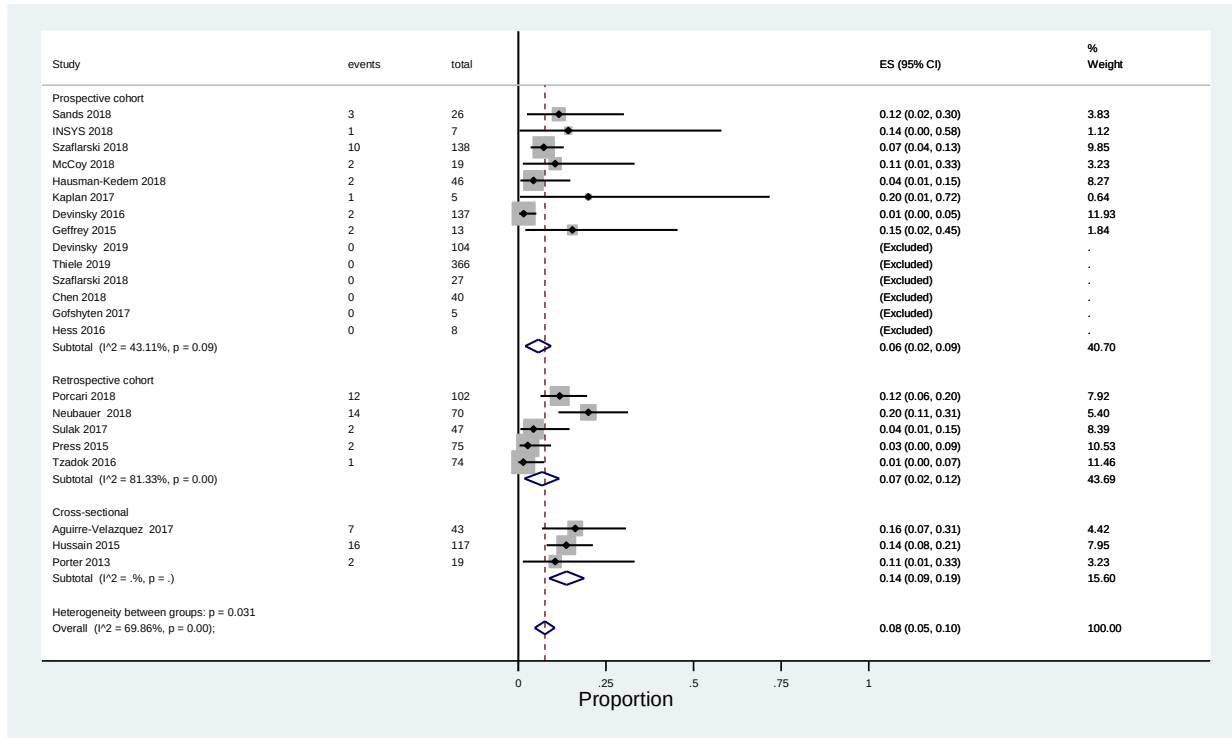
Note: freedom from all seizure types

A. All studies^a

Author, yr	Study design	Population	Treatments	Duration	No. events/no. in group (%) ^b	
					Cannabis-based treatment	Control
Devinsky 2017, p. 2011 ²⁰	RCT	Dravet syndrome	• CBD, up to 20 mg/kg/d • Placebo	14 wk	3/61 (5)	0/59 (0)
Devinsky 2019, p. 294 ²	Prospective single-group cohort	Dravet syndrome	• CBD, up to 30 mg/kg/d	Median (range) 274 (1–512) d	Overall: 0/104 (0) Final 12 wk: 3/104 (2.9)	NA
Thiele 2019, p. 419 ¹	Prospective single-group cohort	Lennox-Gastaut Syndrome	• CBD, up to 30 mg/kg/d	Median (range) 263 (3–430) d	Overall: 0/366 (0) Final 12 wk: 6/366 (1.6)	NA
Sands 2019, p. 47 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 25 mg/kg/d	Mean (range) 21.8 (4–53) mo	3/26 (11.5)	NA
Chen 2018, p. 217 ⁵	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 25 mg/kg/d	12 wk	0/40 (0)	NA
Hausman-Kedem 2018 ²³	Prospective single-group cohort	Drug-resistant epilepsy	• CBD:THC, up to 50 mg/kg/d CBD	Median (range) 18 (3–33) mo	2/46 (4)	NA
INSYS 2018 (NCT02551731) ⁹	Prospective single-group cohort	Infantile spasms	• CBD, up to 40 mg/kg/d	14 d	1/7 (14)	NA
McCoy 2018, p. 1077 ¹⁰	Prospective single-group cohort	Dravet syndrome	• CBD:THC, up to 16 mg/kg/d CBD	20 wk	2/19 (11)	NA
Szaflarski 2018, p. 131 ¹⁴	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d	• 12 wk • 24 wk • 48 wk	• 6/70 (9) • 4/43 (9) • 0/27 (0)	NA
Szaflarski 2018, p. 1540 ¹²	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d	• 12 wk • 24 wk • 48 wk • 72 wk • 96 wk	• 26/431 (6) • 25/412 (6) • 17/282 (6) • 16/197 (8) • 10/138 (7)	NA
Gofshteyn 2017, p. 35 ²⁷	Prospective single-group cohort	FIRES (acute)	• CBD, up to 25 mg/kg/d	4 wk	1/2 (50)	NA
		FIRES (chronic)	• CBD, up to 25 mg/kg/d	• 4 wk • 48 wk	1/5 (20) 0/5 (0)	NA
Kaplan 2017, p.18 ²⁹	Prospective single-group cohort	Sturge-Weber syndrome	• CBD, up to 25 mg/kg/d	• 14 wk • Most recent visit (6–82 wk)	0/5 (0) 1/5 (20)	NA
Devinsky 2016, p. 270 ³⁵	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d	12 wk	2/137 (1)	NA
Hess 2016, p. 1617 ³⁶	Prospective single-group cohort	Tuberous sclerosis complex	• CBD, up to 50 mg/kg/d	• 3 mo • 12 mo	1/18 (0.6) 0/8 (0)	NA
Geffrey 2015, p. 1246 ³⁸	Prospective single-group cohort	Drug-resistant epilepsy taking	• CBD, up to 25 mg/kg/d	8 wk	2/13 (15)	NA

Author, yr	Study design	Population	Treatments	Duration	No. events/no. in group (%) ^b	
					Cannabis-based treatment	Control
		CLO				
Neubauer 2018, p. 79 ²⁴	Retrospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 16 mg/kg/d	Median (range) 14.0 (6–29) mo	14/70 (20)	NA
Porcari 2018, p. 240 ²⁵	Retrospective comparative cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d • CBD + CLO • CLO	Mean (SD), yr 1.1 (0.8) 1.3 (1.0) 2.5 (1.9)	CBD: 7/48 (15) CBD+CLO: 5/54 (9)	CLO: 8/74 (11)
Tzadok 2016, p. 41 ³⁷	Retrospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 20 mg/kg/d	• ≥ 3 mo	1/74 (1)	NA
Press 2015, p. 49 ³⁴	Retrospective single-group cohort	Drug-resistant epilepsy	• Mixed cannabis-based treatments	Mean (range) 5.59 (1–24) mo	2/75 (3)	NA
Sulak 2017, p. 328 ³¹	Retrospective single-group cohort	Drug-resistant epilepsy ^c	• Mixed cannabis-based treatments	NR	2/47 (4)	NA
Aguirre- Velazquez 2017, p. 1 ²⁶	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments	<1 to 12 mo	7/43 (16)	NA
Hussain 2015, p. 138 ³⁹	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments	Median (IQR) 6.8 (3.8–9.8) mo	16/117 (14)	NA
Porter 2013, p. 574 ⁴⁰	Cross-sectional	Drug-resistant epilepsy	• CBD, up to 28.6 mg/kg/d	> 1 yr	2/19 (11)	NA
Note: CBD = cannabidiol, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, NA = not applicable, RCT = randomized controlled trial, THC = tetrahydrocannabinol. a. Adapted from Elliott et al. 2019. ⁴² b. No. randomized for RCTs; otherwise, no. included in efficacy analysis. c. Washington cohort						

B. Non-randomized studies



Appendix 9: Evidence summary — Seizure frequency

A) Total seizures^a

Author, yr	Study design	Population	Treatments ^b (no. randomized)	Duration (no. in group at each time)	Seizure frequency ^c ; median per month ^d		Effect estimate
					Baseline	After treatment	
Devinsky 2018, p. 1888 ²¹	RCT	Lennox- Gastaut syndrome	- Placebo (76) - CBD 10 mg/kg/d (73) - CBD 20 mg/kg/d (76)	14 wk: Placebo (76); CBD 10 mg/kg/d (73); CBD 20 mg/kg/d (76)	180.6 (IQR: 90.4–431.3) 165.0 (81.3–359.0) 174.3 (82.7–392.4)	NR	Change in median monthly seizure frequency: - Placebo: –18.5% - CBD 10 mg/kg/d: –36.4% - CBD 20 mg/kg/d: –38.4% Median difference v. placebo (95%CI): - CBD: 10 mg/kg/d: –19.5% (–30.4% to –7.5%) - CBD 20 mg/kg/d: –18.8% (–31.8% to –4.4%)
Thiele 2018, p. 1085 ²²	RCT	Lennox- Gastaut syndrome	- Placebo (85) - CBD 20 mg/kg/d (86)	14 wk: Placebo (85); CBD (86)	176.7 144.6	128.7 83.8	Change in median (IQR) monthly seizure frequency: - Placebo: –13.7% (–45.0% to 7.3%) - CBD 20 mg/kg/d: –41.2% (–62.9% to –13.0%) Median difference v. placebo (95%CI): –21.1% (–33.3% to –9.4%)
Devinsky 2017, p. 2011 ²⁰	RCT	Dravet syndrome	- Placebo (59) - CBD 20 mg/kg/d (61)	14 wk: Placebo (59); CBD (61)	41.5 24.0	31.1 13.7	Adjusted median change: - Placebo: –9% - CBD: –28.6% Median difference v. placebo (95%CI): –19.2% (95%CI –39.25% to –1.17%)
Thiele 2019, p. 419 ¹	Prospective single-group cohort	Lennox- Gastaut syndrome	CBD, up to 30 mg/kg/d (366)	12 wk (364) 24 wk (334) 36 wk (314) 48 wk (209)	NR	NR	Change in median monthly seizure frequency (IQR) from baseline ^e : 12 wk: –48% (–75%, 12%) 24 wk: –55% (–81%, –25%) 36 wk: –58% (–81%, –24%) 48 wk: –57% (–82%, –22%)
Devinsky 2019, p. 294 ²	Prospective single-group cohort	Dravet syndrome	CBD, up to 30 mg/kg/d (104)	12 wk (102) 24 wk (93) 36 wk (87) 48 wk (75)	NR	NR	Change in median monthly seizure frequency (IQR) from baseline ^e : 12 wk: –40% (–82%, 3%) 24 wk: –49% (–84%, –5%) 36 wk: –39% (–82%, 17%) 48 wk: –51% (–86%, 7%)
Porcari 2018, p.	Retrospective	Drug-	CBD, up to 50	Mean (SD), yr	Mean (range)	Mean (SE)	Change in seizures from baseline:

Author, yr	Study design	Population	Treatments ^b (no. randomized)	Duration (no. in group at each time)	Seizure frequency ^c ; median per month ^d		Effect estimate
					Baseline	After treatment	
240 ²⁵	comparative cohort	resistant epilepsy	mg/kg/d (48) • CBD + CLO (54) • CLO (74)	1.1 (0.8), (48) 1.3 (1.0), (54) 2.5 (1.9), (74)	89 (0–675) 372 (0.3–4680) 437 (0.2–10,800)	63 (21) 252 (88) 198 (58)	• CBD alone: –30% • CBD + CLO: –33% • CLO: –55%
Szaflarski 2018, p. 131 ¹⁴	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d (77)	• 12 wk (69) • 24 wk (43) • 48 wk (27)	Per 2 wk period: 44.8 (IQR: 10.2–232.2)	Per 2 wk period: • 12 wk: 23 (IQR: 45, 86.8) • 24 wk: 25.7 (3, 80.4) • 48 wk: 9.2 (4.5, 55)	Change in median seizure frequency per 2 wk period from baseline: • 12 wk: –49% • 24 wk: –43% • 48 wk: –79%
Szaflarski 2018, p. 1540 ¹²	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d (607)	• 12 wk (431) • 24 wk (412) • 48 wk (282) • 72 wk (197) • 96 wk (138)	72 (IQR: 22–196)	NR	Change in median monthly seizure frequency (90%CI) from baseline: • 12 wk: –48% (–56%, –42%) • 24 wk: –46% (–50%, –40%) • 48 wk: –47% (–56%), –42% • 72 wk: –53% (–65%, –47%) • 96 wk: –49% (–61%, –40%)
Gofshteyn 2017, p. 35 ²⁷	Prospective single-arm cohort	FIRES (chronic)	• CBD up to 25 mg/kg/d (5)	48 wk (5)	NR	NR	Change in mean (SD) monthly seizures from baseline: 4 wk: –90.94% (19.9%) 48 wk: –63.3% (29.3%)
INSYS 2017 ²⁸ (NCT02324673)	Prospective, comparative cohort	Drug-resistant epilepsy	• CBD 10 mg/kg/d (20) • CBD 20 mg/kg/d (20) • CBD 40 mg/kg/d (21)	11 d 10 mg/ml (19) 20 mg/ml (13) 40 mg/kg/d (19)	NR	NR	Mean (SD), seizures per day: CBD 10 mg/kg/d: –0.8 (1.55) CBD 20 mg/kg/d: –0.8 (1.59) CBD 40 mg/kg/d: –2.9 (7.69)
Devinsky 2016, p. 270 ³⁵	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d (214)	12 wk (137)	60 (range: 22.0–131.8)	NR	Change in median (IQR) monthly seizure frequency from baseline: –34.6% (–66.7% to –9.8%)
Hess 2016, p. 1617 ³⁶	Prospective single-arm cohort	Tuberous sclerosis complex	• CBD up to 50 mg/kg/d (18)	3 mo (8)	22.0 (IQR: 14.8–57.4) per wk	13.2 (IQR: 5.06–22.1) per wk	Change in median (IQR) weekly seizure frequency from baseline: –48.8% (–69.1% to –11.1%)
Geffrey 2015, p. 1246 ³⁸	Prospective single-arm cohort	Drug-resistant epilepsy taking CLO	• CBD, up to 25 mg/kg/d (13)	8 wk (13)	NR	NR	Mean (SD) change in monthly seizures from baseline: –51% (56%)

Author, yr	Study design	Population	Treatments ^b (no. randomized)	Duration (no. in group at each time)	Seizure frequency ^c ; median per month ^d		Effect estimate
					Baseline	After treatment	
Suraev 2017, p. 334 ³²	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products (51)	Mean (SD) 15.75 (15.65) mo (51)	Mean (SD) 12.8 (16.7) 30.6 (196.4)	Mean (SD) 2.5 (73.2) NA	Change in seizures from baseline with cannabis-based product: –80%
Note: CBD = cannabidiol, CI = confidence interval, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, NR = not reported, RCT = randomized controlled trial, SD = standard deviation, SE = standard error. a. Adapted from Elliott et al. 2019.⁴² b. Number randomized for RCTs; otherwise, number of participants included in efficacy analysis. c. Total seizures, includes convulsive and non-convulsive seizures. d. Unless otherwise stated. e. Change from baseline seizure frequency in prior RCT.							

B. Tonic-clonic seizure frequency^a

Author, yr, page no.	Study design	Population	Treatments (no. in group ^b)	Duration	Seizure frequency; median per month		Effect estimate
					Baseline	After treatment	
Devinsky 2018, p. 1888 ²¹	RCT	Lennox-Gastaut syndrome	• Placebo (34) • CBD 10 mg/kg/d (37) • CBD 20 mg/kg/d (41)	14 wk	NR	NR	Median difference (95% CI) v. placebo in monthly seizures • CBD 10 mg/kg/d: –39.92% (–64.55% to –19.66%) • CBD 20 mg/kg/d: –27.95% (–51.99% to –2.86%)
Devinsky 2017, p. 2011 ²⁰	RCT	Dravet syndrome	• Placebo (52) • CBD 20 mg/kg/d (55)	14 wk	NR	NR	Median difference (95% CI) v. placebo in monthly seizures –22.01% (–42.52% to –2.11%)
Thiele 2018, p. 1085 ²²	RCT	Lennox-Gastaut syndrome	• Placebo (53) • CBD 20 mg/kg/d (49)	14 wk	NR	NR	Median difference (95% CI) v. placebo in monthly seizures –22.77 (–44.94% to 0.37%)
Devinsky 2016, p. 270 ³⁵	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d (89)	12 wk	10 (4–25) ^c	NR	Change in median (95% CI) monthly seizure frequency from baseline: –16.0% (–60.1% to 35.3%)
Hess 2016, p. 1617 ³⁶	Prospective single-arm cohort	Tuberous sclerosis syndrome	• CBD up to 50 mg/kg/d (6)	12 mo	NR	NR	Change in median (95% CI) weekly seizure frequency from baseline: –91.4% (–100% to –13.9%)
Note: CBD = cannabidiol, CI= confidence interval, NR = not reported, RCT = randomized controlled trial. a. Adapted from Elliott et al. 2019.⁴² b. Number randomized for RCTs; otherwise, number of participants included in efficacy analysis. c. Unclear if reported data are median (range) or median (IQR).							

Treatment response

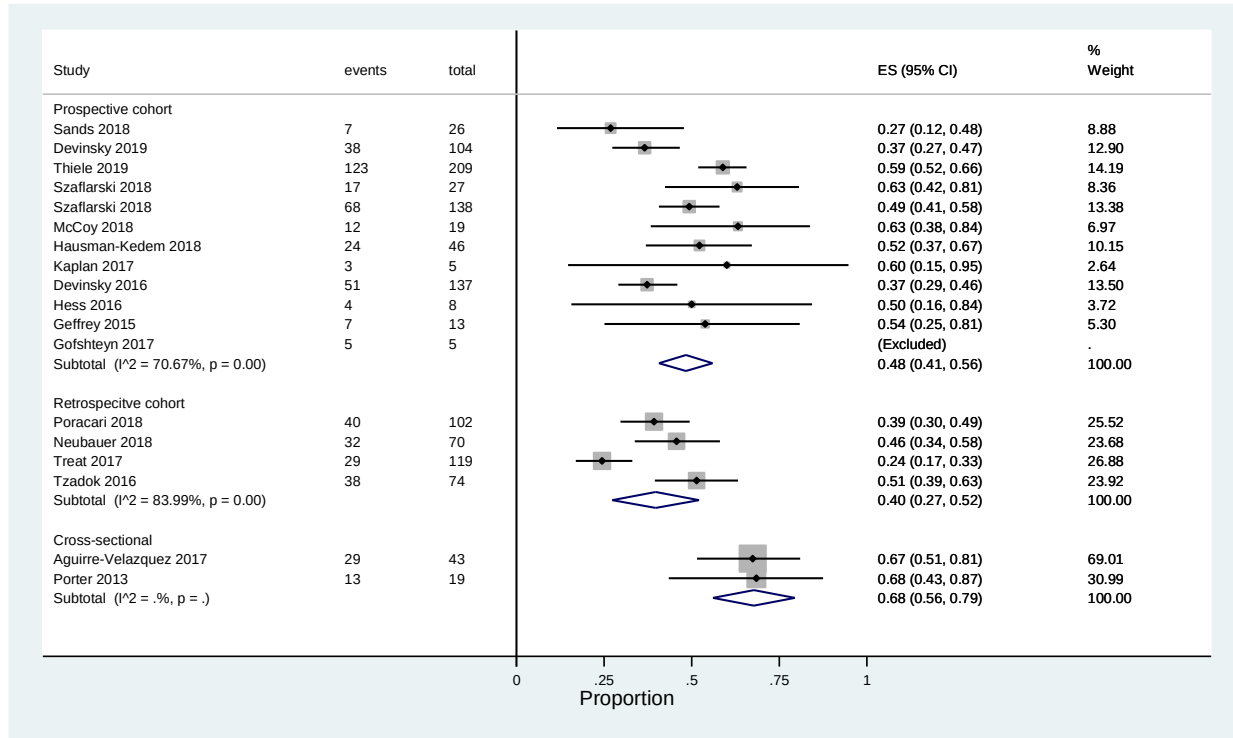
Note: $\geq 50\%$ reduction in total seizures from baseline period

A. All studies^a

Author, yr	Study design	Population	Treatments	Duration	No. of responders /no. randomized ^b (%)	
					Cannabis-based treatment	Control
Thiele 2018, p. 1085 ²²	RCT	Lennox-Gastaut syndrome	• Placebo • CBD, 20 mg/kg/d	14 wk	32/86 (37)	18/85 (21)
Devinsky 2019, p. 294 ²	Prospective single-group cohort	Dravet syndrome	• CBD, up to 30 mg/kg/d	12 wk 24 wk 36 wk 48 wk	47/102 (46) 45/93 (48) 38/87 (44) 38/75 (51)	NA
Sands 2019, p. 474	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 25 mg/kg/d	3 mo 6 mo 9 mo 12 mo 18 mo 24 mo 36 mo	10/26 (38.4) 15/26 (56.7) 11/26 (42.3) 10/26 (38.4) 11/26 (42.3) 9/26 (34.6) 7/26 (26.9)	NA
Thiele 2019, p. 419 ¹	Prospective single-group cohort	Lennox-Gastaut syndrome	• CBD, up to 30 mg/kg/d	12 wk 24 wk 36 wk 48 wk	175/364 (48) 184/334 (55) 182/314 (58) 123/209 (59)	NA
Hausman-Kedem 2018, p.544 ²³	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD:THC, , up to 50 mg/kg/d of CBD	Mean 15.6 mo	24/46 (52)	NA
McCoy 2018, p. 1077 ¹⁰	Prospective single-group cohort	Dravet syndrome	• CBD:THC, up to 16 mg/kg/d CBD	20 wk	12/19 (63)	NA
Szaflarski 2018, p. 131 ¹⁴	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d	12 wk 24 wk 48 wk	42/69 (61) 21/43 (49) 17/27 (63)	NA
Szaflarski 2018, p. 1540 ¹²	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d	12 wk 24 wk 48 wk 72 wk 96 wk	211/431 (49) 202/412 (48) 135/282 (48) 102/197 (52) 68/138 (49)	NA
Kaplan 2017, p.18 ²⁹	Prospective single-arm cohort	Sturge-Weber syndrome	• CBD, up to 25 mg/kg/d	14 wk Last visit (6–82 wk)	2/4 (50) 3/5 (60)	NA
Gofshteyn 2017, p. 35 ²⁷	Prospective single-arm cohort	FIRES (acute)	• CBD, up to 25 mg/kg/d	48 wk	1/2 (50)	NA
		FIRES (chronic)		4 wk 48 wk	5/5 (100) 5/5 (100)	NA
Devinsky 2016, p. 270 ³⁵	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d	12 wk	51/137 (37)	NA

Author, yr	Study design	Population	Treatments	Duration	No. of responders /no. randomized ^b (%)	
					Cannabis-based treatment	Control
Hess 2016, p. 1617 ³⁶	Prospective single-arm cohort	Tuberous sclerosis complex	• CBD, up to 50 mg/kg/d	3 mo 12 mo	9/18 (50) 4/8 (50)	NA
Geffrey 2015, p. 1246 ³⁸	Prospective single-arm cohort	Drug-resistant epilepsy taking CLO	• CBD, up to 25 mg/kg/d	8 wk	7/13 (54)	NA
Porcari 2018, p. 240 ²⁵	Retrospective comparative cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d • CBD + CLO • CLO	Mean, yr: 1.1 1.3 2.5	CBD: 16/48 (33) CBD+CLO: 24/54 (44)	CLO: 28/74 (38)
Neubauer 2018, p. 79 ²⁴	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD, up to 16 mg/kg/d	Median 14.0 mo	32/70 (46)	NA
Tzadok 2016, p. 41 ³⁷	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD-enriched cannabis oil, up to 20 mg/kg/d CBD	≥ 3 mo	38/74 (51)	NA
Treat 2017, p. 123 ³³	Retrospective single-arm cohort	Drug-resistant epilepsy	• Mixed cannabis-based products	Mean (range) 11.7 (0.3–57) mo	29/119 (24)	NA
Aguirre- Velazquez 2017, p. 1 ²⁶	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products	<1 to 12 mo	29/43 (67)	NA
Porter 2013, p. 574 ⁴⁰	Cross-sectional	Drug-resistant epilepsy	• CBD, up to 28.6 mg/kg/d	> 1 yr	13/19 (68)	NA
Note: CBD = cannabidiol, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, NA = not applicable, RCT = randomized controlled trial, THC = tetrahydrocannabinol. a. Adapted from Elliott et al. 2019. ⁴² b. Number randomized for RCTs; otherwise, number of participants included in efficacy analysis.						

B. Treatment response in non-randomized studies



Appendix 10: Evidence summary — Quality of life (children)

A. All studies^a

Author, yr.	Study design	Population	Treatments (no. randomized) ^b	Duration	Quality of life; mean (SD)		Effect estimate
					Baseline	After treatment	
Thiele 2018, p. 1085 ²²	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD, 20 mg/kg/d (86)	14 wk	NR	NR	Adjusted ^c difference between groups after treatment: 3.7 (95% CI –3.3 to 10.7) ^c
Devinsky 2018, p. 1888 ²¹	RCT	Lennox-Gastaut syndrome	• Placebo (76)^e • CBD, 10 mg/kg/d (73) • CBD, 20 mg/kg/d (76)	14 wk	NR	NR	Adjusted ^c mean difference (95%CI) between groups after treatment: ^d • 10 mg/kg/d v. placebo: 1.6 (–4.5 to 7.8) • 20 mg/kg/d v. placebo –5.1 (–11.4 to 1.2)
Devinsky 2017, p. 2011 ²⁰	RCT	Dravet syndrome	• Placebo (59) • CBD, 20 mg/kg/d (61)	14 wk	NR	NR	Mean difference (95%CI) between groups after treatment: 1.5 (–3.8 to 6.8) ^d
McCoy 2018, p. 1077 ¹⁰	Prospective single-group cohort	Dravet syndrome	• CBD:THC, up to 16 mg/kg/d CBD (19)	20 wk	39.60 (11.1)	46.02 (14.2)	Statistically significant improvement in quality in life after treatment (p = 0.045) ^d
Rosenberg 2017, p. e96 ³⁰	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d (48)	12 wk	31.8 (7.8)	45.74 (8.50)	Mean (SD) difference before-after treatment: 8.12 (9.85); p < 0.001
Kaplan 2017, p.18 ²⁹	Prospective single-group cohort	Sturge-Weber syndrome	• CBD, up to 25 mg/kg/d (5)	Up to 82 wk	NR	NR	"All subjects reported improvements in QoL for most of their time on CBD. All three subjects who have continued on CBD reported their QoL at last visit being "a lot better" since starting CBD." ^f
Note: CBD = cannabidiol, CI = confidence interval, NR = not reported, QoL = quality of life, RCT = randomized controlled trial, SD = standard deviation, THC = tetrahydrocannabinol. a. Adapted from Elliott et al. 2019.⁴² b. Number randomized for RCTs; otherwise, number of participants included in efficacy analysis. c. Adjusted for baseline score and age group d. 100-point Quality of Life in Childhood Epilepsy score; positive score favours CBD. e. Analysis included 38 participants in the placebo group, 36 in 10 mg/kg/d group, and 33 in 20 mg/kg/d group. f. Likert scale ranging from –3 to 3 ("A lot worse" to "A lot better"); no data reported.							

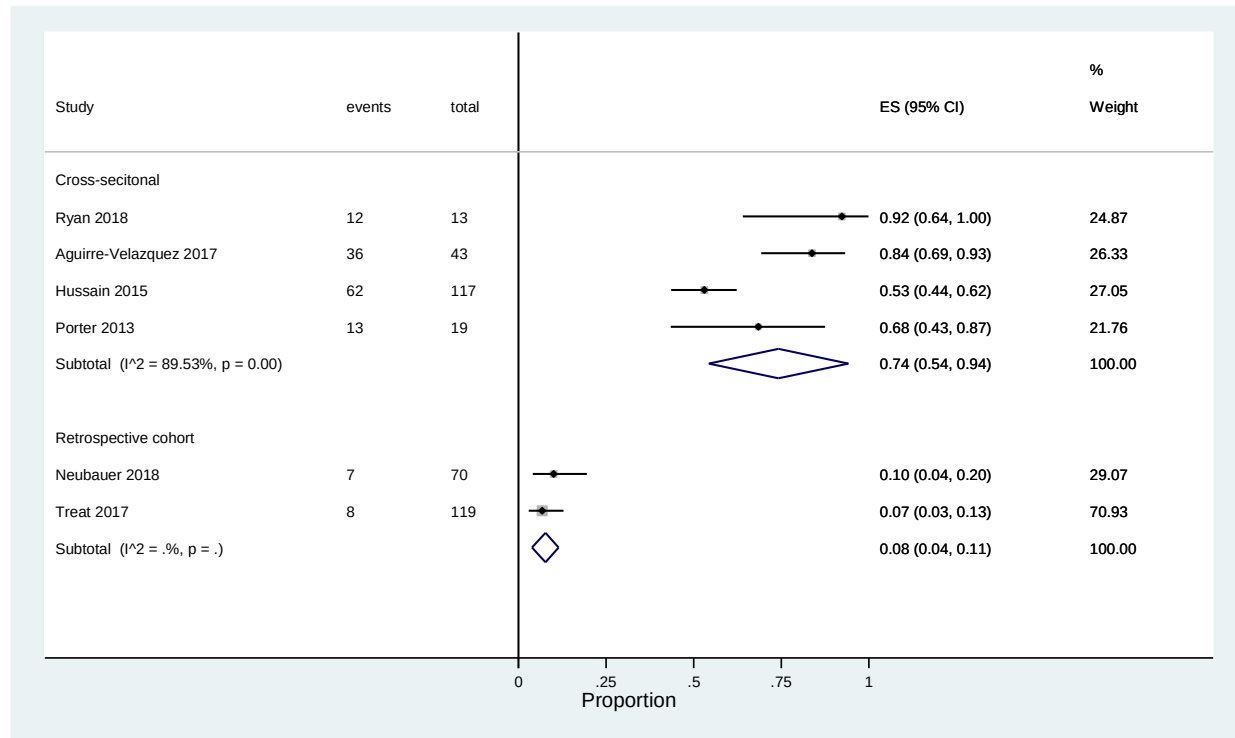
Appendix 11: Evidence summary — Sleep

A. Evidence summary — All studies^a

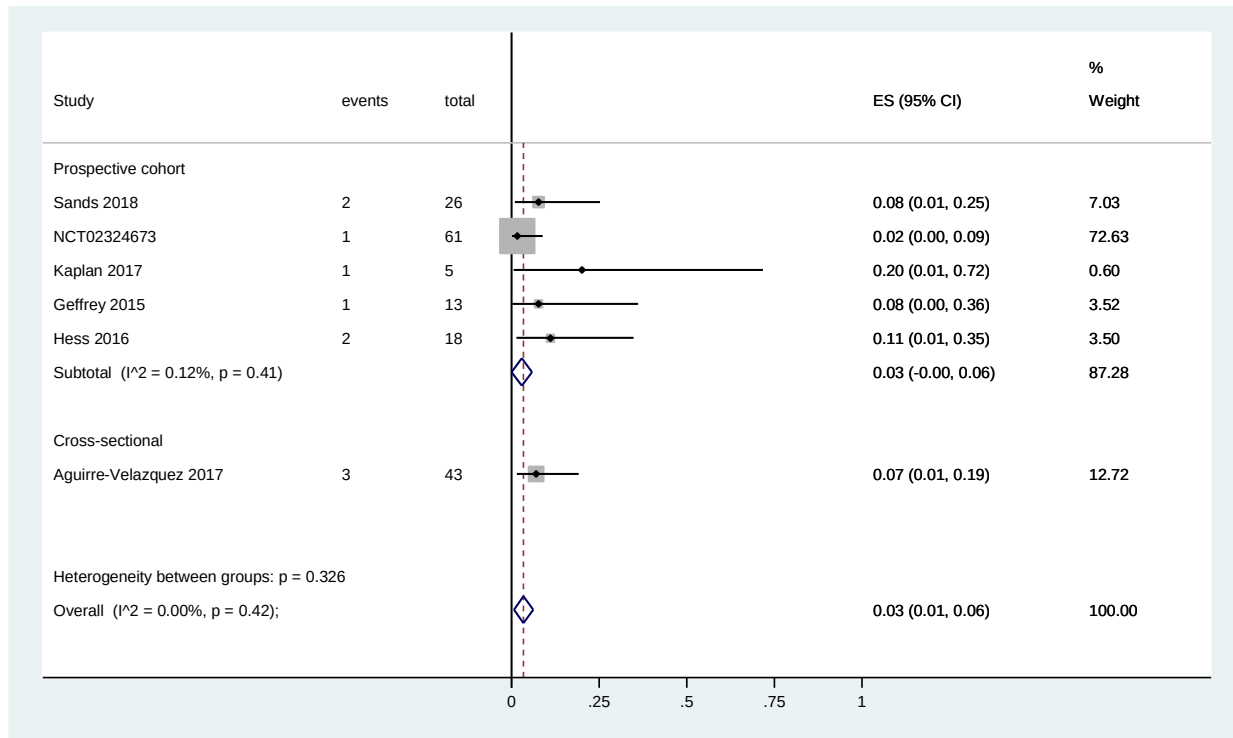
Author, yr	Study design	Population	Treatments (no. in group ^b)	Duration	Reported finding
Sleep Disruption Rating Scale score^c					Mean difference (95%CI) between groups after treatment
Thiele 2018, p. 1085 ²²	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD, 20 mg/kg/d (86)	14 wk	−0.2 (−1.1 to 0.7) ^d
Devinsky 2018, p. 1888 ²¹	RCT	Lennox-Gastaut syndrome	• Placebo (76) • CBD 10 mg/kg/d (73) • CBD 20 mg/kg/d (76)	14 wk	• 10 mg/kg/d v. placebo: −0.8 (−1.7 to 0.1) ^d • 20 mg/kg/d v. placebo: −0.3 (−1.2 to 0.6) ^d
Devinsky 2017, p. 2011 ²⁰	RCT	Dravet syndrome	• Placebo (59) • CBD, 20 mg/kg/d (61)	14 wk	−0.4 (−1.5 to 0.7) ^e
Impaired sleep					Reported finding
Thiele 2018, p. 1085 ²²	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD, 20 mg/kg/d (86)	14 wk	Sleep apnea: 1 participant (1.2%) in the cannabidiol group; none reported in placebo group
Sands 2019, p. 47 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 25 mg/kg/d (26)	Mean (range) 21.8 (4-53) mo	Insomnia reported by 2 (7.7%) of participants
INYS 2017 ²⁸ (NCT02324673)	Prospective comparative cohort	Drug-resistant epilepsy	• CBD 10 mg/kg/d (20) • CBD 20 mg/kg/d (20) • CBD 40 mg/kg/d (21)	10 d ^f	Sleep apnea: 1 participant (4.8%) in the CBD 40 mg/kg/d group; none in the other dosage groups
Geffrey 2015, p. 1246 ³⁸	Prospective single-group cohort	Drug-resistant epilepsy taking CLO	• CBD, up to 25 mg/kg/d (13)	8 wk	“Restless sleep” was reported for 1 participant (7.7%) who received CBD and CLO
Hess 2016, p. 1617 ³⁶	Prospective single-group cohort	Tuberous sclerosis complex	• CBD, up to 50 mg/kg/d (18)	Up to 12 mo	“Poor sleep” was reported for 2 participants (11.1%) who received CBD
Kaplan 2017, p. 18 ²⁹	Prospective single-group cohort	Sturge-Weber syndrome	• CBD, up to 25 mg/kg/d (5)	Up to 82 wk	“Sleep difficulties” were reported for 1 participant (20%) who received CBD
Aguirre-Velazquez 2017, p. 1 ²⁶	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (43)	Range <1 to 12 mo	“Broken sleep” was reported for 3 participants (7.0%) who received mixed cannabis-based products
Improved sleep					Reported finding
Neubauer 2018, p. 79 ²⁴	Single-arm retrospective	Drug-resistant epilepsy	• CBD, up to 16 mg/kg/d (70)	Median (range) 14.0 (6.0–29.3) mo	Better sleep was reported for 7 (10%) participants who received CBD

Author, yr	Study design	Population	Treatments (no. in group ^b)	Duration	Reported finding
	cohort				
Treat 2017, p. 123 ³³	Retrospective single-arm cohort	Drug-resistant epilepsy	• Mixed cannabis-based treatments (119)	Mean (range) 11.7 (0.3–57) mo	Better sleep was reported for 8 (6.7%) participants who received mixed cannabis-based products
Ryan 2018, p. 1 ³	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (13)	NA	• “Improved a great deal”: 5 (38%) • “Improved a lot”: 4 (31%) • “Improved a moderate amount”: 2 (15%) • “Improved a little”: 1 (8%) • “Did not improve or worsen”: 1 (8%) • “Worsened”: 0 (0%)
Aguirre-Velazquez 2017, p. 1 ²⁶	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (43)	Range <1 to 12 mo	“Improvement in sleep” was reported for 83% of participants who received mixed cannabis-based products
Hussain 2015, p. 138 ³⁹	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (117)	Median (IQR) 6.8 (3.8–9.8) mo	“Improvement in sleep” was reported for 53% of participants who received mixed cannabis-based products
Porter 2013, p. 574 ⁴⁰	Cross-sectional	Drug-resistant epilepsy	• CBD, up to 28.6 mg/kg/d (19) • Stiripentol (22)	Range: 2 wk to > 1 yr	Better sleep was reported for 13 (68.4%) participants who received mixed cannabis-based products; better sleep was reported for 6 participants (27.3%) who received stiripentol
Note: CBD = cannabidiol, CI = confidence interval, CLO = clobazam, IQR = interquartile range, RCT = randomized controlled trial. a. Adapted from Elliott et al. 2019.⁴² b. No. randomized for RCTs; otherwise, no. included in analysis. c. Sleep Disruption Rating Scale score, assessed on a numerical rating scale from 0 to 10, with higher scores indicating greater disruption. Negative mean difference favours cannabidiol. d. Adjusted for baseline score and age group. e. Adjusted; covariates not reported. f. Treatment for 10 days, followed by withdrawal period for up to 7 days. Participants who enrolled into a subsequent rollover study may not have had adverse event data collected after day 11.					

B. Improved sleep reported in non-randomized studies



C. Impaired sleep reported in non-randomized studies

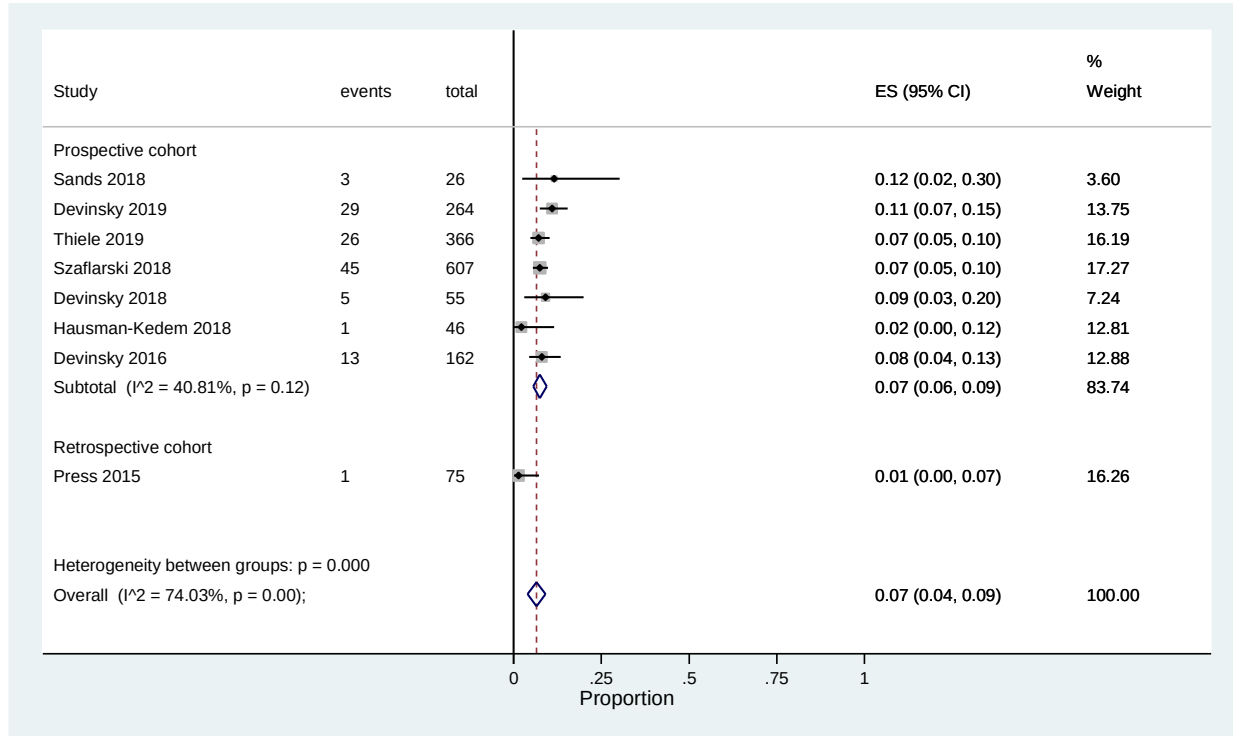


Appendix 12: Evidence summary — Status epilepticus

A. All studies^a

Author, yr	Study design	Population	Duration	Treatment	No. participants /no. in group ^b (%)
Thiele 2018, p. 1085 ²²	RCT	Lennox-Gastaut syndrome	14 wk	• Placebo • CBD, 20 mg/kg/d	1/85 (1.2) 1/86 (1.2)
Devinsky 2018, p. 1888 ²¹	RCT	Lennox-Gastaut syndrome	14 wk	• Placebo • CBD 10 mg/kg/d • CBD 20 mg/kg/d	3/76 (3.9) 7/67 (10.4) 4/82 (4.9) ^c
Devinsky 2017, p. 2011 ²⁰	RCT	Dravet syndrome	14 wk	• Placebo • CBD, 20 mg/kg/d	3/59 (5.1) 3/61 (4.9)
Devinsky 2019, p. 294 ²	Prospective single-group cohort	Dravet syndrome	Median (range) 274 (1–512) d	• CBD (total) • CBD ≤ 20 mg/kg/d • CBD > 20 mg/kg/d	29/264 (11) 17/190 (8.9) 12/74 (16.2)
Thiele 2019, p. 419 ¹	Prospective single-group cohort	Lennox-Gastaut syndrome	Median (range) 263 (3–430) d	• CBD (total) • CBD ≤ 20 mg/kg/d • CBD > 20 mg/kg/d	26/366 (7.1) 11/192 (5.7) 15/174 (8.6)
Devinsky 2018, p. 131 ⁶	Prospective single-group cohort	CDKL deficiency, Aicardi, Dup15Q, Doose syndromes	Up to 144 wk	• CBD, up to 50 mg/kg/d	5/55 (9) ^d
Hausman-Kedem 2018, p. 544 ²³	Prospective single-arm cohort	Drug-resistant epilepsy	Median (range) 18 (3–33) mo	• CBD:THC; up to 50 mg/kg/d CBD	1/46 (2.2)
Sands 2019, p. 47 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	Mean (range) 21.8 (4–53) mo	• CBD, up to 25 mg/kg/d	3/26 (11.5)
Szaflarski 2018, p. 1540 ¹² (Laux 2019, p. 13 ¹³)	Prospective single-group cohort	Drug-resistant epilepsy	Median (range) 48 (2–146) wk	• CBD, up to 50 mg/kg/d	45/607 (7.4)
		Dravet and Lennox-Gastaut syndromes ^e	Median (range) 80 (1–146) wk	• CBD, up to 50 mg/kg/d	14/152 (9)
Devinsky 2016, p. 270 ³⁵	Prospective single-arm cohort	Drug-resistant epilepsy	12 wk	• CBD, up to 50 mg/kg/d	13/162 (8.0)
Press 2015, p. 49 ³⁴	Retrospective single-arm cohort	Drug-resistant epilepsy	Mean (range) 5.59 (1–24) mo	• Mixed cannabis-based products	1/75 (1.3)
Note: CBD = cannabidiol, THC = tetrahydrocannabinol. a. Adapted from Elliott et al. 2019.⁴² b. No. randomized for RCTs; otherwise, no. included in safety analysis. c. 6 participants in the 10 mg/kg/d group received a dose above the target and were included in the 20 mg/kg/d group for the safety analysis d. Includes patients from Devinsky 2016.³⁵ e. Laux et al.¹³ reported on a subgroup of participants with Dravet and Lennox Gastaut syndrome. These participants were also included in the earlier report by Szaflarski 2018, p. 1540.¹²					

B. Status epilepticus among children administered CBD in non-randomized studies



Appendix 13: Evidence summary — Death

All studies^a

Author, yr ^b	Study design	Population	Duration	Treatment (no. in group) ^c	Deaths	Reported cause
Thiele 2018, p. 1085 ²²	RCT	Lennox-Gastaut syndrome	14 wk	• Placebo (85) • CBD, 20 mg/kg/d (86)	1 death in the CBD group; zero deaths in the placebo group	Respiratory failure (reported to be unrelated to study drug)
Devinsky 2019, p. 294 ²	Prospective single-group cohort	Dravet syndrome	Median (range) 274 (1–512) d	• CBD, up to 30 mg/kg/d (264)	2 deaths	Both owing to SUDEP and reported to be unrelated to study drug
Thiele 2019, p. 419 ¹	Prospective single-group cohort	Lennox-Gastaut syndrome	Median (range) 263 (3–430) d	• CBD, up to 30 mg/kg/d (366)	4 deaths	Respiratory failure as a complication of aspiration pneumonia (1), bowel obstruction with necrotic bowel and severe septic shock (1), seizure disorder as primary cause with severe cerebral and pulmonary edema as secondary causes (1), and complications of seizure disorder due to perinatal hypoxic ischemic encephalopathy (1); All deaths were reported to be unrelated to study drug
McCoy 2018, p. 1077 ¹⁰	Prospective single-group cohort	Dravet syndrome	20 wk	• CBD:THC, up to 16 mg/kg/d CBD (20)	1 death	SUDEP (reported to be unrelated to study drug)
Szaflarski 2018, p. 1540 ¹²	Prospective single-group cohort	Drug-resistant epilepsy	Median (range) 48 (2–146 wk)	• CBD, up to 50 mg/kg/d (607) ^d	12 deaths ^e	2 deaths due to SUDEP ^f (cause of 10 deaths NR); All deaths reported to be unrelated to study drug
Gofshteyn 2017, p. 35 ²⁷	Prospective single-arm cohort	FIRES	48 wk	• CBD, up to 25 mg/kg/d (acute: 2; chronic: 5)	1 death was reported in a child treated during the acute stage; no deaths in the chronic stage	Multi-organ failure (thought to be related to prolonged isoflurane exposure)
Devinsky 2016, p. 270 ³⁵	Prospective single-arm cohort	Drug-resistant epilepsy	12 wk	• CBD, up to 50 mg/kg/d (214)	1 death	SUDEP (reported to be unrelated to the study drug)
Neubauer 2018, p. 79 ²⁴	Retrospective, single-arm cohort	Drug-resistant epilepsy	Median (range) 14.0 (6.0–29.3) mo	• CBD, up to 16 mg/kg/d (70)	2 deaths	Multiple cavernomas (died suddenly during sleep; 1); bronchopneumonia (1)
Press 2015 ³⁴	Retrospective, single-arm cohort	Drug-resistant epilepsy	Mean (range) 5.59 (1–24) mo	• CBD, CBD + other oral cannabis extract, THCA only, or "other" (75)	1 death	NR

Sulak 2017, p. 328 ³¹	Case series ⁸	Drug- resistant epilepsy	NR	• THCA (2 mg/kg/d) (4‡)	1 death	SUDEP
Note: CBD = cannabidiol, FIRES = Febrile Infection-Related Epilepsy syndrome, NR = not reported, RCT = randomized controlled trial, SUDEP = sudden unexpected death in epilepsy, THCA = tetrahydrocannabinolic acid, THC = tetrahydrocannabinol. a. Adapted from Elliott et al. 2019.⁴² b. An additional four studies^{6,19,20,28} reported that no deaths occurred during the study period. c. Treatments described in Table 1. No. randomized for RCTs; otherwise, no. included in safety analysis. d. Pooled results from 25 US Expanded Access Programs (EAP); updated analysis of Devinsky 2016³⁵, which included 11 EAP programs and 214 children. e. Also reported in Laux et al. 2019¹³ f. Of the 12 reported deaths, one may have been previously reported in Devinsky 2016.³⁵ g. Case series of 4 children with epilepsy who received “herbal cannabinoid treatment.”						

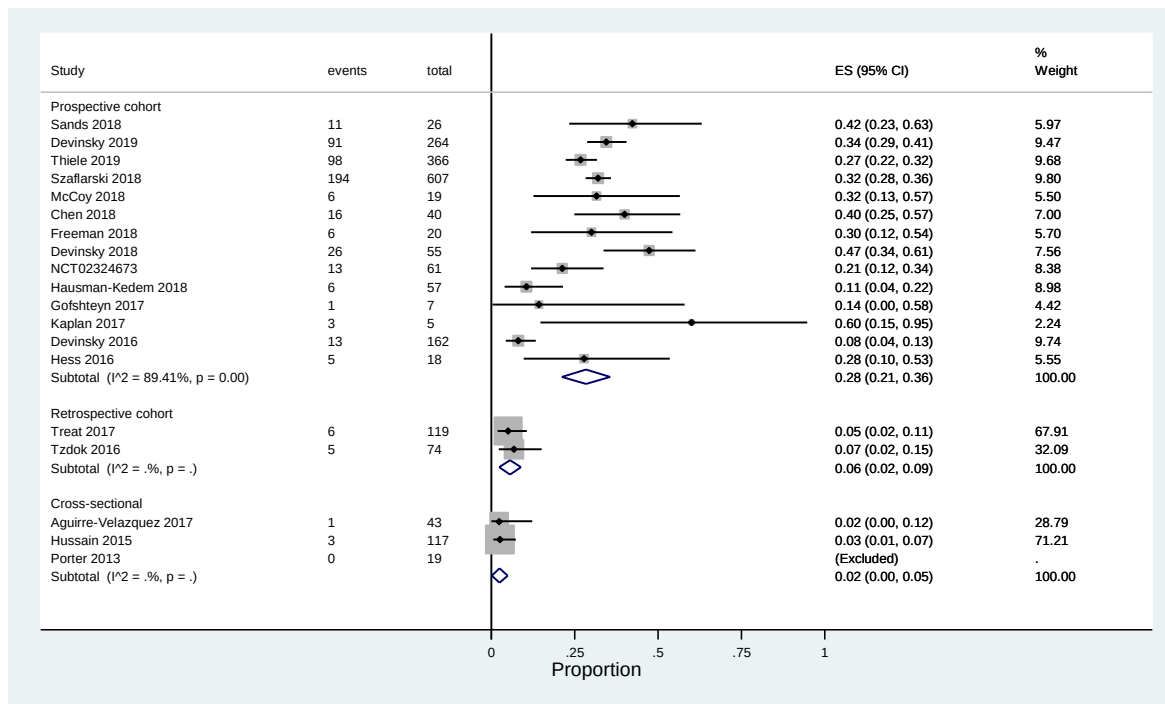
Appendix 14: Evidence summary — Gastrointestinal adverse events

A. All studies^a

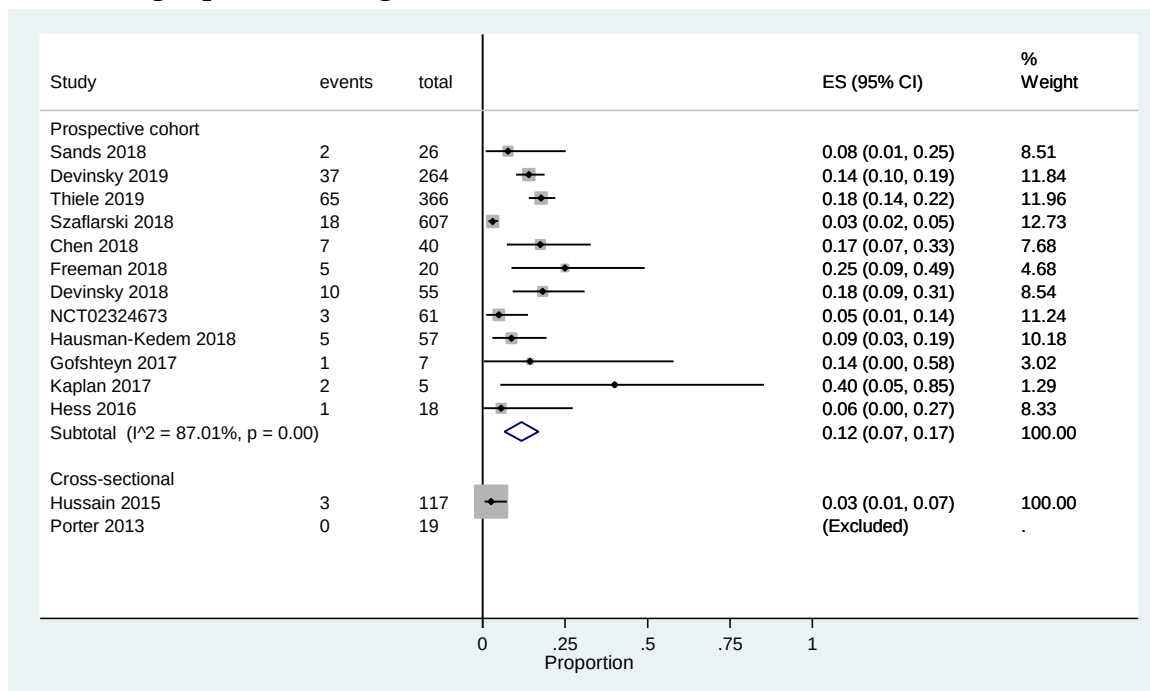
Author, yr	Study design	Population	Treatments (no. in group) ^b	Duration	No. (%) of participants	
					Vomiting	Diarrhea
Thiele 2018, p. 1085 ²²	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD, 20 mg/kg/d (86)	14 wk	14 (16) 9 (10)	7 (8) 16 (19)
Devinsky 2018, p. 1888 ²¹	RCT	Lennox-Gastaut syndrome	• Placebo (76) • CBD 10 mg/kg/d (67) • CBD 20 mg/kg/d (82) ^c	14 wk	9 (12) 4 (6) 10 (12)	6 (8) 7 (10) 12 (15)
Devinsky 2018, p. e1204 ¹⁹	RCT	Dravet syndrome	• Placebo (7) • CBD 5 mg/kg/d (10) • CBD 10 mg/kg/d (8) • CBD 20 mg/kg/d (9)	3 wk	0 (0) 1 (10) 1 (13) 1 (11)	NR
Devinsky 2017, p. 2011 ²⁰	RCT	Dravet syndrome	• Placebo (59) • CBD, 20 mg/kg/d (61)	14 wk	3 (5) 9 (14.8)	6 (10.2) 19 (31.1)
Devinsky 2019, p. 294 ²	Prospective single-group cohort	Dravet syndrome	• CBD (all doses) (264) • CBD ≤ 20 mg/kg/d (190) • CBD > 20 mg/kg/d (74)	Median (range) 274 (1–512) d	37 (14.0) 24 (12.6) 13 (17.6)	91 (34.5) 60 (31.6) 31 (41.9)
Thiele 2019, p. 419 ¹	Prospective single-group cohort	Lennox-Gastaut syndrome	• CBD (all doses) (366) • CBD ≤ 20 mg/kg/d (192) • CBD > 20 mg/kg/d (174)	Median (range) 263 (3–430) d	65 (17.8) 30 (15.6) 35 (20.1)	98 (26.8) 43 (22.4) 55 (31.6)
Sands 2019, p. 47 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 25 mg/kg/d (26)	Mean (range) 21.8 (4–53) mo	2 (7.7)	9 (34.6)
Chen 2018, p. 217 ⁵	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 25 mg/kg/d (40)	Up to 12 wk	7 (17.5)	9 (22.5)
Devinsky 2018, p. 131 ⁶	Prospective single-group cohort	CDKL deficiency, Aicardi, Dup15Q, Doose syndrome	• CBD, up to 50 mg/kg/d (55)	Up to 144 wk	10 (18)	16 (29)
Freeman 2018, p. 228 ⁷	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 20 mg/kg/d (20)	Up to 40 wk	5 (25)	1 (5)
Hausman-Kedem 2018, p.544 ²³	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD:THC (20:1), up to 50 mg/kg/d CBD (57)	Median (range) 18 (3–33) mo	5 (8.8)	1.8%
McCoy 2018, p. 1077 ¹⁰	Prospective single-group cohort	Dravet syndrome	• CBD:THC (50:1), up to 16 mg/kg/d CBD (20)	20 wk	NR	6 (31.6)
Szaflarski 2018, p. 1540 ¹² (Laux 2019, p. 13 ¹³)	Prospective single-group cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d (607)	Median (range) 48 (2–146) wk	18 (3)	176 (29)
		Dravet and Lennox-Gastaut syndromes ^d	• CBD, up to 50 mg/kg/d (152)	Median (range) 80 (1–146) wk	20 (13)	36 (24)
Devinsky 2016, p. 270 ³⁵	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD, up to 50 mg/kg/d (162)	12 wk	NR	13 (8.0)

Author, yr	Study design	Population	Treatments (no. in group) ^b	Duration	No. (%) of participants	
					Vomiting	Diarrhea
Hess 2016, p. 1617 ³⁶	Prospective single-arm cohort	Tuberous sclerosis complex	• CBD, up to 50 mg/kg/d (18)	12 mo	1 (6)	4 (22.2)
Gofshteyn 2017, p. 35 ²⁷	Prospective single-arm cohort	FIRES	• CBD, up to 25 mg/kg/d (7)	48 wk	1 (14)	NR
INYS 2017 ²⁸ (NCT02324673)	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD 10 mg/kg/d (20) • CBD 20 mg/kg/d (20) • CBD 40 mg/kg/d (21)	10 d ^e	2 (10) 1 (5) 0 (0)	1 (5) 2 (10) 7 (33)
Kaplan 2017, p. 18 ²⁹	Prospective single-arm cohort	Sturge-Weber syndrome	• CBD, up to 25 mg/kg/d (5)	Up to 82 wk	2 (40)	1 (20.0)
Treat 2017, p. 123 ³³	Retrospective single-arm cohort	Drug-resistant epilepsy	• Mixed cannabis-based products (119)	Mean (range) 11.7 (0.3–57) mo	6 (5)	
Tzadok 2016, p. 41 ³⁷	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD-enriched cannabis oil, up to 20 mg/kg/d CBD (74)	≥ 3 mo	5 (7)	
Aguirre-Velazquez 2017, p. 1 ²⁶	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products (43)	Up to 12 mo	NR	1 (2.3)
Hussain 2015, p. 138 ³⁹	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products (117)	Median (IQR) 6.8 (3.8–9.8)	3 (3)	NR
Porter 2013, p. 574 ⁴⁰	Cross-sectional	Drug-resistant epilepsy	• Stiripentol (22) • CBD, up to 28.6 mg/kg/d (19)	> 1 yr	2 (9) 0 (0)	NR
Note: CBD = cannabidiol, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, NR = not reported, RCT = randomized controlled trial, THCA = tetrahydrocannabinolic acid, THC = tetrahydrocannabinol. a. Adapted from Elliott et al. 2019.⁴² b. Number randomized for RCTs; otherwise, number of participants included in safety analysis. c. 6 participants in the 10 mg/kg/d group received a dose above the target and were included in the 20 mg/kg/d group for the safety analysis. d. Laux et al.¹³ reported on a subgroup of participants with Dravet and Lennox Gastaut syndrome. These participants were also included in the earlier report by Szafarski 2018, p. 1540.¹² e. Treatment for 10 days, followed by withdrawal period for up to 7 days. Participants who enrolled into a subsequent rollover study may not have had adverse event data collected after day 11.						

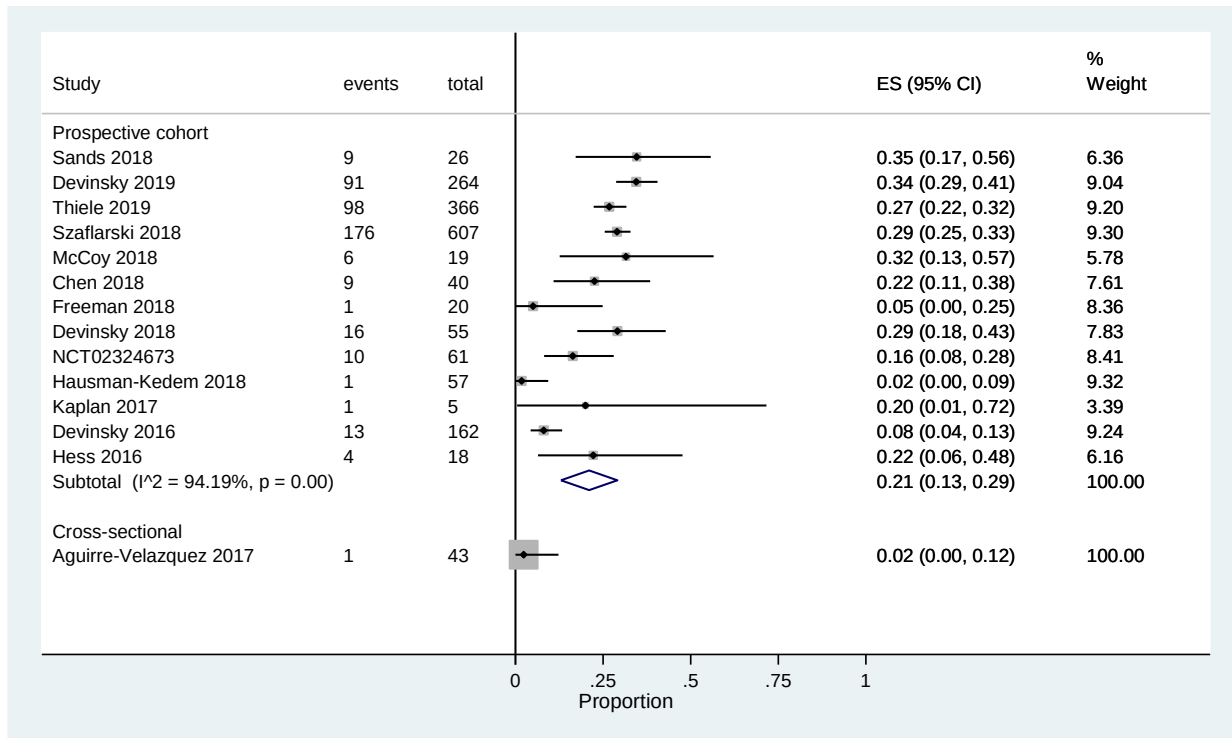
B. Gastrointestinal adverse events (vomiting and/or diarrhea) reported among non-randomized studies



C. Vomiting reported among non-randomized studies



D. Diarrhea reported among non-randomized studies



Appendix 15: Evidence summary — Visits to the emergency room

Author, yr	Study design	Population	Treatments (no. of participants)	Duration	Observation period; no. of visits, ^a mean (range)	
					Baseline	On treatment
Sands 2019, p. 47 ⁴	Prospective single-group cohort	Drug- resistant epilepsy	• CBD, up to 25 mg/kg/d (24)	Mean (range) 21 (4–53) mo	6-months before treatment, total no. of admissions per patient: NR (0–10)	Treatment period: range 4–53 mo, total no. of admissions per patient: NR (0–2)
Chen 2018, p. 217 ⁵	Prospective single-group cohort	Drug- resistant epilepsy	• CBD, up to 25 mg/kg/d (40)	12 wk	1-year before treatment, admissions per mo per patient: 0.29 (0–1.25)	12-wk treatment period: admissions per mo per patient: 0.39 (0–2) ^b
Note: CBD = cannabidiol, NR = not reported. a. Visits to the ER or admitted to hospital. b. Not statistically significant different from the baseline rate.						

Appendix 16: Trial registration records that met the eligibility criteria

Registration number ^{a,b}	Title	Sponsor	Population	Eligible ages, yr	Treatments	Design	Recruitment status	Primary completion date (estimated or actual)	Country
ACTRN12618001706268	A double-blind placebo-controlled study investigating the safety, tolerability, efficacy and pharmacokinetics of EP1, and enriched cannabidiol oil in children and adolescents with medication resistant refractory epilepsy	Cann Pharmaceutical Australia Limited	DRE	2–18 years	Oral solution, CBD:THC 20:1 ratio	Randomized	Not yet recruiting	2022	Australia
NCT02224703	GWPCARE2 A study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome	GW Research Ltd	DS	2–18 yr	CBD (GWP42003-P), high dose, low dose or placebo	Randomized	Unknown	May 2017	Multi-national
NCT02544763	A randomized controlled trial of cannabidiol (GWP42003-P, CBD) for seizures in Tuberous Sclerosis Complex (GWPCARE6)	GW Research Ltd	Tuberous Sclerosis Complex	1–65 yr	CBD (GWP42003-P) 25 mg/kg/d, 50 mg/kg/d or placebo	Randomized	Active, not recruiting	February 2019	US
NCT02607891	A study to investigate possible drug-drug interactions between stiripentol or valproate and cannabidiol in patients with epilepsy	GW Research Ltd	Epilepsy	16–55 yr	CBD (Epidiolex; GWP42003-P), up to 20 mg/kg/d, v. placebo	Randomized	Recruiting	August 2018	Multi-national
NCT02783092	A double-blind trial to evaluate efficacy and safety of cannabidiol as an add-on therapy for treatment in refractory epilepsy	Prati Donaduzzi & Cia Ltd	DRE	2–18	Oral CBD solution, up to 25 mg/kg/d, v. placebo	Randomized	Recruiting	August 2020	Brazil
NCT03421496	A study to assess the efficacy, safety, and tolerability of cannabidiol oral solution with vigabatrin as initial therapy in participants with infantile spasms	INSYS Therapeutics Inc	Infantile spasms	1–24 mo	Oral CBD (40 mg/kg/d) + vigabatrin v. placebo + vigabatrin	Randomized	Recruiting	December 2019	US
NCT03944447	Outcomes mandate national integration with cannabis as medicine	OMNI Medical Services	Chronic conditions, including epilepsy	≥ 7 yr	Cannabis	Prospective cohort, observational	Recruiting	December 2025	US
NCT02229032	Genetic analysis between Charlotte's Web responders versus non-responders in a Dravet population	University of Colorado, Denver	DS	1–50 yr	Charlotte's Web strain of medical marijuana	Cross-sectional	Completed (no results posted)	July 2017	US
NCT02286986	Cannabidiol (CBD) to 27 patients (Aged 2 Years - 19 Years) with drug resistant epilepsy	University of Utah	DRE	2–19 yr	CBD (GWP42003-P)	Single group interventional	Active, not recruiting	January 2019	US
NCT02332655	Cannabidiol expanded access study in	GW	Sturge-Weber	1 mo–45	CBD (Epidiolex)	Single group	Active, not	June 2019	US

Registration number ^{a,b}	Title	Sponsor	Population	Eligible ages, yr	Treatments	Design	Recruitment status	Primary completion date (estimated or actual)	Country
	medically refractory Sturge-Weber syndrome	Pharmaceuticals Ltd.	Syndrome	yr		interventional	recruiting		
NCT02397863	Epidiolex and drug resistant epilepsy in children	Augusta University	DRE	1–18 yr	CBD (Epidiolex)	Single group interventional	Available	December 2019	US
NCT02447198	Cannabidiol (CBD) and pediatric epilepsy	University of Colorado, Denver	Epilepsy	1 mo–17 yr	CBD	Single group interventional	Completed (no results posted)	September 2018	US
NCT02461706	Treatment of drug resistant epilepsy	University of Florida	DRE	“children”	CBD 25 mg/kg/d	Single group interventional	No longer available	NR (last update January 2019)	US
NCT02523183	The use of medicinal cannabinoids as adjunctive treatment for medically refractory epilepsy	University of Colorado, Denver	DRE	1 mo–20 yr	Medical cannabis	Single group interventional	Active, not recruiting	October 2019	US
NCT02544750	An open-label extension trial of cannabidiol (GWP42003-P, CBD) for seizures in Tuberous Sclerosis Complex (GWPCARE6)	GW Research Ltd	Tuberous Sclerosis Complex	1–65 yr	CBD (GWP42003-P), up to 50 mg/kg/d	Open-label extension	Enrolling by invitation	September 2022	US
NCT02556008	Cannabidiol for pediatric epilepsy (compassionate use)	University of California, Los Angeles	Refractory Childhood Epilepsy	NR	Epidiolex, up to 25 mg/kg/d	Single group interventional	No longer available	NR (last updated May 2017)	US
NCT02607904	An open-label extension trial to investigate possible drug-drug interactions between stiripentol or valproate and cannabidiol in patients with epilepsy	GW Research Ltd	Epilepsy	16–55 yr	CBD (GWP42003-P), up to 20 mg/kg/d	Open-label extension	Enrolling by invitation	August 2019	NR
NCT02660255	Safety and tolerability of cannabidiol in subjects with drug resistant epilepsy	GW Pharmaceuticals Ltd.	DRE	1–60 yr	CBD (Epidiolex)	Single group interventional	Approved for marketing	NR (last updated April 2019)	NR
NCT02700412	University of Alabama at Birmingham (UAB) adult CBD program	University of Alabama at Birmingham	DRE	15–99	CBD (Epidiolex), up to 50 mg/kg/d	Single group interventional	Active, not recruiting	April 2021	US
NCT02815540	The effects of cannabidiol (CBD) on electrical and autonomic cardiac function in children with severe epilepsy	Gillette Children's Specialty Healthcare	DS, LGS	2–30 yr	CBD	Single group interventional	Terminated	December 2018	US
NCT02910297	The pharmacokinetics of cannabidiol (CBD) and its effects in children with severe epilepsy	Gillette Children's Specialty Healthcare	DS, LGS	2–30 yr	CBD	Single group interventional	Withdrawn	December 2017	US
NCT02953548	Trial of cannabidiol (CBD; GWP42003-P)	GW Research Ltd	Infantile	1–24 mo	CBD (GWP42003-P), up to	Single group	Active, not	October 2018	Multi-

Registration number ^{a,b}	Title	Sponsor	Population	Eligible ages, yr	Treatments	Design	Recruitment status	Primary completion date (estimated or actual)	Country
	for Infantile Spasms (GWPCARE7)		Spasms		40 mg/kg/d	interventional	recruiting		national
NCT02954887	Phase 3 trial of cannabidiol (CBD; GWP42003-P) for Infantile Spasms: Open-label extension phase (GWPCARE7)	GW Research Ltd	Infantile Spasms	1–24 mo	CBD (GWP42003-P)	Single group interventional	Active, not recruiting	December 2018	Multi-national
NCT02987114	A study to evaluate the safety, tolerability and efficacy of oral administration of PTL101 (cannabidiol) as an adjunctive treatment for pediatric intractable epilepsy	PhytoTech Therapeutics, Ltd.	DRE	2–15 yr	CBD (PLT101), up to 25 mg/kg/d	Single group interventional	Completed (no results posted)	June 2018	Israel
NCT03014440	Study of cannabidiol for drug-resistant epilepsies	University of Pittsburgh	DRE	1–20 yr	CBD (Epidiolex)	Single group interventional	No longer available	NR (last updated April 2017)	NR
NCT03196934	Expanded use of cannabidiol oral solution	MultiCare Health System Research Institute	DRE	1–18 yr	CBD oral solution	Single group interventional	Available	NR (last updated June 2017)	NR
NCT03336242	Cannabidiol oral solution in pediatric participants with treatment-resistant childhood absence seizures	INSYS Therapeutics Inc	Childhood Absence Epilepsy	3–17 yr	CBD oral solution: • 20 mg/kg/d • 30 mg/kg/d • 40 mg/kg/d	Non-randomized, parallel group interventional	Recruiting	May 2019	US
NCT03355300	Long-term safety of pharmaceutical grade synthetic cannabidiol oral solution in pediatric participants with treatment-resistant childhood absence seizures	INSYS Therapeutics Inc	Childhood Absence epilepsy	3–17 yr	CBD oral Solution	Single group interventional	Recruiting	November 2019	US
NCT03467113	A study to assess the safety and tolerability of ZX008 in children and young adults with DS or LGS currently taking CBD	Zogenix Inc	LGS, DS	2–18 yr	CBD + fenfluramine	Single group interventional	Active, not recruiting	February 2020	US
ACTRN12618000516280	Open label study to assess the safety and efficacy of ZYN002 administered as a transdermal gel to children and adolescents (3 to <18 years) with developmental and epileptic encephalopathy (BELIEVE 1)	Zynerba Pharmaceuticals Pty Ltd	Developmental and epileptic encephalopathy	3–18 yr	Transdermal CBD gel, 250 mg/d (weight < 25 kg) or 500 mg/d (>25 kg)	Single group interventional	Recruiting	December 2019	New Zealand

Note: CBD = cannabidiol, DS = Dravet syndrome, LGS = Lennox-Gastaut syndrome, NR = not reported, THC = tetrahydrocannabinol.

a. Adapted from Elliott et al. 2019.⁴²

b. Table includes registration records not matched to included published studies and that did not report study results as of May 17, 2019. Registration records that report otherwise unpublished study results are included in Appendix 4.

Appendix references

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Chapter 4:

Cost-effectiveness of medical cannabis for pediatric drug-resistant epilepsy

CHAPTER OVERVIEW

Chapter 4 addresses the second research question: *Is medical cannabis a cost-effective treatment for pediatric drug-resistant epilepsy compared to current therapeutic options?*

While the available evidence suggests that some cannabis-based products (particularly purified cannabidiol) may be effective in reducing seizures associated with drug-resistant epilepsy (see Chapter 3), the cost-effectiveness of these treatments is not clear. In this chapter, the cost-effectiveness of medical cannabis for pediatric drug-resistant epilepsy compared to current standard therapies was investigated. A broad systematic review was first undertaken to identify existing economic evaluations of cannabis-based products in this population (**Section 4.1, 4.2**). Finding none, a model-based cost-utility analysis was conducted to assess the long-term costs and health outcomes associated with use of cannabinoid oil for the treatment of Dravet syndrome (**Section 4.4**). A second systematic review (**Section 4.3**) was conducted to identify inputs (i.e., health state utility values, resource use, productivity losses) for the cost-utility analysis.

Chapter 4 contains four manuscripts (**Sections 4.1–4.4**), two of which have been published (**Sections 4.1, 4.2**); the remaining manuscripts (**Sections 4.3, 4.4**) have been submitted for publication. Each manuscript is briefly described below, and a more fulsome description is found on the first page of each section.

CHAPTER CONTENTS

Section 4.1 presents the protocol for the systematic review described in Sections 4.2 and 4.3. This manuscript was published in *Systematic Reviews*.

Section 4.2 describes the results of a systematic review related to the cost-effectiveness of cannabis-based products for pediatric drug-resistant epilepsy. Further, this manuscript provides an overview of

decision models that have been previously used to assess the cost-effectiveness of pharmacologic treatments in this population. This manuscript was published in *PharmacoEconomics*.

Section 4.3 presents the findings of a systematic review conducted to identify health state utility values, health care resource use, and productivity losses related to pediatric drug-resistant epilepsy. This manuscript has been submitted for publication in *Cost-Effectiveness and Resource Allocation*.

Section 4.4 presents the findings of a *de novo* cost-utility analysis of the cost-effectiveness of cannabinoid oil for the treatment of Dravet syndrome compared to current standard therapies. This manuscript has been submitted for publication in *PharmacoEconomics*.

Section 4.1

Cost-effectiveness of cannabinoids for pediatric drug-resistant epilepsy:

Protocol for a systematic review of economic evaluations

SECTION OVERVIEW

This section presents a manuscript describing the protocol for two systematic reviews. The first systematic review was performed to identify economic evaluations of cannabis-based products for treatment of drug-resistant epilepsy in children, as well as decision models used in economic evaluations of other pharmacologic treatments in this population (**Section 4.2**). The second review (**Section 4.3**) served to identify inputs for the cost-utility analysis described in **Section 4.4**.

MANUSCRIPT STATUS

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Supporting material

Additional File 1: PRISMA-P checklist

Additional File 2: Search strategy

Author roles and contributions

JE and DC designed the study. BS designed the search strategy. JE drafted the protocol, which was revised by all authors. All authors approved the version of the manuscript submitted for publication.

RELATED THESIS APPENDICES

Appendix G: Published manuscripts. The PDF of the published manuscript is presented in Appendix G.

Cost-effectiveness of cannabinoids for pediatric drug-resistant epilepsy:

Protocol for a systematic review of economic evaluations

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ABSTRACT

Background: Drug-resistant epilepsy negatively impacts quality of life and is associated with increased morbidity and mortality and high costs to the health care system. Cannabis-based treatments may be effective in reducing seizures in this population, but whether they are cost-effective is unclear. In this systematic review, we will search for cost-effectiveness analyses involving the treatment of pediatric drug-resistant epilepsy with cannabis-based products to inform decision-making by public health care payers about reimbursement of such products. We will also search for cost-effectiveness analyses of other pharmacologic treatments for pediatric drug-resistant epilepsy, as well as estimates of health care resource use, costs, and utilities, for use in a subsequent cost-utility analysis to address this decision problem.

Methods: We will search the published and grey literature for economic evaluations of cannabis-based products and other pharmacologic treatments for pediatric drug-resistant epilepsy, as well as resource utilization and utility studies. Two independent reviewers will screen the title and abstract of each identified record and the full-text version of any study deemed potentially relevant. Study and population characteristics, the incremental cost-effectiveness ratio (ICER), as well as total costs and benefits, will be extracted, and quality will be assessed by use of the Drummond and CHEERS checklists; context-specific issues will also be considered. From model-based cost-utility and cost-effectiveness analyses, we will extract and summarize the model structure, including health states, time horizon, and cycle length. From resource utilization studies, we will extract data about the frequency of resource use (e.g., neurology visits, emergency department visits, admissions to hospital). From utility studies, we will extract the utility for each health state, source of the preferences (e.g., child, parent, patient, general public), and the method of elicitation.

Discussion: Drug-resistant epilepsy in children is associated with important costs to the health care system, and decision makers require high-quality evidence on which to base reimbursement decisions. The results of this review will be useful to both decision makers considering the decision

problem of whether to reimburse cannabis-based products through public formularies and to analysts conducting studies in this area.

Systematic review registration: PROSPERO no.: CRD42018099591.

Keywords: cannabis, cannabidiol, cost-effectiveness, pediatric drug-resistant epilepsy, resource use, costs, benefits, utilities

BACKGROUND

Drug-resistant epilepsy (inadequate response to two or more trials of appropriate antiepileptic drugs [1]) affects between 28% and 37% of people with epilepsy [2] and can have profound consequences for affected children and their families, with affected children at increased risk of severe morbidity (e.g., cognitive delay, behavioural problems, autism) and mortality [3]. Pediatric epilepsy is associated with increased contacts with the health-care system, including neurologist visits, visits to the emergency department, and admissions to hospitals [4,5], and children with uncontrolled seizures use more health resources than children with controlled seizures, with costs correlated with epilepsy severity [4,6]. Taken together, resource use by children with epilepsy contributes major costs to the health care system [6,7].

Drug-resistant epilepsy comprises multiple types of pediatric epilepsies, frequently with underlying genetic causes (e.g., Dravet syndrome, Lennox-Gastaut syndrome, West syndrome) [3]. Pediatric epilepsy may also be caused by structural or metabolic (e.g., structural abnormality or chronic metabolic condition) or unknown causes [3]. Because of this variation, and variation in seizure types, there is no standard of care for treatment of pediatric drug-resistant epilepsy, with treatment dependent on the nature of a child's individual disease, which drugs are available in a given jurisdiction, and local practice [8]. Individual antiepileptic drugs may benefit only small groups of patients because of the rare nature of some epilepsy syndromes, and some antiepileptic drugs have designated orphan drug status (e.g., stiripentol for Dravet syndrome [9]). In addition to pharmacologic treatments (i.e., antiepileptic drugs), other treatment options include non-pharmacologic interventions (e.g., surgery to resect the seizure focus, vagus nerve stimulation, deep brain stimulation therapy, ketogenic diet therapy)[3], with increasing interest in the use of alternative therapies, including cannabinoids [10,11].

Interest in the use of cannabis for the treatment of pediatric epilepsy has increased over the last decade, with recent clinical studies suggesting that cannabidiol, one of two main cannabinoids in

cannabis, reduces seizure burden in some epilepsy syndromes [12,13]. The first pharmaceutical-grade cannabidiol product intended to treat Dravet syndrome and Lennox-Gastaut syndrome was recently approved by the US Food and Drug Administration [14], and it is expected that public payers will soon be faced with decisions as to whether to include such products on their formularies. Economic evaluations can provide important information to decision makers as they make such reimbursement and funding decisions [15]. As such, the objective of this systematic review is to provide a comprehensive overview of the cost-effectiveness of cannabis-based treatments for pediatric drug-resistant epilepsy and to search for inputs for a *de novo* cost-utility analysis to address this decision problem in the Canadian context.

Research aims

There are three aims of this study:

1. Identify and assess the applicability of existing economic evaluations of cannabis-based products for the treatment of pediatric drug-resistant epilepsy;
2. Identify and assess the suitability of existing models that have been used in the economic evaluation of other pharmacologic treatments in this population;
3. Identify model inputs (e.g., resource use, utilities) from existing economic evaluations of pharmacologic treatments or from stand-alone studies in this population.

The findings of aims 2 and 3 will be used to inform a *de novo* cost-utility analysis intended to address the decision problem of whether Canadian public health care payers should reimburse cannabis-based products for the treatment of drug-resistant epilepsy in children with Dravet syndrome.

METHODS

This systematic review protocol has been registered in PROSPERO (CRD42018099591) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)

statement (Additional File 1) [16]. All screening and data extraction will be performed by use of standardized and piloted forms in Distiller SR (Evidence Partners).

Search strategy

The search strategy was developed in consultation with an experienced medical information specialist and the research team (Additional File 2). The search was peer reviewed by another senior librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist prior to execution [17]. Databases to be searched include Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE and Embase Classic+Embase. The Cochrane Library (HTA database, NHSEED, DSR, DARE, and CENTRAL), Wiley version, will also be searched. The search strategies will be adjusted to the individual database and will include a combination of controlled vocabulary (e.g., Medical Subject Headings) and keywords; no date restrictions will be applied. Grey literature searches will be undertaken using the relevant economic web sites and databases listed in Grey Matters [18].

Eligibility criteria

We will include studies that meet the criteria described below. Conference abstracts and non-English language records will be excluded; however, studies performed in Canada but reported in French will be eligible. Studies that report mixed populations of children and adults will be included if they report data separately for participants aged less than 19 years or if, based on descriptive statistics, we can determine that most patients (i.e., >80%) are aged less than 19 years.

Research aim 1:

Population: Children (aged less than 19 years) with any form of drug-resistant epilepsy (inadequate response to two or more trials of appropriate antiepileptic drugs [1]).

Intervention: Any type of cannabis or cannabis-based product, cannabinal, cannabidiol (CBD), tetrahydrocannabinol (THC), or combinations of these agents, administered by any route (e.g., oral, inhalation), involving any strain of cannabis and any ratio of THC to CBD.

Comparator: Pharmacologic (i.e., antiepileptic drugs) or non-pharmacologic treatments (i.e., ketogenic diet, epilepsy surgery, vagus nerve stimulation) for pediatric drug-resistant epilepsy.

Study designs: Full economic evaluations (i.e., cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-minimization analysis) and health technology assessments that include a full economic evaluation. Both trial-based and model-based economic evaluations will be eligible for inclusion.

Research aim 2:

Population: Children (aged less than 19 years) with any form of drug-resistant epilepsy [1].

Interventions and comparators: Pharmacologic treatments for pediatric drug-resistant epilepsy compared with other pharmacologic or non-pharmacologic treatments.

Study designs: Full economic evaluations and health technology assessments that involve model-based cost-utility or cost-effectiveness evaluations.

Research aim 3:

Population: Children with any form of drug-resistant epilepsy (resource utilization, utility, productivity studies) or adult caregivers of children with drug-resistant epilepsy (utility, productivity studies).

Study designs: Resource utilization studies involving at least 5 children, utility studies, productivity studies; full economic evaluations identified as part of Aim 1 or 2.

Screening and study selection

Two independent reviewers will screen the title and abstract of each identified record and the full-text version of any study deemed potentially relevant, with disagreements resolved by discussion.

Outcomes

Research aim 1: Total and incremental costs; direct, indirect (i.e., productivity costs), and drug-related costs; total and incremental quality-adjusted life years (QALYs); and incremental cost-effectiveness ratios (ICERs).

Research aim 2: Model structure (e.g., description of the included health states, horizon, cycle length), model inputs (e.g., resource use [e.g., number of neurologist visits, admission to hospital, visits to the emergency department], utility values).

Research aim 3: Resource use, costs, and utility values, by seizure status (e.g., controlled or uncontrolled seizures). From resource utilization studies, the number of resource units used (e.g., number of hospital admissions) will be extracted from all studies; associated costs will be extracted only from studies performed in Canada. Depending on the perspective, costs may include those incurred by the payer (e.g., costs to the health care system) or to society (e.g., costs to patients and caregivers, productivity costs). Productivity costs may include lost productivity, lost leisure time, and lost income by caregivers of affected children, as well as productivity losses by children with drug-resistant epilepsy. Utilities may be related to either affected children or their caregivers.

Data extraction

Data will be extracted by one reviewer, and the completeness and accuracy verified by a second reviewer. We will extract study characteristics (e.g., study design, location, decision problem, perspective [i.e., patient, hospital, health care, society], funding source), as well as population characteristics (e.g., epilepsy syndrome, age, comorbidities, setting or context) and details about the interventions and comparators. Details about the model structure, including health states, time horizon, and cycle length, will be extracted from model-based cost-effectiveness and cost-utility analyses, as well as model inputs, including resource use and utilities. From utility studies, we will extract the utility value for each health state, as well as details about the source of the utilities (e.g., population characteristics, setting), method of elicitation (e.g., time trade-off, standard gamble,

preference-based multi-attribute classification system), and description of the health state. From resource utilization studies, we will extract details about the source of the resource use (e.g., population characteristics, setting, number of participants), and study design, along with the frequency of use of each type of reported service.

Quality and risk of bias assessment

We will evaluate the quality of the included economic evaluations by use of the 10-item Drummond checklist [19] and the CHEERS statement [20]. We will also evaluate whether the economic evaluations adequately considered context-specific issues, which may influence the ability of an evaluation to address the decision problem. For example, this may include how the evaluations accounted for changes to treatment regimens or patient weight gain during the analysis horizon. Each study will be appraised independently by two reviewers, with conflicts resolved by discussion.

Synthesis

The extracted data, including study and patient characteristics and study quality, will be summarized descriptively. Depending on study type, model characteristics, resource use, costs, QALYs, and cost-effectiveness results (e.g., ICER) will be summarized. To facilitate comparison between studies, all costs will be reported in 2018 Canadian dollars. First, if necessary, costs will be converted to Canadian Dollars using purchasing power parity for the year of each study and then adjusted to 2018 based on the Bank of Canada Inflation calculator. Where possible, data will be reported separately by drug-resistant epilepsy syndrome and by seizure status (e.g., controlled, uncontrolled).

DISCUSSION

Epilepsy is a major public health concern, affecting about 50 million people worldwide [21]. Because drug-resistant epilepsy is associated with important costs to the health care system [6,7], it is crucial that the cost-effectiveness of new and existing treatments be evaluated using the best available evidence. This review will provide a comprehensive overview of the cost-effectiveness of current

pharmacologic treatments, including cannabis-based treatments, for drug-resistant epilepsy in children, and will serve to inform the subsequent development of a *de novo* cost-effectiveness analyses in this population.

Abbreviations: CBD = cannabidiol, ICER = incremental cost-effectiveness ratios, QALY = quality-adjusted life year, THC = tetrahydrocannabinol.

Declarations

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Availability of data and materials: Not applicable.

Author's contributions: JE and DC designed the study. BS designed and will execute the search strategy. JE drafted the protocol, which was revised by all authors. All authors approved the version of the manuscript submitted for publication.

Ethics approval and consent to participate: Not applicable.

Competing interests: None declared for Jesse Elliott, Becky Skidmore, Tammy Clifford, Beth Potter, George Wells, or Doug Coyle. Bláthnaid McCoy is principal investigator of a study assessing the use of cannabidiol for treatment of Dravet syndrome in children.

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Additional Files

Additional File 1: PRISMA-P checklist (.pdf)

Additional File 2: Search strategy (.pdf)

Additional File 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplemental file 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

Additional File 2: Search strategy

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2018 June 11>, Ovid MEDLINE(R) ALL <1946 to June 11, 2018>

Search Strategy:

- 1 exp Epilepsy/ (337212)
- 2 (epileps* or epilept*).tw,kf. (314061)
- 3 seizure*.tw,kf. (277032)
- 4 convulsi*.tw,kf. (66672)
- 5 falling sickness*.tw,kf. (55)
- 6 comitial disease*.tw,kf. (3)
- 7 (petit mal or grand mal or absence status).tw,kf. (7552)
- 8 Landau-Kleffner Syndrome*.tw,kf. (1004)
- 9 Lennox Gastaut Syndrome*.tw,kf. (3116)
- 10 Dravet Syndrome*.tw,kf. (1866)
- 11 West syndrome*.tw,kf. (2669)
- 12 Doose syndrome*.tw,kf. (157)
- 13 Ohtahara syndrome*.tw,kf. (459)
- 14 Sturge-Weber Syndrome/ (3570)
- 15 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kf. (7823)
- 16 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw,kf. (732)
- 17 SMEI.tw,kf. (419)
- 18 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw,kf. (1072)
- 19 Lafora.tw,kf. (1308)
- 20 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kf. (679)
- 21 ((infantile or nodding) adj2 spasm?).tw,kf. (5772)
- 22 ((flexor or "in flexion") adj2 spasm?).tw,kf. (313)
- 23 ((lightning or salaam) adj2 attack?).tw,kf. (15)
- 24 hypsarrhythmi*.tw,kf. (1936)
- 25 or/1-24 [EPILEPSY] (560609)
- 26 Adolescent/ (3369665)
- 27 exp Child/ (4503995)
- 28 exp Infant/ (2130677)
- 29 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kf. (4316665)
- 30 (newborn* or neonat*).tw,kf. (833360)
- 31 (pediatric* or paediatric*).tw,kf. (776024)
- 32 or/26-31 (8172802)
- 33 25 and 32 [PEDIATRIC EPILEPSY] (203882)
- 34 exp Technology assessment, biomedical/ (23249)
- 35 (technology assessment* or HTA or HTAs).tw,kf. (17211)
- 36 health technology assessment.jw. (3141)
- 37 or/34-36 [HTAs] (37651)
- 38 33 and 37 [PAEDIATRIC EPILEPSY - HTAs] (71)
- 39 exp Epilepsy/ec [Economics] (540)
- 40 Economics/ (257845)
- 41 exp "Costs and Cost Analysis"/ (538452)
- 42 Economics, Nursing/ (38348)
- 43 Economics, Medical/ (44003)
- 44 Economics, Pharmaceutical/ (10619)
- 45 exp Economics, Hospital/ (799622)
- 46 Economics, Dental/ (37552)

47 exp "Fees and Charges"/ (68883)
 48 exp Budgets/ (39309)
 49 budget*.ti,ab,kf. (59686)
 50 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
 economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or
 financed).ti,kf. (419450)
 51 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
 economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or
 financed).ab. /freq=2 (585534)
 52 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (322118)
 53 (value adj2 (money or monetary)).ti,ab,kf. (4814)
 54 exp models, economic/ (14513)
 55 economic model*.ab,kf. (6529)
 56 markov chains/ (15421)
 57 markov.ti,ab,kf. (42108)
 58 monte carlo method/ (58618)
 59 monte carlo.ti,ab,kf. (83017)
 60 exp Decision Theory/ (12808)
 61 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (45992)
 62 exp Delivery of health Care/ec [economics] (49499)
 63 ((healthcare or health care or resource?) adj3 (utili#ation? or utilise? or utilize? or utili#ing)).ti,ab,kf. (65949)
 64 (resource? adj3 ("use" or used or uses or using)).ti,ab,kf. (57658)
 65 (resource? adj3 (unit or units)).ti,ab,kf. (1764)
 66 (resource? adj3 (value? or valuation?)).ti,ab,kf. (2929)
 67 ((utility or utili#ation) adj (study or studies)).ti,ab,kf. (2946)
 68 (ICER or ICERs).ti,ab,kf. (11261)
 69 or/39-68 [ECONOMICS, COST-UTILITY] (1992079)
 70 33 and 69 [PAEDIATRIC EPILEPSY - ECONOMICS, COST-UTILITY] (3310)
 71 "Value of Life"/ (135868)
 72 Quality of Life/ (553323)
 73 quality of life.ti,kf. (155404)
 74 ((instrument or instruments) adj3 quality of life).ab. (7082)
 75 Quality-Adjusted Life Years/ (31484)
 76 quality adjusted life.ti,ab,kf. (26122)
 77 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. (43237)
 78 disability adjusted life.ti,ab,kf. (5604)
 79 (daly or dalys).ti,ab,kf. (5292)
 80 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sftthirtysix or sfthirty
 six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.
 (58225)
 81 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short
 form6).ti,ab,kf. (3888)
 82 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or
 short form eight).ti,ab,kf. (1041)
 83 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform
 twelve or short form twelve).ti,ab,kf. (12539)
 84 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform
 sixteen or short form sixteen).ti,ab,kf. (82)
 85 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform
 twenty or short form twenty).ti,ab,kf. (868)
 86 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. (36071)
 87 (hye or hyes).ti,ab,kf. (178)
 88 (health* adj2 year* adj2 equivalent*).ti,ab,kf. (97)
 89 (pqol or qls).ti,ab,kf. (911)
 90 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf. (1165)
 91 nottingham health profile*.ti,ab,kf. (2545)
 92 sickness impact profile.ti,ab,kf. (2238)
 93 exp health status indicators/ (292343)
 94 (health adj3 (utilit* or status)).ti,ab,kf. (140789)

95 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. (26067)
 96 Patient Preference/ (20266)
 97 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or
 instruments)).ti,ab,kf. (20490)
 98 disutilit*.ti,ab,kf. (1083)
 99 rosser.ti,ab,kf. (199)
 100 willingness to pay.ti,ab,kf. (10950)
 101 standard gamble*.ti,ab,kf. (1818)
 102 (time trade off? or time tradeoff?).ti,ab,kf. (3037)
 103 (tto or ttos).ti,ab,kf. (2341)
 104 (hui or hui1 or hui2 or hui3).ti,ab,kf. (3154)
 105 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. (33522)
 106 Absenteeism/ (25724)
 107 absentee*.ti,ab,kf. (13411)
 108 Presenteeism/ (798)
 109 presentee*.ti,ab,kf. (2638)
 110 productivit*.ti,ab,kf. (108615)
 111 ((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kf. (235562)
 112 ((work* or employ*) adj5 abilit*).ti,ab,kf. (23476)
 113 (time adj1 away).ti,ab,kf. (1386)
 114 Sick Leave/ (9808)
 115 ((sick or medical) adj leave).ti,ab,kf. (10506)
 116 or/71-115 [QoL/DISEASE BURDEN] (1571112)
 117 33 and 116 [PAEDIATRIC EPILEPSY - QoL/DISEASE BURDEN] (6990)
 118 38 or 70 or 117 [HTAs/ECONOMICS/QoL/DISEASE BURDEN] (9727)
 119 exp Animals/ not (exp Animals/ and Humans/) (16386162)
 120 118 not 119 [ANIMAL-ONLY REMOVED] (6980)
 121 120 use medall [MEDLINE RECORDS] (4123)
 122 exp epilepsy/ (337212)
 123 (epileps* or epilept*).tw,kw. (319442)
 124 seizure*.tw,kw. (279367)
 125 convulsi*.tw,kw. (67865)
 126 falling sickness*.tw,kw. (58)
 127 comitial disease*.tw,kw. (3)
 128 (petit mal or grand mal or absence status).tw,kw. (7453)
 129 Landau-Kleffner Syndrome*.tw,kw. (1041)
 130 Lennox Gastaut Syndrome*.tw,kw. (3173)
 131 Dravet Syndrome*.tw,kw. (1914)
 132 West syndrome*.tw,kw. (2795)
 133 Doose syndrome*.tw,kw. (169)
 134 Ohtahara syndrome*.tw,kw. (473)
 135 sturge-weber syndrome/ (3570)
 136 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kw. (7950)
 137 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or
 biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy
 syndrome* or naito oyanagi disease*).tw,kw. (742)
 138 SMEI.tw,kw. (443)
 139 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or
 myoencephalopathy ragged-red fibre disease*).tw,kw. (1101)
 140 Lafora.tw,kw. (1320)
 141 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kw. (685)
 142 ((infantile or nodding) adj2 spasm?).tw,kw. (5916)
 143 ((flexor or "in flexion") adj2 spasm?).tw,kw. (312)
 144 ((lightning or salaam) adj2 attack?).tw,kw. (15)
 145 hypsarrhythmi*.tw,kw. (1968)
 146 or/122-145 [EPILEPSY] (562925)
 147 juvenile/ (40218)
 148 exp adolescent/ (3369840)
 149 exp child/ (4503995)

150 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school*
 or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-
 school*).tw,kw. (4326831)
 151 (newborn* or neonat*).tw,kw. (829311)
 152 (pediatric* or paediatric*).tw,kw. (796794)
 153 or/147-152 (8032752)
 154 146 and 153 [PEDIATRIC EPILEPSY] (203319)
 155 biomedical technology assessment/ (22142)
 156 (technology assessment* or HTA or HTAs).tw,kw. (17805)
 157 health technology assessment.jw. (3141)
 158 or/155-157 [HTAs] (37034)
 159 154 and 158 [PAEDIATRIC EPILEPSY - HTAs] (70)
 160 exp epilepsy/ec [Economics] (540)
 161 economics/ (257845)
 162 cost/ (104904)
 163 exp health economics/ (776721)
 164 budget/ (36915)
 165 budget*.ti,ab,kw. (60026)
 166 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
 economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or
 financed).ti,kw. (440284)
 167 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
 economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or
 financed).ab. /freq=2 (585534)
 168 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. (326140)
 169 (value adj2 (money or monetary)).ti,ab,kw. (4826)
 170 statistical model/ (233242)
 171 economic model*.ab,kw. (6749)
 172 probability/ (137107)
 173 markov.ti,ab,kw. (42814)
 174 monte carlo method/ (58618)
 175 monte carlo.ti,ab,kw. (84136)
 176 decision theory/ (2611)
 177 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. (46752)
 178 ((healthcare or health care or resource?) adj3 (utili#ation? or utilise? or utilize? or utili#ing)).ti,ab,kw. (66568)
 179 (resource? adj3 ("use" or used or uses or using)).ti,ab,kw. (57797)
 180 (resource? adj3 (unit or units)).ti,ab,kw. (1771)
 181 (resource? adj3 (value? or valuation?)).ti,ab,kw. (2947)
 182 ((utility or utili#ation) adj (study or studies)).ti,ab,kw. (3047)
 183 (ICER or ICERs).ti,ab,kw. (11300)
 184 or/160-183 [ECONOMICS, COST-UTILITY] (2176315)
 185 154 and 184 [PAEDIATRIC EPILEPSY - ECONOMICS, COST-UTILITY] (3834)
 186 socioeconomics/ (134357)
 187 exp quality of life/ (585448)
 188 quality of life.ti,kw. (181629)
 189 ((instrument or instruments) adj3 quality of life).ab. (7082)
 190 quality-adjusted life year/ (31484)
 191 quality adjusted life.ti,ab,kw. (26277)
 192 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. (43556)
 193 disability adjusted life.ti,ab,kw. (5618)
 194 (daly or dalys).ti,ab,kw. (5370)
 195 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sftthirtysix or sftthirty
 six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty
 six).ti,ab,kw. (58463)
 196 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short
 form6).ti,ab,kw. (3900)
 197 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or
 short form eight).ti,ab,kw. (1043)

198 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or
 shortform twelve or short form twelve).ti,ab,kw. (12582)
 199 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or
 shortform sixteen or short form sixteen).ti,ab,kw. (82)
 200 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or
 shortform twenty or short form twenty).ti,ab,kw. (867)
 201 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw. (36232)
 202 (hye or hyes).ti,ab,kw. (182)
 203 (health* adj2 year* adj2 equivalent*).ti,ab,kw. (100)
 204 (pqol or qls).ti,ab,kw. (913)
 205 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw. (1173)
 206 nottingham health profile/ (394)
 207 nottingham health profile*.ti,ab,kw. (2557)
 208 sickness impact profile/ (9156)
 209 sickness impact profile.ti,ab,kw. (2275)
 210 health status indicator/ (24834)
 211 (health adj3 (utilit* or status)).ti,ab,kw. (142207)
 212 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.
 (26188)
 213 Patient Preference/ (20266)
 214 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or
 instruments)).ti,ab,kw. (20560)
 215 disutilit*.ti,ab,kw. (1086)
 216 rosier.ti,ab,kw. (200)
 217 willingness to pay.ti,ab,kw. (11074)
 218 standard gamble*.ti,ab,kw. (1838)
 219 (time trade off? or time tradeoff?).ti,ab,kw. (3066)
 220 (tto or ttos).ti,ab,kw. (2352)
 221 (hui or hui1 or hui2 or hui3).ti,ab,kw. (3168)
 222 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. (33591)
 223 absenteeism/ (25724)
 224 absentee*.ti,ab,kw. (13617)
 225 presenteeism/ (798)
 226 presentee*.ti,ab,kw. (2699)
 227 productivit*.ti,ab,kw. (109229)
 228 ((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kw. (235647)
 229 ((work* or employ*) adj5 abilit*).ti,ab,kw. (23541)
 230 (time adj1 away).ti,ab,kw. (1389)
 231 medical leave/ (5661)
 232 ((sick or medical) adj leave).ti,ab,kw. (10652)
 233 or/186-232 [QoL/DISEASE BURDEN] (1345906)
 234 154 and 233 [PAEDIATRIC EPILEPSY - QoL/DISEASE BURDEN] (5407)
 235 159 or 185 or 234 [HTAs/ECONOMICS/QoL/DISEASE BURDEN] (8755)
 236 animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp
 vertebrate/ (48151623)
 237 exp human/ or exp human experimentation/ or exp human experiment/ (37022786)
 238 236 not 237 (11130520)
 239 235 not 238 [ANIMAL-ONLY REMOVED] (8679)
 240 conference abstract.pt. (3034537)
 241 239 not 240 [CONFERENCE ABSTRACTS REMOVED] (7205)
 242 241 use emcxd [EMBASE RECORDS] (4490)
 243 121 or 242 [BOTH DATABASES] (8613)
 244 limit 243 to yr="2010-current" (4067)
 245 remove duplicates from 244 (3064)
 246 243 not 244 (4546)
 247 remove duplicates from 246 (3682)
 248 245 or 247 [TOTAL UNIQUE RECORDS] (6746)
 249 248 use medall [MEDLINE UNIQUE RECORDS] (4087)
 250 248 use emcxd [EMBASE UNIQUE RECORDS] (2659)

Section 4.2

Decision models for assessing the cost-effectiveness of treatments for pediatric drug-resistant epilepsy: A systematic review of economic evaluations

SECTION OVERVIEW

This section presents a manuscript that describes the findings of a systematic review that was undertaken to identify existing economic evaluations of cannabis-based products for pediatric drug-resistant epilepsy. This review also served to identify and appraise decision models previously used in economic evaluations of pharmacologic treatments in this population, in order to inform the development of a subsequent cost-utility analysis (**Section 4.4**). The protocol described in **Section 4.1** was followed for the conduct of this review.

MANUSCRIPT STATUS

This manuscript has been published:

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Supporting material

Appendix 1: PRISMA checklist

Appendix 2: Search strategy

Appendix 3: Included and excluded studies

Appendix 4: Reporting quality of the included studies — CHEERS

Appendix 5: Study-level quality assessment

Author roles and contributions

JE, TC, DC, BP, BM, GW and DC designed the study. BS developed and executed the search strategy. JE, SVK and DC selected studies for inclusion and extracted data. JE analyzed the data

and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication.

RELATED THESIS APPENDICES

Appendix G: Published manuscripts. The PDF of the published manuscript is presented in Appendix G.

Decision models for assessing the cost-effectiveness of treatments for pediatric drug-resistant epilepsy: A systematic review of economic evaluations

Running head: Decision models for pediatric drug-resistant epilepsy

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Keywords: pediatric drug-resistant epilepsy, cannabis, economic evaluation, systematic review, decision model

ABSTRACT

Background: Drug-resistant epilepsy affects about one-third of children with epilepsy and is associated with high costs to the health care system, yet the cost-effectiveness of most treatments is unclear. Use of cannabis-based products for epilepsy is increasing, and the cost-effectiveness of such strategies relative to conventional pharmacologic treatments must be considered.

Objective: The objective of this systematic review was to identify economic evaluations of cannabis-based treatments for pediatric drug-resistant epilepsy. We also sought to identify and appraise decision models that have been used in economic evaluations of pharmacologic treatments (i.e., antiepileptic drugs) in this population.

Methods: Electronic searches of MEDLINE, Embase, and the Cochrane library, as well as a targeted grey literature search, were undertaken (June 11, 2018). Model-based full economic evaluations involving cannabis-based treatments or pharmacologic treatments for drug-resistant epilepsy in children were eligible for inclusion. Two independent reviewers selected studies for inclusion, and study quality was assessed by use of the Drummond and CHEERS checklists. Study findings, as well as model characteristics, are narratively summarized.

Results: Nine economic evaluations involving children with drug-resistant epilepsy were identified; however, none involved cannabis-based treatments. All studies involved pharmacologic treatments compared to other pharmacologic treatments or to non-pharmacologic treatments (i.e., ketogenic diet, epilepsy surgery, vagus nerve stimulation). Few studies have assessed the cost-effectiveness of pharmacologic treatments in specific drug-resistant epilepsy syndromes, including Dravet and Lennox-Gastaut syndromes. Five included studies involved use of Markov models with a similar structure (i.e., health states based on seizure frequency relative to baseline). There was wide range of methodological quality, and few studies fully addressed context-specific issues such as weight gain and treatment switching.

Conclusion: Whether cannabis-based treatments for pediatric drug-resistant epilepsy represent good value for money has yet to be investigated. Economic evaluations of such treatments are needed and should address issues of particular importance in pediatric epilepsy, including weight gain over time, switching or discontinuation of treatments, effectiveness of interventions and comparators, and long-term effectiveness beyond the duration of available clinical studies.

PROSPERO: CRD42018099591

Key points

1. The cost-effectiveness of cannabis-based treatments for pediatric drug-resistant epilepsy has yet to be evaluated.
2. Few studies have evaluated the cost-effectiveness of pharmacologic treatments for pediatric drug-resistant epilepsy.
3. The quality of existing cost-effectiveness evaluations in this area is variable, and few studies have addressed context-specific issues such as weight gain and treatment switching.

1. Introduction

Epilepsy is a chronic neurologic disorder that affects about 50 million people worldwide.[1] As such, the goal of treatment is to reduce seizures and improve quality of life with minimal adverse effects.[2] Although most people with epilepsy respond well to pharmacologic treatments, about one-third have a drug-resistant form [3] (failure of two or more adequate trials of antiepileptic drugs [AEDs][4]). The consequences of drug-resistant epilepsy, especially among children, are severe, including cognitive delay, behavioural problems, autism, poor quality of life, and an increased risk of death.[5–7] Children with drug-resistant epilepsy use more health care resources than those whose seizures are controlled,[8,9] contributing high costs to the health care system.[10,11]

There are multiple types of drug-resistant epilepsy, for example Dravet syndrome and Lennox-Gastaut syndrome, each with individual seizure profiles. As such, there is no one standard of care,[12] and treatment options include both pharmacologic (e.g., AEDs) and non-pharmacologic interventions (e.g., epilepsy surgery, ketogenic diet [KD], vagus nerve stimulation [VNS]). Parents of children with epilepsy also report use of complementary and alternative medicines,[13] including cannabis-based treatments, after failure of conventional AEDs to control seizures,[14] and recent clinical studies suggest that some cannabis-based treatments may reduce seizures among children with drug-resistant epilepsy.[15–18]

In this systematic review, we sought to identify and appraise economic evaluations of cannabis-based treatments for drug-resistant epilepsy in children. We also sought to identify decision models that have been used in economic evaluations of pharmacologic treatments in this population, in order to inform the development of a *de novo* cost-utility analysis of cannabis-based treatments for Dravet syndrome.

2. Methods

The systematic review protocol was registered in PROSPERO (CRD42018099591) and published.[19] The focus of this paper is economic evaluations of cannabis-based products and decision models that have been used to evaluate the cost-effectiveness of pharmacologic treatments for drug-resistant epilepsy in children. This report follows the PRISMA guidelines (Appendix 1).[20] All screening and data extraction were performed using Distiller SR (Evidence Partners).

2.1 Eligibility criteria: We included studies that meet the following criteria:

2.1.1 Population: Children aged less than 19 years with drug-resistant epilepsy, according to the International League Against Epilepsy (ILAE) definition (failure of two or more adequate trials of AEDs).[4] Because few studies reported use of a definition, we also included those that described the target population as having “resistant,” “refractory,” or “intractable” epilepsy, focused on specific drug-resistant epilepsy syndromes (e.g., Dravet syndrome, Lennox Gastaut syndrome), or involved interventions intended to treat drug-resistant epilepsy (i.e., KD, epilepsy surgery, VNS).

2.1.2 Interventions and comparators: We included studies involving any form of cannabis-based treatment (e.g., cannabidiol) compared with any pharmacologic (i.e., AEDs) or non-pharmacologic treatment (i.e., KD, epilepsy surgery, VNS) intended to treat drug-resistant epilepsy. In order to appraise decision models that have been used in this population, we also included studies that compared pharmacologic treatments with other pharmacologic treatments or non-pharmacologic treatments. Economic evaluations that compared non-pharmacologic interventions with other non-pharmacologic interventions were beyond the scope of this review.

2.1.3 Outcomes: Outcomes of interest were total and incremental costs, including direct, indirect (i.e., productivity costs), and drug-related costs; total and incremental quality-adjusted life years (QALYs); and incremental cost-effectiveness ratios (ICERs). Additionally, outcomes of interest from Markov model-based analyses were model structure (e.g., description of the included health states,

horizon, cycle length) and model inputs (i.e., resource use [e.g., number of neurologist visits, admission to hospital, visits to the emergency department], utility values).

2.1.4 Study designs: We included model-based full economic evaluations (i.e., cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-minimization analysis) and health technology assessments that include a full economic evaluation involving a decision model. Stand-alone resource utilization and utility studies were not included in this analysis.

2.2 Search strategy and study selection

Using the OVID platform, we searched Ovid MEDLINE, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase Classic + Embase, as well as the Cochrane Library on Wiley, from inception to June 11, 2018. Search strategies were adjusted across databases and used a combination of controlled vocabulary (e.g., “Epilepsy,” “Costs and Cost Analysis,” “Quality of Life”) and keywords (e.g., “seizure,” “cost,” “QALY”). The strategy (Appendix 2) was peer reviewed by use of the PRESS Checklist [21] A targeted grey literature search was performed, by searching relevant economic web sites and databases included in CADTH’s Grey Matters.[22] The title and abstract of each identified record were screened by two independent reviewers (J.E, S.V.K.), and the full text of any record deemed potentially relevant was examined in duplicate (J.E, D.C.). We excluded conference abstracts and non-English language records. Disagreements were resolved by discussion.

2.3 Risk of bias and quality of the evidence

Two independent reviewers (J.E., D.C.) evaluated the quality of included economic evaluations by use of the 10-item Drummond checklist [22] and the 24-item Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[23] For both checklists, items were graded as “yes,” “no,” or “not applicable.” The Drummond checklist assesses whether appropriate methodology was used in the conduct of the economic evaluation and assesses the validity of the results, while the CHEERS checklist focuses on issues related to reporting. Because a study authored

by J.E. and D.C. was among the included studies, a third reviewer evaluated the quality of this study. Disagreements were resolved by discussion.

Both the CHEERS and Drummond checklists are generic instruments and may not identify context-specific issues that are important to specific decision problems.[24] We identified an additional five issues pertinent to economic evaluations in pediatric drug-resistant epilepsy: First, we considered whether weight gain had been incorporated into the decision model, if appropriate (i.e., time horizon longer than one year). Given that pharmacologic treatments are frequently dosed based on patient weight, and that a child's weight may increase considerably over the analysis horizon, failure to consider weight gain may be a source of bias. Second, we considered whether discontinuation or switching of treatments was addressed. Changing treatments is common among children with drug-resistant epilepsy, with new treatments added or current treatments discontinued in an attempt to control seizures. Third, we considered whether the assumptions made about effectiveness were unbiased across all study treatments. Fourth, we assessed whether all relevant clinical data were incorporated into the model. Finally, we assessed assumptions made about the effectiveness beyond the duration of existing clinical studies.

2.4 Data extraction and synthesis

Study data were extracted by one author (J.E.) and verified for completeness and accuracy by a second reviewer (D.C.), with disagreements resolved by discussion. We extracted study characteristics, including design, location, modeling method (i.e., decision tree or Markov model), and intervention/comparator details. Study findings (e.g., ICERs), as well as study and population characteristics, model inputs, and quality, are summarized descriptively. To facilitate comparison between studies, all costs are expressed in 2018 Canadian dollars (1 \$CAN = 0.7721 USD, 0.6538 Euro). If necessary, costs were converted to Canadian Dollars using purchasing power parity for the year of the study and then adjusted to 2018 based on the Bank of Canada Inflation calculator. Data are reported separately by drug-resistant epilepsy syndrome, where available.

3. RESULTS

3.1 Search results

The literature search yielded 7460 unique records (Figure 1). Of these, 465 were reviewed for eligibility in full-text format. Ten economic evaluations met the inclusion criteria (Appendix 3); however, it was unclear whether one study [25] was a model- or trial-based evaluation and it was not included in the evidence summary. Thus, the evidence base for this review comprised nine full economic evaluations based on decision models involving treatments for drug-resistant epilepsy in children.[26–34] No studies assessed the cost-effectiveness of cannabis-based treatments for pediatric drug-resistant epilepsy.

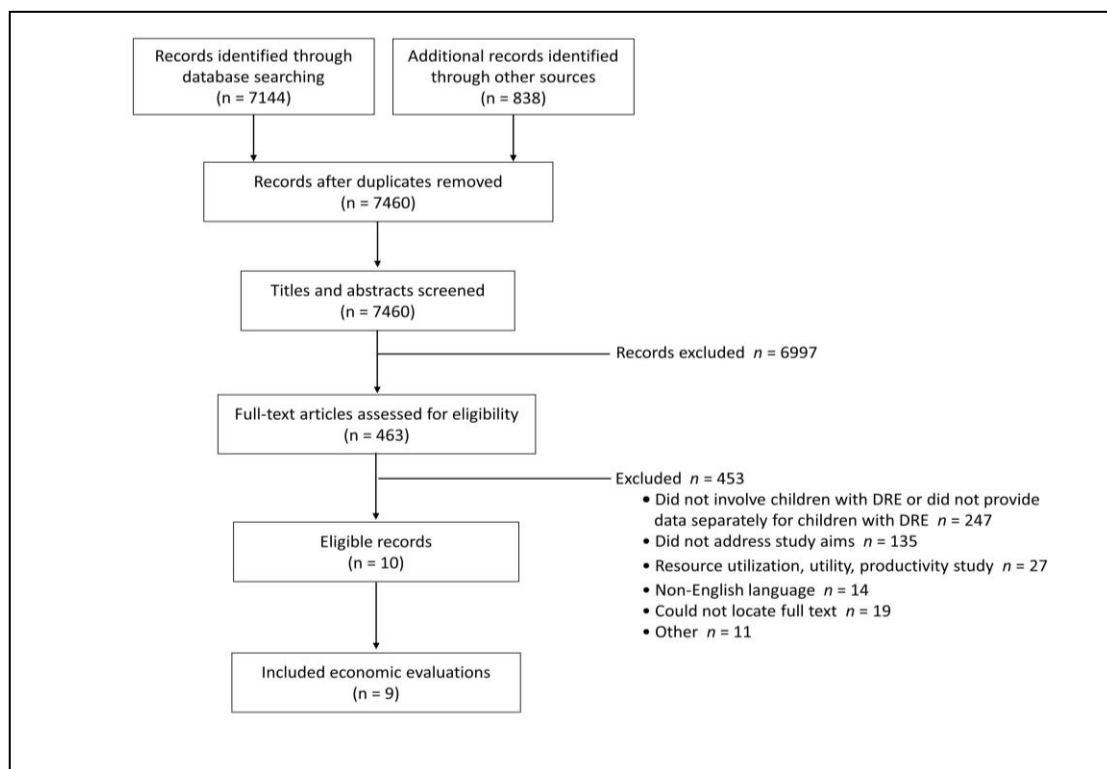


Figure 1: PRISMA flowchart showing study selection. DRE = drug-resistant epilepsy.

3.2 General characteristics of included studies

Each of the nine included economic evaluations evaluated the cost-effectiveness of pharmacologic treatments for drug-resistant epilepsy, compared to other pharmacologic treatments (four studies [26,28,30,33]) or to VNS, KD, or epilepsy surgery (one study [29]) (Table 1). In the remaining four studies,[27,31,32,34] pharmacologic treatments were grouped as “care as usual” or “medical management”; the pharmacologic treatments included in these “usual care” regimens were not well described (e.g., did not specify which AEDs were involved in the treatments). The included studies comprised five cost-utility analyses,[27–29,32,33] assessing costs per QALY gained, while four studies [26,30,31,34] assessed cost-effectiveness by use of alternative health outcomes, with one study each assessing health gains as percentage of successfully treated patients (defined as >50% seizure reduction),[26] percentage of patients with seizures controlled (not defined),[30] percentage of seizures reduced compared with baseline,[34] or seizure freedom.[31]

Four studies targeted specific patient populations, including Dravet syndrome (one study [28]), Lennox Gastaut syndrome (two studies [26,33]), and tuberous sclerosis complex (TSC; one study [29]), while the remaining studies targeted drug-resistant epilepsy in general.[27,30–32,34] The studies were conducted between 1999 and 2018, and the majority were performed in Canada (four studies [27,28,31,34]) and the UK (two studies [26,33]), with one study each from the US,[29] Iran,[30] and The Netherlands.[32] Most studies were undertaken from the perspective of the health care system (seven studies [26–29,32–34]). One study [31] adopted a government perspective; however, the costs included were related to a societal perspective (direct costs, parent productivity loss, social or community living costs). Finally, the perspective of one study was described as “patient” but was limited to drug-related costs (drug-budget perspective).[30] Five economic evaluations involved a Markov model,[26–28,32,33] while the remainder involved a decision tree.[29–31,34] Of the studies that involved a decision tree, two compared pharmacologic treatment to epilepsy surgery [31,34], one compared pharmacologic treatment (carbamazepine) to ketogenic

diet, vagus nerve stimulation or epilepsy surgery [29], and one compared various pharmacologic treatments over a three-month horizon [30]. Two studies assessed outcomes in terms of seizure reductions through the Engel criteria [29,34] whilst another dichotomized the outcomes as seizure control or no control [30]. For the other study using a decision tree, it was not possible to determine the outcomes modeled [31]. The included economic evaluations were primarily funded by non-industry sources or had no funding (five studies [27–30,32]; 56%), while two studies (22%) reported industry funding [26,33] and two (22%) did not report the funding source.[31,34]

3.3 Critical appraisal

There was a wide range in the methodologic and reporting quality of the included studies, ranging from 4 to 10 points on the Drummond checklist (out of 10 points; Figure 2) and 7 to 22 points on the CHEERS checklist (out of 24 points; Appendix 4). In general, most studies (>75%) specified the decision problem, target population, and adopted perspective, and described the decision model and assumptions; however, few provided sufficient description of the competing interventions (44%) or established the effectiveness of the interventions (33%). Overall, few studies (33%) fully reported model inputs, and only two studies (22%) reported efforts to validate model structure and/or inputs [28,32]. Among the included cost-utility analyses, few studies (40%) described the population and methods used to elicit preferences for the health states. Although most authors addressed the limitations of their analyses, few addressed issues of concern such as generalizability of the findings to other jurisdictions or across epilepsy syndromes.

Most of the included studies performed sensitivity analyses, however the type and parameters tested varied across studies (Table 2). All studies assessed the impact of at least one alternative model input, including costs, utilities and/or effectiveness estimates, through deterministic or probabilistic sensitivity analyses or scenario analyses; fewer studies assessed the impact of alternative structural assumptions.[26–28,31,33]

Table 1: Characteristics of the included studies

Author, year	Population	Study design	Perspective	Location	Funding	Modelling method	Analysis horizon	Intervention and comparators
Elliott 2018 [28]	Dravet syndrome	CUA	Health care system	Canada	None	Markov model	10 years	1. Adjunctive stiripentol 2. Clobazam + valproate
Fallah 2016 [29]	DRE secondary to TSC	CUA	Health care system	US	None	Decision tree	5 years	1. Carbamazepine 2. Ketogenic diet 3. Vagus nerve stimulation 4. Epilepsy surgery
de Kinderen 2015 [32]	DRE	CUA	Health care system	The Netherlands	The Netherlands Organization for Health Research and Development	Markov model	12 months; 5 years	1. Ketogenic diet 2. Vagus nerve stimulation 3. Care as usual
Bowen 2012 [27]	DRE	CUA	Health care system	Canada	Ontario Ministry of Health and Long-Term Care	Markov model	20 years	1. Surgery* 2. Medical management
Gharibnaseri 2012 [30]	DRE	CEA	Drug budget	Iran	Tehran University of Medical Sciences	Decision tree	3 months	1. Conventional AEDs 2. Newer AEDs†
Widjaja 2011 [34]	DRE	CEA	Health care system	Canada	NR	Decision tree	1 year	1. Surgery 2. Medical management
Benedict 2010 [26]	Lennox Gastaut syndrome	CEA	Health care system	UK	Eisai Ltd.	Markov model	3 years	1. Rufinamide 2. Topiramate 3. Lamotrigine 4. Standard treatment
Verdian 2010 [33]	Lennox Gastaut syndrome	CUA	Health care system	UK	Eisai Ltd.	Markov model	3 years	1. Rufinamide 2. Topiramate 3. Lamotrigine 4. Standard treatment
Keene 1999 [31]	DRE	CEA	Societal	Canada	NR	Decision tree	25 years	1. Epilepsy surgery 2. Medical management
Note: CEA = cost-effectiveness analysis, CUA = cost-utility analysis, DRE = drug resistant epilepsy, NR = not reported, TSC = tumour sclerosis complex. *Cost-effectiveness of surgery v. medical management among children considered eligible for surgery. Additional analyses addressed cost-effectiveness of referral for epilepsy surgery, which was outside the scope of the current review. †Conventional AEDs: carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate; newer AEDs: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin, zonisamide.								

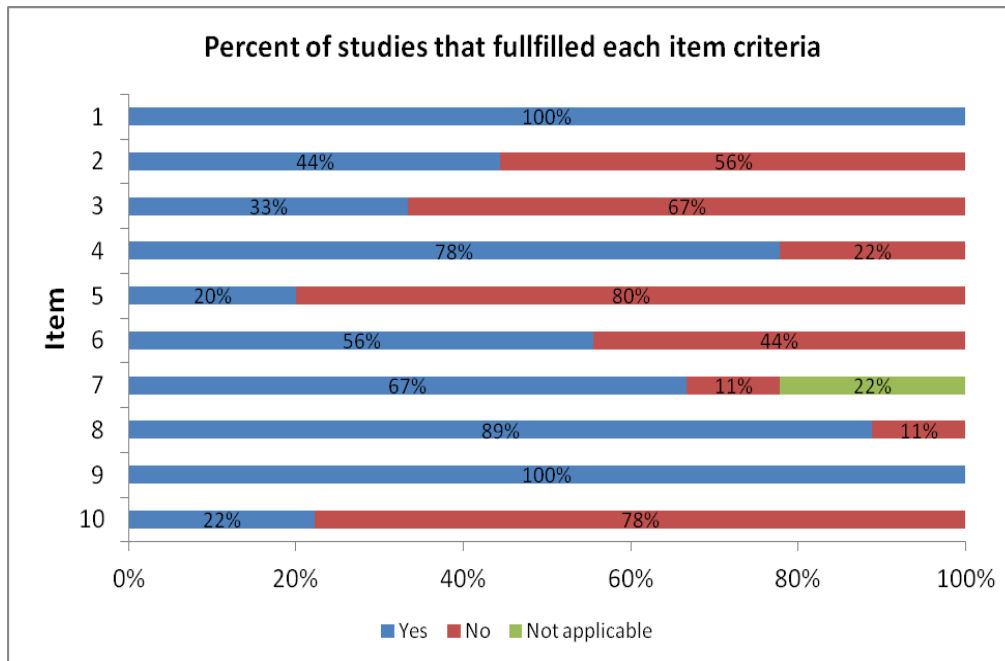


Figure 2: Methodological quality of the included economic evaluations, evaluated by use of the Drummond checklist. Items: 1. Well-defined question. 2. Well-described competing alternatives. 3. Established effectiveness. 4. Important and relevant costs and consequences identified. 5. Measurement accurately performed. 6. Costs and consequences valued credibility. 7. Discounting. 8. Incremental analysis performed. 9. Allowance made for uncertainty. 10. All items of concern to users discussed.

Table 2: Sensitivity analysis descriptions

Author, year	Reference case modelling method	Type of sensitivity analysis	Parameters for sensitivity analyses
Elliott 2018 [28]	Markov model; probabilistic	Scenario analyses; probabilistic	• Drug costs, dose • Patient age • Correlation between utility values • Discount rate • Analysis horizon
Fallah 2016 [29]	Decision tree; deterministic	Probabilistic sensitivity analysis; one-way sensitivity analysis; two-way sensitivity analysis	<i>Probabilistic sensitivity analysis</i> • Drug costs • Effectiveness estimates • Utilities <i>One-way sensitivity analysis</i> • Costs • Effectiveness outcomes • Utilities <i>Two-way sensitivity analysis</i> • Cost of VNS implantation and battery replacement
Benedict 2010 [26]	Markov model; probabilistic	One-way sensitivity analysis	• Analysis horizon • Hospitalization rate for drop seizures • Discount rate
Verdian 2010 [33]	Markov model; deterministic	Probabilistic sensitivity analysis; one-way sensitivity analysis; scenario analysis	<i>Probabilistic sensitivity analysis</i> : Model parameters <i>One-way sensitivity analysis</i> : Uncertainty of model parameters <i>Scenario analysis</i> • Drug unit costs • Discount rates • Analysis horizon
Gharibnaseri 2012 [30]	Decision tree; deterministic	Scenario analysis	• Drug costs • Effectiveness endpoint
de Kinderen 2015 [32]	Markov model; probabilistic	Probabilistic sensitivity analysis; deterministic sensitivity analysis	<i>Probabilistic sensitivity analysis</i> • Costs • Utilities • Transition probabilities <i>Deterministic sensitivity analysis</i> : KD costs
Widjaja 2011 [34]	Decision tree; deterministic	One-way sensitivity analysis; probabilistic sensitivity analysis	<i>One-way sensitivity analyses</i> • Effectiveness estimates • Treatment costs • AEs associated with surgical treatment <i>Probabilistic sensitivity analysis</i> : Model parameters
Keene 1999 [31]	Decision tree; deterministic	Scenario analysis, one-way sensitivity analysis	• Discount rates • Effectiveness estimates • Employment rates • Surgical costs • Post-surgery use of antiepileptic medications
Bowen 2012 [27]	Markov model; deterministic	One-way sensitivity analysis	• Analysis horizons • Discount rate • Utility values

3.3.1 Context-specific issues

(1) Weight gain: Of the included studies, only one considered the impact of increasing patient weight on the ICER. In sensitivity analyses, Elliott and colleagues [28] varied the starting age of the patient cohort, incorporating child weight by use of the World Health Organization's weight-for-age 50th percentile value.[35] The remaining studies assumed a fixed weight over the analysis horizon or did not report assumptions about patient weight. Although the dose of antiepileptic drugs may not be adjusted at every clinical encounter, over time the weight-based dose would be expected to increase as a child ages and increases in weight. Among the decision models included in this review, the analysis horizon ranged from 3 to 20 years, and the failure to consider weight gain may underestimate total drug costs, especially for studies with a horizon longer than 10 years.

(2) Treatment discontinuation or switching: Four studies addressed switching treatments during the analysis horizon,[26,28,32,33] while the remaining studies assumed that no changes occurred [29,30,34] or did not report whether changes were permitted.[27,31] Elliott and colleagues [28] assumed that patients with Dravet syndrome whose seizures did not respond to adjunctive stiripentol treatment within the first six months of treatment would discontinue stiripentol and continue on clobazam and valproate alone. Similarly, both Benedict and colleagues [26] and Verdian and colleagues [33] assumed that patients with Lennox-Gastaut syndrome whose seizures were not adequately controlled by rufinamide, topiramate, or lamotrigine would switch to “standard treatment” (the patient's AEDs taken at baseline) [26] or to the mix of AEDs used in the placebo arm of a clinical trial [33]; in both cases, the specific AEDs that made up the standard treatment arm were not described. Finally, de Kinderen and colleagues [32] assumed that patients who withdrew from the KD would return to a normal diet, while patients with a VNS could have it switched off or removed; however, no changes were made to AED treatments in the “care as usual” group.

Among studies that did not permit switching between treatments, Gharibnaseri and colleagues [30] considered remaining on a treatment regimen for the three months' duration of the analysis as part of

their effectiveness outcome, while Widjaja and colleagues [34] assumed that medication type and dose would remain constant for the first year following epilepsy surgery; whether patients in the medical management arm could switch antiepileptic drugs was not reported. Finally, Fallah and colleagues [29] assumed that patients would stay on a chosen treatment for the five-year study duration.

(3) Effectiveness of usual care: In six studies,[26,27,31–34] pharmacologic treatments were included as “usual care,” “standard treatment” or “medical management” without detailed description of the antiepileptic drugs included in the treatment regimens, and one study [30] compared individual “newer” AEDs to older AEDs as a group (including carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate). Two studies [30,34] derived effectiveness estimates from retrospective reviews of clinical data at single centres, while two studies [26,32] derived estimates of the effectiveness of usual pharmacologic care from the control arms of RCTs. Other studies assumed that patients in the medical treatment arm would not improve (i.e., continue to have inadequately controlled seizures),[27] assumed a “spontaneous remission rate” of 10%,[31] or did not describe assumptions related to the efficacy of standard medical care.[33]

The comparators in two studies were specific AEDs regimens.[28,29] Elliott and colleagues [28] compared adjunctive stiripentol to a regimen of clobazam and valproate alone in children with Dravet syndrome, while Fallah and colleagues [29] compared carbamazepine to KD, VNS, or epilepsy surgery in children with TSC. Elliott and colleagues [28] estimated the effectiveness of clobazam and valproate from a pooled analysis of the control arms of two RCTs,[36,37] while the effectiveness estimate for carbamazepine used by Fallah and colleagues [29] was derived from a retrospective review of clinical data for children with TSC at a single centre.[38]

(4) Clinical effectiveness: In general, meta-analyses of RCTs involving head-to-head comparisons of the competing interventions are considered to provide the highest level of evidence to inform decision-models.[39] However, because of the rare nature of some drug-resistant epilepsy syndromes

and because few RCTs have been performed in some populations,[40] we considered the source of data used to derive effectiveness estimates and how studies addressed a lack of RCTs, if applicable. Of the nine included studies, three used data derived from RCTs to inform their model,[26,32,33] either by pairwise [32] or indirect treatment comparison pooling.[26,33] One study [28] derived effectiveness estimates by use of individual patient data from a multi-centre prospective observational cohort,[41] despite the availability of RCT data, owing to a longer follow-up duration in the observational study compared with the RCTs. Three studies [27,30,34] used data from retrospective observational studies, owing to a lack of RCTs for the model comparators, while two studies [29,31] did not provide sufficient information about the source of the effectiveness data.

(5) Long-term clinical effectiveness: Among seven of the included decision models,[26–29,31–33] the analysis horizon was longer than the duration of the studies used to estimate effectiveness. As such, assumptions were required about the continuation of effect beyond the available data. Four studies [26,28,29,33] assumed that the effectiveness (i.e., transition probabilities) would be consistent beyond the observed duration, assuming no waning of treatment effect. In contrast, one study [32] assumed that there would be no change to seizure status after the first 24 months of treatment, such that a patient in the seizure free state would remain in that state for the remainder of the five-year horizon. One study [27] assumed that all patients in the medical management arm would remain drug-refractory (i.e., no improvement) over the entire 20 year horizon, while patients in the other comparator arms would continue to move through model states based on transition probabilities from the first year of treatment. One study [31] did not report assumptions about maintenance of effect beyond the available data, despite a 25-year horizon.

3.4 Decision-model characteristics

Of the included studies, five involved use of a Markov model (Table 3).[26–28,32,33] Each model involved three health states related to the frequency of seizures relative to a baseline period; death was the final absorbing state in each model. Each model included a state in which patients

experienced no improvement (one study [27]) or limited improvement (<50% reduction in seizures; four studies [26,28,32,33]). The models used in three studies [26,27,32] included a seizure-free state, while two studies [26,33] used a >75% seizure reduction as the state with greatest improvement. Most models involved a three-month cycle (three studies [26,32,33]), while one study each used a one-month [28] and another a one-year cycle.[27] No study justified the chosen cycle length. The analysis horizon ranged from 12 months to 20 years, and most studies provided justification for the chosen time horizon, based on the availability of data (three studies [26,32,33]) or transition to adult care (one study [28]). Four studies [26–28,33] tested the impact of alternative horizons in sensitivity analyses.

Table 3: Structure of Markov models

Author, year	Time horizon	Cycle length	Discount rate	Health states
Elliott 2018 [28]	10 years	1 month	Costs and benefits: 1.5%	• 0% to 49% reduction of seizures from baseline • 50% to 99% reduction • Seizure free • Death
de Kinderen 2015 [32]	12 months; 5 years	3 months	Costs: 4%; benefits: 1.5%	• < 50% seizure reduction • ≥ 50% seizure reduction • Seizure free • Death
Bowen 2012* [27]	20 years	1 year	Costs and benefits: 5%	• No improvement • Seizure reduction • Seizure free • Death
Benedict 2010 [26]	3 years	3 months	Costs: 3.5%; benefits not discounted	• <50% seizure reduction from baseline • 50% to 75% reduction • >75% reduction • Death
Verdian 2010 [33]	3 years	3 months	Costs and benefits: 3.5%	• <50% seizure reduction • 50% to <75% reduction • 75% reduction from baseline. • Death
*Starting at the point of epilepsy surgery.				

3.5 Decision-model inputs

3.5.1 Costs

Each study included at least some costs directly related to the provision of health care (Table 4). One study included only drug costs in their evaluation,[30] without consideration of other costs or resources that may differ between competing treatments, while one study [32] assumed that drug costs would be equivalent between competing treatments (pharmacologic treatment along, or in combination with KD or VNS), thus omitting drug costs from their analysis. Most studies included costs related to visits to a neurologist or epileptologist (78%), while fewer studies included visits to a primary care physician (33%) or emergency department (33%) (Table 4). Admission to hospital or intensive care unit was included in 56% and 22% of analyses, respectively; one study [28] included costs related to ambulance transfer to hospital. Nursing-related costs were included in 44% of studies, although additional studies may have captured nursing costs as part of hospital-related costs. Diagnostic procedures were included in 22% of studies, and professional services (e.g., learning disability specialist, clinical psychologist) were included in 33% of studies.

One study [31] included indirect costs as part of their analysis, which was described as a governmental perspective but was more broad, including parental productivity losses as well as costs related to social or community living. No studies included costs related to patient productivity losses, either as losses during childhood or future losses during adulthood.

3.5.2 Utility values

The cost-utility analyses included in this review [27–29,32,33] used health state utility values derived from three studies, reported in three conference abstracts [42–44] and one full publication.[45] Of these, two studies [42,43,45] assessed utilities among adults with epilepsy: in one study,[45] patients in each health state (ranging from “suboptimal” seizure control to seizure free) were asked how much time they would be willing to give up to live their remaining years in “excellent health,” while one study [42,43] assessed EQ5D scores among adults with recurrent seizures after six months of

adjunctive AED treatment. One study [44] assessed preferences for states related to Lennox-Gastaut syndrome, elicited by time-trade off from members of the general population. None of the included cost-utility analyses considered health effects on caregivers or other family members.

Table 4: Direct and indirect costs included in the economic evaluations

Cost category	References	Proportion of studies (no. of studies/total studies)
Direct costs		
Drug costs	[26–31,33,34]	89% (8/9)
Non-pharmacologic intervention costs†	[27,29,31,32,34]	56% (5/9)
Hospitalization	[27,28,32–34]	56% (5/9)
Intensive care unit	[26,33]	22% (2/9)
Emergency department visits	[28,33,34]	33% (3/9)
Ambulance transfer visits	[28]	11% (1/9)
General practitioner or pediatrician visits	[26,28,33]	33% (3/9)
Neurologist or pediatric epileptologist visits	[26–29,32–34]	78% (7/9)
Nursing‡	[26,32–34]	44% (4/9)
Diagnostic procedures	[33,34]	22% (2/9)
Professional services¶	[26,33,34]	33% (3/9)
Indirect costs		
Productivity (parental)	[31]	11% (1/9)
Social or community living	[31]	11% (1/9)
†Including costs of epilepsy surgery, VNS (insertion and/or battery replacement, removal), ketogenic diet (may include vitamin supplements, keto sticks), follow-up after surgery ‡Epilepsy nurse or not specified. ¶Including occupational therapy, psychotherapy, respite care, home care, learning disability specialist, psychiatry clinics, clinical psychologist, professional services type not specified.		

3.6 Study findings

3.6.1 Cannabis-based treatments: No completed economic evaluations of cannabis-based treatments for pediatric drug-resistant epilepsy were located. We identified one in-progress cost-effectiveness analysis of cannabidiol for seizures associated with Dravet and Lennox Gastaut syndromes; no results are available at this time.[46]

3.6.2 Pharmacologic treatments: Nine studies of pharmacologic treatments for pediatric drug-resistant epilepsy were included in this review. Main outcomes, costs, and incremental cost-

effectiveness ratios are summarized in Table 5. Below we summarize the findings separately by epilepsy syndrome, where possible.

Dravet syndrome: One study [28] assessed the cost-effectiveness of adjunctive stiripentol compared with clobazam and valproate in children with Dravet syndrome whose seizures had not previously responded to clobazam and valproate. From the perspective of the Canadian public health care system, adjunctive use of stiripentol was both more effective and more costly compared with use of clobazam and valproate alone, resulting in an incremental cost of \$154,336 per QALY gained with stiripentol treatment.

Lennox-Gastaut syndrome: Two studies [26,33] assessed the cost-effectiveness of adjunctive rufinamide, topiramate, or lamotrigine compared with standard treatment with older AEDs among children with Lennox-Gastaut syndrome from the perspective of the UK health care system. For treatment of drop seizures, Benedict and colleagues [26] estimated that rufinamide, topiramate, and lamotrigine were each less costly and more effective than standard-therapy with older AEDs. Compared with topiramate, rufinamide was associated with an ICER of \$132 for each 1% increase in successfully treated patients (drop seizures reduced by at least 50%), while lamotrigine and standard treatment were dominated. For total seizures, standard treatment and topiramate were dominated by lamotrigine, and rufinamide was associated with an ICER of \$5,526 for each 1% increase in successfully treated patients. Similarly, Verdian and colleagues [33] estimated that the addition of rufinamide to a background of standard AEDs would be more costly than the addition of either topiramate or lamotrigine, with an estimated ICER of \$52,955 compared to topiramate and \$399,214 compared with lamotrigine per QALY gained.

Table 5: Results of included cost-effectiveness and cost-utility analyses (Costs in 2018 CDN\$*)

Author, year; population	Total (incremental) benefits	Total (incremental) costs	Total (incremental) drug-related costs	Incremental cost-effectiveness results
Dravet syndrome				
Elliott 2018 [28]	QALYs • Clobazam+Valproate: 3.77 (REF) • Stiripentol: 4.37 (0.60)	• Clobazam+Valproate: 56,504 (REF) • Stiripentol: 149,406 (92,902)	• Clobazam+Valproate: 6,356(REF) • Stiripentol: 107,399 (101,043)	<i>Incremental cost per QALY gained with stiripentol: \$154,336</i>
Tuberous sclerosis complex				
Fallah 2016 [29]	QALYs • Carbamazepine: 4.14 (ref) • KD: 3.60 (-0.54) • VNS: 3.89 (-0.25) • Surgery: 4.38 (0.25)	• Carbamazepine: 9,050 (ref) • KD: 18,544 (9,494) • VNS: 69,914 (60,864) • Surgery: 101,108 (92,058)	NR	<i>Incremental cost per QALY gained:</i> • KD: Dominated • VNS: Dominated • Surgery: \$369,712
Lennox-Gastaut syndrome				
Benedict 2010 [26]	% of patients successfully treated (at least 50% reduction) <u>Drop seizures</u> Topiramate: 7.2% (NR) Lamotrigine: 5.2% (NR) Rufinamide: 11.3% (NR) Standard therapy: 3.3% (NR) <u>Total seizures</u> Lamotrigine: 6.9% (NR) Standard therapy: 2.3% (NR) Topiramate: 5.6% (NR) Rufinamide: 7.7% (NR)	<u>Drop seizures</u> Topiramate: 130,318 (NR) Lamotrigine: 130,953 (NR) Rufinamide: 130,978 (NR) Standard therapy: 132,140 (NR) <u>Total seizures</u> Lamotrigine: 95,216 (NR) Standard therapy: 98,561 (NR) Topiramate: 99,052 (NR) Rufinamide: 99,748 (NR)	NR	<i>Incremental cost per 1% increase in successfully treated patients</i> <u>Drop seizures</u> Topiramate: REF Lamotrigine: Dominated Rufinamide: 132 Standard therapy: Dominated <u>Total seizures</u> Lamotrigine: REF Standard therapy: Dominated Topiramate: Dominated Rufinamide: 5,526
Verdian 2010 [33]	QALYs Rufinamide: 1.44 Topiramate: 1.36 Lamotrigine: 1.42 <i>Incremental QALYs for Rufinamide:</i> v. Topiramate: 0.079 v. Lamotrigine 0.021	Rufinamide: 64,439 Topiramate: 60,231 Lamotrigine: 56,165 <i>Incremental costs for Rufinamide:</i> v. Topiramate: 1632 v. Lamotrigine 3209	Rufinamide: 16,579 (NR) Topiramate: 10,290 (NR) Lamotrigine: 7,018 (NR)	<i>Incremental cost per QALY gained for rufinamide</i> v. topiramate: 52,955 v. lamotrigine: 399,214
Drug-resistant epilepsy; type not specified				
de Kinderen 2015 [32]	QALYs <u>12 months</u> KD: 0.693 (NR) VNS: 0.688 (NR) CAU: 0.662 (NR) <u>5 years</u> KD: 3.338 (NR) VNS: 3.395 (NR) CAU: 3.153 (NR)	<u>12 months</u> KD: 20,931 (NR) VNS: 29,708 (NR) CAU: 4,930 (NR) <u>5 years</u> KD: 46,131 (NR) VNS: 47,095 (NR) CAU: 22,412 (NR)	NA†	<u>12 months:</u> KD: Dominant over VNS KD v. CAU: 517,306 VNS v. CAU: 955,979 <u>5 years:</u> KD v. VNS: 16,967 KD v. CAU: 128,283 VNS v. CAU: 102,133
Gharibnaseri 2012 [30]	<i>Proportion of patients with seizures controlled</i> • Conventional AEDs: NR (REF) • Gabapentin NR (-0.52)	• Conventional AEDs: NR (ref) • Gabapentin NR (179) • Lamotrigine NR (97) • Levetiracetam NR (203)	NR	<i>Incremental cost per patient with seizures controlled, v. conventional AEDs:</i> • Gabapentin: Dominated • Lamotrigine: 744

	• Lamotrigine NR (0.13) • Levetiracetam NR (-0.52) • Oxcarbazepine NR (0.15) • Topiramate NR (0.36) • Vigabatrin NR (0.15) • Zonisamide: NR (-0.52)	• Oxcarbazepine NR (135) • Topiramate NR (885) • Vigabatrin NR (768) • Zonisamide NR (169)		• Levetiracetam: Dominated • Oxcarbazepine: 898 • Topiramate: 2,458 • Vigabatrin: 5,123 • Zonisamide: Dominated
Bowen 2012 [27]	QALYs Medical management: NR (REF) Surgery: NR (0.892)	Medical management: NR (REF) Surgery: NR (-\$1,967)	NR	Surgery was dominant over medical management
Widjaja 2011 [34]	% seizure reduction Surgery: 76.53% (NR) Medical treatment: 34.33% (NR)	Surgery: \$35,877 (NR) Medical treatment: \$17,649 (NR)	Surgery: \$2,162 (NR) Medical treatment: \$2,007 (NR)	Incremental cost per 1% seizure reduction gained with surgery: \$432
Keene 1999 [31]	NR	Surgery: \$14,235,807 Medical: \$18,568,446	NR	NR
Note: KD = ketogenic diet, NR = not reported, QALY = quality-adjusted life year, REF = reference group, VNS = vagus nerve stimulation. *(1 \$CAN = 0.7721, USD, 0.6538 Euro). †Cost of antiepileptic drugs were assumed to be equal for all three comparators.				

Tuberous Sclerosis Complex: One study [29] assessed the cost-effectiveness of adjunctive carbamazepine, KD, VNS implantation, and resective surgery for the treatment of drug-resistant epilepsy in children with TSC whose seizures had not responded to two previous AEDs. Compared to adding carbamazepine, KD and VNS implantation were both more costly and less effective (dominated), while resective surgery was associated with an incremental cost of \$369,712 per QALY gained.

Unspecified types of drug-resistant epilepsy: Five studies assessed the cost-effectiveness of treatments for drug-resistant epilepsy in children without specifying a specific syndrome.[27,30–32,34] One study [30] compared the addition of newer AEDs (gabapentin, levetiracetam, lamotrigine, oxcarbazepine, topiramate, vigabatrin, zonisamide) to a regimen including older AEDs (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate), considering only costs related to AEDs: lamotrigine, oxcarbazepine, topiramate, and vigabatrin were associated with ICERs of \$744, \$898, \$2458, and \$5123 per patient with controlled seizures; while gabapentin, levetiracetam and zonisamide were dominated by conventional AEDs.

The remaining four studies [27,31,32,34] included pharmacologic treatments as comparators to KD, VNS implantation, or surgery (Table 1); each of these studies grouped pharmacologic treatments as “medical management” or “care as usual” without fully describing the AED regimens used. Among these studies, pharmacologic treatment was less effective and less costly than surgery,[27,34] KD,[32] and VNS.[32] Compared with medical management, surgery was associated with an ICER of \$432 per 1% reduction in seizures,[34] and KD and VNS were associated with an ICER of \$517,306 and \$955,979, respectively, per QALY gained [32] (Table 5). One study, undertaken from a government perspective, reported that surgery was less costly and more “cost-efficient” than pharmacologic treatment; however, effectiveness data and the ICER were not reported.[31]

4. Discussion

The first objective of this review was to identify economic evaluations of cannabis-based treatments for drug-resistant epilepsy in children; however, no such completed studies were located. One ongoing health technology assessment of cannabidiol for the treatment of Lennox-Gastaut and Dravet syndromes was located, with results expected in late 2019.[46] A 2018 systematic review of cannabis-based treatments for chronic illnesses in adults similarly found no economic evaluations of such treatments for epilepsy.[47]

Our second objective was to identify and appraise decision models that had been used in full economic evaluations of pharmacologic treatments for children with drug-resistant epilepsy, in order to inform a subsequent de novo cost-utility analysis. Our findings highlight a lack of studies in this population, with a total of nine eligible studies, including two in Lennox-Gastaut syndrome [26,33] and one each in Dravet syndrome [28] and TSC.[29] Because of important differences in patient populations, modelling approaches and assumptions, and study comparators, it is difficult to compare cost-effectiveness across studies and interventions. Furthermore, we observed wide variation in the quality of published economic evaluations in this clinical area, and decision makers should consider

the study quality and it is relevant to clinical practice in their jurisdiction when evaluating whether an intervention is cost-effective.

There were important differences in methodologies among the included studies, including the modeling approach used (i.e., decision tree, Markov model), model assumptions, and included costs. However, among studies that involved use of a Markov model, the health states were relatively consistent, despite differences in cycle length and analysis horizons. Few studies considered issues specific to pediatric epilepsy, including weight gain and changing treatments during the analysis horizon. As well, although most studies were undertaken from a health care perspective, the resources included varied widely between studies. Most included visits to a neurologist or epileptologist (78%); however, few studies included visits to a general practitioner, emergency department, or admission to hospital (33%–56%). This is an important consideration, because costs related to hospitalization account for a large portion of direct costs in some drug-resistant epilepsy syndromes and may vary depending on intervention [48]; as such, a failure to include such costs may introduce bias into the economic evaluation. Recent studies have reported costs associated with some drug-resistant epilepsy syndromes, including Dravet syndrome [49,50], which may help to inform future economic evaluations in this population.

Health care decision makers will soon be faced with the decision of whether to reimburse cannabis-based products through public formularies. The first pharmaceutical-grade cannabidiol product, Epidiolex, recently received approval from the US Food and Drug Administration,[51] and cannabis producers in other jurisdictions have developed high-concentration cannabidiol products that have shown promise in clinical studies.[52] In order to evaluate whether such interventions represent good value for money compared to currently available treatments, it is imperative that both the costs and benefits of both the new interventions as well as the currently existing treatments are considered. In our review, we found that cost-effectiveness has been evaluated for few of the currently available pharmacologic treatments for drug-resistant epilepsy in children, despite being listed on public

formularies. This finding is consistent with a 2017 systematic review [53] which identified few economic evaluations of treatments drug-resistant epilepsy in children.

Drug-resistant epilepsy affects an estimated 16 million people worldwide. Despite this, some drug-resistant epilepsy syndromes are individually rare (e.g., Dravet syndrome, Lennox-Gastaut syndrome), and there are limited clinical trials to support the efficacy of most treatments, especially among children.[54,55] Some authors have argued that treatments for rare diseases should not be held to the same standards as drugs to treat common diseases, instead following the rule of rescue without consideration of the cost per benefit gained.[56] However, a recent survey found that Canadians place more value on drug effectiveness and safety, as well as the ability to improve quality and quantity of life, compared with rarity of the target condition.[57] Because of this, as well as high opportunity costs, drugs to treat rare diseases, including drug-resistant epilepsy syndromes, should be rigorously evaluated and must show good value for money through cost-effectiveness evaluations. In Table 6, we provide recommendations for future economic evaluations in this area.

Table 6: Recommendations for model-based economic evaluations of treatments for pediatric drug-resistant epilepsy

Element	Issue	Recommendation
General		
Population	Drug-resistant epilepsy comprises multiple individual epilepsy syndromes, and there may be heterogeneity across syndromes (e.g., natural history, response to interventions).	The target population should be specified. Studies that target a broad population of “drug-resistant epilepsy” should explore heterogeneity through stratified analyses. Generalizability of findings across epilepsy syndromes should be addressed as a study limitation, if appropriate.
Comparators	The choice of comparator may vary by drug-resistant epilepsy syndrome and may depend on jurisdiction.	Study comparators should be described in sufficient detail (e.g. specific AEDs and doses) such that decision makers can evaluate the relevance of comparators to clinical care in their jurisdiction.
Modelling	Assumptions made during model development may impact the cost-effectiveness ratio.	The model should be consistent with the current clinical understanding of the target condition, and model assumptions should be clearly stated and justified. During the model design phase, analysts should consult with a clinical expert with experience caring for children with drug-resistant epilepsy.
Measurement and valuation of health	Health state utility values should reflect the model health states for the target population. Sources of utilities may include affected children, adult caregivers, clinical experts, or the general public.	The source of preferences should be clearly stated and justified for the chosen utility values. Alternate sources of utilities should be tested in scenario analyses, if available.
Resource use and costs	All relevant resources and associated costs should be considered; choice of resources and costs may depend on perspective and jurisdiction.	Analysts should consult with a clinical expert in their jurisdiction to ensure that all relevant resources have been considered. If appropriate given the choice of perspective, analysts should consider both the impacts on the productivity of adult caregivers and affected children.
Context-specific issues		
Weight gain	Drug dosages are frequently based on patient weight; failure to consider weight gain may underestimate drug costs.	For studies with an analysis horizon longer than one year, patient weight gain should be considered. This may be most relevant for studies involving young children and those with uncontrolled seizures.
Treatment discontinuation/switching	Patients with drug-resistant epilepsy whose seizures do not respond to treatment may discontinue the intervention or switch to an alternative treatment	Medication switches should be considered, including any costs associated with switching. The duration of treatment before discontinuation or switching should be specified and justified.
Effectiveness of usual care	“Usual care” may vary by jurisdiction and epilepsy syndrome, and insufficient description of usual care as a comparator does not allow decision makers to assess relevance to their jurisdiction.	The interventions that comprise “usual care” should be explicitly described. Any assumptions about the effectiveness of usual care should be justified.
Clinical effectiveness	There may be limited information about the clinical effectiveness of interventions for drug-resistant epilepsy, owing to the rarity of some individual syndromes.	Choice of data should be based on fitness for purpose, credibility and consistency; use of a hierarchy[39] may be useful in selecting data.
Long-term effectiveness	Decision analyses with a long-term horizon may require assumptions about the maintenance of effect beyond the duration of treatment reported in available clinical studies.	Assumptions about the effectiveness of interventions beyond the duration of clinical observation should be explicitly reported.

4.1 Strengths and limitations

We undertook a systematic review of the published and grey literature to identify relevant economic evaluations, and the protocol was registered a priori. However, several limitations should be considered. First, the review was limited to studies reported in English, which may have excluded relevant studies. Second, because we sought to identify and appraise decision models that had been used to evaluate the cost-effectiveness of pharmacologic treatments for drug-resistant epilepsy, we excluded trial-based economic evaluations. Although RCTs provide important information that can be used in the context of a decision-model, trial-based economic evaluations are unlikely to include all relevant comparators, have a short analysis horizon, and include costs not relevant to clinical practice.[58] Third, the included studies were of variable quality, and few adequately considered context-specific issues, which may bias their findings. Finally, the generalizability of the findings from most of the included studies is limited, because most did not specify a specific epilepsy syndrome. Drug-resistant epilepsy is a heterogeneous population, defined based on response to AEDs,[4] not on clinical characteristics or seizure profile. Similarly, about half of the reviewed studies included pharmacologic treatments as “care as usual” or “medical treatment” without adequately describing the treatment regimen. However, the decision models used in such studies are likely to be generalizable across epilepsy syndromes, with inputs tailored to the specific populations and interventions of interest.

5. Conclusion

Although cannabis-based treatments may be effective in reducing seizures associated with drug-resistant epilepsy, the cost-effectiveness of such treatments relative to other currently available treatments has yet to be investigated. Few economic evaluations of treatments for drug-resistant epilepsy have been conducted, and this review highlights areas where additional research is needed. Future studies will be improved by addressing issues of particular importance in economic evaluations of pediatric epilepsy.

Data Availability Statement: All data generated or analysed during this study are included in this published article (and its supplementary information files).

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Author's contributions: JE, TC, DC, BP, BM, GW and DC designed the study. BS developed and executed the search strategy. JE, SVK and DC selected studies for inclusion and extracted data. JE analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication.

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Appendix 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, Appendix 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 2, Appendix 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

Appendix 2: Search strategy

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2018 June 11>, Ovid MEDLINE(R) ALL <1946 to June 11, 2018>

Search Strategy:

-
- 1 exp Epilepsy/ (337212)
 - 2 (epileps* or epilept*).tw,kf. (314061)
 - 3 seizure*.tw,kf. (277032)
 - 4 convulsi*.tw,kf. (66672)
 - 5 falling sickness*.tw,kf. (55)
 - 6 comitial disease*.tw,kf. (3)
 - 7 (petit mal or grand mal or absence status).tw,kf. (7552)
 - 8 Landau-Kleffner Syndrome*.tw,kf. (1004)
 - 9 Lennox Gastaut Syndrome*.tw,kf. (3116)
 - 10 Dravet Syndrome*.tw,kf. (1866)
 - 11 West syndrome*.tw,kf. (2669)
 - 12 Doose syndrome*.tw,kf. (157)
 - 13 Ohtahara syndrome*.tw,kf. (459)
 - 14 Sturge-Weber Syndrome/ (3570)
 - 15 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kf. (7823)
 - 16 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw,kf. (732)
 - 17 SMEI.tw,kf. (419)
 - 18 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw,kf. (1072)
 - 19 Lafora.tw,kf. (1308)
 - 20 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kf. (679)
 - 21 ((infantile or nodding) adj2 spasm?).tw,kf. (5772)
 - 22 ((flexor or "in flexion") adj2 spasm?).tw,kf. (313)
 - 23 ((lightning or salaam) adj2 attack?).tw,kf. (15)
 - 24 hypsarrhythmi*.tw,kf. (1936)
 - 25 or/1-24 [EPILEPSY] (560609)
 - 26 Adolescent/ (3369665)
 - 27 exp Child/ (4503995)
 - 28 exp Infant/ (2130677)
 - 29 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kf. (4316665)
 - 30 (newborn* or neonat*).tw,kf. (833360)
 - 31 (pediatric* or paediatric*).tw,kf. (776024)
 - 32 or/26-31 (8172802)
 - 33 25 and 32 [PEDIATRIC EPILEPSY] (203882)
 - 34 exp Technology assessment, biomedical/ (23249)
 - 35 (technology assessment* or HTA or HTAs).tw,kf. (17211)
 - 36 health technology assessment.jw. (3141)
 - 37 or/34-36 [HTAs] (37651)
 - 38 33 and 37 [PAEDIATRIC EPILEPSY - HTAs] (71)
 - 39 exp Epilepsy/ec [Economics] (540)
 - 40 Economics/ (257845)
 - 41 exp "Costs and Cost Analysis"/ (538452)
 - 42 Economics, Nursing/ (38348)
 - 43 Economics, Medical/ (44003)
 - 44 Economics, Pharmaceutical/ (10619)
 - 45 exp Economics, Hospital/ (799622)
 - 46 Economics, Dental/ (37552)
 - 47 exp "Fees and Charges"/ (68883)
 - 48 exp Budgets/ (39309)
 - 49 budget*.ti,ab,kf. (59686)

50 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
 economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or
 financed).ti,kf. (419450)
 51 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
 economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab.
 /freq=2 (585534)
 52 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (322118)
 53 (value adj2 (money or monetary)).ti,ab,kf. (4814)
 54 exp models, economic/ (14513)
 55 economic model*.ab,kf. (6529)
 56 markov chains/ (15421)
 57 markov.ti,ab,kf. (42108)
 58 monte carlo method/ (58618)
 59 monte carlo.ti,ab,kf. (83017)
 60 exp Decision Theory/ (12808)
 61 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (45992)
 62 exp Delivery of health Care/ec [economics] (49499)
 63 ((healthcare or health care or resource?) adj3 (utili#ation? or utilise? or utilize? or utili#ing)).ti,ab,kf. (65949)
 64 (resource? adj3 ("use" or used or uses or using)).ti,ab,kf. (57658)
 65 (resource? adj3 (unit or units)).ti,ab,kf. (1764)
 66 (resource? adj3 (value? or valuation?)).ti,ab,kf. (2929)
 67 ((utility or utili#ation) adj (study or studies)).ti,ab,kf. (2946)
 68 (ICER or ICERs).ti,ab,kf. (11261)
 69 or/39-68 [ECONOMICS, COST-UTILITY] (1992079)
 70 33 and 69 [PAEDIATRIC EPILEPSY - ECONOMICS, COST-UTILITY] (3310)
 71 "Value of Life"/ (135868)
 72 Quality of Life/ (553323)
 73 quality of life.ti,kf. (155404)
 74 ((instrument or instruments) adj3 quality of life).ab. (7082)
 75 Quality-Adjusted Life Years/ (31484)
 76 quality adjusted life.ti,ab,kf. (26122)
 77 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. (43237)
 78 disability adjusted life.ti,ab,kf. (5604)
 79 (daly or dalys).ti,ab,kf. (5292)
 80 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty
 six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty
 six).ti,ab,kf. (58225)
 81 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short
 form6).ti,ab,kf. (3888)
 82 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short
 form eight).ti,ab,kf. (1041)
 83 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform
 twelve or short form twelve).ti,ab,kf. (12539)
 84 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform
 sixteen or short form sixteen).ti,ab,kf. (82)
 85 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform
 twenty or short form twenty).ti,ab,kf. (868)
 86 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. (36071)
 87 (hqe or hyes).ti,ab,kf. (178)
 88 (health* adj2 year* adj2 equivalent*).ti,ab,kf. (97)
 89 (pqol or qls).ti,ab,kf. (911)
 90 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf. (1165)
 91 nottingham health profile*.ti,ab,kf. (2545)
 92 sickness impact profile.ti,ab,kf. (2238)
 93 exp health status indicators/ (292343)
 94 (health adj3 (utilit* or status)).ti,ab,kf. (140789)
 95 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. (26067)
 96 Patient Preference/ (20266)
 97 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or
 instruments)).ti,ab,kf. (20490)
 98 disutilit*.ti,ab,kf. (1083)
 99 rosser.ti,ab,kf. (199)

100 willingness to pay.ti,ab,kf. (10950)
101 standard gamble*.ti,ab,kf. (1818)
102 (time trade off? or time tradeoff?).ti,ab,kf. (3037)
103 (tto or ttos).ti,ab,kf. (2341)
104 (hui or hui1 or hui2 or hui3).ti,ab,kf. (3154)
105 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. (33522)
106 Absenteeism/ (25724)
107 absentee*.ti,ab,kf. (13411)
108 Presenteeism/ (798)
109 presentee*.ti,ab,kf. (2638)
110 productivit*.ti,ab,kf. (108615)
111 ((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kf. (235562)
112 ((work* or employ*) adj5 abilit*).ti,ab,kf. (23476)
113 (time adj1 away).ti,ab,kf. (1386)
114 Sick Leave/ (9808)
115 ((sick or medical) adj leave).ti,ab,kf. (10506)
116 or/71-115 [QoL/DISEASE BURDEN] (1571112)
117 33 and 116 [PAEDIATRIC EPILEPSY - QoL/DISEASE BURDEN] (6990)
118 38 or 70 or 117 [HTAs/ECONOMICS/QoL/DISEASE BURDEN] (9727)
119 exp Animals/ not (exp Animals/ and Humans/) (16386162)
120 118 not 119 [ANIMAL-ONLY REMOVED] (6980)
121 120 use medall [MEDLINE RECORDS] (4123)
122 exp epilepsy/ (337212)
123 (epileps* or epilept*).tw,kw. (319442)
124 seizure*.tw,kw. (279367)
125 convulsi*.tw,kw. (67865)
126 falling sickness*.tw,kw. (58)
127 comitial disease*.tw,kw. (3)
128 (petit mal or grand mal or absence status).tw,kw. (7453)
129 Landau-Kleffner Syndrome*.tw,kw. (1041)
130 Lennox Gastaut Syndrome*.tw,kw. (3173)
131 Dravet Syndrome*.tw,kw. (1914)
132 West syndrome*.tw,kw. (2795)
133 Doose syndrome*.tw,kw. (169)
134 Ohtahara syndrome*.tw,kw. (473)
135 sturge-weber syndrome/ (3570)
136 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kw. (7950)
137 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw,kw. (742)
138 SMEI.tw,kw. (443)
139 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw,kw. (1101)
140 Lafora.tw,kw. (1320)
141 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kw. (685)
142 ((infantile or nodding) adj2 spasm?).tw,kw. (5916)
143 ((flexor or "in flexion") adj2 spasm?).tw,kw. (312)
144 ((lightning or salaam) adj2 attack?).tw,kw. (15)
145 hypsarrhythmi*.tw,kw. (1968)
146 or/122-145 [EPILEPSY] (562925)
147 juvenile/ (40218)
148 exp adolescent/ (3369840)
149 exp child/ (4503995)
150 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kw. (4326831)
151 (newborn* or neonat*).tw,kw. (829311)
152 (pediatric* or paediatric*).tw,kw. (796794)
153 or/147-152 (8032752)
154 146 and 153 [PEDIATRIC EPILEPSY] (203319)
155 biomedical technology assessment/ (22142)
156 (technology assessment* or HTA or HTAs).tw,kw. (17805)

157 health technology assessment.jw. (3141)
158 or/155-157 [HTAs] (37034)
159 154 and 158 [PAEDIATRIC EPILEPSY - HTAs] (70)
160 exp epilepsy/ec [Economics] (540)
161 economics/ (257845)
162 cost/ (104904)
163 exp health economics/ (776721)
164 budget/ (36915)
165 budget*.ti,ab,kw. (60026)
166 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or
financed).ti,kw. (440284)
167 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab.
/freq=2 (585534)
168 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. (326140)
169 (value adj2 (money or monetary)).ti,ab,kw. (4826)
170 statistical model/ (233242)
171 economic model*.ab,kw. (6749)
172 probability/ (137107)
173 markov.ti,ab,kw. (42814)
174 monte carlo method/ (58618)
175 monte carlo.ti,ab,kw. (84136)
176 decision theory/ (2611)
177 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. (46752)
178 ((healthcare or health care or resource?) adj3 (utili#ation? or utilise? or utilize? or utili#ing)).ti,ab,kw. (66568)
179 (resource? adj3 ("use" or used or uses or using)).ti,ab,kw. (57797)
180 (resource? adj3 (unit or units)).ti,ab,kw. (1771)
181 (resource? adj3 (value? or valuation?)).ti,ab,kw. (2947)
182 ((utility or utili#ation) adj (study or studies)).ti,ab,kw. (3047)
183 (ICER or ICERs).ti,ab,kw. (11300)
184 or/160-183 [ECONOMICS, COST-UTILITY] (2176315)
185 154 and 184 [PAEDIATRIC EPILEPSY - ECONOMICS, COST-UTILITY] (3834)
186 socioeconomics/ (134357)
187 exp quality of life/ (585448)
188 quality of life.ti,kw. (181629)
189 ((instrument or instruments) adj3 quality of life).ab. (7082)
190 quality-adjusted life year/ (31484)
191 quality adjusted life.ti,ab,kw. (26277)
192 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. (43556)
193 disability adjusted life.ti,ab,kw. (5618)
194 (daly or dalys).ti,ab,kw. (5370)
195 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sftthirtysix or sftthirty
six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty
six).ti,ab,kw. (58463)
196 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short
form6).ti,ab,kw. (3900)
197 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or
short form eight).ti,ab,kw. (1043)
198 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform
twelve or short form twelve).ti,ab,kw. (12582)
199 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform
sixteen or short form sixteen).ti,ab,kw. (82)
200 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform
twenty or short form twenty).ti,ab,kw. (867)
201 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw. (36232)
202 (hye or hyes).ti,ab,kw. (182)
203 (health* adj2 year* adj2 equivalent*).ti,ab,kw. (100)
204 (pqol or qls).ti,ab,kw. (913)
205 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw. (1173)
206 nottingham health profile/ (394)
207 nottingham health profile*.ti,ab,kw. (2557)

208 sickness impact profile/ (9156)
 209 sickness impact profile.ti,ab,kw. (2275)
 210 health status indicator/ (24834)
 211 (health adj3 (utilit* or status)).ti,ab,kw. (142207)
 212 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.
 (26188)
 213 Patient Preference/ (20266)
 214 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or
 instruments)).ti,ab,kw. (20560)
 215 disutilit*.ti,ab,kw. (1086)
 216 rosser.ti,ab,kw. (200)
 217 willingness to pay.ti,ab,kw. (11074)
 218 standard gamble*.ti,ab,kw. (1838)
 219 (time trade off? or time tradeoff?).ti,ab,kw. (3066)
 220 (tto or ttos).ti,ab,kw. (2352)
 221 (hui or hui1 or hui2 or hui3).ti,ab,kw. (3168)
 222 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. (33591)
 223 absenteeism/ (25724)
 224 absentee*.ti,ab,kw. (13617)
 225 presenteeism/ (798)
 226 presentee*.ti,ab,kw. (2699)
 227 productivit*.ti,ab,kw. (109229)
 228 ((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kw. (235647)
 229 ((work* or employ*) adj5 abilit*).ti,ab,kw. (23541)
 230 (time adj1 away).ti,ab,kw. (1389)
 231 medical leave/ (5661)
 232 ((sick or medical) adj leave).ti,ab,kw. (10652)
 233 or/186-232 [QoL/DISEASE BURDEN] (1345906)
 234 154 and 233 [PAEDIATRIC EPILEPSY - QoL/DISEASE BURDEN] (5407)
 235 159 or 185 or 234 [HTAs/ECONOMICS/QoL/DISEASE BURDEN] (8755)
 236 animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp
 vertebrate/ (48151623)
 237 exp human/ or exp human experimentation/ or exp human experiment/ (37022786)
 238 236 not 237 (11130520)
 239 235 not 238 [ANIMAL-ONLY REMOVED] (8679)
 240 conference abstract.pt. (3034537)
 241 239 not 240 [CONFERENCE ABSTRACTS REMOVED] (7205)
 242 241 use emczd [EMBASE RECORDS] (4490)
 243 121 or 242 [BOTH DATABASES] (8613)
 244 limit 243 to yr="2010-current" (4067)
 245 remove duplicates from 244 (3064)
 246 243 not 244 (4546)
 247 remove duplicates from 246 (3682)
 248 245 or 247 [TOTAL UNIQUE RECORDS] (6746)
 249 248 use medall [MEDLINE UNIQUE RECORDS] (4087)
 250 248 use emczd [EMBASE UNIQUE RECORDS] (2659)

Appendix 3: Included and excluded studies (full-text review)

Included studies

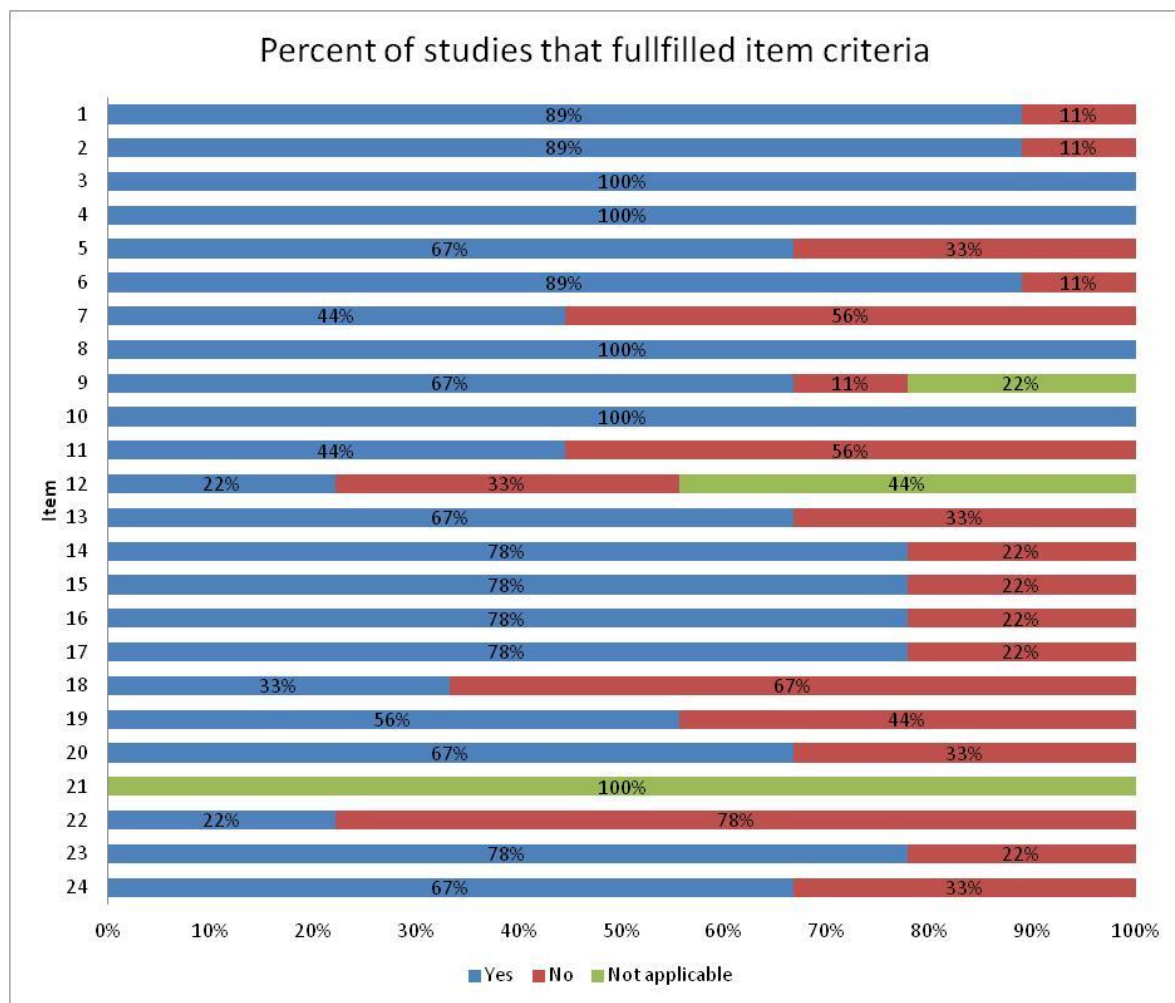
1. Benedict B, Verdian L, MacLaine G. The cost effectiveness of rufinamide in the treatment of Lennox-Gastaut syndrome in the UK. *PharmacoEconomics*. 2010;28:185-99.
2. Bowen JM, Snead O Carter, Chandra K, Blackhouse G, Goeree R. Epilepsy care in Ontario: An economic analysis of increasing access to epilepsy surgery. *Ont Health Technol Assess Ser* [Internet] 2012 July 12;12(18):1-41. Available: www.hqontario.ca/Portals/0/Documents/evidence/reports/econ-epilepsy-surgery.pdf (accessed: 2018 November 6).
3. Clements KM, Skornicki M, O'Sullivan AL. Cost-effectiveness analysis of antiepileptic drugs in the treatment of Lennox-Gastaut syndrome. *Epilepsy Behav*. 2013;29:184-9.
4. de Kinderen RJ, Postular D, Aldenkamp AP, et al. Cost-effectiveness of the ketogenic diet and vagus nerve stimulation for the treatment of children with intractable epilepsy. *Epilepsy Res*. 2015;110:119-31.
5. Elliott J, McCoy B, Clifford T, Wells GA, Coyle D. Economic evaluation of stiripentol for Dravet syndrome: A cost-utility analysis. *PharmacoEconomics*. 2018;6:1253-1261.
6. Fallah A, Weil AG, Wang S, Lewis E, Baca CB, Mathern GW. Cost-utility analysis of competing treatment strategies for drug-resistant epilepsy in children with Tuberous Sclerosis Complex. *Epilepsy Behav*. 2016;63:79-88.
7. Gharibnaseri Z, Kebriaeezadeh A, Nikfar S, Zamani G, Abdollahiasl A. Cost-effectiveness of adding-on new antiepileptic drugs to conventional regimens in controlling intractable seizures in children. *Daru* 2012;(20):17.
8. Keene D, Ventureyra EC. Epilepsy surgery for 5- to 18-year old patients with medically refractory epilepsy--is it cost efficient?. *Childs Nerv Syst*. 1999;15:52-54.
9. Verdian L, Yi Y. Cost-utility analysis of rufinamide versus topiramate and lamotrigine for the treatment of children with Lennox-Gastaut Syndrome in the United Kingdom. *Seizure*. 2010;19(1):1-11.
10. Widjaja E, Li B, Schinkel CD, et al. Cost-effectiveness of pediatric epilepsy surgery compared to medical treatment in children with intractable epilepsy. *Epilepsy Res*. 2011;94(1-2):61-8.

Excluded studies

The full list of excluded studies is available by request from the corresponding author.

Appendix 4: Reporting quality of the included studies — CHEERS

Assessed by use of the 23-item CHEERS checklist. Items: 1. Identified as an economic evaluation. 2. Structured abstract. 3. Clearly stated context. 4. Target population described. 5. Setting and location of decision described. 6. Perspective stated. 7. Comparators described. 8. Horizon described. 9. Discount rate stated for benefits and costs. 10. Health outcomes described. 11. Source of effectiveness data described. 12. Measurement and valuation of preference based outcomes described. 13. Resources and costs described. 14. Currency, price, and conversions reported. 15. Model described. 16. Assumptions described. 17. Analytical methods described. 18. Study parameters described. 19. Incremental costs and outcomes reported. 20. Uncertainty characterized. 21. Differences between subgroups described. 22. Findings, limitations, generalizability, and current knowledge described. 23. Sources of funding described. 24. Conflicts of interest stated. Note: Judgement of “Can’t say” was grouped with “No” in this figure.



Appendix 5: Study-level quality assessment

DRUMMOND checklist

	Elliott 2018	Fallah 2016	de Kinderen 2015	Bowen 2012	Gharibn-aseri 2012	Widjaja 2011	Benedict 2010	Verdian 2010	Keene 1999
1. Well-defined question	YES	YES	YES	YES	YES	YES	YES	YES	YES
2. Well-described competing alternatives	YES	YES	NO	NO	NO	NO	YES	YES	NO
3. Established effectiveness	YES	NO	NO	NO	NO	NO	YES	YES	NO
4. Important and relevant costs and consequences identified	YES	YES	NO	YES	NO	YES	YES	YES	YES
5. Measurement accurately performed	YES	YES	YES	NO	YES	NO	YES	NO	NO
6. Costs and consequences valued credibility	YES	Can't say	YES	NO	YES	Can't say	YES	YES	Can't say
7. Discounting	YES	No	YES	YES	NA	NA	YES	YES	YES
8. Incremental analysis performed	YES	YES	YES	YES	YES	YES	YES	YES	NO
9. Allowance made for uncertainty	YES	YES	YES	YES	YES	YES	YES	YES	YES
10. All items of concern to users discussed	YES	NO	YES	NO	NO	NO	NO	NO	NO
Total score	10	6	7	5	5	4	9	8	4

CHEERS checklist

	Elliott 2018	Fallah 2016	de Kinderen 2015	Bowen 2012	Gharibn- aseri 2012	Widjaja 2011	Benedict 2010	Verdian 2010	Keene 1999
1. Identified as an economic evaluation	YES	YES	YES	YES	YES	YES	YES	YES	NO
2. Structured abstract	YES	YES	YES	YES	YES	YES	YES	YES	NO
3. Clearly stated context	YES	YES	YES	YES	YES	YES	YES	YES	YES
4. Target population described	YES	YES	YES	YES	YES	YES	YES	YES	YES
5. Setting and location of decision described	YES	NO	YES	YES	YES	YES	NO	YES	No
6. Perspective stated	YES	YES	YES	YES	NO	YES	YES	YES	YES
7. Comparators described	YES	YES	No	NO	NO	NO	YES	YES	NO
8. Horizon described	YES	YES	YES	YES	YES	YES	YES	YES	YES
9. Discount rate stated for benefits and costs	YES	No	YES	YES	NA	NA	YES	YES	YES
10. Health outcomes described	YES	YES	YES	YES	YES	YES	YES	YES	YES
11. Source of effectiveness data described	YES	YES	NO	NO	NO	NO	YES	YES	NO
12. Measurement and valuation of preference-based outcomes described	NO	NO	NO	YES	NA	NA	NA	YES	NA
13. Resources and costs described	YES	YES	YES	NO	YES	NO	YES	YES	NO
14. Currency, price, and conversions reported	YES	YES	YES	NO	YES	NO	YES	YES	YES
15. Model described	YES	YES	YES	YES	NO	YES	YES	YES	NO
16. Assumptions described	YES	YES	YES	YES	NO	YES	YES	YES	NO
17. Analytical methods described	YES	YES	YES	YES	NO	YES	YES	YES	NO
18. Study parameters described	YES	YES	YES	NO	NO	NO	NO	NO	NO

19. Incremental costs and outcomes reported	YES	YES	NO	YES	NO	YES	NO	YES	NO
20. Uncertainty characterized	YES	YES	YES	NO	NO	YES	YES	YES	NO
21. Differences between subgroups described	NA	NA	NA	NA	NA	NA	NA	NA	NA
22. Findings, limitations, generalizability, and current knowledge described	YES	NO	YES	NO	NO	NO	NO	No	NO
23. Sources of funding stated	YES	YES	YES	YES	YES	NO	YES	YES	NO
24. Conflicts of interest stated	YES	YES	NO	YES	YES	NO	YES	YES	NO
Total score	22	19	18	16	11	13	18	21	7

Section 4.3

A systematic review of health state utility values, health care resource use, and productivity costs associated with pediatric drug-resistant epilepsy

SECTION OVERVIEW

This section presents the findings of a systematic review that was undertaken to identify inputs for the cost-utility analysis presented in **Section 4.4**. Specifically, this review was intended to identify studies that have assessed preferences for health states (utility values), health care resource use, and/or productivity costs (e.g., due to presenteeism, absenteeism, loss of leisure time) related to pediatric drug-resistant epilepsy. The protocol presented in **Section 4.1** was followed for the conduct of this review.

MANUSCRIPT STATUS:

This manuscript has been submitted for publication:

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Supporting material

Additional File 1: PRISMA checklist

Additional File 2: Search strategy

Additional File 3: Included and excluded studies

Additional File 4: Characteristics – health state utility values

Additional File 5: Quality assessment – health state utility values

Additional File 6: Characteristics – health care resource use

Additional File 7: Quality assessment – health care resource use

Additional File 8: Cost data

Author roles and contributions

JE, TC, DC, BP, BM, GW and DC designed the study. BS developed and executed the search strategy. JE, SVK and DC selected studies for inclusion and extracted data. JE analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication.

A systematic review of health state utility values, health care resource use, and productivity costs associated with pediatric drug-resistant epilepsy

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Keywords: pediatric drug-resistant epilepsy, utility, health care resource use, productivity, systematic review

Abbreviations:

QALY = quality-adjusted life year; SD = standard deviation

Additional Files

Additional File 1

File name: Additional file 1; format: Word (.docx); title: PRISMA checklist; description: Completed PRISMA checklist.

Additional File 2

File name: Additional file 2; format: Word (.docx); title: Search Strategy; description: literature search strategy.

Additional File 3

File name: Additional file 3; format: Word (.docx); title: Included and excluded studies; description: List of studies included at full-text review.

Additional File 4

File name: Additional file 4; format: Word (.docx); title: Characteristics –health state utility values; description: Characteristics of included studies that assessed health state utility values related to drug-resistant epilepsy in children.

Additional File 5

File name: Additional file 5; format: Word (.docx); title: Quality assessment –health state utility values; description: Study-level quality assessment for studies that assessed health state utility values related to pediatric drug-resistant epilepsy.

Additional File 6

File name: Additional file 6; format: Word (.docx); title: Characteristics –health care resource use; description: Characteristics of included studies that assessed health care resource use among children with drug-resistant epilepsy.

Additional File 7

File name: Additional file 7; format: Word (.docx); title: Quality assessment – health care resource use; description: Quality assessment of studies reporting health care resource use by children with drug-resistant epilepsy

Additional File 8

File name: Additional file 8; format: Word (.docx); title: Cost data; description: Included studies that provided cost data but not disaggregated resource use.

DECLARATIONS

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable.

Competing interests: None declared.

Acknowledgements: Not applicable

ABSTRACT

Background: Drug-resistant epilepsy has profound consequences for children with this diagnosis, as well as their families, and is associated with major costs to the health care system. Despite this, we know little about preferences for health states, use of health care resources, and productivity loss associated with pediatric drug-resistant epilepsy.

Methods: We performed a systematic review to identify studies that have assessed preferences for health states (utility values), health care resource use, and/or productivity (e.g., presenteeism, absenteeism, loss of leisure time) related to pediatric drug-resistant epilepsy. We searched MEDLINE, Embase, the Cochrane library, and grey literature sources (June 11, 2018) and included studies that reported productivity or utility values for children with drug-resistant epilepsy or adult caregivers, as well as studies that reported health care resource use by affected children.

Results: Twenty-six studies met the eligibility criteria. Few studies focused on specific epilepsy syndromes: most included children with various types of drug-resistant epilepsy or receiving a specific intervention. Four studies reported health state utility values, with preferences elicited from adults in the general public, clinical experts, or from adult caregivers. There was considerable variation in the health states assessed and in the resulting utility values, ranging from 0.70 for severe seizure disorder to 1.00 for seizure freedom. Fourteen studies reported health care resource use, with admission to hospital and emergency room visits most frequently assessed. Among children with Dravet syndrome, tuberous sclerosis complex, or non-specified drug-resistant epilepsy, hospital admissions ranged from 0.5 to 2.1 per child per year, visits to the emergency room ranged from 1.9 to 2.1, and outpatient visits ranged from 11.13 to 24.1. Vagus nerve stimulation and ketogenic diet reduced hospital admissions and emergency room visits, with no change in neurologist visits. Productivity loss was reported in one study, with a loss of 381 and 616 hours per person per year for absenteeism and presenteeism, respectively, among caregivers of children with Dravet syndrome.

Conclusions: An important research gap that has implications for economic evaluations in the context of pediatric drug-resistant epilepsy has been identified, as related to health state utility values, use of health care resources and productivity loss.

Registration: PROSPERO no. CRD42018099591

BACKGROUND

Epilepsy affects about 50 million people worldwide,¹ with an estimated incidence of about 90–212 per 100,000 in the first year of life.² Although most people with epilepsy respond well to antiepileptic drugs, about one-third have a drug-resistant form³ (failure of two or more adequate trials of antiepileptic drugs⁴). The term “drug-resistant epilepsy” encompasses many individual syndromes (e.g., Dravet syndrome, Lennox-Gastaut syndrome), each with its own seizure profile and recommended treatments.⁵ Individually, some of these syndromes are rare (e.g., Dravet syndrome: 1 in 15000 to 1 in 40,000 children^{6,7}), which has contributed to a paucity of clinical research in this area, including clinical trials⁸ and economic evaluations of interventions.⁹

The consequences of pediatric drug-resistant epilepsy are severe, for both the affected child and family members. Children with drug-resistant epilepsy face severe morbidity,^{10,11} including increased risk of cognitive delay, behavioral problems, autism, and poor quality of life.^{2,5} Health-related quality of life is lower among children with drug-resistant epilepsy compared to children with non-drug-resistant epilepsy and to children without epilepsy, with a higher frequency of seizures associated with a lower quality of life.¹² Other family members, including parents and siblings, are also affected by pediatric drug-resistant epilepsy, with reduced quality of life, high levels of stress, and a negative impact on relationships both within and outside the family.¹³ Parents may also experience worry over their financial situation,^{13,14} frequently missing work, switching or quitting jobs, or losing a job because of their care-giving responsibilities,¹⁵ potentially leading to reduced productivity in the workplace (i.e., absenteeism, presenteeism), or lost leisure time.

Pediatric drug-resistant epilepsy is associated with major costs to the health care system.^{16–18}

Children with uncontrolled seizures use more health care resources compared to those with controlled or no seizures,^{17,19} yet few interventions for drug-resistant epilepsy have been subject to economic evaluation.⁹ As such, we have limited information about the relative costs and benefits of available treatment options. In this review, we sought to identify and appraise studies that would

provide insight into the impact of drug-resistant epilepsy on the use of health care resources and preferences for health states relevant to drug-resistant epilepsy in children. In particular, we sought to identify studies that have assessed health state utility values, health care resources use, and productivity losses (i.e., absenteeism, presenteeism, lost leisure time) related to pediatric drug-resistant epilepsy. The results of this systematic review will be of use to health economists working in this clinical area, by providing an up-to-date summary of data that can be used to inform economic evaluations in this population.

METHODS

The protocol for this review was registered in PROSPERO (CRD42018099591) and published.²⁰

This report follows the PRISMA guidelines for systematic reviews (Additional File 1).²¹

Search strategy

The search strategy was developed by an experienced medical information specialist (B.S.). Using the OVID platform, we searched MEDLINE, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, and Embase Classic + Embase. We also searched the Cochrane Library on Wiley. All searches were performed from database inception to June 12, 2018. We adjusted the search strategies across each database and used a combination of controlled vocabulary (e.g., “Epilepsy,” “Costs and Cost Analysis,” “Quality of Life”) and keywords (e.g., “seizure,” “cost,” “QALY”). The strategy was peer reviewed by use of the PRESS Checklist²² and has been provided in Additional File 2.²¹ We also performed a targeted search of the grey literature, by searching relevant economic web sites and databases included in Grey Matters.²³ Additionally, we hand-searched the reference list of relevant economic evaluations⁹ to identify additional eligible studies. Because we intend to use the results of this review to inform a *de novo* cost-utility analysis from the perspective of a Canadian decision maker, studies performed in Canada but reported in French were considered eligible for inclusion;²¹ however, studies published in other non-English languages were excluded.

Study selection

Two reviewers (J.E, S.V.K.) screened the title and abstract of each identified record against the eligibility criteria. Briefly, we included studies that had assessed health state utility values, health care resource use, or productivity associated with drug-resistant epilepsy in children. The full inclusion and exclusion criteria are described in Table 1. The full text of any record deemed potentially relevant was examined in duplicate (J.E, D.C.). All screening was performed using Distiller SR (Evidence Partners), and disagreements were resolved by discussion. We included studies that reported at least one of the following: (1) utility values for states related to pediatric drug-resistant epilepsy in affected children or their adult caregivers (i.e., parents), (2) health care resource use by children with drug-resistant epilepsy, or (3) productivity losses incurred by children with drug-resistant epilepsy or their adult caregivers. We also included economic evaluations and health technology assessments that assessed health state utility values, resource use, or productivity as part of their study.

Data extraction and quality assessment

Data were extracted from eligible studies by one author (J.E.) and verified for completeness and accuracy by a second reviewer (D.C.). From all studies, we extracted study characteristics (e.g., author, year of publication, country, study design, inclusion criteria) and participant characteristics (age, % male). As well, we extracted the following information from each study design:

Utility studies: respondent (i.e., child v. parent proxy), number and source of respondents (e.g., general public, clinical expert), response rate, measurement and valuation approach, health state description, utility value and measure of variability (e.g., standard deviation [SD]).

Table 1: Study eligibility criteria

Element	Inclusion	Exclusion
Population	Children aged less than 19 years with drug-resistant epilepsy*: - defined as the failure of two or more adequate trials of antiepileptic drugs [‡] ; - reported as being “resistant,” “refractory,” or “intractable”; - focused on specific drug-resistant epilepsy syndromes (e.g., Dravet syndrome, Lennox Gastaut syndrome); - involved interventions intended to treat drug-resistant epilepsy (i.e., ketogenic diet, epilepsy surgery, vagus nerve stimulation)	Studies that included both adults and children but did not report data separately for children
Interventions/comparators	All, including no intervention	
Outcome measures	Health state utility values Health care resource use Costs associated with health care use [†] Productivity costs [‡]	
Study design	Utility elicitation studies: direct or indirect measurement Resource utilization studies: prospective or retrospective cohort, medical chart review, database analyses, cross-sectional surveys Productivity: prospective or retrospective observational cohort, cross-sectional surveys Health technology assessment¶ Economic evaluation¶	Non-primary studies (e.g., editorial, narrative review) Systematic reviews of economic evaluations** Resource utilization studies involving fewer than 5 children
Restrictions	English language	Non-English studies ^{††}
*Studies involving adult caregivers of children with drug-resistant epilepsy were eligible for health state utility studies and productivity studies; utility studies could involve members of the general public provided that the health states being valued pertained to pediatric drug-resistant epilepsy. †Costing studies performed in Canada only. ‡Productivity costs due to absenteeism, presenteeism, or lost leisure time, incurred by the child or an adult caregiver. ¶Health technology assessments and economic evaluations that included measurement of resource use, productivity, or health state utility values as part of the study design were eligible for inclusion. **Systematic reviews of economic evaluations of pharmacologic treatments for pediatric epilepsy were hand-searched for eligible studies. ††Studies performed in Canada but reported in French were eligible for inclusion.		

Resource utilization studies: observation period, comparison group (if applicable), resources assessed (e.g., admission to hospital, emergency department visit), effect estimate and measure of variability, and time period (e.g., number of visits per child per year); data were extracted separately for seizure-related and non-seizure related resource use, if provided. Data were standardized to a one-year period for reporting.

Productivity studies: type of productivity (child or parent; absenteeism, presenteeism, lost leisure time), number of respondents, response rate, survey instrument, effect estimate and measure of variability (e.g., SD).

Study quality was assessed by use of the criteria proposed by the NICE Decision Support Unit²⁴ for studies reporting health state utility values. The quality of studies reporting health care resource use was similarly evaluated by use of the NICE criteria, with modifications to reflect a focus on resource use. Quality was assessed by two reviewers (J.E., D.C), and disagreements were resolved by discussion.

RESULTS

Search results

In total, 7460 records were screened after removal of duplicates (Figure 1). Of these, 463 were selected for full-text review, and 27 met the full eligibility criteria (25 unique studies; Additional File 3).^{15,17,25–49} We identified one additional utility study⁵⁰ by hand searching relevant economic evaluations. Of the 26 included studies, four assessed preferences for health states related to pediatric drug-resistant epilepsy (five publications^{25,35,42,44,50}). Resource utilization, alone or in combination with costs, was assessed in 14 studies (15 publications^{15,17,26,28,32,34,35,37,40,41,45–49}), while an additional eight studies^{27,29–31,33,36,38,39} reported costs but not the number of resources consumed. One study reported on parental productivity (two publications^{15,41}); no studies reported productivity of children with drug-resistant epilepsy. Few studies focused on specific epilepsy syndromes, including Dravet syndrome,^{15,41} infantile spasms,⁴⁵ tuberous sclerosis complex,^{26,34} and Lennox-Gastaut syndrome⁵⁰; the remaining studies included children with various types of drug-resistant epilepsy.

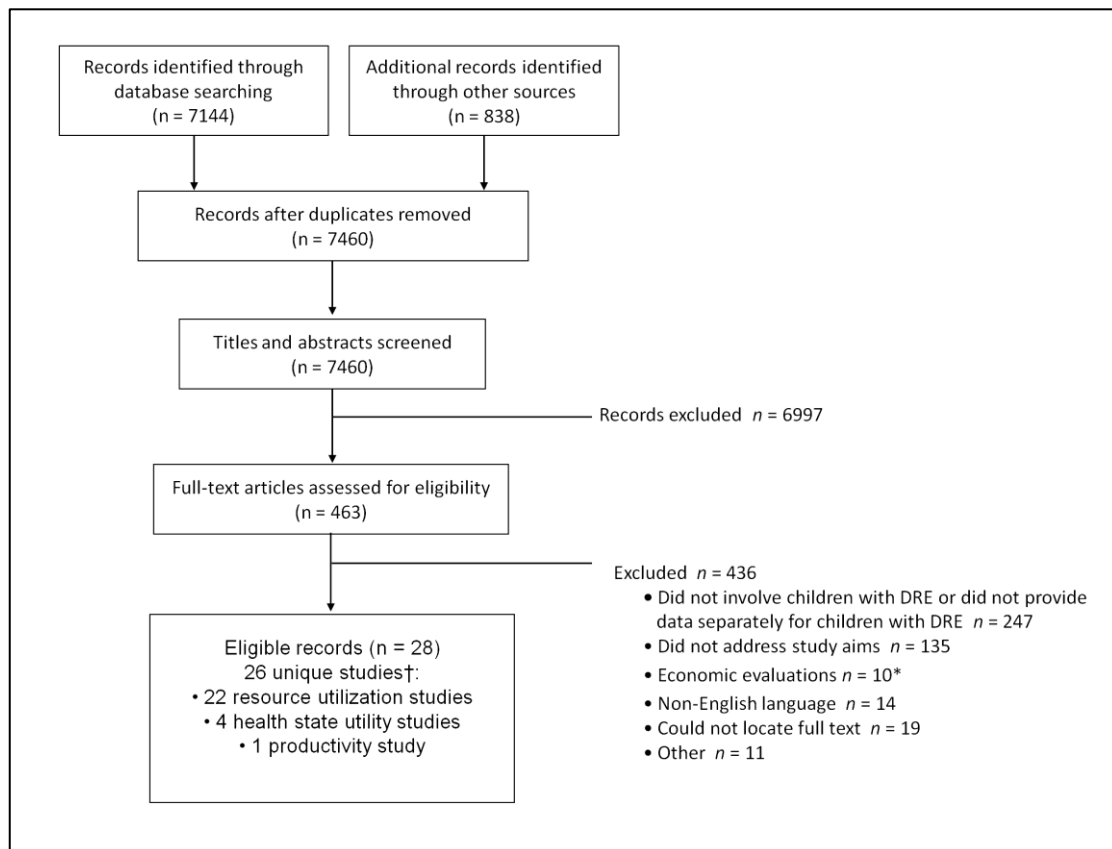


Figure 1: PRISMA flow diagram showing selection of studies. *Hand searched for relevant studies; one additional study was identified. †One study reported both resource utilization and productivity.

Health state utility values

In total, four studies reported health state utility values related to epilepsy in children (Table 2, Additional File 4).^{42–44,50} The included studies employed a variety of methods and designs to elicit preferences for health states: one study⁴² assessed quality of life of children and their adult caregivers as part of a randomized controlled trial of the ketogenic diet versus care as usual, one study⁴³ reported on the development of a catalogue of utility values for a wide range of pediatric diseases, and two studies^{44,50} reported utility values elicited as part of cost-utility analyses. Both direct and indirect methods were used to value health states, including time trade-off,^{43,50} standard gamble,⁴³ visual analogue scale,⁵⁰ EQ-5D,^{42,44,50} EQ-5D-Y,⁴² and TAPQOL/TACQOL⁴²; several studies

involved use of more than one method. One study⁴² used proxy respondents (adult parents) to approximate child preferences for health states, one study⁴⁴ sought the opinion of neurologists experienced in caring for children with epilepsy, while two studies^{43,50} assessed the preferences of adults from the general population. The characteristics of each study and results of quality assessment are described in Additional File 4 and 5, respectively.

There were considerable differences in the health states assessed by each study and the resulting utility values (Table 2, Additional File 5). Wijnen and colleagues⁴² reported utility values before and after receipt of ketogenic diet for up to 16 months or care as usual for 4 months among children with intractable seizures. Among children, there was little change in reported utilities with either receipt of the ketogenic diet (0.753 at baseline, 0.750 at 16 months) or care as usual (baseline: 0.745, 4 months: 0.753). Interestingly, utilities among parents decreased in both the ketogenic diet and care as usual groups (ketogenic diet: baseline: 0.875, 16 months: 0.838; care as usual: baseline: 0.808, 4 months: 0.791).

Carroll and colleagues⁴³ reported utilities related to mild, moderate, and severe seizure disorder, each based on the number of seizures experienced (mild: 1–2 per year; moderate: monthly seizures; severe: 3–4 seizures daily despite taking “medications to reduce the number of seizures”). Utilities ranged from 0.86 for mild seizure disorder to 0.70 for severe seizure disorder.

Connock and colleagues⁴⁴ sought preferences of clinical experts with experience in caring for children with epilepsy to assess utilities related to six broadly defined outcomes of epilepsy treatment, ranging from seizure freedom to an “unacceptable” frequency of seizures, with or without learning disabilities. Utilities were highest for the health states that encompassed “seizure freedom and acceptable side effects, such that the drug is continued (0.981) and “seizure freedom following withdrawal of a successful drug or successful surgery (1.00), while utilities were lowest for states with “unacceptable side effects” (0.767) or “unacceptable frequency of seizures” (0.782); utilities were lower for children with disabilities for each health state (Table 2).

Finally, Verdian and colleagues⁵⁰ report utility values related to Lennox-Gastaut syndrome, with health states related to seizure frequency. Preferences for health states were elicited from adults in the general public by use of time-trade off, visual analogue scale, and EQ-5D (Table 2). Each of the four included health states described the frequency of drop seizures experienced on a weekly basis: the anchor health state was uncontrolled seizures (21–28 drop seizures per week), with the remaining states based on percentage reduction in seizures with treatment. Utility scores for the anchor state were highest with the time trade-off method (0.461), while the visual analogue and EQ-5D gave lower preferences for this state (both 0.02). Across all three methods, the utility weight increased as seizures decreased, with the highest utility reported for a reduction of at least 75% in seizure frequency (0.699) (Table 2).

Table 2: Utility values for children with drug-resistant epilepsy

Author, year	Health states*	Utility value, mean (SD)	
Wijnen 2017	Before treatment, after 4 months of treatment (KD or CAU), after 16 months of treatment (KD); utilities assessed for both affected children and parents	KD GROUP - TACQOL/TAPQOL (child): - Baseline: 0.753 (NR) 4 months: 0.748 (NR) 16 months: 0.750 (NR) - EQ-5D-Y (child):† - Baseline: 0.53 (NR) 4 months: 0.60 (NR) 16 months: 0.73 (NR) - EQ-5D (parent; UK tariff): - Baseline: 0.875 (NR); 4 months: 0.853 (NR) 16 months: 0.838 (NR) - EQ-5D (parent; Dutch tariff): - Baseline: 0.881 (NR) 4 months: 0.866 (NR) 16 months: 0.865 (NR)	CAU GROUP‡ - TACQOL/TAPQOL (child): - Baseline: 0.745 (NR) 4 months: 0.753 (NR) - EQ-5D-Y (child)‡: - Baseline: 0.68 (NR) 4 months: 0.65 (NR) - EQ-5D (parent; UK tariff): - Baseline: 0.808 (NR); 4 months: 0.791 (NR) - EQ-5D (parent; Dutch tariff): - Baseline: 0.831 (NR) 4 months: 0.815 (NR)
Carroll 2009	- Mild seizure disorder (1–2 seizures/yr) - Moderate seizure disorder (monthly seizures) - Severe seizure disorder (3–4 seizures/d, drug-resistant)	- Mild - SG: 0.85 (0.21) - TTO: 0.86 (0.21) - Moderate - SG: 0.84 (0.21) - TTO: 0.83 (0.22)	- Severe - SG: 0.70 (0.25) - TTO: 0.71 (0.27)
Verdian 2008⁵⁰	States defined by the number of tonic-atonic (drop attack) seizures per wk and percentage reduction following treatment; Lennox-Gastaut syndrome - Health state 1 (uncontrolled seizures): 21–28 seizures per wk - Health state 2: < 50% reduction - Health state 3: ≥ 50% to <75% reduction - Health state 4: ≥ 75% reduction	- Health state 1 - TTO: 0.393 (NR) - VAS: 0.02 (NR) - EQ-5D: 0.02 (NR) - Health state 2 - TTO: 0.461 (NR) - VAS: 0.414 (NR) - EQ-5D: 0.100 (NR) - Health state 3 - TTO: 0.605 (NR) - VAS: 0.556 (NR) - EQ-5D: 0.500 (NR)	- Health state 4 - TTO: 0.699 (NR) - VAS: 0.677 (NR) - EQ-5D: 0.596 (NR) Disutility scores: - Concentration problems: 0.108 (NR) - Weight loss: 0.135 (NR) - Somnolence: 0.174 (NR) - Rash: 0.190 (NR) - Nausea/vomiting: 0.193 (NR)
Connock 2006	- Patient has unacceptable side effects of the drug such that the drug will be withdrawn (AES) - Patient experiences an unacceptable frequency of seizures such that a change of therapy will be initiated and the drug withdrawn (USF) - Patient experiences an acceptable reduction in seizures and acceptable side-effects, such that the drug is continued (PAR) - Patient experiences seizure freedom and acceptable side effects, such that the drug is continued (EFFd) - Patient experiences seizure freedom following withdrawal of a successful drug or successful surgery (EFFw) - Patient is not seizure free but prefers to remain untreated (UNT)	- AES - No learning disability: 0.767 (0.1825) - Learning disability: 0.603 (0.2416) - USF: - No learning disability: 0.782 (0.1972) - Learning disability: 0.675 (0.1830) - PAR: - No learning disability: 0.908 (0.1144) - Learning disability: 0.782 (0.09)	- EFFd: - No learning disability: 0.981 (0.0525) - Learning disability: 0.830 (0.1016) - EFFw: - No learning disability: 1.000 (0.0000) - Learning disability: 0.857 (0.1000) - UNT: - No learning disability: 0.846 (0.1375) - Learning disability: 0.707 (0.1938)

Note: CAU = care as usual, KD = ketogenic diet, NR = not reported, SD = standard deviation, SG = standard gamble, TAPQOL = TNO-AZL Preschool Children's Quality of Life, TACQOL = TNO-AZL Children's Quality of Life, TTO = time trade off, VAS = visual analogue scale.

*Health states are fully described in Additional File 5.

†QoL in the CAU group was last measured at 4 mo, and observations were carried forward to 16 mo.

‡EQ-5D-Y measured for 11 children (of 26) at baseline for the KD group, 11 (of 22) at baseline in the CAU group, and 4 (of 26) in the KD group at follow-up.

Health care resource use

In total, use of health care resources was assessed in 14 studies^{17,26,28,32,34,35,37,40,41,45–49}; of these, one study²⁸ did not provide data for a defined observation period and is not included in the evidence synthesis. The ages of the included children ranged from 1 to 18 years (Table 3); where reported, the mean ages were between 3 and 12 years. A variety of study designs were represented, including retrospective review of medical charts^{26,35,37,49} or administrative databases,^{31,38,40,42,49,51} cross-sectional surveys of parents or caregivers,^{34,41} and prospective observational cohort⁴⁶ (Additional File 6). Although all studies included children with drug-resistant epilepsy, some focused on specific epilepsy syndromes (Dravet syndrome,⁴¹ infantile spasms,⁴⁵ tuberous sclerosis complex^{26,34}), while the remainder focused on children who received a specific intervention (vagus nerve stimulation,^{32,35,37,47,48} ketogenic diet,^{40,49} or who had any type of drug-resistant epilepsy^{17,46}) (Table 3). Most studies focused on the use of two or three resources,^{26,32,34,35,40,45,48,49} while few studies assessed use of four or more resources.^{41,47} Among the included studies, admission to hospital was the most frequently assessed resource,^{26,32,34,37,40,41,45–49} followed by emergency room visits^{32,34,35,40,41,45,47–49}; use of other resources, such as ambulance transfer, were infrequently assessed.⁴¹ The characteristics of each study and results of quality assessment are described in Additional File 6 and 7, respectively. Of note, the quality of the included studies was variable, with most involving a small number of participants, and at high risk of selection bias.

Health care resource utilization data are summarized in Table 3. Among children with Dravet syndrome, tuberous sclerosis complex, or non-specified drug-resistant epilepsy, hospital admissions ranged from 0.5 to 2.1 per child per year^{26,34,41,46}, emergency room visits ranged from 1.9 to 2.1 per child per year^{34,41}, outpatient visits ranged from 11.13 to 24.1 per child per year^{17,34,41}, while one study each reported in-home visits (46 per child per year),⁴¹ ambulance use (ground: 0.67; air: 0.07)⁴¹ and admissions to the intensive care unit (0.06).²⁶

Among children who received vagus nerve stimulation or ketogenic diet, hospital admissions before intervention ranged from fewer than one visit per year to about two visits per year^{32,35,37,40,47–49}; Table 3); in each study, admissions decreased following intervention. Similarly, ER visits decreased following initiation of vagus nerve stimulation or ketogenic diet^{32,35,40,47,49}, while the number of outpatient physician and neurologist visits were relatively consistent before and after intervention^{32,47}. Notably, no study reported health care resource use by seizure frequency or severity.

Table 3: Health care resource use by children with drug-resistant epilepsy

Study¶	Population (no. in group); mean age (SD)	Group	No. visits per 12-month period*, mean (SD)							Hours per yr per person; mean (SD)
			Hospital admission	ER visits	Outpatient/ physician visits	Neurologist visits	In-home visits	Ambulance transfer	ICU admission	Productivity
Children not undergoing a specific intervention										
Whittington 2018	DS (34); 11.7 (5.8)	—	1.13 (2.16)	1.90 (2.27)	11.13 (9.07)	—	46.23 (137.64)	Ground: 0.67 (1.58); air: 0.07 (0.25)	—	Absenteeism: 381 (704); presenteeism: 616 (719); lost leisure time: 2047 (2929) **
Rentz 2015	TSC (179); 7.1 (4.6)	—	2.1 (1.3)	2.1 (1.3)	24.1 (27.5)	—	—	—	—	—
Cramer 2014	DRE (422); 6.6 (2.7)	—	—	—	Total: 17.3 (NR); epilepsy related: 4.7 (NR)	—	—	—	—	—
Lennert 2012	TSC (95); 3.1 (7.8)	—	Total: 0.50 (NR); neurologic-related: 0.28 (NR); TSC– related: 0.18 (NR); other: 0.04 (NR)	—	—	—	—	—	0.06 (NR)	—
Guerrini 2001	DRE (42); NR (range 5–14)	—	0.8 (NR)	—	—	—	—	—	—	—
Children undergoing vagus nerve stimulation										
Patel 2018	Undergoing VNS (34); 10.5 (NR)	Pre-VNS	1.56 (NR)	2.88 (NR)	—	1.68 (NR)	—	—	—	—
		Post-VNS	0.24 (NR)	2.64 (NR)	—	1.8 (NR)	—	—	—	—
Aburahma 2015	DRE, undergoing VNS (28); 9.4 (NR)	Pre-VNS	—	36 (NR)	—	—	—	—	13‡	—
		Post-VNS	—	8.76 (NR)	—	—	—	—	0	—
Kalanithi 2014	Undergoing VNS (93); 10.6 (NR)	Pre-VNS	1.08 (NR)	—	—	—	—	—	—	—
		Post-VNS	Total: 0.66 (NR), seizure-related: 0.65 (NR)	Total: 1.11 (NR); Seizure-related: 0.80 (NR)	—	—	—	—	—	—
Helmers 2012	DRE, undergoing VNS (445); Aged 1-11	Pre-VNS	Aged 1–11 yr: Total: 0.012 (NR), seizure- related: 0.012 (NR); Age 12–17 yr: total:	Aged 1–11 yr: 0.032 (NR); Age 12–17 yr: 0.028 (NR)	Aged 1–11 yr: Total: 1.096 (NR), seizure- related: 0.304 (NR); Age 12–17 yr: total:	Aged 1–11 yr: 0.044 (NR); Age 12–17 yr: 0.044 (NR)	—	—	—	—

Study¶	Population (no. in group); mean age (SD)	Group	No. visits per 12-month period*, mean (SD)							Hours per yr per person; mean (SD)
			Hospital admission	ER visits	Outpatient/physician visits	Neurologist visits	In-home visits	Ambulance transfer	ICU admission	Productivity
	yr group: 7.1 (2.6); Aged 12-17 yr group: 14.6 (1.7)		0.012 (NR), seizure-related: 0.008 (NR)		0.856 (NR), seizure-related: 0.228 (NR)					
		Post-VNS	Aged 1–11 yr: Total: 0.012 (NR), seizure-related: 0.008 (NR); Age 12–17 yr: total: 0.008 (NR), seizure-related: 0.004 (NR)	Aged 1–11 yr: Total: 0.028 (NR); Age 12–17 yr: total: 0.016 (NR)	Aged 1–11 yr: Total: 1.16 (NR), seizure-related: 0.36 (NR); Age 12–17 yr: total: 0.082 (NR), seizure-related: 0.2 (NR)	Aged 1–11 yr: Total: 0.04 (NR); Age 12–17 yr: total: 0.04 (NR)	—	—	—	—
Ryzi 2012	Undergoing VNS (15); median 14.6 (2.5)	Pre-VNS	1.0 (0.6)	—	—	—	—	—	—	—
		Post-VNS	0.3 (0.5)	—	—	—	—	—	—	—
Children receiving ketogenic diet										
Kayyali 2016	DRE, receiving KD (37); 4 (2.78)	Pre-KD	Total: 1.44 (NR); seizure related: 1.08 (NR); non-seizure related: Pre-KD 0.36 (NR)	Total: 1.8 (NR); seizure related: 1.08 (NR); non-seizure related: Pre-KD 0.72 (NR)	—	—	—	—	—	—
		Post-KD	Total: 0.84 (NR); seizure related: 0.36 (NR); non-seizure related: Pre-KD 0.48 (NR)	Total: 1.08 (NR); seizure related: 0.36 (NR); non-seizure related: Pre-KD 0.84 (NR)	—	—	—	—	—	—
Whiting 2017	Receiving KD† (166); 5.8 (4.5)	Pre-KD	2.1 (SE 0.27)	4.6 (SE 0.60)	—	—	—	—	—	—
		Post-KD	1.3 (SE 0.24)	2.1 (SE 0.25)	—	—	—	—	—	—
Children receiving other interventions										
Gold 2016	Infantile spasms, received repository corticotrop-hin injection (252); 5.8 (4.5)	Before diagnosis	Received intervention within 30 days of diagnosis: 0.8 (2); Received intervention > 30 days after diagnosis: 2.4 (4)	—	—	—	—	—	—	—
		After diagnosis	Received intervention within 30 days of diagnosis: 2.2 (1.9); Received	Received intervention within 30 days of diagnosis: total	—	—	—	—	Received intervention within 30 days of diagnosis: 0.3	—

Study¶	Population (no. in group); mean age (SD)	Group	No. visits per 12-month period*, mean (SD)							Hours per yr per person; mean (SD)
			Hospital admission	ER visits	Outpatient/physician visits	Neurologist visits	In-home visits	Ambulance transfer	ICU admission	Productivity
			intervention > 30 days after diagnosis: 2.4 (2.0)	visits 1.0 (1.7), IS-related visits: 0.2 (0.5); Received intervention > 30 days after diagnosis: total visits 1.1 (1.5), IS-related visits: 0.2 (0.5)					(0.7); Received intervention > 30 days after diagnosis: 0.5 (1.5)	
Note: DRE = drug-resistant epilepsy, DS = Dravet syndrome, ER = emergency room, ICU = intensive care unit, IS = infantile spasm, KD = ketogenic diet, SD = standard deviation, TSC = tuberous sclerosis complex, VNS = vagus nerve stimulation. Additional participant characteristics are available in Additional File 6. *Standardized to a 12-month period. †Included a comparison group (n = 167) who did not receive KD: Hospitalizations in the matched “pre-KD” period: 0.5 (SE 0.09); matched on-diet period: 0.3 (SE 0.06); ER visits in the matched “pre-KD” period: 1.7 (SE 0.22); matched on-diet period: 1.3 (SE 0.19). ‡"In 5 patients who had frequent status epilepticus events, the total number of intensive care unit admissions dropped from 13 admissions in the 3 years prior to implantation to none in the last 3 years after implantation." ¶One additional study (MacCracken 1999) reported hospital admissions and ED visits among 13 patients in the US before and after receipt of ketogenic diet. The duration of patient observation before KD was initiated was not reported, and the on-diet period ranged from 5 wks to 2.75 yr. **Among adult caregivers: Absenteeism, presenteeism: n = 24 (those who reported employment); lost leisure time: n = 33										

Productivity

Productivity costs associated with pediatric drug-resistant epilepsy was assessed in one study (Table 3).^{15,41} In a survey of parents of children with Dravet syndrome, parents reported a mean loss of 381 (SD 704; n = 24) hours of work per year per person (absenteeism). Presenteeism was estimated to account for 616 (SD 719; n = 24) hours per person per year, while a loss of 2047 (SD 2929; n = 34) hours per person per year of leisure time was reported. No study assessed productivity loss among children with drug-resistant epilepsy.

DISCUSSION

In this review, we identified 26 studies that reported health state utility values, health care resource use, or productivity costs associated with pediatric drug-resistant epilepsy. Of these, most focused on the use of health care resources, while few studies assessed preferences for health states or productivity costs. No studies assessed child productivity or children's preferences for health states.

Economic evaluation is widely used to inform discussions about reimbursement policies related to health care interventions. Because economic evaluation hinges on the comparison of costs and consequences of the available treatment options,⁵² the source and types of information included can have an important effect on the subsequent estimate of cost-effectiveness.⁵³ The evaluation of interventions intended for use in children presents additional challenges beyond those common to economic evaluations of treatments for adult conditions, including the dependency of children on others (i.e., parents or caregivers), differing health care needs and patterns of disease depending on developmental stage, and the impact of adults on access to and use of health care resources.⁵⁴

Because children are not independent of their parents or caregivers, the health effects and costs incurred by other family members may also require consideration, which is consistent with guidelines from Canada⁵⁵ and the United Kingdom⁵⁶ for economic evaluations of health care interventions.

The measurement of health benefits in terms of QALYs requires estimation of preferences for relevant health states (utility weights). However, for economic evaluations of interventions for pediatric conditions, an important question is whether utility weights should be based on adult or child preferences for the relevant health states. While some posit that utilities should be based on children's preferences,⁵⁷ others argue that adults, as tax payers and voting members of society, should be the source of utility weights.⁵⁸ This can have important implications, given that children and adults may not value health states in the same way⁵⁹ and the source of preferences has the potential to affect decisions about whether a treatment is considered cost-effective.⁶⁰ Of the four utility studies identified in this review, only Wijnen and colleagues⁴² sought to elicit children's preferences,⁴² with the other studies relied on adults to value pediatric health states. However, although Wijnen and colleagues⁴² set out to obtain child-reported EQ-5D-Y values, they were only able to do so for a small subset of participants. This may have been owing to the age of children in their study (range 1.1 to 16.5 yr): EQ-5D-Y is indicated for self-response by children aged 8 years and older, with proxy respondents recommended for younger children.⁶¹ Indeed, most generic multi-attribute utility systems are recommended for use by children in specific age groups and may require the use of proxy respondents for the youngest age groups,⁶² and there is no valid instrument for use by children of all ages.⁵⁷ Because children may value health states differently compared with adult respondents, this a lack of data from children represents an important gap in our understanding of the impact of drug-resistant epilepsy on children and should be considered when conducting economic evaluations in this area.

Among the studies that reported health state utility values, there was considerable variation in terms of the health states assessed. Wijnen and colleagues⁴² reported changes in utilities before and after receipt of the ketogenic diet, but did not provide utilities for specific health states (e.g., based on frequency of seizures). Similarly, Carroll and colleagues⁴³ described three seizure disorders (mild, moderate, severe) but did not capture all of the health states that would be relevant to a decision

model in drug-resistant epilepsy. Connock and colleagues⁴⁴ and Verdian and colleagues⁵⁰ went further in describing health states in terms of the number of seizures experienced⁵⁰ or in terms of the outcomes of treatment (“acceptable” or “unacceptable” seizure frequency and adverse events⁴⁴). As such, the utilities reported by Connock⁴⁴ and Verdian⁵⁰ may be most informative for future economic evaluations in this population. However, it should be noted that drug-resistant epilepsy is a heterogeneous population, defined based on response to antiepileptic drugs,⁴ and, with the exception of Lennox-Gastaut syndrome, preferences for health states associated with specific drug-resistant epilepsy syndromes (e.g., Dravet syndrome) have yet to be assessed.

Pediatric drug-resistant epilepsy contributes high costs to the health care system,^{16–18} and health care resource use is higher among children with uncontrolled seizures relative to those with controlled seizures.^{17,19} Despite this, none of the studies identified in our review reported resource use by seizure frequency, which may be partly owing to the rare nature of these conditions and the small sample size of the studies. Similarly, resource use among children with specific epilepsy syndromes has not been well studied, with only three of the included studies assessing resource use among children with specific epilepsy syndromes.^{26,34,41} This represents a gap in the literature that has important implications for model-based economic evaluations, and analysts may have to look more broadly for health care resource use related to seizure status, and assumptions may be required about the relevance of such estimates to specific drug-resistant epilepsy syndromes. For example, because of a lack of published data about resource use among children with drug-resistant epilepsy, previous decision models by our group⁶³ and others⁶⁴ have incorporated estimates not specific to children with drug-resistant epilepsy.¹⁹ If such alternative data sources are required, any assumptions should be explicitly stated, and the limitations and implications of such an approach should be discussed.

The responsibility of caring for a child who is ill may have a considerable effect on the productivity of one or both parents, including absenteeism, presenteeism, or a change in work situation, including reduced work hours, quitting, or taking a part time job with less pay.⁵⁴ The inclusion of such

productivity costs within an economic evaluation has the potential to affect whether an intervention is considered cost-effective.⁶⁵ If a decision maker wishes to adopt a societal perspective (i.e., includes indirect/productivity costs in the determination of cost-effectiveness), this reflects a willingness to trade health benefits for productivity benefits, signaling that the objective of the health care budget is to maximize the productivity, not the health, of the relevant population. Such reduced parental productivity has been noted in Dravet syndrome, a catastrophic form of drug-resistant epilepsy, in which at least one parent is typically unable to work full time.¹⁴ Additionally, we know little about the effects of drug-resistant epilepsy on the productivity of affected children. Although children are not productive in the usual sense (i.e., contribution to the workforce or society), child productivity may be conceptualized in terms of school performance, with reduced school performance potentially limiting future productivity in adulthood.⁵⁴ However, there is no consensus about how to best measure and value child productivity.⁵⁴ In this systematic review, we found only one study that had assessed the productivity of parents of children with Dravet syndrome; no studies have assessed productivity associated with other drug-resistant epilepsy syndromes or among affected children. Given that productivity costs have the potential to influence whether a treatment is considered cost-effective, the lack of evidence related to productivity costs, either among parents or children with drug-resistant epilepsy, is an important gap in the evidence base.

Strengths and limitations

We performed a systematic review of the literature to identify studies that had assessed health state utility values, health care resource use, and productivity costs associated with pediatric drug-resistant epilepsy. However, several limitations should be noted. First, few studies reported use of a definition of drug-resistant epilepsy, and many employed a definition that differed from the ILAE definition.⁴ As such, we also included studies that described the target population as having “resistant,” “refractory,” or “intractable” epilepsy, focused on specific drug-resistant epilepsy syndromes (e.g., Dravet syndrome, Lennox Gastaut syndrome), or involved interventions intended to treat drug-

resistant epilepsy (i.e., ketogenic diet, epilepsy surgery, vagus nerve stimulation). Second, we included studies published in English, which may have resulted in some relevant studies being overlooked. However, we performed a comprehensive search of published and grey literature, and few studies were excluded because of publication in a language other than English. Similarly, although we set out to exclude conference abstracts, no studies were excluded for this reason. One relevant abstract⁵⁰ was identified while hand-searching relevant economic evaluations, and we included this abstract because of the limited number of studies that have assessed health state utility values associated with drug-resistant epilepsy in children. Fourth, among the studies that assessed health care resource use, several reported costs associated with resource use but did not provide data in a disaggregated way (e.g., number of hospital admissions and unit cost per admission (Additional File 8)).^{27,29–31,33,36,38,39} Because of differences in treatment patterns and standards of care across jurisdictions, cost data provided as a single monetary value is likely unusable as an input for economic evaluations across jurisdictions. However, the cost data from these studies may be of interest to analysts in the jurisdictions in which the studies were performed. Finally, as described above, few studies have considered the impact of spillover from the affected children to other family members. This represents an important gap in our understanding of the true effects and costs associated with drug-resistant epilepsy in children.

Conclusion

Health state utility values, health care resource use, and productivity costs associated with drug-resistant epilepsy in children have not been thoroughly investigated. This has important implications for both assessing the current impact of this condition on the health care system and for the conduct of economic evaluations of interventions intended to treat pediatric drug-resistant epilepsy. Additional research is therefore needed to provide such information across drug-resistant epilepsy syndromes.

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Author's contributions: JE, TC, DC, BP, BM, GW and DC designed the study. BS developed and executed the search strategy. JE, SVK and DC selected studies for inclusion and extracted data. JE analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication.

Availability of data and materials: The dataset(s) supporting the conclusions of this article is(are) included within the article (and its additional file(s)).

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Additional File 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6, Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Additional file 4, 6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Additional file 5, 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2, 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

Additional File 2: Search strategy

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2018 June 11>, Ovid MEDLINE(R) ALL <1946 to June 11, 2018>

Search Strategy:

-
- 1 exp Epilepsy/ (337212)
 - 2 (epileps* or epilept*).tw,kf. (314061)
 - 3 seizure*.tw,kf. (277032)
 - 4 convulsi*.tw,kf. (66672)
 - 5 falling sickness*.tw,kf. (55)
 - 6 comitial disease*.tw,kf. (3)
 - 7 (petit mal or grand mal or absence status).tw,kf. (7552)
 - 8 Landau-Kleffner Syndrome*.tw,kf. (1004)
 - 9 Lennox Gastaut Syndrome*.tw,kf. (3116)
 - 10 Dravet Syndrome*.tw,kf. (1866)
 - 11 West syndrome*.tw,kf. (2669)
 - 12 Doose syndrome*.tw,kf. (157)
 - 13 Ohtahara syndrome*.tw,kf. (459)
 - 14 Sturge-Weber Syndrome/ (3570)
 - 15 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kf. (7823)
 - 16 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy syndrome* or naito oyanagi disease*).tw,kf. (732)
 - 17 SMEI.tw,kf. (419)
 - 18 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or myoencephalopathy ragged-red fibre disease*).tw,kf. (1072)
 - 19 Lafora.tw,kf. (1308)
 - 20 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kf. (679)
 - 21 ((infantile or nodding) adj2 spasm?).tw,kf. (5772)
 - 22 ((flexor or "in flexion") adj2 spasm?).tw,kf. (313)
 - 23 ((lightning or salaam) adj2 attack?).tw,kf. (15)
 - 24 hypsarrhythmi*.tw,kf. (1936)
 - 25 or/1-24 [EPILEPSY] (560609)
 - 26 Adolescent/ (3369665)
 - 27 exp Child/ (4503995)
 - 28 exp Infant/ (2130677)
 - 29 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school* or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-school*).tw,kf. (4316665)
 - 30 (newborn* or neonat*).tw,kf. (833360)
 - 31 (pediatric* or paediatric*).tw,kf. (776024)
 - 32 or/26-31 (8172802)
 - 33 25 and 32 [PEDIATRIC EPILEPSY] (203882)
 - 34 exp Technology assessment, biomedical/ (23249)
 - 35 (technology assessment* or HTA or HTAs).tw,kf. (17211)
 - 36 health technology assessment.jw. (3141)
 - 37 or/34-36 [HTAs] (37651)
 - 38 33 and 37 [PAEDIATRIC EPILEPSY - HTAs] (71)
 - 39 exp Epilepsy/ec [Economics] (540)
 - 40 Economics/ (257845)
 - 41 exp "Costs and Cost Analysis"/ (538452)
 - 42 Economics, Nursing/ (38348)
 - 43 Economics, Medical/ (44003)
 - 44 Economics, Pharmaceutical/ (10619)
 - 45 exp Economics, Hospital/ (799622)
 - 46 Economics, Dental/ (37552)
 - 47 exp "Fees and Charges"/ (68883)
 - 48 exp Budgets/ (39309)
 - 49 budget*.ti,ab,kf. (59686)

50 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
 economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or
 financed).ti,kf. (419450)
 51 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
 economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab.
 /freq=2 (585534)
 52 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (322118)
 53 (value adj2 (money or monetary)).ti,ab,kf. (4814)
 54 exp models, economic/ (14513)
 55 economic model*.ab,kf. (6529)
 56 markov chains/ (15421)
 57 markov.ti,ab,kf. (42108)
 58 monte carlo method/ (58618)
 59 monte carlo.ti,ab,kf. (83017)
 60 exp Decision Theory/ (12808)
 61 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (45992)
 62 exp Delivery of health Care/ec [economics] (49499)
 63 ((healthcare or health care or resource?) adj3 (utili#ation? or utilise? or utilize? or utili#ing)).ti,ab,kf. (65949)
 64 (resource? adj3 ("use" or used or uses or using)).ti,ab,kf. (57658)
 65 (resource? adj3 (unit or units)).ti,ab,kf. (1764)
 66 (resource? adj3 (value? or valuation?)).ti,ab,kf. (2929)
 67 ((utility or utili#ation) adj (study or studies)).ti,ab,kf. (2946)
 68 (ICER or ICERs).ti,ab,kf. (11261)
 69 or/39-68 [ECONOMICS, COST-UTILITY] (1992079)
 70 33 and 69 [PAEDIATRIC EPILEPSY - ECONOMICS, COST-UTILITY] (3310)
 71 "Value of Life"/ (135868)
 72 Quality of Life/ (553323)
 73 quality of life.ti,kf. (155404)
 74 ((instrument or instruments) adj3 quality of life).ab. (7082)
 75 Quality-Adjusted Life Years/ (31484)
 76 quality adjusted life.ti,ab,kf. (26122)
 77 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. (43237)
 78 disability adjusted life.ti,ab,kf. (5604)
 79 (daly or dalys).ti,ab,kf. (5292)
 80 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty
 six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty
 six).ti,ab,kf. (58225)
 81 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short
 form6).ti,ab,kf. (3888)
 82 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short
 form eight).ti,ab,kf. (1041)
 83 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform
 twelve or short form twelve).ti,ab,kf. (12539)
 84 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform
 sixteen or short form sixteen).ti,ab,kf. (82)
 85 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform
 twenty or short form twenty).ti,ab,kf. (868)
 86 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. (36071)
 87 (hye or hyes).ti,ab,kf. (178)
 88 (health* adj2 year* adj2 equivalent*).ti,ab,kf. (97)
 89 (pqol or qls).ti,ab,kf. (911)
 90 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf. (1165)
 91 nottingham health profile*.ti,ab,kf. (2545)
 92 sickness impact profile.ti,ab,kf. (2238)
 93 exp health status indicators/ (292343)
 94 (health adj3 (utilit* or status)).ti,ab,kf. (140789)
 95 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. (26067)
 96 Patient Preference/ (20266)
 97 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or
 instruments)).ti,ab,kf. (20490)
 98 disutilit*.ti,ab,kf. (1083)
 99 rosser.ti,ab,kf. (199)
 100 willingness to pay.ti,ab,kf. (10950)

101 standard gamble*.ti,ab,kf. (1818)
102 (time trade off? or time tradeoff?).ti,ab,kf. (3037)
103 (tto or ttos).ti,ab,kf. (2341)
104 (hui or hui1 or hui2 or hui3).ti,ab,kf. (3154)
105 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. (33522)
106 Absenteeism/ (25724)
107 absentee*.ti,ab,kf. (13411)
108 Presenteeism/ (798)
109 presentee*.ti,ab,kf. (2638)
110 productivit*.ti,ab,kf. (108615)
111 ((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kf. (235562)
112 ((work* or employ*) adj5 abilit*).ti,ab,kf. (23476)
113 (time adj1 away).ti,ab,kf. (1386)
114 Sick Leave/ (9808)
115 ((sick or medical) adj leave).ti,ab,kf. (10506)
116 or/71-115 [QoL/DISEASE BURDEN] (1571112)
117 33 and 116 [PAEDIATRIC EPILEPSY - QoL/DISEASE BURDEN] (6990)
118 38 or 70 or 117 [HTAs/ECONOMICS/QoL/DISEASE BURDEN] (9727)
119 exp Animals/ not (exp Animals/ and Humans/) (16386162)
120 118 not 119 [ANIMAL-ONLY REMOVED] (6980)
121 120 use medall [MEDLINE RECORDS] (4123)
122 exp epilepsy/ (337212)
123 (epileps* or epilept*).tw,kw. (319442)
124 seizure*.tw,kw. (279367)
125 convulsi*.tw,kw. (67865)
126 falling sickness*.tw,kw. (58)
127 comitial disease*.tw,kw. (3)
128 (petit mal or grand mal or absence status).tw,kw. (7453)
129 Landau-Kleffner Syndrome*.tw,kw. (1041)
130 Lennox Gastaut Syndrome*.tw,kw. (3173)
131 Dravet Syndrome*.tw,kw. (1914)
132 West syndrome*.tw,kw. (2795)
133 Doose syndrome*.tw,kw. (169)
134 Ohtahara syndrome*.tw,kw. (473)
135 sturge-weber syndrome/ (3570)
136 ((sturge* or weber) adj2 (disease* or syndrome*)).tw,kw. (7950)
137 (myoclonic encephalopath* or action myoclonus-renal failure syndrome* or atypical inclusion-body disease* or
biotin-responsive encephalopath* or haw river syndrome* or may white syndrome* or myoclonus-nephropathy
syndrome* or naito oyanagi disease*).tw,kw. (742)
138 SMEI.tw,kw. (443)
139 (MERRF or fukuhara disease* or fukuhara disorder* or myoencephalopathy ragged-red fiber disease* or
myoencephalopathy ragged-red fibre disease*).tw,kw. (1101)
140 Lafora.tw,kw. (1320)
141 ((Unverricht adj1 Lundborg) or Baltic Myoclonus or Unverricht disease* or Unverricht syndrome*).tw,kw. (685)
142 ((infantile or nodding) adj2 spasm?).tw,kw. (5916)
143 ((flexor or "in flexion") adj2 spasm?).tw,kw. (312)
144 ((lightning or salaam) adj2 attack?).tw,kw. (15)
145 hypsarrhythmi*.tw,kw. (1968)
146 or/122-145 [EPILEPSY] (562925)
147 juvenile/ (40218)
148 exp adolescent/ (3369840)
149 exp child/ (4503995)
150 (boy or boys or girl or girls or infant* or infanc* or baby or babies or child* or toddler* or preschool* or pre-school*
or school-age* or adolescen* or teen or teens or teenager* or youth or youths or highschool* or high-
school*).tw,kw. (4326831)
151 (newborn* or neonat*).tw,kw. (829311)
152 (pediatric* or paediatric*).tw,kw. (796794)
153 or/147-152 (8032752)
154 146 and 153 [PEDIATRIC EPILEPSY] (203319)
155 biomedical technology assessment/ (22142)
156 (technology assessment* or HTA or HTAs).tw,kw. (17805)
157 health technology assessment.jw. (3141)
158 or/155-157 [HTAs] (37034)

159 154 and 158 [PAEDIATRIC EPILEPSY - HTAs] (70)
160 exp epilepsy/ec [Economics] (540)
161 economics/ (257845)
162 cost/ (104904)
163 exp health economics/ (776721)
164 budget/ (36915)
165 budget*.ti,ab,kw. (60026)
166 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or
financed).ti,kw. (440284)
167 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab.
/freq=2 (585534)
168 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. (326140)
169 (value adj2 (money or monetary)).ti,ab,kw. (4826)
170 statistical model/ (233242)
171 economic model*.ab,kw. (6749)
172 probability/ (137107)
173 markov.ti,ab,kw. (42814)
174 monte carlo method/ (58618)
175 monte carlo.ti,ab,kw. (84136)
176 decision theory/ (2611)
177 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. (46752)
178 ((healthcare or health care or resource?) adj3 (utili#ation? or utilise? or utilize? or utili#ing)).ti,ab,kw. (66568)
179 (resource? adj3 ("use" or used or uses or using)).ti,ab,kw. (57797)
180 (resource? adj3 (unit or units)).ti,ab,kw. (1771)
181 (resource? adj3 (value? or valuation?)).ti,ab,kw. (2947)
182 ((utility or utili#ation) adj (study or studies)).ti,ab,kw. (3047)
183 (ICER or ICERs).ti,ab,kw. (11300)
184 or/160-183 [ECONOMICS, COST-UTILITY] (2176315)
185 154 and 184 [PAEDIATRIC EPILEPSY - ECONOMICS, COST-UTILITY] (3834)
186 socioeconomics/ (134357)
187 exp quality of life/ (585448)
188 quality of life.ti,kw. (181629)
189 ((instrument or instruments) adj3 quality of life).ab. (7082)
190 quality-adjusted life year/ (31484)
191 quality adjusted life.ti,ab,kw. (26277)
192 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. (43556)
193 disability adjusted life.ti,ab,kw. (5618)
194 (daly or dalys).ti,ab,kw. (5370)
195 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty
six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty
six).ti,ab,kw. (58463)
196 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short
form6).ti,ab,kw. (3900)
197 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or
short form eight).ti,ab,kw. (1043)
198 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform
twelve or short form twelve).ti,ab,kw. (12582)
199 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform
sixteen or short form sixteen).ti,ab,kw. (82)
200 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform
twenty or short form twenty).ti,ab,kw. (867)
201 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw. (36232)
202 (hye or hyes).ti,ab,kw. (182)
203 (health* adj2 year* adj2 equivalent*).ti,ab,kw. (100)
204 (pqol or qls).ti,ab,kw. (913)
205 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw. (1173)
206 nottingham health profile/ (394)
207 nottingham health profile*.ti,ab,kw. (2557)
208 sickness impact profile/ (9156)
209 sickness impact profile.ti,ab,kw. (2275)
210 health status indicator/ (24834)

211 (health adj3 (utilit* or status)).ti,ab,kw. (142207)
 212 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.
 (26188)
 213 Patient Preference/ (20266)
 214 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or
 instruments)).ti,ab,kw. (20560)
 215 disutilit*.ti,ab,kw. (1086)
 216 rosser.ti,ab,kw. (200)
 217 willingness to pay.ti,ab,kw. (11074)
 218 standard gamble*.ti,ab,kw. (1838)
 219 (time trade off? or time tradeoff?).ti,ab,kw. (3066)
 220 (tto or ttos).ti,ab,kw. (2352)
 221 (hui or hui1 or hui2 or hui3).ti,ab,kw. (3168)
 222 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. (33591)
 223 absenteeism/ (25724)
 224 absentee*.ti,ab,kw. (13617)
 225 presenteeism/ (798)
 226 presentee*.ti,ab,kw. (2699)
 227 productivit*.ti,ab,kw. (109229)
 228 ((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kw. (235647)
 229 ((work* or employ*) adj5 abilit*).ti,ab,kw. (23541)
 230 (time adj1 away).ti,ab,kw. (1389)
 231 medical leave/ (5661)
 232 ((sick or medical) adj leave).ti,ab,kw. (10652)
 233 or/186-232 [QoL/DISEASE BURDEN] (1345906)
 234 154 and 233 [PAEDIATRIC EPILEPSY - QoL/DISEASE BURDEN] (5407)
 235 159 or 185 or 234 [HTAs/ECONOMICS/QoL/DISEASE BURDEN] (8755)
 236 animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp
 vertebrate/ (48151623)
 237 exp human/ or exp human experimentation/ or exp human experiment/ (37022786)
 238 236 not 237 (11130520)
 239 235 not 238 [ANIMAL-ONLY REMOVED] (8679)
 240 conference abstract.pt. (3034537)
 241 239 not 240 [CONFERENCE ABSTRACTS REMOVED] (7205)
 242 241 use emczd [EMBASE RECORDS] (4490)
 243 121 or 242 [BOTH DATABASES] (8613)
 244 limit 243 to yr="2010-current" (4067)
 245 remove duplicates from 244 (3064)
 246 243 not 244 (4546)
 247 remove duplicates from 246 (3682)
 248 245 or 247 [TOTAL UNIQUE RECORDS] (6746)
 249 248 use medall [MEDLINE UNIQUE RECORDS] (4087)
 250 248 use emczd [EMBASE UNIQUE RECORDS] (2659)

Additional File 3: Included and excluded studies (full-text review)

*Indented lines indicate that the study is connected to the study immediately above.

Included studies

1. Aburahma SK, Alzoubi FQ, Hammouri HM, et al. Vagus nerve stimulation therapy in a developing country: a long term follow up study and cost utility analysis. *Seizure*. 2015;25:167.
2. Campbell JD, Whittington MD, Kim CH, et al. Assessing the impact of caring for a child with Dravet syndrome: Results of a caregiver survey. *Epilepsy Behav*. 2018;80:152.
3. Whittington MD, Knupp KG, Vanderveen G, et al. The direct and indirect costs of Dravet Syndrome. *Epilepsy Behav*. 2018;80:109.
4. Carroll AE, Downs SM. Improving decision analyses: Parent preferences (utility values) for pediatric health outcomes. *Journal of Pediatrics*. 2009;155:21.
5. Connock M, Frew E, Evans BW, et al. The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review. *Health Technol Assess*. 2006;10:1-139.
6. Cramer JA, Wang ZJ, Chang E, et al. Healthcare utilization and costs in children with stable and uncontrolled epilepsy. *Epilepsy Behav*. 2014;32:135-41.
7. Gold LS, Schepman PB, Wang WJ, et al. Healthcare costs and resource utilization in patients with infantile spasms treated with H.P. Acthar Gel. *Advances in Therapy*. 2016;33:1293.
8. Guerrini R, Battini R, Ferrari AR, et al. The costs of childhood epilepsy in Italy: comparative findings from three health care settings. *Epilepsia*. 2001;42:641.
9. Helmers SL, Duh MS, Guerin A, et al. Clinical outcomes, quality of life, and costs associated with implantation of vagus nerve stimulation therapy in pediatric patients with drug-resistant epilepsy. *Europ J Paediatr Neurol*. 2012;16:449.
10. Kalanithi PS, Arrigo RT, Tran P, et al. Rehospitalization and emergency department use rates before and after vagus nerve stimulation for epilepsy: use of state databases to provide longitudinal data across multiple clinical settings. *Neuromodulation*. 2014;17:60.
11. Kayyali HR, Luniova A, Abdelmoity A. Ketogenic diet decreases emergency room visits and hospitalizations related to epilepsy. *Epilepsy Res Treat*. 2016;1.
12. Lennert B, Farrelly E, Sacco P, et al. Resource utilization in children with tuberous sclerosis complex and associated seizures: a retrospective chart review study. *J Child Neurol*. 2013;28:461.
13. Luoni C, Canevini MP, Capovilla G, et al. A prospective study of direct medical costs in a large cohort of consecutively enrolled patients with refractory epilepsy in Italy. *Epilepsia*. 2015;56:1162.
14. MacCracken KA, Scalisi JC. Development and evaluation of a ketogenic diet program. *J American Dietetic Assoc*. 1999;99:1554.

15. Majoie HJ, Berfelo MW, Aldenkamp AP, et al. Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome: clinical results, neuropsychological effects, and cost-effectiveness. *J Clin Neurophysiol* 2001;18:419.
16. Mandel A, Ballew M, Pina-Garza JE, et al. Medical costs are reduced when children with intractable epilepsy are successfully treated with the ketogenic diet. *J American Dietetic Assoc.* 2002;102:396.
17. Oldham MS, Horn PS, Tsevat J, et al. Costs and clinical outcomes of epilepsy surgery in children with drug-resistant epilepsy. *Pediatric Neurol.* 2015;53:216.
18. Patel A, Wang L, Gedela S. Health care utilization following vagus nerve stimulation therapy in pediatric epilepsy patients from a pediatric accountable care organization. *J Child Neurol.* 2018;33:136.
19. Pina-Garza JE, Montouris GD, Vekeman F, et al. Assessment of treatment patterns and healthcare costs associated with probable Lennox-Gastaut syndrome. *Epilepsy Behav.* 2017;73:46.
20. Rentz AM, Skalicky AM, Liu Z, et al. Tuberous sclerosis complex: a survey of health care resource use and health burden. *Pediatric Neurol* 2015;52:435.
21. Riechmann J, Strzelczyk A, Reese JP, et al. Costs of epilepsy and cost-driving factors in children, adolescents, and their caregivers in Germany. *Epilepsia.* 2015;56:1388.
22. Ryzi M, Brazdil M, Novak Z, et al. Long-term vagus nerve stimulation in children with focal epilepsy. *Acta Neurologica Scandinavica.* 2013;127:316.
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26. Wijnen BFM, de Kinderen RJA, Lambrechts DAJE, et al. Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy. *Epilepsy Res.* 2017;132:91.
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Excluded studies

The full list of excluded studies (k = 436) is available by request from the corresponding author.

Additional File 4: Characteristics – health state utility values

Characteristics of included studies that assessed health state utility values related to drug-resistant epilepsy in children.

Author, year	Location	Study design	Sample size	Target population	Respondent	Source	Approach (measurement and valuation)
Wijnen 2017¹ (de Kinderen 2016²)	The Netherlands	RCT, KD for 16 mo v. CAU for 4 mo	KD: n = 26; CAU: n = 22	1–18 yr, with intractable seizures (i.e. failure of at least 2 AEDs), not eligible for epilepsy surgery	Child, parent proxy, parent*	Economic evaluation alongside an RCT evaluating KD compared with CAU at an epilepsy centre; enrollment July 2010 to Aug 2014	CHILD utilities: TAPQOL (children aged 1-5 years; parent proxy), TACQOL (children aged 6-16 years; parent proxy), EQ-5D-Y PARENT/CAREGIVER utilities: EQ-5D (UK and Dutch tariffs)
Carroll 2009³	US	Cross-sectional	n = 4016 Response rate: 88%	Children with mild (1–2 seizures per yr), moderate (monthly seizures), or severe seizure disorder (3–4 seizures/d, drug-resistant)†	Adults from the general public (85% female), with at least one child aged <18 yrs	Pediatricians' offices, urgent care centres, health fairs, state fairs	Time trade off and standard gamble; narrative vignettes were presented to each participant; each health state was assessed at least 255 times
Verdian 2008⁴	UK	Cross-sectional	n = 119 Response rate: NR	Lennox Gastaut Syndrome	General public, 48% were caregivers or parents of children aged 4–18 years	NR	Time trade off, visual analogue scale, EQ-5D (tariff NR)
Connock 2006⁵	NR	Expert opinion; as part of a HTA of pharmacologic treatments for pediatric epilepsy	n = 22 Response rate: NR	Average child with focal epilepsy, aged 7–12 yr with no motor impairment, with or without learning disability	Clinical experts with experience caring for children with epilepsy	NR	Modified version EQ-5D; scores were converted to utilities by use of the MVH A1 tariff (derived from a TTO survey of the general population of the UK)

Note: AED = antiepileptic drug, CAU = care as usual, HTA = health technology assessment, KD = ketogenic diet, NR = not reported, RCT = randomized controlled trial, TAPQOL = TNO-AZL Preschool Children's Quality of Life, TACQOL = TNO-AZL Children's Quality of Life, TTO = time trade off.

*Depending on instrument.

†Of the 29 pediatric health states included in the model, three pertained to seizure disorders.

References (Additional File 4):

1. Wijnen BFM, Kinderen RJA de, Lambrechts DAJE, et al. Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy. *Epilepsy Res.* 2017;132:91.
2. Kinderen RJ de, Lambrechts DA, Wijnen BF, et al. An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: An interim analysis. *Epilepsia.* 2016;57(1):41.
3. Carroll AE, Downs SM. Improving decision analyses: parent preferences (utility values) for pediatric health outcomes. *J Pediatr.* 2009;155(1):21-25.e5.
4. Verdian L, Oyee J, Heyes A, Tolley K, Yi Y. Eliciting preferences for health states associated with Lennox-Gastaut syndrome (LGS) (Abstract 1.352) Abstract presented at: 62nd meeting of the American Epilepsy Society. 2008 Dec 5-9; Seattle, Washington.
www.aesnet.org/meetings_events/annual_meeting_abstracts/view/8833.
5. Connock M, Frew E, Evans B, Bryan S, Cummins C, Po ALW. The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review. *Heal Technol Assess.* 2006;10(7):1-139.

Additional File 5: Quality assessment – health state utility values

Study-level quality assessment for studies that assessed health state utility values related to pediatric drug-resistant epilepsy

STUDY	Wijnen 2017 ¹ (de Kinderen 2016 ²)
Criteria	Comment
Sample size	• KD group: 26 children received KD for up to 16 months; • CAU group: 22 children received CAU for 4 months, with the option to receive KD after that time. Utilities at 4 mo were carried forward to 16 mo. • Number of parents NR
Respondent selection and recruitment	• Potential participants were screened for exclusion criteria by their own attending paediatrician, neurologist or paediatric neurologist, and only eligible for ketogenic diet were subsequently referred to the ketogenic diet team and evaluated for RCT eligibility • The trial population includes only those who were eligible to receive KD but not epilepsy surgery
Inclusion/exclusion criteria	Aged 1–18 yrs; having uncontrolled seizures after trying 2 or more AEDs; not eligible for epilepsy surgery; no fatty acid oxidation disorders and related diseases; no diabetes and hyperinsulinism; no long QT syndrome; no hypercholesterolemia or hypertriglyceridemia; no severe liver, kidney, or pancreas diseases; no renal tubular acidosis; no severe behavioral disorder; no malnutrition; no treatment with topiramate or acetazolamide; and no positive family history or other risk factors for kidney stones or acidosis.
Response rate to instrument used	• Number of parents who completed the EQ-5D NR; unclear if utilities were assessed for one parent per child • “Measuring utilities with the EQ-5D-Y seemed only possible in a minority of patients in our sample. We, therefore, used the QoL scores of the TAPQOL and TACQOL (age-dependent) to calculate QALYs for the patients.” (EQ-5D-Y was completed for 11 children in each group at baseline, and 4 children in the CAU group at 12 months follow-up. Authors do not state why it was not possible to measure utilities with EQ-5D-Y for all patients.)
Loss to follow-up	• KD group: 58% of patients completed the 16-month treatment period (9 patients were excluded from the KD group for utility calculation owing to loss to follow-up) • CAU group: NR
Missing data	“Results from the CAU group, both costs and effects, at 4 months were extrapolated to 16 months using last observation carried forward. If data were totally absent, mean imputation per randomization group was used to impute missing Quality Adjusted Life Years (QALYs). For incomplete cases, last observation was carried forward.”
Health state descriptions	NA; utilities based on receiving KD or CAU; utilities were assessed before treatment, after 4 months of treatment (CAU and KD), after 16 months of treatment (KD only); utilities assessed for both affected children and parents
Other considerations	• Single-centre RCT performed in the Netherlands • Interventions received in the care as usual group were not well described. Children in this group continued to receive their pre-trial AEDs. Type and dosage of AEDs were not reported, and there were differences between the KD and CAU group with respect to the number of AEDs used at the start of the study and the number of AEDs tried in the past. • Parent proxy used to assess QoL • Utilities provided at 16 mo for both groups; however, QoL in the CAU group was last measured at 4 mo and observations were carried forward to 16 mo.
STUDY	Carroll 2009 ³
Criteria	Comment
Sample size	4016; Each participants’ preferences were assessed for 3 health states out of 29 health states included in the study (each state was assessed > 255 times, with most assessed > 400 times)
Respondent selection and recruitment	“Recruiting locations included local pediatric physicians’ offices in Indianapolis, as well as local urgent care centers, health fairs, and other events occurring in or around the city of Indianapolis that had the potential to draw large groups of parents, such as the Indiana State Fair (http://www.in.gov/statefair/) and the Indiana Black Expo (http://www.indianablackexpo.com). Recruitment took place between 2006 and 2008.” “Each individual who agreed to participate in the study was given a \$5 gift card.” • Most participants were mothers (85%), and 97% were identified as either Caucasian or African American; 60% of participants had at least some college education
Inclusion/exclusion	Aged > 18 yr, had at least 1 child under age 18 at the time of the study, and spoke English

criteria	• If the participant's child had 1 of the randomly selected health states, then a new set of 3 health states was randomly selected
Response rate to instrument used	88% (4016/4561 approached)
Loss to follow-up	NA
Missing data	Whether any data were missing was NR
Health state descriptions	Mild seizure disorder: "About once each year or two, <child's name> would have a seizure. During the seizure, he/she would partially lose consciousness, seeming "out of it." His/her right arm and leg would become stiff and then begin shaking. This would usually last about a minute. He/she would take medications twice a day to reduce the number of seizures, but when he/she is sick with a fever, they would probably occur more often. After each seizure, he/she would feel tired and normal, but usually would not remember what happened. The seizures would rarely disrupt school, and as long as he/she remained on the medication, he/she would be able to drive." Moderate seizure disorder: "About once a month, <child's name> would have a seizure. During the seizure, he/she would become unconscious and have violent shaking of his/her arms and legs. His/her back would arch and his/her eyes would roll back. This would last 3-8 minutes each time. He/she would take medications four times a day to prevent the seizures from happening more often, but when he/she is sick with a fever, they would occur more often anyway. After each seizure, he/she would feel tired and "out of it," and sometimes forget what was happening right before the seizure started. The seizures would rarely disrupt school, but he/she would not be able to drive when older because of the seizures." Severe seizure disorder: "Three to four times a day, <child's name> would have a seizure. During the seizure, he/she would become unconscious and have violent shaking of his/her arms and legs. His/her back would arch and his/her eyes would roll back. This would last 3-8 minutes each time. He/she would take medications to reduce the number of seizures, but would still have them 3-4 times every day. After each seizure, he/she would feel tired and "out of it," and sometimes forget what was happening right before the seizure started. The seizures would disrupt school and make it difficult to learn. He/she would not be able to drive when he/she is older because of the seizures."
Other considerations	• Utilities were assessed by use of standard gamble and time-trade off. Authors note "With a few exceptions, the mean utility values measured by the 2 methods were reasonably similar."
STUDY	Verdian 2008⁴
Criteria	Comment
Sample size	119
Respondent selection and recruitment	Members of the general public; 48% were caregivers/parents of children aged 4 to 18. Source of the participants was not described, nor were any demographic characteristics
Inclusion/exclusion criteria	NR
Response rate to instrument used	NR
Loss to follow-up	NA
Missing data	NR
Health state descriptions	"HSs were defined by tonic-atonic (drop attack) seizure frequency (SF). For LGS outcomes, the anchor state (HS-1) for uncontrolled disease was described by frequency of 21-28 seizures per week; HS-2 a reduction of < 50% in SF following adjunctive treatment; HS-3 a reduction of >=50% and <75% in SF and HS-4 a >=75% reduction in SF following adjunctive treatment."
Other considerations	• Findings available only in a conference abstract • Utilities assessed by use of time trade off, visual analogue scale, and EQ-5D (tariff NR)
STUDY	Connock 2006⁵
Criteria	Comment
Sample size	22
Respondent selection and recruitment	Not described how clinical experts were identified, selected, or recruited
Inclusion/exclusion criteria	Not explicitly stated. Authors "sought views from clinical experts with experience in the care of children with epilepsy".
Response rate to instrument used	NR

Loss to follow-up	NA
Missing data	NR
Health state descriptions	6 “broadly defined outcomes of treatment for epilepsy in childhood”: • The patient experiences unacceptable side-effects of the drug (that cannot be controlled by adjusting the dose) such that the drug will be withdrawn (AES). • After an adequate trial of the drug, the patient still experiences an unacceptable frequency of seizures such that a change of therapy will be initiated and the drug withdrawn (i.e. not considered to be having sufficient beneficial effect) (USF). • The patient experiences an acceptable reduction in frequency of seizures and acceptable side-effects, such that the drug is continued (PAR). • The patient experiences seizure freedom and acceptable side effects, such that the drug is continued (EFFd). • The patient experiences seizure freedom following withdrawal of a successful drug or successful surgery (EFFw). • The patient is not seizure free but prefers to remain untreated (UNT).
Other considerations	• Instrument: Modified version EQ-5D; scores were converted to utilities by use of the MVH A1 tariff (derived from a TTO survey of the general population of the UK) • Respondents were “asked to consider how good or bad each state is for an average child with focal epilepsy, between the ages of 7 and 12 years, and with no motor impairments.”
Note: HS = health state, LGS = Lennox-Gastaut syndrome, NR = not reported, QoL = quality of life.	

References (Additional File 5):

1. Wijnen BFM, Kinderen RJA de, Lambrechts DAJE, et al. Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy. *Epilepsy Res.* 2017;132:91.
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www.aesnet.org/meetings_events/annual_meeting_abstracts/view/8833.
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Additional File 6: Characteristics – health care resource use

Characteristics of included studies that assessed health care resource use among children with drug-resistant epilepsy

Study	Country	Study design	Inclusion criteria	n	Mean age, yr (SD); % male	Observation/recall period	Comparison
Whittington 2018¹ (Campbell 2018²)	USA	Survey of caregivers whose children received care for Dravet syndrome at Children's Hospital Colorado; survey open for 3 wk in 2016	Caregivers of children with Dravet syndrome (friend or family member)	34	11.7 (5.8); NR	Previous 12 mo	NA
Patel 2018³	USA	Retrospective analysis of claims data from an accountable care organization caring for Medicaid patients in Ohio (Partners for Kids)	Children (0–19 yr) with a CPT code for VNS initial placement (64568) and Medicaid enrollment, with continuous enrollment for at least 6 mo	13	10.5 (range 4–18); 62%	12 mo before and after initial VNS placement	Before, after VNS insertion
Kayyali 2016⁴	USA	Retrospective chart review of pediatric patients who received ketogenic diet for refractory epilepsy at a tertiary pediatric epilepsy center, 2009–2013	Epilepsy was diagnosed and treated by a pediatric neurologist or epileptologist for ≥12 months prior to KD; patient's epilepsy had not responded to conventional pharmacological therapy before KD; patient had received KD for ≥ 12 mo	37	4 (2.78); 57%	≥ 12 mo before and after starting KD	Before, after KD
Whiting 2017⁵	CAN	Retrospective analysis of Ontario, Canada, administrative data; children identified by chart review at the Children's Hospital of Eastern Ontario (Ottawa), The Hospital for Sick Children (Toronto), and McMaster Children's Hospital (Hamilton); KD patient were compared to matched group of children with epilepsy who did not receive KD, 2000–2010	KD group: Patients who initiated KD between 2000 and 2010 No KD: children with epilepsy who did not receive KD (1:1 match to patients in the KD group; matched on epilepsy diagnosis during the study period, sex, rural/nonrural status of the child's residence at index event date, date of birth within one year, and fiscal year of study start).	KD group: 166 No KD group: 167	KD group: 5.8 (4.5); 54% No KD group: 5.8 (4.5); 54%	Mean 1.5 (SD 0.68) yr	Before, after KD; children who did not receive KD

Study	Country	Study design	Inclusion criteria	n	Mean age, yr (SD); % male	Observation/recall period	Comparison
Gold 2016⁶	USA	Retrospective analysis of claims data (Truven Health MarketScan, Commercial Claims and Encounters Database, and the Truven Health MarketScan Multi-State Medicaid Database)	Patients in the MarketScan Research Database who received treatment for infantile spasms (ICD-9-CM diagnosis code: 345.60) between April 1, 2007 and December 31, 2012 who were less than 2 years old at the time of the diagnosis	252	<30 days: 0.62 (0.49); 61% >30 days: 0.64 (0.48); 54%	3 mo before, 12 mo after diagnosis	Prescription for repository corticotropin injection (Acthar gel) within 30 days of diagnosis, >30 days after diagnosis
Rentz 2015⁷	USA	Web-based survey, recruitment via e-mail and social networking web sites associated with the Tuberous Sclerosis Alliance, a US-based patient advocacy organization, May to June 2012	Caregivers: 18 yr or older, care for someone diagnosed with TSC, able to read English and participate in a web-based survey	179†	7.1 (4.6); 15.6%‡	Previous 12 mo	NA
Aburahma 2015⁸	Jordan	Retrospective chart review and caregiver recall for children who underwent VNS implantation at King Abdullah University Hospital and Jordan University Hospital, 2007–2011	NR	28	9.4 (range 2–19); 57%	≥ 3 yr	Before, after VNS insertion
Cramer 2014⁹	USA	Retrospective analysis of claims data (Truven Health Analytics MarketScan), 2007-2009	Aged <12 yr with epilepsy (ICD-9-CM 345.xx or 780.39), received at least one AED, and had ≥2 epilepsy-related claims (ICD-9-CM codes: 345.xx or 780.39; ≥30 days apart) during the identification period (2008), and received the same AED (monotherapy or combination) for ≥12 months (controlled epilepsy) or added additional AED(s) during the identification period (uncontrolled epilepsy)	Uncontrolled epilepsy: 422	6.6 (2.7) yr; 54%	1 year after index prescription	Controlled, unstable epilepsy

Study	Country	Study design	Inclusion criteria	n	Mean age, yr (SD); % male	Observation/recall period	Comparison
Kalanithi 2014 ¹⁰	USA	Retrospective analysis of claims data for children who underwent VNS surgery; California Inpatient (CA-SID) and Ambulatory Surgery (CA-ASD) databases, 2005–2008	Patients with epilepsy (ICD-9 345.x, 780.39) and an ICD-9 code for the placement, revision, and removal of VNS and/or implantable pulse generator (ICD-9 04.92, 04.93, 86.94, 86.05; CA-SID) or CPT code (64573, 61885, 64585, 61888; CA-ASD)	93	10.6 (range 1–17); 52%	12 mo before, 12 mo after VNS insertion	Before, after VNS insertion
Lennert 2012 ¹¹	USA	Retrospective chart review, patients who received care at the Minnesota Epilepsy Group, PA, 1973–2010	Patients with tuberous sclerosis complex-related seizure diagnosis	95	3.1 (7.8); 49.5%	5 yr after TSC diagnosis	NA
Helmerts 2012 ¹²	USA	Retrospective analysis of claims data, Medicaid data from Florida, Iowa, Kansas, Missouri, New Jersey	≥ 1 neurologist visits with a diagnosis of epilepsy (ICD-9: 345.xx) or nonfebrile convulsions (ICD-9: 780.3, 780.39), ≥ 1 pharmacy dispensation of an AED, ≥ 1 procedure claim for VNS implantation, ≥ 6 mo continuous enrollment before and after VNS implantation	Group 1 (1–11 yr): 238 Group 2 (12–17 yr): 207	Group 1: 7.1 (2.6); 51.3% Group 2: 14.6 (1.7); 52.7%	Up to 3 yr	NA
Guerrini 2001 ¹³	Italy	Prospective observational cohort	Patients with diagnosed epilepsy (repeated provoked seizures 24 h apart); included a subgroup of patients with DRE (i.e., patients with seizures in the preceding 2 years, judged by their physicians to be drug resistant).	DRE: 42	DRE: 64% aged 5–14 yr; 57.1%	12 mo	NA
MacCracken 1999 ¹⁴	USA	Survey of parents whose children received KD (1995–1998), duration of diet ranged from 5 wk to 2.75 yr	Ineffective pharmacologic control of seizures, unwanted side effects from AEDs, or limited alternatives for further treatment	13	Range 1.1–12.6 yr; NR	NR**	Before, after KD
Ryzi 2013 ¹⁵	Czech Republic	Retrospective review of patient charts and seizure diaries, Epilepsy Centre Brno centre, Czech Republic, 1999–2008	Aged less than 18 yr at the time of VNS implantation, confirmed electroclinical diagnosis of refractory focal cryptogenic or symptomatic epilepsy (without the possibility of resective	15	Median 14.6 +/- 2.5 yr	Up to 5 yr after VNS insertion	Before, after VNS implantation

Study	Country	Study design	Inclusion criteria	n	Mean age, yr (SD); % male	Observation/recall period	Comparison
			surgery), and follow-up for ≥ 12 mo after VNS implantation				
Note: AED = antiepileptic drug, CPT = current procedural terminology, DRE = drug-resistant epilepsy, KD = ketogenic diet, NA = not applicable, NR = not reported, SD = standard deviation, TSC = tuberous sclerosis complex, VNS = vagus nerve stimulation. *KD group and matched controls were followed for the same amount of time that the corresponding KD group patient was followed for. The index date for the noKD group was defined relative to the date of epilepsy diagnosis to ensure the matched pairs had epilepsy for the same amount of time in the observation window. †Pediatric sample. Study also included 497 participants aged 19 years and older who answered on their own behalf. ‡Unclear if the reported percentage applies to the caregivers or children. **Treatment period 5 wk to 2.75 yr.							

References (Additional File 6)

1. Whittington MD, Knupp KG, Vanderveen G, Kim C, Gammaitoni A, Campbell JD. The direct and indirect costs of Dravet Syndrome. *Epilepsy Behav.* 2018;80:109-113.
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13. Guerrini R, Battini R, Ferrari AR, et al. The costs of childhood epilepsy in Italy: comparative findings from three health care settings. *Epilepsia*. 2001;42(5):641.
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15. Ryzi M, Brazdil M, Novak Z, et al. Long-term vagus nerve stimulation in children with focal epilepsy. *Acta Neurol Scand*. 2013;127(5):316.

Additional File 7: Quality assessment – health care resource use

Quality assessment of studies reporting health care resource use

STUDY	Whittington 2018¹
Criteria	Comment
Study design; country	Electronic survey of caregivers of children with Dravet syndrome at the Children's Hospital Colorado, survey open for 3 wk in 2016; US
Sample size	34
Respondent selection and recruitment/Data source	"Eligible caregivers were contacted using the email address recorded in the DS patient's electronic medical record. If an email address was not available in the electronic health record, a study coordinator contacted the caregivers by telephone to see if they were interested in participating in the study and asked for their email address to send the survey."
Inclusion/exclusion criteria	"DS caregivers were eligible to participate if they provided care for a friend or a family member with DS seen at Children's Hospital Colorado"; Exclusion criteria: not reported
Response rate to instrument used	"The survey was emailed to 60 DS caregivers, of which 34 (57% response rate) responded. Of the 34 responders, 30 (88%) fully completed the survey"
Recall/observation period	Recall of resource use: previous 12 months; productivity and leisure time: one week
Loss to follow-up	Not applicable
Missing data	Not reported how missing data were addressed; 88% of surveys were complete
Main considerations	Single study site, low response rate to survey, missing data not addressed; recall period up to 1 year
STUDY	Patel 2018²
Criteria	Comment
Study design	Retrospective analysis of claims data; US
Sample size	13
Respondent selection and recruitment/Data source	Claims data from Partners for Kids, an accountable care organization caring for Medicaid patients in Ohio; largest pediatric accountable care organization in the US
Inclusion/exclusion criteria	Inclusion criteria: patients (0–19 yr) with a CPT code of vagus nerve stimulation initial placement (64568) and Medicaid enrollment and eligibility with continuous enrollment for at least 6 months were included; Exclusion criteria: >19 years of age. Patients with a vagus nerve stimulation battery replacement (CPT code 61885), less than 6 months eligibility, less than 6 months continuous enrollment
Response rate to instrument used	Not applicable
Recall/observation period	12 months before and after an initial vagus nerve stimulation placement
Loss to follow-up	Not reported
Missing data	Authors excluded patients with less than 6 months of continuous enrollment "as completeness of the data could not be known"; not reported how many potential participants were excluded for this reason
Main considerations	Data from a single organization, small sample size, validation of codes not reported, data on clinical characteristics and confounding variables not available, patients with less than 6 months continuous data excluded, data not reported by epilepsy syndrome or severity
STUDY	Kayyali 2016³
Criteria	Comment
Study design; country	Retrospective chart review, single centre ("tertiary pediatric epilepsy center"); US
Sample size	37
Respondent selection and recruitment/Data	Chart review

source	
Inclusion/exclusion criteria	Inclusion: (1) epilepsy was diagnosed and treated by a pediatric neurologist or epileptologist for ≥ 12 months prior to KD; (2) patients failed to respond to conventional pharmacological therapy before starting the diet; (3) patients were treated with the KD for ≥ 12 months; Exclusion criteria not reported
Response rate to instrument used	Not applicable
Recall/observation period	Observation: 12 months before and after starting KD
Loss to follow-up	Not reported
Missing data	Not reported
Main considerations	Single centre, small sample size, not stated how patients were identified, missing data and loss to follow-up not reported, data not reported by epilepsy syndrome or severity
STUDY	Whiting 2017⁴
Criteria	Comment
Study design; Country	Retrospective review of medical chart and administrative claims data; Canada
Sample size	Total 333 children; KD group: 166 patients; matched group without KD: 167 patients
Respondent selection and recruitment/Data source	Patients were identified from The Children's Hospital of Eastern Ontario (Ottawa), The Hospital for Sick Children (Toronto), and McMaster Children's Hospital (Hamilton); "An encoded version of the patients' Ontario Health Insurance Plan (OHIP) number was used to deterministically link patients to health administrative data from several Ontario-wide databases available at the Institute for Clinical Evaluative Sciences (ICES), capturing Ontario residents' contact with the province's universal healthcare system across time. The following databases were used: Ontario Registered Persons Database (RPDB) for demographic variable, OHIP physician claims data to identify matched controls for the children receiving the diet, Discharge Abstract Database (DAD) to obtain inpatient visits, and costs related to these visits, ERCLAIM for health care utilization in the ED setting and National Ambulatory Care Reporting System (NACRS; available starting fiscal year 2003) for the ED cost analysis." Ambulatory Care Reporting System (NACRS; available starting fiscal year 2003) for the ED cost analysis.
Inclusion/exclusion criteria	"A list of all patients who received KD during the study period was generated via medical records search at all three of the study locations. Search terms included epilepsy, seizure disorder, ketogenic diet, and dietician consult. This list was cross-referenced with a list kept by dietitians and a list of patients for whom an EEG had been obtained, to ensure that all patients who received KD were identified." Study also included a cohort of patients who did not receive KD for comparison: "The noKD children were selected based on a 1:1 match of KD group patients. To make the two groups more comparable, matching was performed based on epilepsy diagnosis during the study period, sex, rural/nonrural status of the child's residence at index event date (Kralj 2009), date of birth within one year, and fiscal year of study start. Additionally, each match was followed for the same amount of time that the corresponding KD group patient was followed for." Since the noKD group did not have a naturally defined index date, their index date was defined relative to the date of epilepsy diagnosis to ensure the matched pairs had epilepsy for the same amount of time in the observation window" Exclusion criteria: "Patients in the KD database who initiated the diet between January 1, 2000 and December 31, 2010 were excluded from the study if they had an invalid OHIP number (i.e. out of province patient). Patients were also excluded if their diet status at the time of data abstraction or if date of epilepsy diagnosis were missing. Patients who died during the observation period or who were not eligible to receive OHIP coverage in the defined observation window were also excluded"
Response rate to instrument used	Not applicable
Recall/observation period	2000 to 2010; "A look-back window and look-ahead window was defined in reference to the index date. For each patient in the KD group, the look-ahead window was defined as the minimum of two dates: date of KD termination, and two years (730 days) postindex date. The length of the look-back window was mirrored, unless it extended past a patient's date of birth. In this case, the beginning of the look-back window, the patient's study start date, was equated to the date of birth."
Loss to follow-up	Not reported

Missing data	Participants missing information on diet status at the end of the study, missing information on their date of epilepsy diagnosis or because they were deceased during the study period were excluded (n = 10).
Main considerations	Matched “noKD” group had epilepsy for a shorter duration of time; limited characteristics and confounding variables reported for the “noKD” group, data not reported by epilepsy syndrome or severity
STUDY	Gold 2016⁵
Criteria	Comment
Study design; country	Retrospective analysis of claims data; US
Sample size	252
Respondent selection and recruitment/Data source	Truven Health MarketScan Commercial Claims and Encounters Database and the Truven Health MarketScan Multi-State Medicaid Database. "These databases contained inpatient, outpatient, pharmacy claims, and insurance coverage data for patients across the US who are enrolled in commercial insurance plans"
Inclusion/exclusion criteria	"We included patients in the MarketScan Research Database who received treatment for IS (ICD-9-CM diagnosis code: 345.60) between April 1, 2007 and December 31, 2012 who were less than 2 years old at the time of the IS diagnosis." Exclusion: "Patients with subsequent diagnoses of tuberous sclerosis complex (TSC; ICD-9-CM diagnosis code: 759.5) were excluded from our analyses" "we also excluded patients who were not enrolled in their health plans continuously for at least 3 months prior and 12 months after the index date." "756 were excluded, because they did not receive prescriptions for Acthar."
Response rate to instrument used	Not applicable
Recall/observation period	Patients enrolled in databases between April 1, 2007 and December 31, 2012; patients were followed for 3 months before IS diagnosis and 12 months after diagnosis
Loss to follow-up	1949 participants were excluded from the data set because they did not have complete follow-up information for at least 3 months before and 12 months after diagnosis
Missing data	Excluded: "We also excluded 2000 patients, because their ages were missing or they were not less than 2 years old at the time of their IS diagnoses. "we excluded patients who were not enrolled in their health plans for 1 year after the index event."
Main considerations	Participants were assigned to a treatment group based on administrative data (prescription receipt v. medication use); limited information on clinical characteristics or confounding variables available (data not reported by epilepsy syndrome or severity)
STUDY	Rentz 2015⁶
Criteria	Comment
Study design; country	"Cross-sectional, non-intervention web-based survey study"; US
Sample size	179 caregivers of pediatric patients; also included 497 participants aged 19 years and older
Respondent selection and recruitment/Data source	"Participants were recruited via e-mail and social networking web sites associated with the Tuberous Sclerosis Alliance, a US-based patient advocacy organization, between May and June 2012"
Inclusion/exclusion criteria	"Eligibility criteria for patients included a minimum age (18 years or older), TSC diagnosis, ability to read English and participate in a web-based survey, and ability and willingness to provide online assent. Eligible caregivers had to be 18 years or older, care for someone diagnosed with TSC, able to read English and participate in a web-based survey, and able and willing to provide online assent. " Exclusion: "Prospective survey participants were excluded if they reported cognitive impairment or other health impairment that would interfere with completing a TSC-related online survey or if they refused to provide online assent."
Response rate to instrument used	Not reported
Recall/observation period	Survey administered May and June 2012; recall period: 6–12 months
Loss to follow-up	Not applicable
Missing data	Not reported

Main considerations	Participants were recruited by an advocacy agency and may not be reflective of wider patient sample, the minimum age stated in the eligibility criteria appears to apply only to those answering the survey on their own behalf; diagnosis based on self-report and not verified, response rate and percentage of missing data not reported, data based on participant recall over the previous 6-12 months
STUDY	Aburahma 2015⁷
Criteria	Comment
Study design; country	Retrospective review, including review of medical records and caregiver recall; Jordan
Sample size	28
Respondent selection and recruitment/Data source	"Data regarding frequency of emergency room visits, ward admissions, and intensive care unit admissions pre and post VNS implantation was collected retrospectively from patients' medical records and from caregivers" "This is a retrospective review of all children who underwent VNS implantation at King Abdullah University Hospital, and Jordan University Hospital. King Abdullah University Hospital is an urban, JCI Aa accredited, tertiary referral hospital in the north of Jordan, and Jordan University Hospital is a JCI A accredited tertiary referral hospital in the capital Amman"
Inclusion/exclusion criteria	Not reported
Response rate to instrument used	Not applicable
Recall/observation period	Data collected for children who had VNS implanted between 2007 and 2011; "All patients were followed for a minimum of three years, 22 patients had follow-up of five or more years"
Loss to follow-up	Not reported
Missing data	Not reported
Main considerations	Small sample size, data collected from two tertiary referral centres, codes or methods of identifying patients and procedures/resource use not reported; inclusion/exclusion criteria not reported, method of addressing missing data not stated, data not reported by epilepsy syndrome or severity
STUDY	Cramer 2014⁸
Criteria	Comment
Study design; country	Retrospective review of claims data; US
Sample size	422 with uncontrolled epilepsy ("The term 'uncontrolled' was used for patients who added an additional AED to their existing regimen since seizure frequency was not in the database." "We defined additional AED therapy as ≥ 3 months of baseline therapy, followed by ≥ 3 months with both baseline and additional AED(s)."
Respondent selection and recruitment/Data source	Truven Health Analytics MarketScan database
Inclusion/exclusion criteria	Inclusion: "Patients <12 years old, diagnosed with epilepsy and treated with at least one AED in the identification (ID) period, calendar year 2008, were included. We identified all patients with ≥ 2 medical claims with epilepsy (ICD-9-CM codes: 345.xx or 780.39; ≥ 30 days apart) in any diagnosis field in the ID period and who had either 1) the same AED (monotherapy or combination) for ≥ 12 months or 2) added additional AED(s) in the ID period. We defined additional AED therapy as ≥ 3 months of baseline therapy, followed by ≥ 3 months with both baseline and additional AED(s). Included AEDs were as follows: carbamazepine, clonazepam, divalproex, valproate, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, vigabatrin, and zonisamide." Exclusion criteria: "Patients were excluded if they were not continuously enrolled or had a diagnosis of chronic pain, fibromyalgia, bipolar disorder, or migraines in the study period. These diagnoses were excluded because AEDs may be prescribed for these conditions"
Response rate to instrument used	Not applicable
Recall/observation period	2007 to 2009; 1 yr after index prescription
Loss to follow-up	Authors excluded 5799 children who were not continuously enrolled in the baseline or postindex

	period
Missing data	"The database contains every claim for an individual's enrollment period. There are no missing data since a payment is processed only if a claim exists."
Main considerations	Codes for identification of epilepsy have not been validated, data on clinical characteristics and confounding variables not available (data not reported by severity or epilepsy syndrome), patients without continuous enrollment excluded, data not reported by epilepsy syndrome or severity, patients who switched AEDs during the study period were excluded
STUDY	Kalanithi 2014⁹
Criteria	Comment
Study design; country	Retrospective analysis of claims data; US
Sample size	93
Respondent selection and recruitment/Data source	"The HCUP is a federal-state-industry partnership that represents the largest set of encounter-based longitudinal hospital care data in the United States. Two data sets, the California Inpatient (CA-SID) and Ambulatory Surgery (CA-ASD) databases, were assayed for all VNS surgeries from 2005 to 2008" "For the 365 days following implantation, CA-SID, CA-ASD, and the California State Emergency Department databases were surveyed for any recorded utilization." Study includes both pediatric and adult patients; data extracted and assessed for pediatric sample only
Inclusion/exclusion criteria	"Patients were selected by diagnosis code for epilepsy (International Classification of Diseases [ICD]-9 345.x, 780.39) and the following: for CA-SID, ICD-9 procedure codes used were for placement, revision, and removal of vagus nerve stimulator and/or implantable pulse generator (ICD-9 04.92, 04.93, 86.94, 86.05), and for CA-ASD, CPT codes were used (64573, 61885, 64585, 61888)." Exclusion criteria: not reported
Response rate to instrument used	Not applicable
Recall/observation period	2005–2009; "For the 365 days following implantation, CA-SID, CA-ASD, and the California State Emergency Department databases were surveyed for any recorded utilization". "The one-year post-VNS rate of hospitalization and ED use was compared to these rates in the year prior to VNS implantation"
Loss to follow-up	Not stated. Patients were included for the assessment of resource use if they had complete data for one year before and after VNS insertion
Missing data	Patients with missing data were excluded from analysis.
Main considerations	Codes used for identification of patients have not been validated in the study databases, not stated how many children were excluded for not having one year before and after VNS implantation, on clinical characteristics and confounding variables not available (data not reported by epilepsy syndrome or severity)
STUDY	Lennert 2012¹⁰
Criteria	Comment
Study design; country	Retrospective chart review; USA
Sample size	95
Respondent selection and recruitment/Data source	Patients with TSC-related seizure diagnosis who received care at the Minnesota Epilepsy Group, PA, 1973–2010
Inclusion/exclusion criteria	"To be included in this cohort, patients were required to be diagnosed with a tuberous sclerosis complex-related seizure disorder within the first 6 months after tuberous sclerosis complex diagnosis. Patients were excluded if they were diagnosed with a tuberous sclerosis complex-unrelated seizure disorder." Patients with less than 6 months of data were excluded.
Response rate to instrument used	Not applicable
Recall/observation period	5 yr after diagnosis of TSC
Loss to follow-up	Unclear; authors state that "only 115 charts were available at Minnesota Epilepsy Group that met the aforementioned criteria." But included 95 children in the analysis population
Missing data	Not stated

Main considerations	Not clear how patients with TSC were identified, data from a single centre, data not reported by seizure severity
STUDY	Helmerts 2012¹¹
Criteria	Comment
Study design; country	Retrospective analysis of claims data; US
Sample size	238 children aged 1–11 year; 207 children aged 12–17 yr
Respondent selection and recruitment/Data source	“The data for this study came from Medicaid, which is a US government health-insurance program designed to serve low income citizens, the blind, and those with chronic disabling conditions.” “Medicaid data from five states: Florida (FL), Iowa (IA), Kansas (KS), Missouri (MO), and New Jersey (NJ) was combined and analyzed for this study.” Data provided separately for children aged 1-11 (mean age 7.1) and 12-17 (mean age 14.6) years
Inclusion/exclusion criteria	“a) ≥ 1 neurologist visits with a diagnosis for epilepsy (ICD-9: 345.xx) or nonfebrile convulsions (ICD-9: 780.3, 780.39); b) at least one 1 pharmacy dispensings for an AED; c) at least one procedure claims for VNS implantation; and d) at least 6-months of continuous enrollment before and after the implantation date of VNS.” Exclusion criteria: not reported
Response rate to instrument used	Not applicable.
Recall/observation period	“The observation period for each patient extended from the index date until removal of the device, death, Medicaid data end date (KS: June 30, 2009, NJ: December 31, 2008, FL: June 30, 2008, MO: June 30, 2008, and IA: June 30, 2006), or end of the study period (maximum 3 years of follow-up), whichever occurred first.” Observation period: Aged 1-11 yr: 28.3 (SD 10.2) months after VNS insertion; 12-17 yr: 29.8 (SD 9.4) months after VNS insertion
Loss to follow-up	Not stated
Missing data	Not stated
Main considerations	Not stated if codes have been validated, data were limited to Medicaid programs in five states, not stated how many children were excluded for not having continuous enrollment during the study period, data on clinical characteristics and confounding variables not available (data not reported by epilepsy syndrome or severity)
STUDY	Guerrini 2001¹²
Criteria	Comment
Study design; country	Prospective observational cohort; Italy
Sample size	189 total, 42 with drug-resistant epilepsy
Respondent selection and recruitment/Data source	Participants were recruited at 3 study centres (university department, general hospital, outpatient department). “Over a 12-month period, patients or their parents at each follow-up appointment reported data regarding... outpatient evaluations, and hospital admissions in an ad hoc diary.”
Inclusion/exclusion criteria	“Patients were included in the study if their epilepsy fulfilled a standard diagnostic definition (i.e., repeated un-provoked seizures 24 h apart.” Included participants were “grouped in the following categories: (a) newly diagnosed patients; (b) patients with epilepsy in remission; (c) patients with active non-drug resistant epilepsy; and (d) those with drug-resistant epilepsy (patients with seizures in the preceding 2 years, judged by their physicians to be drug resistant).” Exclusion criteria: not reported
Response rate to instrument used	Not applicable
Recall/observation period	Observation over 12 months
Loss to follow-up	No losses
Missing data	Not stated
Main considerations	Small sample size, unclear selection criteria (definition of “drug-resistant” epilepsy was not reported and was based physician judgement), unclear if consecutive patients were recruited, not stated how missing data were addressed, data not reported by epilepsy syndrome or severity

STUDY	Ryzi 2013¹³
Criteria	Comment
Study design; country	Retrospective review of patient files and seizure diaries; Czech Republic
Sample size	15
Respondent selection and recruitment/Data source	Epilepsy Centre Brno centre, Czech Republic
Inclusion/exclusion criteria	Inclusion criteria: "1. patient age younger than 18 at the time of VNS implantation; 2. confirmed electroclinical diagnosis of refractory focal cryptogenic or symptomatic epilepsy (without the possibility of resective surgery); and 3. available outcome of at least 12 months after VNS implantation." Exclusion criteria: not reported
Response rate to instrument used	Not applicable
Recall/observation period	1999-2008; preoperative period: average 3.9 +/- 2.0 yr (range 1–7 yr); post-operative period: 5.6 yr +/-2.2 yr (range 1–9 yr)
Loss to follow-up	Not stated
Missing data	Not stated
Main considerations	Single centre, small sample size, not stated how missing data were addressed, patients with less than 12 months of follow-up were excluded (not reported how many patients were excluded for this reason), data not reported by epilepsy syndrome or severity
Note: AED = antiepileptic drug, CPT = current procedural terminology DS = Dravet syndrome, IS = infantile spasms, KD = ketogenic diet, TSC = tuberous sclerosis complex, VNS = vagus nerve stimulation.	

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Additional File 8: Cost data

Included studies that provided cost data but not disaggregated resource use

Study	Country	Population	Costs reported (valuation year and currency)
Luoni 2015¹	Italy	Drug-resistant epilepsy	• 0–5 yr, median (range): direct medical cost 5,151 (109–31,551); AED cost 408 (25–2,392); hospital admission costs 3,092 (0–27,315) • 6–11 yr: direct medical cost 2,239 (201–16,692); AED cost 578 (43–7,649); hospital admission costs 0 (0–11,338) • 12–16 yr: direct medical cost 3,096 (226–34,549); AED cost 1,046 (77–4,023); hospital admission costs 0 (0–29,377) (2013 Euro)
Sun 2015²	USA	Tuberous sclerosis complex undergoing surgical resection of subependymal giant cell astrocytoma, 91% with seizures; mean baseline age of 11.6 years	“The mean direct medical costs were \$8543 (inpatient: \$3770; outpatient: \$3473; medication: \$1300) for the pre-surgery year, and \$85,397 (inpatient: \$71,562; outpatient: \$11,497; medication: \$2338) for the post-surgery year.” (2010 US dollars)
Strzelczyk 2014³	Germany	Dravet syndrome; mean age: 12.3±7.5 years	Total direct costs: €6506; medication: €1559, Non-AED costs: €4946, [Hospitalization: €4483, emergency transport €391, outpatient care: €46] (2011 Euro)
Pina-Garza 2017⁴	USA	Probable Lennox-Gastaut syndrome; mean age 16.3 yr	Health care costs: \$28,461–\$40,193 per patient per year (PPPY); medical costs: medical costs: \$25,303–\$37,342 PPPY; Home-based care (aged 1–18 year): \$12,396 to \$18,360 PPPY; Long-term care: \$1648 to \$5933 PPPY; pharmacy costs: \$1592–\$5630 PPPY (US dollars, year not stated [data collected between 1997 and 2013])
Mandel 2002⁵	USA	Drug-resistant epilepsy receiving ketogenic diet	“Total costs affiliated with care for the 15 children were: \$352,820.20 for the prediet period, \$41,221.91 for the diet initiation, and \$149,436.86 for the post-diet initiation phase.” (US dollars, year not stated [data collected in 1998])
Riechmann 2015⁶	Germany	Children with epilepsy, including drug-resistant epilepsy	“Total direct costs summed up to €1,619 ± €4,375 per participant and 3-month period. Direct medical costs were due mainly to hospitalization (47.8%, €774 ± €3,595 per 3 months), anticonvulsants (13.2%, €213 ± €363), and ancillary treatment (9.1%, €147 ± €344).” (2011 Euro)
Oldham 2015⁷	USA	Children with drug-resistant epilepsy referred for surgery	“The median (25th–75th percentile) cost of the epilepsy surgery hospitalization was \$118,400 (\$101,900–\$143,800). “Median annual follow-up costs, not including the cost of the surgical hospitalization, were not significantly different between the surgical group and the medical group in the first year (\$13,000 [\$7700–\$43,800] versus \$16,200 [\$7700–\$28,400], P = NS) or second year of follow-up (\$9200 [\$4300–\$19,700] versus \$7600 [\$5200–\$34,600], P = NS). However, among surgical patients who achieved complete remission from seizures (ILAE class 1), annual median follow-up costs were lower as compared with medical patients in the first year (\$8000 [\$5700–\$11,800] versus \$16,200 [\$7700–\$28,400], P = 0.04) and second year of follow-up (\$5200 [\$2700–\$10,700] versus \$7600 [\$5200–\$35,000], P = 0.05).” (2012 US dollars)
Majoie 2001⁸	The Netherlands	Lennox-Gastaut syndrome	“The total cost of VNS is 13,024. Euros, including the cost of the device, the surgical procedure, and all necessary presurgical investigations.” (2000 Euro)
Note: AED = antiepileptic drug, VNS = vagus nerve stimulation.			

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Section 4.4

Economic evaluation of cannabinoid oil for Dravet syndrome: A cost-utility analysis

SECTION OVERVIEW

In this section, a manuscript describing a *de novo* cost-utility analysis of the use of cannabinoid oil as a treatment for Dravet syndrome is presented. Dravet syndrome is a severe form of pediatric epilepsy that is associated with important morbidity and costs to the health care system and, although cannabinoid oils are increasingly being used for the treatment of Dravet syndrome, the cost-effectiveness of this approach is unknown. Thus, a cost-utility analysis was performed in order to compare the cost-effectiveness of cannabinoid oil with stiripentol and clobazam plus valproate, two current treatment options for this disease. The findings of the systematic reviews presented in **Sections 4.2 and 4.3** were used to inform the study.

MANUSCRIPT STATUS

This manuscript has been submitted for publication at *PharmacoEconomics*:

Elliott J, McCoy B, Clifford T, Potter BK, Wells GA, Coyle D. Economic evaluation of cannabinoid oil for Dravet syndrome: A cost-utility analysis. *PharmacoEconomics* (submitted January 13, 2020).

Supporting material

Appendix 1: CHEERS Checklist

Appendix 2: Results of scenario analyses

Author roles and contributions

All of the authors contributed to the conception and planning of the study. JE and DC developed the model and performed all analyses. JE drafted the manuscript, and all authors contributed to its critical revision. All authors approved the version of the manuscript submitted for publication.

RELATED THESIS APPENDICES

Appendix C: Abstracts submitted for conference presentation. Findings from this study have been submitted to the 2020 CADTH Symposium (Toronto, Ontario); Submitted September 2019.

Elliott J. Clifford T, Potter B, McCoy B, Wells GA, Coyle DC. Does cannabidiol represent good value for money? A cost-utility analysis of cannabidiol for Dravet syndrome.

Appendix E: Economic evaluation of stiripentol for Dravet syndrome: A cost-utility analysis.

This appendix presents the findings of a cost-utility analysis of stiripentol for the treatment of Dravet syndrome, which was undertaken during JE's PhD coursework and was subsequently refined and published (**Elliott J.**, et al. *PharmacoEconomics* 2015;36:1253-1261). The model used for the analysis in Section 4.4 was initially developed for this project and was submitted for peer-review as part of this publication.

Economic evaluation of cannabinoid oil for Dravet syndrome: A cost-utility analysis

Running head: Cost-effectiveness of cannabinoid oil for Dravet syndrome

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Keywords: cannabinoid oil; Dravet; cannabis; drug-resistant epilepsy; cost-effectiveness

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Contributors: All of the authors contributed to the conception and planning of the study. JE and DC developed the model and performed all analyses. JE drafted the manuscript, and all authors contributed to its critical revision. All authors approved the version of the manuscript submitted for publication.

Conflicts of interest: Bláthnaid McCoy was principal investigator in a study of cannabinoids for treating epilepsy in children with Dravet syndrome. None declared for all other authors.

Financial support: No specific funding was received for this study.

Data Accessibility Statement: All data generated or analyzed during this study are included in this published article (and its online supplementary information files).

Key points for decision makers

1. Cannabinoid oils are being increasingly used to treat Dravet syndrome, a severe form of drug-resistant epilepsy, yet the long-term costs and outcomes of this approach are unknown.
2. Cannabinoid oil (20:1 cannabidiol [CBD] to delta-9-tetrahydrocannabinol [THC]) may be a more cost-effective choice compared with treatments involving clobazam and valproate or stiripentol, which are reimbursed on several Canadian provincial formularies.
3. The opportunity costs associated with not funding cannabinoid oil should be considered.

Abstract

Introduction: Cannabinoid oils are being increasingly used to treat Dravet syndrome, yet the long-term costs and outcomes of this approach are unknown. Thus, we examined the cost-effectiveness of cannabinoid oil for Dravet syndrome, compared with stiripentol and clobazam/valproate.

Methods: We performed a probabilistic cost-utility analysis from the perspective of the Canadian public health care system, comparing cannabinoid oil with (a) stiripentol and (b) clobazam and valproate. Costs and quality adjusted life years (QALYs) were estimated using a Markov model that followed a cohort of children from 5–18 years of age through model states related to seizure frequency. Model inputs were obtained from the literature. The cost-effectiveness of cannabinoid oil, stiripentol, and clobazam/valproate was assessed through sequential analysis. The influence of perspective and other assumptions were explored in scenario analyses. All costs are expressed in 2019 Canadian Dollars.

Results: The incremental cost per QALY gained with use of cannabinoid oil, from the health care system perspective, was \$32,399 compared with clobazam and valproate. Stiripentol was dominated by cannabinoid oil, producing fewer QALYs at higher costs. At a willingness-to-pay threshold of \$50,000, cannabinoid oil was the optimal treatment in 76% of replications. From a societal perspective, cannabinoid oil dominated stiripentol and clobazam/valproate. The interpretation of the results was insensitive to model and input assumptions.

Conclusion: Compared with clobazam/valproate, cannabinoid oil is cost-effective for treatment of Dravet syndrome, if a decision maker is willing to pay at least \$32,399 for each QALY gained. Cannabinoid oil is a more cost-effective choice than stiripentol, which is currently listed on several Canadian provincial formularies. The opportunity costs of continuing to fund stiripentol but not cannabinoid oil should be considered.

1. Introduction

Dravet syndrome, a severe and catastrophic form of pediatric drug-resistant epilepsy, affects about 1 in 15,700 children [1], with the onset of seizures typically during the child's first year [2,3]. Although drug-resistant epilepsies are, by definition, resistant to drug therapy [4], the goal of treatment is to reduce seizures and improve quality of life with minimal adverse effects [5]. Owing partly to the high seizure burden, as well as the associated physical and cognitive effects, quality of life is reduced for children with Dravet syndrome compared to children with other forms of drug-resistant epilepsy or controlled epilepsy [6]. Quality of life is also reduced among parents of children with Dravet syndrome [6], owing in part to high levels of stress and worry over their financial situation [7,8]. Indeed, parents of children with Dravet syndrome report frequently missing work, switching or quitting jobs, or losing a job because of their care-giving responsibilities [6,9]. Dravet syndrome is also associated with high costs to the health care system, and children with Dravet syndrome incur more health care costs compared to children in seizure remission or with other forms of drug-resistant epilepsy [6].

In addition to antiepileptic drugs, children with epilepsy may be given various forms of complementary and alternative medicine in an attempt to control their seizures [10]. Medical cannabis, one form of complementary and alternative medicine, has garnered intense interest over the past decade owing to media reports of children whose drug-resistant seizures have responded to medical cannabis when other treatments have failed. Indeed, parents describe trying cannabis as an alternative or supplement to traditional antiepileptic drugs because "nothing else is working" [11]. Recent studies have suggested that some cannabis-based products, particularly those high in cannabidiol, may be effective in reducing seizures associated with drug-resistant epilepsy [12]. However, most studies have involved a relatively short treatment duration, and the long-term costs and outcomes of such treatment are unclear.

In the present study, we sought to address the decision problem related to the cost effectiveness of cannabinoid oil for the treatment for pediatric Dravet syndrome. Specifically, we evaluated the cost-effectiveness of cannabinoid oil from the perspective of the Canadian publicly funded health care system, compared to treatment with stiripentol and with clobazam plus valproate.

2. Methods

2.1 Decision problem

The use of cannabinoid oil for seizures associated with Dravet syndrome is increasing. The problem relates to the decision of whether cannabinoid oil is cost-effective from the perspective of the Canadian publicly funded health care system. To address this decision problem, we undertook a model-based cost-utility analysis (CUA) that compared cannabinoid oil with two treatment options for Dravet syndrome that are currently reimbursed under some Canadian provincial drug plans (stiripentol; clobazam plus valproate). Because this analysis was conducted from the perspective of the Canadian health care system, effectiveness was based on a cannabinoid oil currently available in Canada (CanniMed 1:20 Oil). We followed Canadian guidelines for economic evaluation of health technologies [13] and recent recommendations for decision modeling in pediatric epilepsy [14]. The Consolidated Health Economics Evaluation Reporting Standards (CHEERS) statement [15] was followed for reporting (Appendix 1).

2.2 Analytic framework

We performed a probabilistic analysis utilizing a four-state Markov model developed within Microsoft Excel to simulate the outcomes associated with use of cannabinoid oil; this model has been previously used in the economic evaluation of stiripentol [16]. The face validity of the model and the relevance of model inputs for the Canadian context was verified through consultation with a pediatric neurologist (B.M.). The model was internally validated for all mathematical calculations, parameter estimates, and coding by a second author. External validity of the model was explored by comparing the results of the model with the results of available clinical studies [17].

Briefly, the model includes four states, three of which relate to the frequency of seizures relative to a baseline period: seizure free (SF; 100% reduction in seizures from baseline), not seizure free (NSF; 50%–99% reduction), and not adequately controlled (NAC; 0%–49% reduction); death is the final absorbing state (Figure 1). At the start of the analysis, all patients were assumed to be in the NAC state (uncontrolled seizures), which is consistent with previous treatment failure. In the following one-month cycles, patients moved between the states dependent on the assigned transition probabilities. Patients whose seizures did not respond to cannabinoid oil or stiripentol for 6 cycles (i.e., those who remained in the NAC state for 6 cycles) were assumed to discontinue treatment and continue on clobazam and valproate alone. Patients whose seizures responded to treatment with cannabinoid oil or stiripentol (i.e., in the SF or NSF states) continued treatment in subsequent cycles. A one-month cycle length was chosen to reflect the frequent movement between model states in this population, and a 13-year horizon was chosen such that the cohort would be considered adults (aged 18 years) at the end of the analysis period. Additional time horizons were tested in scenario analyses (1 yr, 20 yr).

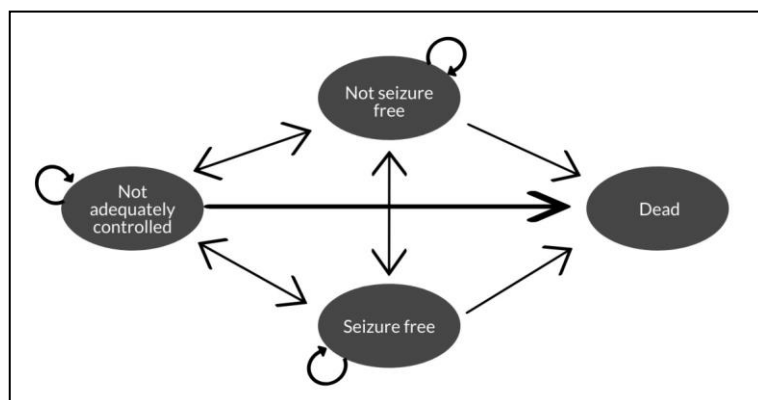


Figure 1: Schematic of Markov model showing movement of patients between states.

Note: Seizure free = 100% reduction in seizures from baseline; not seizure free = 50%–99% reduction; not adequately controlled = 0%–49% reduction.

Table 1: Input parameters for the economic model

Parameter	Base estimate	Probability distribution	Source
Utilities			
<i>Child^b, EQ-5D</i>			
NAC	0.060	1 - Lognormal (0.94, 0.03)	Verdian 2008 [18]
NSF	0.500	1 - Lognormal (0.50, 0.03)	
SF	0.596	1 - Lognormal (0.404, 0.03)	
<i>Adult caregivers^c, EQ-5D-3L</i>			
NAC	0.900	1 - Lognormal (0.90, 0.02)	Strzelczyk 2019 [6]
NSF	0.949	Derived	
SF	0.960	1 - Lognormal (0.96, 0.02)	
Health care resource use, monthly			
<i>Resource use if NAC or NSF</i>			
General practitioner visit	0.540	Gamma (39.3, 0.04) / 3	Strzelczyk 2019 [6]
Neurologist visit	0.627	Gamma (66.35, 0.03) / 3	
Physiotherapy	2.273	Gamma (44.7, 0.15) / 3	
Speech therapy	1.267	Gamma (42.8, 0.09) / 3	
Occupational therapy	1.497	Gamma (49.65, 0.09) / 3	
Emergency department visit	0.158	Gamma (23.82, 0.08) / 12	Whittington 2018 [19]
Hospital admission (non-SE)	0.094	Gamma (9.31, 0.12) / 12	
Land ambulance transfer to hospital	0.056	Gamma (6.11, 0.11) / 12	
<i>Resource use if SF</i>			
General practitioner visit	0.040	Gamma (7.38, 0.02) / 3	Strzelczyk 2019 [6]
Neurologist visit	0.050	Gamma (8.35, 0.02) / 3	
Physiotherapy	0.393	Gamma (9.01, 0.13) / 3	
Speech therapy	0.383	Gamma (9.66, 0.12) / 3	
Occupational therapy	0.373	Gamma (9.11, 0.12) / 3	
Drug costs^a, per mg			
Cannabidiol	\$0.108	Fixed	CanniMed (1:20 ratio of delta-9-tetrahydrocannabinol to cannabidiol) ^e
Stiripentol	\$0.026	Fixed	British Columbia PharmaCare Formulary ^f
Clobazam	\$0.011	Fixed	Ontario Drug Benefit Formulary ^g
Valproate	\$0.0002	Fixed	
Lorazepam	\$0.035	Fixed	
Health care resource costs^a			
General practitioner visit	\$77.20	Fixed	Ontario Schedule of Benefits ^h
Neurologist visit	\$78.80	Fixed	
Emergency department visit	\$97.60	Fixed	Ontario Schedule of Benefits ^h
Hospital admission (SE)	\$7083.63	Gamma (3.75, 1891)	Ontario Case Costing Initiative [20]
Hospital admission (non-SE)	\$5590.25	Gamma (15.77, 355)	
Land ambulance transfer to hospital	\$216	Fixed	Municipal Benchmarking Network Canada [21]
Physiotherapy	\$96.04	Fixed	
Speech therapy	\$146.12	Fixed	Health Data Branch Web Portal ⁱ
Occupational therapy	\$136.65	Fixed	

Transition probabilities			
<i>Cannabinoid oil</i>	IPD	Dirichlet method	Huntsman 2019 [22]
<i>Stiripentol</i>	IPD	Dirichlet method	Inoue 2015 [23]
<i>Clobazam + valproate</i>			STICLO France [24]; STICLO Italy [25]
NSF to NAC	0.94	Beta (29, 2)	
NAC to NSF	0.06	Beta (2, 29)	
Probability of status epileptics			
Cannabinoid oil	0.049	Beta (3, 58)	Devinsky 2017 [26]
Stiripentol	0.045	Beta (1, 21)	STICLO France [24]
Clobazam + valproate	0.050	Beta (1, 19)	
Mortality rate, annual			
SUDEP	0.009	Gamma (10, 0.0009)	Cooper 2015 [27]
Non-SUDEP	0.007	Gamma (7,0.0009)	
Productivity			
Absenteeism, hours lost per caregiver per yr	381	Gamma (7.03, 4.52)	Whittington 2018 [19]
Presenteeism, hours lost per caregiver per yr	616	Gamma (17.62, 2.91)	
Valuation of time lost	\$29.70/hr	Fixed	Statistics Canada ^d [28]

Note: IPD = individual patient data, NAC = not adequately controlled, NICE = National Institute for Health and Care Excellence, NSF = not seizure free, SE = status epilepticus, SF = seizure free, SUDEP = sudden unexpected death in epilepsy.

a. Costs are valued in 2019 Canadian dollars.

b. Utilities for Lennox-Gastaut syndrome, elicited from 119 members of the general public for health states based on frequency of tonic-atonic seizures (drop seizures). We assumed that the utility reported for $\geq 75\%$ reduction would be equivalent to the SF state in our model, and that the value for 50%–75% reduction would be equivalent to the NSF state (50%–99% reduction). For the NAC state (<50% seizure reduction), we averaged the values reported by Verdian et al [18] for “uncontrolled” and less than 50% seizure reduction.

c. Utilities for adult caregivers of children with Dravet syndrome reported by Strzelczyk 2019 [6] were assumed to correspond to the “not adequately controlled” state in the model. Utilities reported for caregivers of children in seizure remission were assumed to correspond to the “seizure free” model state. Utilities for adult caregivers of children in the “not seizure free” state were unavailable; we assumed that the utility value would be higher than for the “not adequately controlled” state, based on the proportion increase observed for children.

d. Average employee wage, both sexes, age 25–40.

e. CanniMed 1:20 oil: www.cannimed.ca/collections/medical-marijuana-oil. Cost input was based on price per mg CBD.

f. British Columbia PharmaCare Formulary: <https://pharmacareformularysearch.gov.bc.ca/>

g. Ontario Drug Benefit Formulary: <https://www.formulary.health.gov.on.ca/formulary/>

h. Ontario Schedule of Benefits: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/physserv_mn.html

Costs and QALYs were discounted at a rate of 1.5% per year following Canadian guidelines [13], and we tested the impact of alternative discount rates in scenario analyses (0%, 3%). The model was run for 10,000 replications, with model inputs represented by probability distributions (Table 1). Uncertainty was based on sampling error where available; if no measure of uncertainty was available, we assumed a standard error of 25% of the mean [13]. Costs and QALYs were estimated for each replication, and sequential analysis was conducted to assess which of cannabinoid oil, stiripentol, and clobazam and valproate were cost effective at different potential threshold values of a QALY.

2.3 Patient population

The target population was Canadian pediatric patients with Dravet syndrome whose seizures had not previously responded to treatment with clobazam and valproate. In the reference case, the typical patient (5 years of age) was based on a recent cohort study [22] involving children aged 1–10 years with drug-resistant epileptic encephalopathy and a minimum of one major seizure per week or four major seizures per month. In order to account for child growth, the weight of the cohort was increased at yearly intervals, based on the World Health Organization's growth charts for Canada [29], using the 50th percentile weight for each age.

2.4 Comparators

We compared cannabinoid oil (CanniMed 1:20 Oil) on a background of clobazam and valproate to (a) treatment with stiripentol (on a background of clobazam and valproate) and to (b) treatment with clobazam plus valproate alone. The cannabinoid oil contains a 20:1 ratio of cannabidiol to delta-9-tetrahydrocannabinol (THC), with an estimated concentration of 16.0 to 24.0 mg/ml (www.cannimed.ca/collections/medical-marijuana-oil). Patients were assumed to be taking 12 mg/kg/d cannabidiol, consistent with the upper dose in a recent clinical study [22]. The impact of alternative doses were explored in scenario analyses (5, 8, 16 mg/kg/d). Patients were assumed to be taking the maximum Health Canada-approved dose of clobazam (1 mg/kg/d to a maximum of 40 mg/d) and valproate (60 mg/kg/d). Similarly, we assumed that patients would be taking the maximum Health-Canada approved dose of stiripentol (50 mg/kg/d) on a background of clobazam and valproate (doses as above).

2.5 Model inputs

2.5.1 Efficacy

Studies assessing the clinical effectiveness of cannabinoid oil were identified from a living systematic review [30] of cannabis-based products for the treatment of pediatric epilepsy. Transition probabilities were derived from published individual patient data from seven children aged 1–10

years in a single-arm cohort study of patients with Dravet and Lennox Gastaut taking cannabinoid oil on a mixed background of antiepileptic drugs for up to 5 months [22]. Similarly, transition probabilities for stiripentol were derived from individual patient data from a cohort of 24 patients with Dravet syndrome taking stiripentol (50 mg/kg/d) on a background of clobazam and valproate for up to 56 weeks [23]. For both cannabinoid oil and stiripentol, we compared the percentage change in seizures for each patient in each one-month period relative to the preceding period and derived the probability of moving between model states (e.g., moving from the NAC to NSF or SF states, staying in the NAC state). Uncertainty around the transition probabilities was represented by Dirichlet distributions [31]. For clobazam and valproate, we pooled data from the control arms of the STICLO randomized controlled trials [24,25], which involved the use of placebo on a background of clobazam and valproate. For each comparator, we assumed that the transition probabilities would be consistent beyond the end of the observed data. The rates of sudden unexpected death in epilepsy (SUDEP) and non-SUDEP in Dravet syndrome were obtained from the literature [27] and were converted to monthly probabilities [32]. We assumed that patients experiencing seizures (i.e., in the NAC or NSF states) were at risk of SUDEP and non-SUDEP, while patients in the seizure-free state were assumed to be at risk of non-SUDEP only.

2.5.2 Adverse events

Patients experiencing seizures (i.e., in the NAC or NSF states) were assumed to be at risk of status epilepticus (prolonged seizure lasting 30 minutes or longer, or intermittent seizures totaling 30 min or more without regaining consciousness between seizures [2]). The probability of status epilepticus was obtained from the cannabidiol arm of a randomized controlled trial involving patients with Dravet syndrome [26] and from the STICLO France trial [24] for stiripentol, clobazam and valproate; the probability of status epilepticus was represented by Beta distributions. No additional adverse events were included in this analysis.

2.5.3 Health state utility values

A recent systematic review of the literature [14] found no health state utility values specific to children with Dravet syndrome. As such, we used utility values from another form of catastrophic pediatric drug-resistant epilepsy (Lennox-Gastaut syndrome) which had been elicited from members of the general public by use of the EQ-5D, time-trade-off, and visual analogue scale for health states related to seizure frequency [18]. Utilities derived from the EQ-5D were used in the reference case, and the impact of alternative utilities were tested in scenario analyses. We assumed correlation between utility values by use of the Cholesky decomposition matrix ($\rho = 0.75$) to ensure rank ordering of states [33] and tested the impact of correlation in scenario analyses.

Because Dravet syndrome affects the health and quality of life of family members of children with the diagnosis, we included health state utilities for parents in the model, following Canadian guidelines to consider health effects on caregivers [13]. A recent study [6] reported utility values for carers of children with Dravet syndrome, as well as for children in seizure remission, which we assumed would correspond to the NAC (uncontrolled seizures) and SF states in our model, respectively (Table 1). We assumed that the utility value for the NSF state would be higher than that for the NAC state in the same proportion as for the child utilities reported by Verdian and colleagues [18]. The influence of incorporating utilities for adult caregivers on the ICER was tested in scenario analyses.

2.5.4 Cost variables

The perspective of the reference case was that of a Canadian public health care payer. As such, direct costs (e.g., costs associated with each medication, health care resource use) were included in the reference case. The costs associated with diagnosis of Dravet syndrome were not included because we assumed that all participants had diagnosis of Dravet syndrome and that this would not differ between study arms. We assumed that medication changes would be managed as part of routine clinic visits and that no additional costs would be incurred as a result of changing therapy; similarly,

we assumed that patients would receive authorization for medical cannabis use as part of a routine clinic visit and that there would be no additional costs associated with the use of cannabinoid oil oils.

Medication costs were obtained from provincial formularies for stiripentol, clobazam, and valproate (Table 1). The price of 1:20 cannabinoid oil was obtained from the manufacturer's website (www.cannimed.ca/collections/medical-marijuana-oil). Health care resource use was based on two recent studies involving children with Dravet syndrome [6,19] and included emergency department visits, admission to hospital, general practitioner and neurologist visits, treating status epilepticus, and transfer to hospital by ambulance (Table 1).

A societal perspective was adopted in a secondary analysis to evaluate the impact of including indirect costs (i.e., parental productivity costs [absenteeism, presenteeism], physiotherapy, speech therapy, occupational therapy). Parents of children in the NAC and NSF states were assumed to incur lost time due to absenteeism or presenteeism; no productivity losses were incurred by parents of children in the seizure-free state. Estimates of hours lost per caregiver per year due to presenteeism and absenteeism were obtained from a recent survey of 24 caregivers of children with Dravet syndrome in the US [19]. We valued the lost time for the Canadian context by use of the average hourly employment wage of a Canadian worker [34], and we accounted for the friction effects with respect to productivity by applying an elasticity of labour of 0.69 [35].

All costs were valued in 2019 Canadian Dollars by use of the Bank of Canada's Inflation Calculator (www.bankofcanada.ca/rates/related/inflation-calculator/; October 2019: 1 Canadian Dollar = 0.757 US dollars)

2.6 Scenario analyses

We performed several probabilistic scenario analyses to test the impact of the model assumptions on the findings. First, we considered the impact on the ICER of adopting a societal perspective. Second, we explored the impact of alternative model inputs (cannabidiol dose, cannabinoid oil price, cohort

starting age, utility values) and structural assumptions (correlation between utility values, inclusion of parent utilities, discount rate, analysis time horizon). Scenario analyses to test structural and input assumptions were performed from the perspective of the health care system.

3. Results

3.1 Health care system perspective: Over a 13-year horizon, the use of cannabinoid oil was more costly than clobazam and valproate (\$275,434 v. \$130,165) but was less costly than stiripentol (\$292,487) (Table 2). The cost of cannabinoid oil accounted for 78% of total costs, compared with 72% for stiripentol and 3% for clobazam and valproate. Cannabinoid oil was the most effective treatment in terms of QALYs (15.12), followed by stiripentol (13.37) and clobazam and valproate (10.64). The incremental cost per QALY gained for cannabinoid oil versus clobazam and valproate was \$32,399. At a willingness-to-pay threshold of \$50,000 per QALY gained, cannabinoid oil was the optimal treatment in 76% replications (Fig 2); if the willingness-to-pay threshold is \$100,000, cannabinoid oil was optimal in 85% of replications. Because stiripentol was more expensive and produced fewer QALYs, it was dominated by cannabinoid oil.

3.2 Scenario analyses

3.2.1 Societal perspective: The results of the analysis were different when conducted from a societal perspective. Over the 13-year horizon, costs were lower with cannabinoid oil (\$386,239) than stiripentol (\$542,431) or clobazam and valproate (\$428,076). Productivity losses were considerably lower with cannabinoid oil, accounting for 14% of total costs, compared with 34% and 51% for stiripentol and clobazam and valproate respectively. Under this scenario, cannabinoid oil was dominant over both stiripentol and clobazam and valproate, producing more QALYs at lower costs (Table 2).

Table 2: Summary of results^a

			Incremental cost per QALY gained (ICER) (\$)	
Comparator	QALYs	COSTS (\$)	vs. Clobazam + Valproate	Sequential ICER
Health care system perspective (Reference case)				
Clobazam + Valproate	10.64	130,165	--	--
Cannabinoid oil	15.12	275,434	32,399	32,399
Dominated therapies				
Stiripentol	13.37	292,478	59,402	Dominated by cannabinoid oil
Societal perspective				
Cannabinoid oil	15.12	386,239	−9,331	−9,331
Dominated therapies				
Clobazam + Valproate	10.64	428,075	–	Dominated by cannabinoid oil
Stiripentol	13.37	542,431	41,851	Dominated by cannabinoid oil
Note: ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year				
ªResults are based on probabilistic analysis and are discounted at 1.5% per annum. Costs and ICERs are reported in 2019 Canadian dollars.				

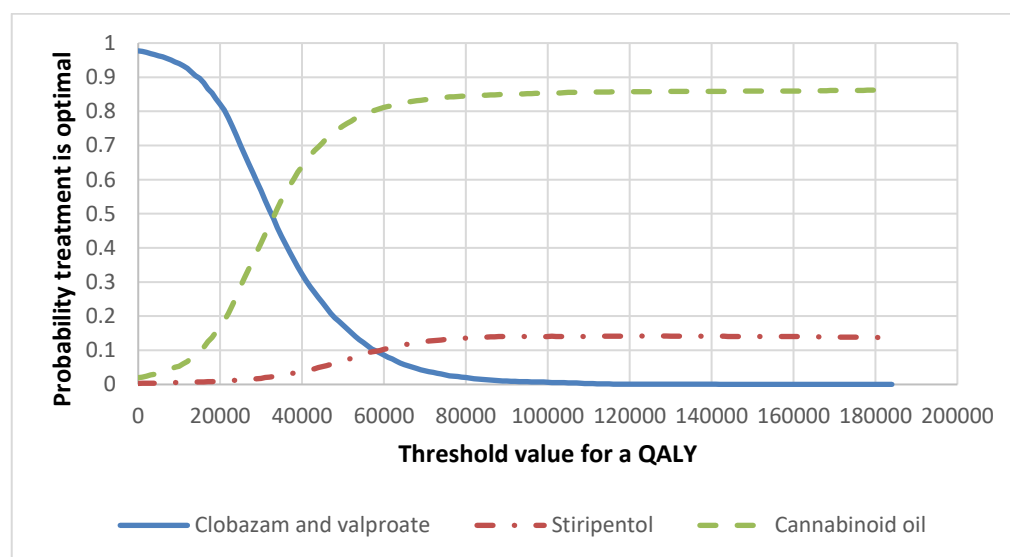


Figure 2: Cost-effectiveness acceptability curve: reference case (health care system perspective). Threshold values are given in 2019 Canadian dollars. QALY = quality-adjusted life year.

3.2.2 Model and input assumptions: Appendix 2 presents the results of the detailed scenario analyses. The interpretation of the results was insensitive to all model structural assumptions (correlation of utilities, discount rate, inclusion of parent utilities, time horizon). Results varied with most input assumptions but not to the extent that the interpretation would change. At the highest dose of cannabidiol tested (16 mg/kg/d), stiripentol was subject to extended dominance through clobazam/valproate and cannabinoid oil (ICER for stiripentol v. clobazam/valproate: \$64,518; ICER for cannabinoid oil v. clobazam/valproate: of \$50,406).

4. Discussion

Our results suggest that, from the perspective of the Canadian health care system, cannabinoid oil is a cost-effective treatment compared to clobazam and valproate for children with Dravet syndrome, if the decision maker is willing to pay at least \$32,399 for each QALY gained. Compared with stiripentol, cannabinoid oil resulted in more QALYs gained at a lower cost, suggesting that cannabinoid oil is more cost-effective than stiripentol at all willingness-to-pay thresholds. From a societal perspective, cannabinoid oil produced greater health gains at lower costs compared with either treatment, owing primarily to lower parental productivity losses with cannabidiol use. These findings were robust to all model assumptions, although the limited availability of clinical data for the effectiveness of cannabinoid oil should be considered in the interpretation of the findings.

These findings need to be placed in context of other studies; however, few treatments for pediatric drug-resistant epilepsy have been subject to economic evaluation [14,36]. In a recent systematic review [14], we identified only one study that had assessed the cost-effectiveness of treatments for Dravet syndrome [16], finding that stiripentol was not cost-effective from the perspective of the Canadian health care system (ICER \$151,310). Importantly, in the context of pediatric drug-resistant epilepsy, the cost-effectiveness has not been evaluated for any of the cannabis-based products currently available in Canada [14], despite growing interest among parents and health care providers as well as recent Canadian recommendations supporting its use in Dravet and Lennox-Gastaut

syndrome [37]. In a recent submission to NICE, the manufacturer of Epidiolex (a purified form of cannabidiol) suggested an ICER of £36,046 per QALY gained with Epidiolex compared with conventional management over a 15-year horizon; however, several limitations were noted by the review panel in terms of methodology and data assumptions [38]. It is not clear if the effectiveness, and hence the cost-effectiveness, of Epidiolex is generalizable to the cannabis-based products available in Canada owing to differences in formulations. Canadian cannabis oils, in contrast to Epidiolex, contain small amounts of THC (e.g., 20:1 ratio of cannabidiol to THC), and some hypothesize that the presence of other cannabinoids and terpenes may have a synergistic effect (“entourage effect”) [39].

Our findings were sensitive to the analysis perspective: from the health care system perspective, cannabinoid oil was dominant over stiripentol and was cost-effective compared with clobazam/valproate at a willingness-to-pay of at least \$32,399. However, when considered from the societal perspective, cannabinoid oil was dominant over both stiripentol and clobazam/valproate treatment, suggesting that cannabinoid oil would be the optimal choice regardless of the willingness-to-pay threshold, a difference which was largely owing to lower parental productivity losses with cannabinoid oil compared to the other treatments. Choice of perspective has been similarly observed to change the interpretation of cost-effectiveness in other studies [40] and the impact of including societal costs (e.g., productivity) should be carefully considered, as it assumes a willingness to accept lower population health gains in order to maximize productivity.

4.1 Strengths and limitations

We followed Canadian guidelines for economic evaluation [13] and the CHEERS reporting guideline [15]. Further, we followed recent recommendations for model-based economic evaluations of treatments for drug-resistant epilepsy in children [14]. We addressed uncertainty in the model through probabilistic analysis, and we adopted the perspective of a public health care payer in the

reference case with an assumed objective of maximizing population health, while evaluating the impact of adopting a more broad societal perspective in sensitivity analyses.

Several limitations should be noted. First, Dravet syndrome is a rare disease and, as such, limited data were available for several model inputs, including clinical effectiveness, utility values, and health care resource use. Importantly, few cannabis-based products available in Canada have been subject to evaluation in clinical trials, and limited effectiveness data are available. We incorporated individual patient data for 7 children with Dravet and LGS syndrome who received cannabinoid oil for 7 months [22]; as additional clinical data become available, uncertainty about the clinical effectiveness may be reduced. At the time of this study, utility values for Dravet syndrome were not available, nor were estimates of health care resource use for Canadian children with Dravet syndrome. As such, we incorporated utilities for another severe form of pediatric epilepsy, Lennox-Gastaut Syndrome. Although these syndromes share similarities, quality of life may be lower among children with Dravet syndrome compared with other forms of drug-resistant epilepsy [6], and it is unknown whether preferences are consistent across syndromes. However, in scenario analyses, we found that the results were insensitive to utility values across a range of inputs. Similarly, we assumed that resource use of patients in Canada would be similar to that in the US [19] and Germany [6]. Future analyses would be strengthened by incorporating data for Canadian Dravet patients.

Second, we did not include adverse events beyond status epilepticus in our model. In clinical trials, the side effects were generally mild and resolved with the reduction of cannabidiol, clobazam or valproate dose [17,22]. Reducing the dose of clobazam and/or valproate would not be expected to alter our findings given the low cost of both drugs, and the findings were robust to changes in cannabidiol dose.

Third, we assumed that authorization for medical cannabis use would be obtained as part of a routine clinic visit. In practice, some children with drug-resistant epilepsy may receive authorization from a

cannabis clinic or from another health care professional, which would add additional costs to cannabinoid treatment.

Finally, we assumed that children who discontinued stiripentol or cannabinoid oil because of a lack of seizure control would remain on clobazam and valproate alone. However, it is likely that such patients would initiate an alternative treatment in an attempt to control their seizures; this may include a trial of other antiepileptic drugs.

4.2 Conclusion

In this cost-utility analysis, we found that cannabinoid oil is a cost-effective treatment for Dravet syndrome at a willingness-to-pay threshold of at least \$32,399, resulting in a gain of 4.5 QALYs over a 13-year period compared over clobazam and valproate. The use of cannabinoid oil for treatment of drug-resistant epilepsy is increasing, and these findings will be of use to decision makers considering whether to reimburse such products on public formularies. Because cannabinoid oil is a more cost-effective choice than stiripentol, which is currently listed on several Canadian provincial formularies, the opportunity costs of continuing to fund stiripentol but not cannabinoid oil should be considered.

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Appendix 1: CHEERS Checklist

Section/item	Item No	Recommendation	Reported on page no.
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	9
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	5, 11
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	6
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	7
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	9
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	10-11

based outcomes			
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	11
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Table 1, 12
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	5, Fig. 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	5-6
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	5-6
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2
Characterising	20a	<i>Single study-based economic evaluation:</i> Describe the effects	NA

uncertainty		of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Table 2, appendix 2
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	15-17
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	1
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	18

Appendix 2: Results of scenario analyses

Scenario	Result
Base case	At a willingness to pay threshold (λ) < \$32,399: Clobazam/valproate is optimal At λ > \$32,399: Cannabidiol is optimal Stiripentol is dominated by cannabidiol (produces less QALYs at a higher cost)
Societal perspective	Clobazam/valproate and stiripentol are dominated by cannabidiol
Cannabidiol dose reduced to 5 mg/kg/d	At λ < \$7,328: Clobazam/valproate is optimal At λ > \$7,328: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Cannabidiol dose reduced to 8 mg/kg/d	At λ < \$17,856: Clobazam/valproate is optimal At λ > \$17,856: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Cannabidiol dose increased to 16 mg/kg/d	Stiripentol is subject to extended dominance through clobazam/valproate and cannabidiol
Cohort starting at age 10 years	At λ < \$52,909: Clobazam/valproate is optimal At λ > \$52,909: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Cohort starting at age 15 years	At λ < \$67,010: Clobazam/valproate is optimal At λ > \$67,010: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Drug costs of cannabidiol reduced by 10%	At λ < \$27,722: Clobazam/valproate is optimal At λ > \$27,722: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Drug costs of cannabidiol reduced by 20%	At λ < \$23,842: Clobazam/valproate is optimal At λ > \$23,842: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Drug costs of cannabidiol reduced by 40%	At λ < \$14,904: Clobazam/valproate is optimal At λ > \$14,904: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Drug costs of cannabidiol reduced by 60%	At λ < \$6,566: Clobazam/valproate is optimal At λ > \$6,566: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Drug costs of cannabidiol reduced by 80%	CV and stiripentol are both dominated by cannabidiol
Utility values are not correlated	At λ < \$31,685: Clobazam/valproate is optimal At λ > \$31,685: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Including only child utilities	At λ < \$37,860: Clobazam/valproate is optimal At λ > \$37,860: Cannabidiol is optimal Stiripentol is dominated by cannabidiol

0% discount rate	At $\lambda < \$33,158$: Clobazam/valproate is optimal At $\lambda > \$33,158$: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
3% discount rate	At $\lambda < \$31,231$: Clobazam/valproate is optimal At $\lambda > \$31,231$: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
1-year time horizon	At $\lambda < \$15,389$: Clobazam/valproate is optimal At $\lambda > \$15,389$: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
20-year time horizon	At $\lambda < \$43,019$: Clobazam/valproate is optimal At $\lambda > \$43,019$: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Time Trade Off utilities	At $\lambda < \$58,416$: Clobazam/valproate is optimal At $\lambda > \$58,416$: Cannabidiol is optimal Stiripentol is dominated by cannabidiol
Visual Analogue Scale utilities	At $\lambda < \$38,082$: Clobazam/valproate is optimal At $\lambda > \$38,082$: Cannabidiol is optimal Stiripentol is dominated by cannabidiol

Chapter 5:

Stakeholder perspectives on the use of medical cannabis for pediatric drug-resistant epilepsy

CHAPTER OVERVIEW

Chapter 5 addresses the third research question: *What are the perspectives of neurologists and parents about the use of medical cannabis for pediatric drug-resistant epilepsy?*

As of 2015, there was a large divide between members of the general public and neurologists with respect to whether the evidence was sufficient to support the use of medical cannabis in the treatment of drug-resistant epilepsy. Although the evidence base has evolved since that time, little is known about the current perspectives of neurologists or parents of children with drug-resistant epilepsy about the use of medical cannabis in this context. As such, two interview-based qualitative studies were undertaken to explore the perspectives and experiences of these key stakeholders.

Chapter 5 contains two manuscripts (**Section 5.1–5.2**), both of which have been submitted for publication. Each manuscript is briefly described below, and a more fulsome description is found on the first page of each section.

CHAPTER CONTENTS

Section 5.1 presents the findings of a qualitative study that explored the perspectives and experiences of neurologists in Canada with the use of medical cannabis as a treatment for pediatric drug-resistant epilepsy.

Section 5.2 presents the findings of a qualitative study that explored the perspectives and experiences of parents whose children with drug-resistant epilepsy have used medical cannabis, including the barriers experienced by parents in accessing medical cannabis via the current Canadian medical cannabis system.

Section 5.1

Neurologists' perspectives on medical cannabis for pediatric drug-resistant epilepsy in Canada: A qualitative interview study

SECTION OVERVIEW

This section presents a manuscript describing an interview-based qualitative study of the perspectives and experiences of neurologists in Canada about the use of medical cannabis in the treatment of pediatric drug-resistant epilepsy. In this study, 12 neurologists who provide care to children with drug-resistant epilepsy were interviewed about their views and experiences with medical cannabis. Based on analysis of the transcribed data, six themes were generated from the content of the interviews: learning about medical cannabis; perceptions about medical cannabis; discussing medical cannabis with parents; experiences with medical cannabis authorization; barriers to authorizing medical cannabis; and the impact of medical cannabis on clinical care.

MANUSCRIPT STATUS

This manuscript has been submitted for publication:

Elliott J, DeJean D, Potter BK, Coyle C, Clifford T, McCoy B, Wells GA. Neurologists' perspectives on medical cannabis for pediatric drug-resistant epilepsy in Canada: A qualitative interview study. *Seizure* (Submitted December 3, 2019; Revised version submitted January 26).

Supporting material

Appendix 1: Interview guide

Standards for Reporting Qualitative Research (SRQR) checklist

Author roles and contributions

All authors contributed to the design of the study and the development of the interview guide. JE carried out all data collection; she analyzed the data (along with DD) and led the writing of the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version submitted for publication.

RELATED THESIS APPENDICES

Appendix C: Abstracts submitted for conference presentation. Findings from this study have been submitted to the 2020 CADTH Symposium (Toronto, Ontario). Submitted: September 2019.

Elliott J, DeJean D, Potter B, Coyle D, Clifford T, McCoy B, Wells GA. Decision-making in the face of uncertainty: Experiences of neurologists and parents with medical cannabis for children with drug-resistant epilepsy.

Appendix F: Ethics approval. Approval for this study was obtained from University of Ottawa's Office of Research Ethics and Integrity (November 23, 2018). Ethics file number H-09-18-1083.

Neurologists' perspectives on medical cannabis for pediatric drug-resistant epilepsy in Canada: A qualitative interview study

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Abstract

Purpose: To understand the experiences with and perspectives of neurologists about the use of medical cannabis in the treatment of pediatric drug-resistant epilepsy.

Methods: In this qualitative study, we interviewed neurologists who provide care to children with drug-resistant epilepsy in Canada. Through semi-structured telephone interviews, we sought participants' views about and experiences with medical cannabis for the treatment of drug-resistant epilepsy in children. Here we present a thematic summary of the interviews.

Results: The 12 interviewed neurologists generally perceived medical cannabis as a viable treatment option for children with drug-resistant epilepsy; however, participants identified important gaps in the evidence and implications for their practices. Six themes were generated from the content of the interviews: learning about medical cannabis; perceptions about medical cannabis; discussing medical cannabis with parents; experiences with medical cannabis authorization; barriers to authorizing medical cannabis; and the impact of medical cannabis on clinical care. Of note, while some neurologists took on all aspects of the children's care, including medical cannabis, others referred interested families to non-neurology health care professionals.

Conclusion: Our findings highlight the diverse opinions and experiences of neurologists in Canada with medical cannabis for the treatment of drug-resistant epilepsy in children, including with the authorization process and caring for children using medical cannabis. Additional education about medical cannabis may be warranted, in order to better prepare neurologists to have informed and open conversations with parents about this treatment option and to provide care for children using medical cannabis.

Keywords: pediatric drug-resistant epilepsy; medical cannabis; cannabidiol; qualitative; neurologist perspectives

Introduction

Cannabis as a treatment for epilepsy dates to the 1800s in the published literature,[1] with increasing interest over the last decade in its use as a treatment for pediatric drug-resistant epilepsy, driven partly by media reports of children whose seizures have responded to cannabis.[2,3,4] Until recently, there was little clinical evidence to support its use in this population,[5] and there were wide differences between the beliefs of health care professionals and the public with respect to effectiveness and safety.[6] A 2015 survey by *Epilepsia* reported a “wide diversity of opinion on the use of medical marijuana in treating people with epilepsy” depending on whether the respondent was a neurologist or a member of the public. At that time, more than two-thirds of neurologists felt that data were insufficient to support its use, although 48% would recommend it to patients whose “severe, catastrophic epilepsy” had not responded to approved therapy.[6] The clinical landscape surrounding medical cannabis has undergone important transformations since 2015. At the time of the *Epilepsia* survey, there had been no randomized controlled trials (RCTs) involving children with epilepsy.[5] As of May 2019, the evidence-base had grown to include 4 RCTs and 31 non-randomized studies involving children,[7] with the findings largely supporting a positive effect for purified cannabidiol (CBD; Epidiolex) in reducing seizures associated with drug-resistant epilepsy. Epidiolex is not available in Canada at this time, despite recently receiving approval by the US Food and Drug Administration [8] and the European Medicines Agency.[9] In Canada, patients with authorization from a health care provider have access to cannabis products including fresh or dried cannabis or cannabis oil (i.e., oil containing cannabinoids extracted from cannabis [CBD-THC oil]).[10] As of December 31, 2019, Health Canada had issued licenses to 165 cannabis producers to sell cannabis products to authorized medical patients, including 61 authorized to sell CBD-THC oils.[11] Notably, these products are not subject to pre-market safety and efficacy review by Health Canada and are not issued a notice of compliance or a drug identification number. While two small cohort studies have recently evaluated the efficacy of two CBD-THC oils, most have not been

evaluated in clinical studies, and it is unknown how Canadian neurologists perceive medical cannabis as a treatment for children with drug-resistant epilepsy.

Objective and significance: Although the evidence-base has changed over the last 5 years, little is known about the current perspectives of neurologists regarding the use of cannabis-based products for the treatment of pediatric epilepsy. In this qualitative interview-based study, we examined the perspectives of neurologists in Canada who provide care to children with drug-resistant epilepsy about the use of medical cannabis.

Methods

This qualitative study used an interpretive description approach [12] and was undertaken as part of a health technology assessment (HTA) of the use of cannabis as a treatment for pediatric drug-resistant epilepsy, and the findings are reported following SRQR checklist.[13]

Interpretive description is an applied qualitative methodology intended to provide rich description of a clinical phenomenon and is commonly used to address questions that are important within the context of clinical health care. By combining aspects of traditional qualitative methodologies (e.g., grounded theory, phenomenology), interpretive description provides a pragmatic way to explore clinical phenomena and to situate the findings within existing research and clinical knowledge.[14]

Interpretive description goes beyond simple description of a phenomenon, by considering the clinical implications of the findings with the aim of creating knowledge that can be applied in clinical practice by providing a “conceptual/thematic description” of the phenomenon.[12,15]

In this study, interpretive description was used to explore the perspectives about medical cannabis of neurologists in Canada whose practices include children with drug-resistant epilepsy, in order to provide insight into the use of medical cannabis in this population. We also sought to better understand the impact of medical cannabis on the health care delivery process and to describe experiences with cannabis authorization. Because medical cannabis regulations vary by country,[17] we focused on neurologists who practice in Canada. We adopted the role of learners and were not

positioned either in favour or opposition of cannabis as a treatment for epilepsy. The research team included qualitative research (D.D., B.K.P) and clinicians who provide care for children with drug-resistant epilepsy (B.M.). We used the reflexive practices of memoing and frequent dialogue between authors to consider ways in which our perspectives were influenced by professional and personal backgrounds, experiences, and assumptions.

This study received ethics approval from the University of Ottawa Research Ethics Board.

Sampling and recruitment

We used purposive and snowball sampling to recruit neurologists practicing in Canada who provide care to children with drug-resistant epilepsy; participants were not required to have previously authorized cannabis use. Participants were identified from an online list of neurologists in Canada (<https://my.aesnet.org/FindaDoctor>) and from among personal contacts of the researchers, and participants were encouraged to tell their colleagues about the study. Practice details, including practice location and years in practice, were verified during participant interviews. We sought to maximize variation in the recruitment process by approaching neurologists from across Canada; we also sought variation in practice duration and gender. All interviews were conducted in English. Recruitment and data collection were concurrent with analysis. Saturation (no new themes, sub-themes, or codes) was reached after the 11th interview; however, we interviewed all 12 neurologists who had expressed an interest in participating, and the analysis considers data from all 12 interviews.

Data collection

All interviews were conducted by J.E. using a semi-structured interview guide (Appendix 1). Telephone interviews were selected for feasibility and to reduce social desirability bias that might result from group interaction. The interview guide was developed by the research team and was informed by a review of the published literature and a framework for undertaking health technology assessments.[18] After providing consent and answering demographic questions, participants were asked open-ended questions intended to capture their experiences and perspectives about medical

cannabis for drug-resistant epilepsy. Interviews were conducted between January and September 2019 and ranged from 20–60 minutes. All interviews were audio-recorded, and field notes taken.

Data analysis

Data collection and analysis were concurrent. All interviews were transcribed verbatim and verified against the original recording, and transcripts were uploaded to NVivo data management software (v. 12 Pro, QSR International). Data analysis was guided by thematic analysis, including repeated reading and familiarization with the transcripts, complete coding across the dataset, and organization of thematically related codes. Codes were generated from the content of the interviews, and the coding structure was recorded in NVivo. All interviews were coded by J.E, and six interviews were independently coded by D.D. Throughout the analysis process, JE and DD discussed codes and coding structures. Findings were viewed through an HTA approach, and attention was paid to the impact of the technology (medical cannabis) on the participants (neurologists) and their interactions with end users (children with drug-resistant epilepsy and their families). In the following section, some quantifying language is used to provide a sense of consistency within themes. For example, the term “most” indicates that a theme was present in at least 10 (of 12) participant accounts, while the term “many” indicates that at least 6 accounts included the theme. The terms “some” or “several” indicate that less than half of participant accounts included a theme; however, the absence of a theme in a participant account does not indicate that a belief was not held, only that it was not raised during the interview.

Results

Twelve neurologists participated in this study, including 7 (58%) who had previously authorized use of medical cannabis for children with drug-resistant epilepsy (Table 1). Most participants were male (75%) and practiced in an academic or teaching hospital (83%). The duration of independent practice ranged from 1–27 years, with most in practice for at least 10 years (58%).

Table 1: Demographic characteristics of study participants

Characteristic	Number (%)
Male	9 (75)
Has previously authorized cannabis use	7 (58)
No. years in practice	
0–9	5 (42)
10–19	6 (50)
≥20	1 (8)
Practice location	
British Columbia	2 (17)
Alberta	1 (8)
Saskatchewan	1 (8)
Manitoba	1 (8)
Ontario	5 (42)
Quebec	1 (8)
Atlantic Canada*	1 (8)
Practice type	
Academic/teaching hospital	10 (83)
Community-based	2 (17)
*Atlantic provinces grouped because of a small number of neurologists in some provinces.	

Thematic summary

Six thematically related categories emerged from our analysis of the data: (1) learning about medical cannabis, (2) perceptions about medical cannabis, (3) discussing medical cannabis with parents, (4) experiences with medical cannabis authorization, (5) barriers to medical cannabis authorization, and (6) the impact of medical cannabis on clinical care. Here we elaborate on those themes, with selected quotations in support of the themes presented in Table 2.

1. Learning about medical cannabis

The medical cannabis field was perceived by participants to be rapidly evolving, and participants expressed a desire to learn more about cannabis, including about cannabis-based products and cannabinoids, noting that increased knowledge would allow them to better counsel patients (Table 2, quotation 1). No participants had received formal training about medical cannabis, and several expressed the need for its addition to medical school curricula. Participants reported learning about medical cannabis by attending rounds, reading journal articles, viewing web seminars, and through discussions with colleagues (quotation 2). Several participants described a desire for guidelines from Canadian professional associations, stating that it would facilitate their practice by allowing them to better counsel patients.

Table 2: Themes and illustrative quotations

Theme	Subtheme	Quote no.	Participant identifier	Illustrative quotations
1. Learning about medical cannabis	Importance of education	1	Neurol 4	“The more that we can understand this, the better, the more avenues I have to counsel my patients. It is very frustrating when [patients] come with something and you say, ‘oh, you know what, I really have no clue.’”
	Sources of knowledge	2	Neurol 4	“Well, I have attended rounds, we've had some people, like [local physician] who prescribes cannabinoids, come a couple of times and give rounds. Then seminars on the web and things like that. Nothing very formal. I haven't attended a fellowship or anything like that, it's been more like rounds and local seminars.”
2. Perceptions about medical cannabis	State of the evidence	3	Neurol 8	“I don't feel that it is being yet ready to be a standard care based on the available data... We are waiting to have some guidance. For any medication, not only for CBD oil, other medications, normally physicians who want to prescribe a medication should have approval from Health Canada. Health Canada will provide safety guidance, dosage, and monitoring.”
		4	Neurol 3	“I think it's kind of a fad right now, and everybody is really interested in it, and although a subset have really benefited, and those are the ones we tend to read about on the parent sites, I would say as a group, I'm not convinced there's really a good sustained effect, and I would predict that within a few years it's going to become a lot less popular.”
		5	Neurol 1	“Most of the studies included kids who had genetic epilepsies or specific syndrome diagnoses, but to my mind, the extrapolation of that is not a challenge because that is often what we encounter with research data, and so extrapolating it to clinical data, in terms of what we would use, what patient population we would consider use in, it would just be reasonable to try in all drug-resistant epilepsy.”
	Line of treatment	6	Neurol 7	“It's something that I'm more likely to consider as opposed to a third line or a fourth line, maybe fifth or sixth, so certainly not at the end, but certainly lower down than I would other anti-epileptic therapies.”
	Gaps in the evidence	7	Neurol 1	“The cannabinoids as a whole are a very complicated substances with hundreds of active chemicals, and we've only begun to scratch the surface in terms of what medical properties are in it. Based on what we know, it looks like cannabidiol can be effective in treating seizures, and there is potential for tiny amounts of cannabinoids such as THC to be effective, but there's a lot we don't know about other components that can be in a variety of different products.”
		8	Neurol 6	“I'm using it in a population where they have intractable epilepsy and therefore the chances of another product making a difference for them is low, about 10-15%, so it doesn't surprise me that it's not a startling success... But it's worth a try.”
	Cost and reimbursement	9	Neurol 4	“Before it wasn't a surprise, it was almost like an assumption. After legalization, some families are like ‘Oh, is that right, oh, okay, I see. No, I was hoping that, now with the legalization that we would have some kind of funding, or that you know, a percentage of it would be funded’ or ‘Oh, but what about the private

				insurance plans, I'm sure they would. Oh! What do you mean that they don't?"
		10	Neurol 5	"I think it needs to have some government or extended healthcare mechanism to fund families where it clearly is working, to have it covered. Now I think it would be reasonable that families maybe should have to pay out-of-pocket to keep it simple to see if it works. But if it works then I think that it saves the healthcare system a lot of money because kids aren't in status, aren't having hospital visits, aren't needing to be on other medications, and so it saves the system and so there should be coverage for like any other drug, if it's efficacious for them."
3. Discussing medical cannabis with parents	Determining parental expectations	11	Neurol 5	"Typically the goal would be looking at seizure control, but certainly families report that there's some more qualitative improvement, or subjective improvement in the level of encephalopathy or alertness that the child has, so those might be secondary measures of the efficacy. And those might be reasons why families maybe don't see a benefit from the seizure point-of-view but overall they feel the child is doing better and so that would be reason enough, if they wanted to, to continue on it with the hope that maybe over time or a slightly higher dose if they're tolerating it, it might control seizures better."
		12	Neurol 9	"This medication is relatively new and counselling is very important for side effects and benefits. 'Cause often parents have false expectations for the medication. They think CBD oil can cure their epilepsy."
		13	Neurol 12	"All the data that they have comes from families testifying how it was miraculous for their kids. So they basically have a one-sided view of that. They don't have the other side of the coin, either the families that it did nothing for their kids or that had side effects. So it takes a lot of work to re-frame that and tell the parents that 'Yes, technically it's a natural product, but can give serious trouble to your kid' and they tend to be very disappointed when we have that approach, but it goes a lot better when I tell them that it's one of the tools that I have at my disposable, but just like everything else it is not miraculous."
		14	Neurol 11	"Think if something did happen, if there was a significant adverse event, I think by virtue of the stigmatization of cannabis and the way that it's come to market and being available for epilepsy, that if ever that was to happen, and I was to be somebody who was put under the microscope to see what was going on, I feel like there would be an additional level of scrutiny looking at this. I recognize that and I've taken on that risk for the patients ... I want to make sure that things are just exceptionally well documented, exceptionally covered, that patients really fully one-hundred percent understand."
	Importance of open communication	15	Neurol 10	"From what I hear from families, the times they are doing that is because when they have tried to talk to their neurologist about treatments that are less evidence-based, they've received such negative response, their perception, the families perception, is that they've been criticized or judged, that then those families proceed without discussing it with their neurologist."
4. Experiences with medical cannabis	Authorization process	16	Neurol 6	"Authorizing, well I just write a prescription. And that's it. So, there's a form the company has ... I fill that in. It asks who I am and my license number and which province I'm in. Asks for the patient's name and the medical diagnosis, and then I give the dosing and the product that I'm prescribing... If I'm prescribing to a

authorization				routine pharmacy, I just use a prescription, I just write the drug and the dosing for the individual and that's that. This just requires a little bit more information, not much more but it does.”
		17	Neurol 1	“It certainly leaves one a bit unsettled about how little you actually have to enter onto the forms, and I think that’s something that should be re-evaluated because it's very important to give the specific instructions and the right products. If you look at any of the websites you’ll see that they can have six different types of oil, one could be just pure THC, and all the labels can look similar, they typically all are numbered in terms of the ratios, and it's very confusing. If you actually look at the website, they all seem to be very similar, all the different oils. And so I think it behooves us to state exactly what we want families to get, but it not necessary, which is a little unsettling.”
	Choosing between licensed producers	18	Neurol 6	“Well, the simple answer...is it's free through [company]. Nobody else has offered it to us free. We were using another supplier, in the past, and there were no problems with it, it's just that they all offer the same product 20:1 CBD to THC, so why should I not use the one that's free?”
		19	Neurol 5	“It makes me a bit uncomfortable, because then I become a salesman, right? For the company that's the nature of it. So, some companies ... offer a very, very significant, like 90% discount for pediatric patients... I point families in that direction but I feel bad because I don't know if that's, you know, ‘get them hooked on our product and then they’ll only buy from us,’ and then they’ll jack up the prices to the regular pricing, I don't know if they'll do that, but given the extreme discount they're doing, I think it seems to be on their, sort of ethical approach to supplying it to kids who need it.”
	Problems with authorization	20	Neurol 1	“The only experience that I've had with families that have had problems with supply have been where companies simply haven't had the products. Some smaller companies have run out of oil for periods of time, and those kind of challenges have arisen for families... Most people haven't had any supply issues if they go with one of the bigger companies, where the issues have arisen is where people have gone for artisanal preparations from smaller companies.”
5. Barriers to medical cannabis authorization	Out of scope	21	Neurol 3	“I don't feel that the smaller proportion of general child neurology patients that I follow, specifically epilepsy patients, there's not sufficient volume for me to prescribe for them. And it would just be a regulatory hassle that I don't want to have to look into. It's a lot easier for me to refer them to someone else who has more expertise in it... I have no objections to CBD oil, I think it's a very reasonable medication to try. But, I also don't put in vagal nerve stimulators, and I don't do brain surgery, and I don't read EEGs, so there's a lot of stuff that is just not part of my practice... becoming more involved in CBD oil is not really something that's of interest.”
	Restrictive policies	22	Neurol 4	“We had a head of division before that was openly opposed or critical about it. So it would have seemed at that point to be a problem. I think it would have been like doing something against the position of the division head.”
		23	Neurol 4	“It was felt that if you, by yourself instead of sharing it in a clinic with another group of colleagues, became

				the only person that would be prescribing it, that you suddenly would be getting the most complex cases. In every way, not just medically complex but the most demanding families or the families that would be complaining if they don't get their way.”
	Referral to other care providers	24	Neurol 3	“What I say to them is, ‘You know if you're interested in CBD oil, then there is a physician in [city] who prescribes it. There are other physicians elsewhere that might prescribe it. You know, there's multiple ways you could, you could access it. I myself don't prescribe it. So if you're interested, I could put a referral through.’”
		25	Neurol 2	“I leave it to the parent to go find one. Unfortunately we're not really allowed to provide even information on the access, so we can say well, you can search Google or something like that, but not ‘Yeah there is this clinic here or there’.”
		26	Neurol 11	“Give me another example in medicine where we do this. We don't do this in other types of medicine, but people are so scared to learn about this stuff and so worried about it, they pass the buck and it's ridiculous. It's not great for patients, it's not safe for them. And then what happens is that creates more unsafe situations than you're dealing with in the first place... I think the onus is on the neurologist if you're seeing neurology patients, you have to do the right thing by them and that is finding the appropriate referral. We do it for any other condition, but for some reason it's ok to refer complex epilepsy patients to a cannabis clinic where an ER doctor with no epilepsy training whatsoever is prescribing cannabis for people. It's crazy, it's wrong.”
		27	Neurol 12	“I do not feel that somebody else should be handling part of the epilepsy care... just like I would not entrust somebody else to manage any other of my medications. Cannabis is one out of a few treatments that the patients are going to receive, and it's going to interact with everyone else. It cannot be managed independently, it has to be managed in concurrence with everything else.”
6. Impact of medical cannabis on clinical care	NA	28	Neurol 4	“When it comes to response to seizures that are not being controlled, if they are still dealing with cannabis, which takes a while to optimize, eh, and they call me and they say, ‘Well, Johnny is still having a lot of seizures, I feel like I need to do something.’ The conversation often will go back to cannabis. So we will say, ‘Well, we could do this, we could do that...Do you feel there is still room to optimize the cannabis oil?’ ... If the answer is yes then they have to touch base again with their cannabis clinic and, as a result of that, there will be a little bit less visits, as they would normally would have, if they were taking only anticonvulsant medication.”
		29	Neurol 10	“And actually, we never receive letters from those clinics. Like if I send a kid to the endocrinologist, if an endocrinologist sees my kid with epilepsy, even if I'm not the referrer, they often send a letter to me that says ‘Tommy was seen and we're starting him on hormone treatment,’ but we never get communication from those clinics and I think that's actually a problem. You can't rely on families, unfortunately, to know what's happening because they sometimes aren't well informed.”

2. Perceptions about medical cannabis

State of the evidence: Opinions varied as to whether there is sufficient evidence to authorize medical cannabis for children with drug-resistant epilepsy, although most neurologists interviewed as part of this study felt that the data are sufficient to support a trial of cannabis. Others expressed concerns about insufficient evidence and lack of guidance (quotation 3). Several neurologists expressed a belief that the benefits of medical cannabis may be oversold (e.g., by the mass media) and that parents' expectations may not be consistent with their clinical experience (quotation 4). One neurologist remarked that "*it's not the magic pill that everyone kind of hopes it could be*" (Neurologist 7).

Some neurologists drew distinctions between the state of the evidence pertaining to different epilepsy syndromes and types of cannabis products. For example, Neurologist 2 stated that "*I think there is some evidence, not enough, and only for Dravet and Lennox-Gastaut syndrome, period.*" Others were more comfortable extrapolating evidence across epilepsy syndromes (quotation 5). Similarly, several participants described inferring effectiveness and adverse events associated with the cannabis oils available in Canada (which contain both CBD and THC in varying ratios [CBD:THC cannabis oils]) from studies involving Epidiolex, a purified CBD product not available in Canada. However, one neurologist cautioned that "*they're not like an apple and apple comparison*" because of the potential entourage effect of additional components (e.g., terpenes, other cannabinoids) in the CBD:THC cannabis oils that are not found in purified CBD (Neurologist 11).

Line of treatment: Participants noted that parents frequently sought cannabis as a first-line treatment; however, it was generally not viewed as a first-line treatment, instead being considered after other treatment options have been explored (quotation 6). Participants described considering cannabis after a failure of least two antiepileptic drugs, although one described initiating discussions about cannabis after one failed drug. One community-based neurologist expressed uncertainty about when in the

treatment course to consider cannabis, wondering if he was waiting longer than his hospital-based colleagues.

Gaps in the evidence: Participants noted areas where additional research is needed, in particular about components of cannabis beyond CBD and long-term effects of cannabis products. Several participants noted that cannabis is a complex substance and that little is known about its medical properties (quotation 7). The lack of evidence about the long-term effects on children was commonly described, and one participant noted that “...*parents have to be willing to take that risk on their own because it's not a long-term tested product*” (Neurologist 5).

Several participants noted that there is a lack of data allowing them to predict which children will benefit from treatment with medical cannabis and some noted that it was “*hit or miss*” which patients would benefit in terms of seizure control. Others were not surprised by the low success rate with medical cannabis given that these children have drug-resistant epilepsy, yet that it was “*worth a try*” (quotation 8).

Costs and reimbursement: The cost of cannabis-based products was described as being an important consideration. Most participants reported discussing costs with families, and some described working with parents to calculate costs based on the projected dose. Several participants noted that the cost of treatment limited their ability to reach a therapeutic dose because parents are typically paying out-of-pocket for the cannabis products. Neurologist 10 summarized the issue as follows: “*Families sometimes don't advance the treatment to a therapeutic dose because the cost is prohibitive and in that case, I think that's all a kind of a waste. It's like going through the trouble of spending your money to take an aspirin a day when really you need eight aspirins a day. Wasting your money, one aspirin a day won't do anything but you'll never get up to eight because you can't afford it.*” Because of this issue, some participants described choosing between licensed producers based on the availability of compassionate discounts for pediatric patients.

The lack of insurance coverage or reimbursement for cannabis-based products was raised by several participants. One neurologist reported that parents were sometimes surprised to learn that cannabis-based products are not typically covered by insurance, especially since the legalization of recreational cannabis in Canada in October 2018 (quotation 9). This was echoed by some neurologists who stated a belief that cannabis-based products should be covered by insurance programs, citing benefits to the health care system (quotation 10).

3. Discussing medical cannabis with parents

Determining expectations: Several neurologists noted that families often value benefits such as the child appearing more alert and that might be sufficient to continue treatment in the absence of seizure control (quotation 11); in contrast, one neurologist described looking for a “*clinically meaningful reduction in seizures*” to determine effectiveness, largely because of the potential for interactions with other medications and the out-of-pocket costs. Participants thus felt that it was important to determine the parents’ expectations prior to initiating cannabis. Further to this, several participants felt that parents may hold overly optimistic beliefs about medical cannabis and described the importance of education in combating “*false expectations*” (quotation 12).

Educating parents: Neurologists described varying levels of knowledge among parents about medical cannabis. Generally, participants felt that parents were more informed about medical cannabis than they are about traditional antiepileptic drugs, although many had potentially false expectations (quotation 12,13). Other neurologists noted that parents were coming to them having heard about cannabis from, for example, a friend or relative and were looking to the neurologist to provide answers to their questions. Educating parents about medical cannabis was felt to empower parents to make informed treatment decisions, and Neurologist 11 described how he wanted parents to “*fully one-hundred percent understand*” the treatment choices that they are making, in part as protection for himself should a serious adverse event occur (quotation 14).

Importance of open communication: Several participants described the importance of open communication with families about all treatments that the child may be taking. However, some voiced concern that some parents may be administering medical cannabis to their children without disclosing its use. Participants speculated that this situation may arise because parents have previously been met with criticism or judgment for wanting to pursue cannabis as a treatment (quotation 15) and that this is indicative of a parent–neurologist “*relationship problem*.” Participants’ concerns about the non-disclosure of cannabis use included not knowing if an observed effect is owing to prescribed treatments or to non-disclosed cannabis use; not knowing if parents are following other care recommendations; parents may not be receiving guidance on dosing; and the potential for the family to be obtaining cannabis from an unlicensed source, with no guarantee of content or quality.

4. Experiences with medical cannabis authorization

Authorization process: Several neurologists described the authorization of medical cannabis as being similar to prescribing traditional pharmacologic drugs. For example, Neurologist 1 reported treating it “*like a prescription*,” writing in “*as much as I can, based on milligrams of CBD or THC or whatever I know about the product*.” This was echoed by others, and some participants noted that completing the authorization form takes time, with more information required than a traditional prescription (quotation 16). One neurologist described being concerned about the limited amount of information required on the authorization form (quotation 17); however, despite not being required to specify a particular product on the authorization form, participants described authorizing specific products for the children in their care, based on colleague recommendations, the CBD:THC ratio in the product, or based on parent request. Most neurologists described authorizing only cannabis oils with high CBD content (e.g., $\geq 20:1$ CBD:THC ratio), although one reported considering additional factors such as terpene content when choosing between products and trialing products with higher relative THC content if an initial high-CBD product was ineffective.

Choosing between licensed producers: As of December 31, 2019, 61 licensed producers held approval from Health Canada to sell medical cannabis oil to registered patients. Participants reported selecting between the producers based on several factors, including colleagues' recommendations, previous experience with a producer, or the number of children registered with a producer. Several participants reported choosing a licensed producer based on cost and the availability of discounts for pediatric patients (quotation 18); however, some described being uncomfortable with this approach (quotation 19), and some felt that a 20:1 CBD:THC oil from one producer may not be the same as a 20:1 oil from another (e.g., because of terpene content).

Problems with authorization: Most participants reported encountering no problems with the authorization process, although some neurologists described encountering supply problems when parents choose products from smaller companies (quotation 20), as well as backorders and delays in registering new patients. A lack of product availability may necessitate a change in licensed producer, which requires the completion of a new authorization form and may result in additional time required by the neurologist.

5. Barriers to medical cannabis authorization

Participants who had not previously authorized medical cannabis described a variety of reasons for not authorizing its use, including personal and institutional factors. **Insufficient evidence or guidance:** Some participants reported not authorizing medical cannabis because of a lack of evidence and/or guidance (quotation 3). **Out of scope:** Others described feeling that authorizing medical cannabis was outside their scope of practice, that they considered it a “*regulatory hassle*” (quotation 21), or that they could not do a “*better job*” than physicians at cannabis clinics. **Restrictive policies:** Some participants described policies at their hospital or within their department that prohibit authorization, while others reported not wanting to be seen as going against people in leadership positions (quotation 22). Several participants noted that consensus had been reached within their department or group to not authorize cannabis and that a unified position was felt to prevent any one

neurologist from being given the most complex cases and/or “*the most demanding families*” (quotation 23).

Referral to other care providers: Participants who do not authorize medical cannabis described referring patients to other health care providers (e.g., neurologist or family physician) or to cannabis clinics, often in the patient’s community (quotation 24), or in one case, to in an adjacent province, stating that there was no closer alternative. Others described hospital or departmental policies that prevented them from referring patients, leaving parents on their own to find a cannabis clinic or care provider to provide authorization (quotation 25). Of note, some neurologists were strongly against the practice of referring patients to non-neurologists for the purpose of obtaining cannabis authorization (quotations 26, 27), citing patient safety as a key concern.

6. Impact of medical cannabis on clinical practice

Most participants reported that caring for children using medical cannabis does not affect their workflow, in terms of the number of patient visits or tests ordered. In one neurologist’s experience, the number of visits may be fewer, at least during the dose-optimization phase, for children who received authorization from another physician (quotation 28). In terms of testing, participants described treating cannabis “*like another drug*,” with no additional testing performed, while some order additional tests at baseline and while titrating the dose or if the child presented in a “*sleepy state*,” or being “*a lot more cautious with the other medications*” prescribed concurrently. Several neurologists described providing counseling and education to families about medical cannabis, which may add to the length of the clinical visit, and one neurologist described offering parents the opportunity to ask follow-up questions via telemedicine after an initial discussion about cannabis. One neurologist described difficulties entering non-formulary medicines into hospital electronic medical records and, for parents who receive authorization at a cannabis clinic, having to rely on parents to supply information about the treatment plan because of a lack of communication from some cannabis clinics (quotation 29).

Discussion

In this qualitative interview study, we explored the experiences and perceptions of neurologists in Canada about the use of medical cannabis for treatment of pediatric drug-resistant epilepsy. Most of the neurologists interviewed for this study viewed medical cannabis as a viable option, particularly after other options had been explored; however, important gaps in the evidence-base were identified, including limited knowledge about the medical properties of cannabinoids beyond CBD, the inability to predict which patients are most likely to benefit from cannabis treatment, and a lack of long-term safety data. Most neurologists reported having overall positive experiences with medical cannabis, although several commented that it's not a magic pill and that the benefits are likely oversold by the media.

In 2013, CNN aired a documentary about Charlotte Figi, a 5-year-old girl with Dravet syndrome.[4] In an attempt to control her drug-resistant seizures, Charlotte's parents initiated a regimen of medical cannabis, reducing her seizures by more than 90%.[19] Charlotte's case received considerable media attention and has led, at least in part, to increased interest among parents in the use of cannabis as an alternative or complementary treatment for epilepsy [3] and to increased requests to physicians for cannabis authorization.[20] Participants in our study also identified the legalization of recreational cannabis in Canada in 2018 as a potential driver of additional interest in medical cannabis. Compared with the public, the medical community has been more slow to adopt cannabis as a treatment for pediatric epilepsy,[21] owing largely to a lack of published clinical studies. Although our study was not intended to quantify support for medical cannabis, we observed that most participants were supportive of a trial of medical cannabis for children whose epilepsy had not responded to other treatments. This is consistent with the findings of a 2019 systematic review, which reported that medical practitioners were largely supportive of the use of medical cannabis across multiple indications, with higher levels of support when other options had been "exhausted." [22]

The Canadian League Against Epilepsy (CLAE) recently published recommendations regarding the use of medical cannabis in the treatment of epilepsy.[23] There are several consistencies between our findings and these recommendations. First, CLAE recommends that patients should make the decision to use cannabis “*in consultation with their health care provider to ensure their safety.*” Neurologists echoed this, voicing concerns that some parents may be administering cannabis to their children without oversight of a health care professional, which could lead to unsafe situations for the child. The use of complementary and alternative medicine is common among children with epilepsy, and parents may not disclose its use.[24] This further supports the need to establish open communication between parents and health care providers.

Second, CLAE “*encourages clinicians and researchers to continue to seek further knowledge and education*” about medical cannabis.[23] Several neurologists in our study also expressed a desire for additional and ongoing education, in order to better counsel their patients. In a 2015 educational needs assessment of Canadian physicians, 64% of respondents perceived a strong need for cannabis education, and 70% felt that receiving cannabis education would better allow them to care for their patients using cannabis.[25] Similarly, a recent systematic review highlighted a lack of self-perceived knowledge among clinicians about medical cannabis,[22] and several groups have called for increased cannabis education.[26,27]

However, there are also several notable differences between our findings and CLAE’s recommendations. First, CLAE acknowledges the differences between purified CBD oil (Epidiolex) and the CBD:THC cannabis oils available in Canada, stating that “evidence is lacking” for products containing both CBD and THC.[23] In contrast, some participants in this study described inferring the safety and effectiveness of CBD:THC cannabis oils based on studies of Epidiolex, which further highlights the need for additional education about the differences between cannabis-based products. Notably, there are important differences between Epidiolex and the products available in Canada. The Canadian CBD:THC oils are whole plant isolates, containing CBD as well as THC in various

ratios, as well as other phytocannabinoids (e.g., cannabichromene, cannabigerol, cannabinol, cannabidivarin), flavonoids, and terpenes.[28] There is also considerable variation in terms of the CBD:THC oils available within Canada. As of December 31, 2019, there were 61 producers licensed to sell such oils to authorized medical patients, most of which offer multiple products with various ratios and concentrations of CBD and THC, including those high in THC (and low in CBD), balanced oils (approximately equal concentration of CBD and THC), and those high in CBD (and low in THC). The concentration of cannabinoids is variable across preparations, such that a cannabinoid oil with a 20:1 ratio of CBD to THC from one producer does not necessarily contain the same concentration of CBD as a 20:1 oil from a different producer. There is also potential for variability in cannabinoid concentration between batches of the same product, leading to uncertainty that may affect dosing, cost, adverse effects, and therapeutic efficacy.[23] These complex issues related to the use CBD:THC oils further reinforce the CLAE's recommendation that clinicians continue to seek additional education about medical cannabis.[23]

Second, some participants described referring patients and their families to cannabis clinics or to health care providers who may not be experienced in caring for patients with epilepsy. However, CLAE recommends that *“treatment with CBD:THC cannabis oil be managed by a physician knowledgeable and experienced with epilepsy care and anti-seizure medications, preferably with experience in CBD:THC cannabis oil.”* Some participants noted departmental policies that prevented them from authorizing cannabis or that neurologists in their group had reached consensus that none would authorize, instead referring patients to cannabis clinics or leaving families to find other health care providers to authorize use. One participant was particularly critical of the practice of referring complex neurology patients to non-neurology health care professionals, stating that *“they owe it to the patient”* to find an appropriate neurology referral if the family wishes to pursue medical cannabis.

Strengths and limitations

The strength of this study lies in the use of qualitative methodology to provide an in-depth exploration of the perspectives of neurologists about the use of medical cannabis for treatment of drug-resistant epilepsy. However, several limitations should be considered. First, neurologists may have been motivated to participate because of strong feelings about medical cannabis. Notably, most participants expressed an overall positive opinion toward its use in this population, although only about half had previously authorized medical cannabis. In order to capture a variety of perspectives, we sought diversity in geographical location, practice type (hospital, community), gender, and practice duration; however, most participants were based in academic centres, which may limit the generalizability of the findings to other settings. We continued recruiting participants until no additional codes were generated from subsequent interviews, although we acknowledge that some perspectives may have been missed. Second, all but one interview was completed before publication of the CLAE recommendations,[23] and it is possible that some participants may have subsequently changed opinions or practices. Third, this study did not capture the perspectives of other providers who may authorize medical cannabis (e.g., family physicians, nurse practitioners). Finally, we recognize that opinions of neurologists in other regions may differ, as support for medical cannabis varies by jurisdiction, depending partly owing to its legal status.[22]

Conclusion

Our findings highlight the opinions and experiences of neurologists with medical cannabis for the treatment of pediatric drug-resistant epilepsy, as well as identified perceived gaps in the evidence base. Additional education about medical cannabis may better prepare neurologists to have informed and open conversations with parents, and further research into the decision-making needs of both neurologists and parents is warranted.

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Appendix 1: Interview guide

- Question 1:** What types of education or training about medical cannabis have you received? What types of research or learning have you done on your own?
- Question 2:** What are your thoughts about the current state of the evidence related to the safety and effectiveness of medical cannabis for use in children with drug-resistant epilepsy?
- Question 3:** Are there any policies in place at your hospital or in your practice about authorizing cannabis use?
- Question 4:** When discussing medical cannabis with parents, is the discussion typically initiated by the parents? Are there any situations where you might propose it as an option?
- Question 5:** Do you find that parents are typically well-informed about medical cannabis or have done their own research before coming to you?
- Question 6:** For children using cannabis in your care, can you tell me about how it affects your usual work flow or the structure of the patient visits?
- Question 7:** Can you tell me about any discussions you have with parents about the cost of cannabis treatment?
- Question 8:** How do you describe the potential risks and benefits of cannabis to interested parents?
- Question 9:** Have you observed any changes in your practice related to medical cannabis since the legalization of recreational cannabis in 2018?
- Question 10:** Have you ever authorized medical cannabis for a child with drug-resistant epilepsy?

For those who have authorized medical cannabis:

- Question 11:** Can you describe the authorization process from your perspective?
- Question 12:** Do you typically specify the licensed producer? How did you choose between producers?
- Question 13:** Do you typically specify the product for the child?
- Question 14:** Do you typically have a trial period for medical cannabis? How do you decide if it is effective?

For those who have not authorized medical cannabis:

Question 15: Could you tell me why you haven't authorized it?

Question 16: For parents interested in obtaining authorization, do you refer them to another health care provider?

Question 17: Are you likely to authorize medical cannabis in the future? Under what circumstances?

Standards for Reporting Qualitative Research (SRQR) checklist

Title and abstract	Page/line no(s).
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	3
Purpose or research question - Purpose of the study and specific objectives or questions	3
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/interpretivist) is also recommended; rationale**	4
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	4
Context - Setting/site and salient contextual factors; rationale**	3,4
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	4
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	4
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	4
Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	4, Appendix 1
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	5, Table 1
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	4

Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	5
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	4

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	5,7
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Table 2

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	17
Limitations - Trustworthiness and limitations of findings	19

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	20
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	20

Reference: O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Academic Medicine* 2014; 89(9).

Section 5.2

Barriers in accessing medical cannabis for children with drug-resistant epilepsy in Canada: A qualitative study

SECTION OVERVIEW

This section presents a manuscript describing the findings of an interview-based qualitative study of the perspectives and experiences of parents whose children with drug-resistant epilepsy have used medical cannabis, with a focus on barriers to access. Although cannabinoid oils have been legal for medical use since mid-2016 in Canada (and other types of cannabis have been legal for almost two decades), there has been no formal study of the experiences of parents in trying to access such products for their children with drug-resistant epilepsy. Thus, interviews were conducted with parents whose children were currently using or had previously used medical cannabis in Canada, and barriers to accessing medical cannabis in the current Canadian system were explored by use of a patient-centered access to care framework. Five dimensions of access were considered: approachability, acceptability, availability, affordability, and appropriateness.

MANUSCRIPT STATUS

This manuscript has been submitted for publication:

Elliott J. DeJean D, Potter BK, Coyle D, Clifford T, McCoy B, Wells GA. Barriers in accessing medical cannabis for children with drug-resistant epilepsy in Canada: A qualitative study. *Epilepsy and Behavior* (Submitted December 24, 2019).

Supporting material

Appendix 1: Interview guide

Author roles and contributions

Author contributors: All authors contributed to the design of the study and the development of the interview guide. JE carried out all data collection, analyzed the data (along with DD), and

led the writing of the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version submitted for publication.

RELATED THESIS APPENDICES

Appendix C: Abstracts submitted for conference presentation. Findings from this study have been submitted to the 2020 CADTH Symposium (Toronto, Ontario). Submitted: September 2019.

Elliott J, DeJean D, Potter B, Coyle D, Clifford T, McCoy B, Wells GA. Decision-making in the face of uncertainty: Experiences of neurologists and parents with medical cannabis for children with drug-resistant epilepsy.

Appendix F: Ethics approval. Approval for this study was obtained from University of Ottawa's Office of Research Ethics and Integrity (November 23, 2018). Ethics file number H-09-18-1083.

Barriers in accessing medical cannabis for children with drug-resistant epilepsy in Canada: A qualitative study

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Abbreviations: CBD = cannabidiol, THC = delta-9-tetrahydrocannabinol

Keywords: pediatric drug-resistant epilepsy; medical cannabis; authorization; cost; insurance

Highlights

- We explored barriers to accessing medical cannabis for children with drug-resistant epilepsy.
- Medical cannabis may fill an unmet need for children with drug-resistant epilepsy.
- Most parents encountered resistance from their child's neurologist about medical cannabis.
- Parents were frustrated that medical cannabis is not eligible for insurance coverage.

Abstract

Introduction: The use of medical cannabis to treat drug-resistant epilepsy in children is increasing; however, there has been limited study of the experiences of parents with the current system of accessing medical cannabis for their children.

Methods: In this qualitative study, we used a patient-centered access to care framework to explore the barriers faced by parents of children with drug-resistant epilepsy when trying to access medical cannabis in Canada. We conducted semi-structured interviews with 19 parents to elicit their experiences with medical cannabis. We analyzed the data according to five dimensions of access, namely approachability, acceptability, availability, affordability, and appropriateness.

Results: Parents sought medical cannabis as a treatment because of a perceived unmet need stemming from the failure of antiepileptic drugs to control their children's seizures. Medical cannabis was viewed as an acceptable treatment, especially compared with adding additional antiepileptic drugs. After learning about medical cannabis from the media, friends and family, or other parents, participants sought authorization for medical use. However, most encountered resistance from their child's neurologist to discuss and/or authorize medical cannabis, and many parents experienced difficulty in obtaining authorization from a member of the child's existing care team, leading them to seek authorization from a cannabis clinic. Participants described spending up to \$2000 per month on medical cannabis, and most were frustrated that it was not eligible for reimbursement through public or private insurance programs.

Conclusions: Parents pursue medical cannabis as a treatment for their children's drug-resistant epilepsy because of a perceived unmet need. However, parents encounter barriers in accessing medical cannabis in Canada, and strategies are needed to ensure that children using medical cannabis receive proper care from health care professionals with training in epilepsy care, antiepileptic drugs, and medical cannabis.

1. Introduction

The use of complementary and alternative medicine among children with epilepsy is common, [1–3] partly owing to uncontrolled seizures [1] and adverse events associated with traditional antiepileptic drugs [2]. The use of medical cannabis, one type of complementary and alternative medicine, has increased over the past decade in parallel with reports of children whose drug-resistant epilepsy has responded to medical cannabis despite the failure of antiepileptic drugs [4,5]. Indeed, the failure of antiepileptic drugs to control seizures is a predictor of parents' willingness to try medical cannabis for their children's epilepsy [6].

Until recently there has been little clinical evidence to support the use of medical cannabis as a treatment for epilepsy, and health care providers may have lower confidence in its effectiveness and safety compared with patients and the public [7]. However, recent randomized controlled trials have suggested that cannabidiol (CBD), one of the active agents in cannabis, may reduce seizures in children with drug-resistant epilepsy [8], and the US Food and Drug Administration and the European Medicines Agency have recently approved Epidiolex, a purified CBD product, for treatment of Dravet and Lennox-Gastaut syndrome, two catastrophic forms of pediatric epilepsy [9,10]. Epidiolex is not available in Canada; instead, Canadian patients have access to cannabinoid oils, which typically include a combination of CBD and delta-9-tetrahydrocannabinol (THC) at various ratios, including high CBD and low THC. While these oils have not been tested in randomized controlled trials, two small open-label cohort studies have suggested that these products may also be effective in reducing seizures associated with drug-resistant epilepsy and have a similar side effect profile to the FDA approved purified CBD product [11,12].

Cannabinoid oils (along with dried and fresh cannabis) have been available to authorized patients via the Canadian medical cannabis system since mid-2016. For authorization, patients or their caregivers must obtain a medical document signed by a licensed health care provider [13]. As such, health care providers act as gate keepers to the medical cannabis system, and some patients have reported

difficulty finding a health care provider to provide authorization [14]. Anecdotally, parents of children with drug-resistant epilepsy face similar barriers to accessing medical cannabis [15], although this has not been formally evaluated. In this qualitative study, we explored the barriers to accessing medical cannabis for treatment of pediatric drug-resistant epilepsy in Canada as experienced by their parents.

2. Methods

This study was performed as part of a health technology assessment focused on the use of cannabis as a treatment for drug-resistant epilepsy in children and its design and methods were informed by interpretive description [16], a qualitative approach that aims to provide a meaningful description of clinical phenomena by describing commonalities and differences between participants' experiences [17]. The research team included members with experience in qualitative research (J.E., D.D., B.K.P) and clinical care of children with epilepsy (B.M.). The research team was not positioned either in favour or opposition of medical cannabis use. The study was approved by the University of Ottawa Research Ethics Board, and participants were not compensated for participation.

2.1 Sampling and recruitment

Eligible participants were parents or primary caregivers of children (aged 18 years or younger when medical cannabis was initiated) with drug-resistant epilepsy (had tried at least two antiepileptic drugs without achieving seizure control [18]) whose children were currently using or had previously used medical cannabis with authorization from a health care provider. Because regulations around the authorization and use of medical cannabis vary by country [19], this study was restricted to parents residing in Canada. Recruitment notices were posted to social media sites (Facebook, Twitter), and participants were encouraged to tell members of their personal networks about the study. Recruitment and data collection were concurrent with analysis. We planned to continue recruitment until saturation was reached (no new themes, sub-themes, or codes identified), which we determined to

have occurred after the 13th interview; however, we interviewed all those who had expressed an interest in participating. Interviews were conducted between January and September 2019.

2.2 Data collection

Semi-structured telephone interviews were conducted by a single researcher (J.E.); the interview guide is available in Appendix 1. Interview questions were open-ended and were intended to capture participants' experiences with the use of medical cannabis for their children's drug-resistant epilepsy, including with the authorization process. The interview questions were developed by the research team following a review of the literature and were informed by a health technology assessment framework [20]. Interviews were conducted between January and September 2019 and ranged from 18 to 105 minutes in duration. All participants provided informed consent prior to the interview, which was audio-recorded.

2.3 Data analysis and analytical framework

Interviews were transcribed verbatim, and the accuracy of the transcription was verified against the original recording before being uploaded to NVivo data management software (v. 12 Pro, QSR International). JE coded all transcripts, and six transcripts were coded independently by a second author (D.D). The data were synthesized by use of framework analysis, a seven-stage process involving (1) verbatim transcription; (2) familiarization with the data; (3) coding; (4) identifying an analytic framework; (5) applying the framework; (6) charting the data into the framework; and (7) interpreting the data [21]. Following an initial review of the data, we identified the patient-centred access to care framework [22] as an appropriate analytic framework to understand the barriers experienced by parents with accessing medical cannabis for their children. The patient-centred access to care framework encompasses five dimensions of access to care: (1) *approachability*; (2) *acceptability*; (3) *availability and accommodation*; (4) *affordability*; and (5) *appropriateness* [22]. In Table 1, we describe how we applied this framework to the concept of access to medical cannabis by

the parents of children with drug-resistant epilepsy; our conceptualizations were informed by our prior work in this area, as well as a review of the relevant literature.

Table 1: Patient-centred access to care framework in the context of medical cannabis for pediatric drug-resistant epilepsy

Dimension	Patient-centred access to care framework [22]	Conceptualization of patient-centred access to medical cannabis for children with drug-resistant epilepsy
<i>Approachability</i>	“Approachability relates to the fact that people facing health needs can actually identify that some form of services exists, can be reached, and have an impact on the health of the individual.”	The ability of parents to discover and learn about medical cannabis as a potential treatment for their child’s epilepsy, as well as their perceived need for medical cannabis
<i>Acceptability</i>	“Acceptability relates to cultural and social factors determining the possibility for people to accept the aspects of the service (e.g. the sex or social group of providers, the beliefs associated to systems of medicine) and the judged appropriateness for the persons to seek care.”	The acceptability of medical cannabis as a treatment to parents, as well as how parents perceive the acceptability of cannabis to their health care providers
<i>Availability</i>	“Availability and accommodation refers to the fact that health services (either the physical space or those working in health care roles) can be reached both physically and in a timely manner.”	The ability of parents to find a health care provider to authorize medical cannabis use, as well as the availability of the chosen cannabis product
<i>Affordability</i>	“Affordability reflects the economic capacity for people to spend resources and time to use appropriate services.”	The relationship between the cost of medical cannabis products and parents’ ability and willingness to pay for them
<i>Appropriateness</i>	“Appropriateness denotes the fit between services and clients need, its timeliness, the amount of care spent in assessing health problems and determining the correct treatment and the technical and interpersonal quality of the services provided.”	The perceived fit between the current model of access to medical cannabis in Canada and the needs of families

3. Results

3.1 Participants

Nineteen parents of children with drug-resistant epilepsy participated in this study. Most were female (84%), aged 41–50 years (68%), and all had obtained at least a college education (Table 2). Among the children of the participants, most were male (63%) and about half had a diagnosis of Lennox-Gastaut or Dravet syndrome (47%). Before starting medical cannabis, most had tried between three and nine antiepileptic drugs without obtaining seizure control (range: 2–14). Most had used medical cannabis for between 1 and 5 years (74%), and most (84%) were current users.

Table 2: Demographic characteristics of the study participants

Characteristic	Number (%)
PARENT	k = 19
Female	16 (84)
Age, yr	
< 40	2 (11)
41–50	13 (68)
> 50	4 (21)
Highest level of education	
College	4 (21)
University	9 (47)
Graduate degree	6 (32)
Residence	
BC	3 (16)
AB	1 (5)
ON	14 (74)
Atlantic Canada	1 (5)
Residence location	
Urban	11 (58)
Rural	8 (42)
CHILD	k = 19
Female	7 (37)
Age at cannabis initiation	
0–9	12 (63)
10–18	7 (37)
Epilepsy syndrome	
Dravet syndrome	7 (37)
Lennox-Gastaut syndrome	2 (10)
Other	10 (53)
Current cannabis use	
Yes	16 (84)
No	3 (16)
Duration of cannabis use	
<1 yr	4 (21)
1–5 years	14 (74)
>5 years	1 (5)
Number of antiepileptic drugs tried before cannabis	
2	3 (16)
3–9	14 (74)
≥10	2 (10)

3.2 Access to medical cannabis

In the following sections, we present the data according to the patient-centred access to care framework [22], based on the dimensions *approachability*, *acceptability*, *availability*, *affordability*, and *appropriateness*, with the conceptualization described in Table 1 leading to the subthemes described within each dimension.

3.2.1 Approachability

Approachability refers to the parents' ability to learn about medical cannabis as a potential treatment for their children's epilepsy (discovering medical cannabis, learning about medical cannabis) and may be influenced by their perception of an unmet need (perceived need).

Perceived need: Drug-resistant epilepsy is, by definition, resistant to antiepileptic drug treatment [18], and parents described an unmet need stemming from a lack of seizure control with the currently available treatments. Parents described feeling like *"nothing seemed to be truly helping at all,"* which was often accompanied by feelings of helplessness from *"knowing very well there was nothing you can do to stop [the seizures]"* and hopelessness *"that we were going to find a med that worked."* Being *"tired of adding more meds"* was common, and parents were generally reluctant to add additional antiepileptic medications to their children's treatment regimen. Parents feared *"losing"* their child owing to increased sedation at higher doses of antiepileptic drugs, and several parents expressed a need to *"do whatever we can to not have that happen"* and to maintain their child's personality:

"Sure we could drug him with all of these different drugs but then you lose him... His personality goes away and he's not as responsive. And so it's more important to us that he's him. And that he can verbalize things even if he's having more seizures. ...We've always said we would rather have him than have a drugged him, drugged into a stupor." (Caregiver 10)

Discovering medical cannabis: Parents learned about cannabis as a potential treatment for epilepsy from their family or friends, from other parents of children with epilepsy (within their geographical community or within online communities), or when searching on the Internet for general information about epilepsy. Medical cannabis was commonly first encountered as a treatment for other conditions:

“I was actually researching marijuana ‘cause my mom was sick with cancer, so I just started looking into it... a year later my sister was diagnosed so I looked even more into it and actually made her some oil [laughs] but that's where I kind of got my initial inclination. I'd seen a lot of overlap with epilepsy in kids, I'd started following a lot of Facebook sites and kind of watching and seeing what was happening” (Caregiver 15)

The CNN documentary “Weed” [23], which highlighted Charlotte Figi’s experiences with medical cannabis, was commonly described as a first encounter with medical cannabis for epilepsy. Parents drew similarities between their children and Charlotte, which heightened their interest in cannabis:

“And the very first scene before they got into it, was this little girl, about [child]'s age, maybe 2 years older than [child] at the time, and she was just seizing in the same way that [child] seizes, it was so eerily familiar. I remember calling my husband down, saying we really should watch this, ‘cause he wasn't super interested in something about another seizure type. And I said no, this little girl from Colorado has Dravet. So we both sat down and watched it. Started chatting after that about, gosh, obviously this is something we wanted to try for [child], because they made it sound quite miraculous.” (Caregiver 2)

Learning about medical cannabis: Most parents attempted to discuss cannabis with their child’s neurologist, either seeking additional information, clarification of information they had received from other sources (e.g., online), or authorization. While some parents described having informative conversations with their child’s neurologist about medical cannabis, most described a reluctance or unwillingness on the part of their neurologist to discuss cannabis:

“Any discussions, any questions that we had...were not responded to very well. There wasn’t ‘Well we don’t really know much about it but let’s find out together.’ There wasn’t a lot of support or encouragement that way, so we did kind of have to go about it ourselves.”
(Caregiver 2)

As a result, parents largely took learning about medical cannabis into their own hands, searching out information from a variety of sources, including from other parents whose children had used medical cannabis and online sources (e.g., Facebook groups, cannabis websites), spending *“a lot of time on the computer.”* Parents cautioned, however, that they had to be careful about the information found online, describing a need to be *“vigilant”* about misinformation and cannabis *“fanatics”*:

“And there’s a lot of misinformation out there in my opinion. ... everybody is expressing opinions and things they do for their kids, but a lot of what people are doing and quote unquote trying is just random. ...You have to be careful. Everybody thinks, not me, but I think the general consensus in the public is that CBD is 100% safe. And it may be, but because it’s combined with THC, people have to be vigilant and careful.” (Caregiver 18)

3.2.2. Acceptability

In the context of medical cannabis, *acceptability* refers to the acceptability of medical cannabis as a treatment to parents and how parents perceive the acceptability of cannabis to their health care providers

Acceptability of medical cannabis to parents: Medical cannabis was viewed as an acceptable treatment option to all parents interviewed, especially compared with adding additional antiepileptic drugs. Some parents qualified this by being willing to try medical cannabis only with the support of a health care provider, ideally a neurologist:

“That would be the dream: to be able to go hand in hand with a neurologist in this journey and maybe they’re not even the experts on cannabis but are willing to work with [cannabis

clinic] and go hand in hand, or even better all in one, with a neurologist who's supportive of cannabis and we can do this journey together.... I just feel like that would be the best."

(Caregiver 2)

Having access to a legal supply of cannabis was also an important consideration to some parents, and some wanted access to a cannabis product intended to treat epilepsy:

"It had to be legal and designed for the purpose ... we wanted something that was associated with epilepsy... We didn't just want to have any random cannabis." (Caregiver 11)

Some parents were hesitant to initiate medical cannabis because of a lack of clinical studies, although most parents described the decision as an easy one to make. Generally, parents were "willing to try anything" and felt that they would have "regretted not trying cannabis"

"When you have a kid who's sick and doesn't respond to regular medications, you'll try anything. You know what I mean? Like, it doesn't even faze us anymore. 'Cause of the stuff you've seen your kid go through, it didn't even, doesn't even cross our minds." (Caregiver 4)

The side effects of medical cannabis were not of great concern to most parents interviewed. For some, it was important to "balance the risk" between the impact of seizures and a lack of evidence about the safety of cannabis use:

"But then also I knew about the whole worry about the impact of cannabis on young brains and such but I really believed that the impact of seizures on my son's young brain was going to be far more damaging than another potential treatment that could stop the seizures. So I really don't think that argument in kids with epilepsy is valid in terms of the relentless seizures that they have. I would be hard pressed to be shown that that's not way worse than the risk of what cannabis could do to their brains." (Caregiver 17)

Anti-biomedical or anti-science views were notably absent among the parents interviewed, although some, as exemplified by Caregiver 9, viewed cannabis as a more natural treatment compared with antiepileptic drugs and expressed a desire to avoid pharmaceutical products:

“I have seen so many side effects of the pharmaceuticals that deep down in my heart I knew that I was going to give him something that was much safer because it’s coming from the earth, at least I know that much. And I know that this is not something that has been synthesized to the point where I need to worry about it. I had some sort of comfort in it. Every time we had to try the pharmaceuticals I was more scared.” (Caregiver 9)

In contrast, others were skeptical that a “natural product” could help their child when pharmaceutical agents had failed. Still others were initially skeptical about the medicinal value of cannabis, in some cases stemming from personal recreational experience.

“I was like, ‘Oh! Medical marijuana. [laughs] Whoever heard of medical marijuana? What do you mean medical marijuana? How is that different from normal marijuana?’ ‘Oh! It’s not different from normal marijuana.’ ‘Oh!’ So then, that sits you back and you’ve got to think about that for a couple months (Caregiver 5)

Concerns about stigma were largely absent among the parents interviewed, with one parent commenting “we weren’t afraid of what people would think in terms of stigma in giving our six-year-old cannabis or anything like that.” (Caregiver 13), while another parent noted the almost lack of reaction from others regarding cannabis use:

“There seems to be no stigma. It’s like nothing, zero. Zero. ...It’s not too much different from us giving her melatonin, it’s for a different purpose melatonin helps her sleep. Bu no, it’s a non-issue. It’s not a big deal.” (Caregiver 18)

However, in contrast, one parent expressed concern about the “social stigma” associated with “getting high,” while another described initially viewing cannabis as “scary” owing to a lack of knowledge about cannabis:

My initial thoughts, obviously it was scary. Not understanding enough about cannabis... 'Cause we were not educated at first...I was afraid that he would have, you know, he would be addicted to cannabis like all the other kids out there [laughs]. Having marijuana, I was afraid because, you know, I didn't want him to be hooked up onto, or addicted to marijuana. Which later on, of course, I realize it's totally different.” (Caregiver 7)

Perceived acceptability by health care providers: Some parents reported that their child’s health care providers were supportive of a trial of medical cannabis:

“I think we’ve been really lucky in that we had a few naysayers at the beginning but our core care team was quite supportive and could see and agree with us that we’ve tried everything that was available for us to try and that this was the next best option.” (Caregiver 17)

However, from most parents’ perspective, medical cannabis was not considered to be an acceptable treatment to their child’s neurologist, at least not initially. Some parents described their neurologists’ reaction as “dismissive,” stating that medical cannabis “certainly wasn't a viable option as far as they were concerned” (Caregiver 2).

“The first time we asked her she kind of laughed, she's was like, ‘No, we're not doing that.’ And I was like, ‘Okay, but what if it works?’ ‘No, no absolutely not.’” (Caregiver 10)

Others reported that their neurologist had “shut the door” in their face, laughed, or attempted to placate them:

“...there was some placating us, our interest. She said ok, she wrote down the website, and I think at the next appointment when we asked her if she’d seen it, she kind of dismissed it, like no, she hadn’t really or hadn't been able to find it or something like that but I think it was sort of like... certainly not an aggressive no at first, but almost very blasé interest in it like ‘Oh ok hadn't really heard of that, nobody's really that serious about it’.... to be honest it went from not really caring to almost dismissing kind of what we had to say, politely and

respectively, but just not really talking about it, to it almost sounding like it was ridiculous to keep bringing this up at appointments.” (Caregiver 2)

As explained by one caregiver, this resistance on the part of neurologist led to frustration among parents, especially when parents considered the other antiepileptic drugs they were being asked to try:

“They kept telling us there’s no safety studies, there’s no this, no that. But really when you look at infants with seizures, there’s never been safety studies on most of the drugs and those combinations and the impact on development brains either... I felt really frustrated when doctors would shut us down when we would approach them about it... for us, we were very uncontrolled with all of the options... watching him lose capacities after every seizure was really difficult to watch so it didn’t feel like that big of a risk to take because we already knew we were losing pieces of him with uncontrolled seizures.” (Caregiver 17)

Some parents were understanding of their health care provider’s resistance, which they saw as being related to a lack of evidence and/or knowledge:

“He said something very enlightened to me actually, he said to me ‘I can’t prescribe something I don’t know of’ and I said to him ‘You’re absolutely right. This is not something that’s taught in medicine school to you. This is such an alien subject, and all of a sudden I’m coming to you for a prescription of it, of course you’re going to be hesitant, because you’re told to live in a code of conduct and you have responsibility.’ I told him that, I appreciate that, and I understand.” (Caregiver 9)

For most parents, resistance from the child’s health care providers did not deter them from pursuing cannabis as a treatment; instead, such reactions led the parents to seek authorization from other providers or from cannabis clinics. In some cases, negative reactions led parents to not disclose cannabis use to their child’s neurologist:

“To [neurologist] cannabis has been the enemy...She doesn't know that we're restarted our journey. Our last meeting with [neurologist] was in August and we started this end of September of this year. So she doesn't know that we have a new doctor, and she doesn't know that we've restarted this journey.” (Caregiver 2)

Others described first initiating cannabis treatment and then informing the neurologist:

“I told her after we'd started it. And no, she wasn't impressed. And then of course said ‘THC is totally bad and this is probably not ideal, but it would be ok to try’... she didn't believe in it of course or anything. However when she saw her, because she'd already been on it for a short time, there were already improvements so she said ‘well she looks healthy, everything is fine so go ahead and do what you're doing’. Begrudgingly [laughs]” (Caregiver 15)

3.2.3. Availability

Availability in this context is conceptualized as the ability of parents to obtain authorization from a health care provider, as well as the availability of the chosen cannabis product (cannabis supply).

Availability of cannabis authorization: Most parents experienced difficulty finding a health care provider to authorize the use of medical cannabis for their child.

“We asked our neurologist for a prescription, which was firmly denied and so we asked for a referral to a doctor who would prescribe and that was also denied. She basically didn't want to go near it.” (Caregiver 15)

Among parents interviewed, just over half ultimately received authorization from a member of their child's already existing health care team (e.g., neurologist, pediatrician, family doctor). Several parents described overcoming their care provider's initial resistance to medical cannabis (*“I kept bringing him and emailing him publications about it, a couple safety studies I had found just around cannabis in general”*; Caregiver 1) or that the provider had changed his or her opinion on

authorization over time. Others, who were unable to obtain authorization from one of their children's current care providers, instead receiving authorization from a physician at a cannabis clinic:

"I said 'Well what about cannabis, is this the point to try the cannabis?' ... she said, 'Okay, maybe.' But she wouldn't do the referral. [laughs] And it's like, 'What do you mean?' And she's like, 'Well, you can do it, but I'm not filling in the referral. You have to go to your family doctor.' We went to the family doctor who said, 'I won't sign the referral, because the potential for brain injury if you're under 25 and taking cannabis is too high.' ... So we went back to neurology and I said, 'Look, this is what we want to do. Our family doctor will not sign the paperwork, I need you to do it.' ... I said, 'all you have to do is send that paper to the cannabis place. That's what they need, just send it...' and so she finally agreed." (Caregiver 10)

Some families were referred to the cannabis clinic by their neurologist, while others self-referred to a clinic, frequently on the recommendation of another parent. Parents described waiting several months for the initial appointment, and some families traveled up to six hours from their home community to find a clinic willing to accept their child as a patient.

Availability of medical cannabis (supply): Shortages of medical cannabis were commonly described by parents, with licensed producers running out of stock or discontinuing their chosen product. Parents called such shortages "terrifying," and some described how they took steps to avoid running out of product. Caregiver 13 recounts how shortages impacted their family:

"A number of our former suppliers have just had zero supply. Whether there's been recalls or just more demand than supply. There was one company that had been keeping a certain amount available for pediatric clients even though they were technically online sold out, but that eventually ended. So that was stressful for us, because we knew that that this was working for [child] and we did not want to have to go without. So we would hoard and

stockpile as much as we could, but there were times when we were cutting it close down to days of not having supply.”

The need to guard against supply shortages was a common theme. Most parents described either re-ordering earlier than needed or ordering more at one time than needed to protect against shortages of their chosen product. Supply shortages forced parents to decide between rationing the product that they had on hand, *“keeping the pace and risk running out completely,”* or changing licensed producers. Parents who were seeing a beneficial effect with one product were reluctant to change products and/or producers, with some parents noting that they had experienced different effects across products.

Recreational cannabis became legal in Canada in October 2018, and many parents described experiencing more product shortages since that time, which was a source of frustration for families:

“After the legalization I realized the oils are getting sold out, the companies are not keeping their part of the end, you know, for medicinal patients the stock should always be available. He had a standing prescription of 30 grams a month, that should always be available with that specific LP [licensed producer] for the oil knowing that he is pediatric patient.”

(Caregiver 9)

Some parents described choosing between licensed producers based on past supply shortages, although this approach wasn’t always successful:

“It was out of stock. The medicine for my kid was out of stock. Actually, that was one reason we switched to [licensed producer 1], we were told that their supply was solid. Because we were having a lot of issues with [licensed producer 2] where they were just out of stock. But [licensed producer 1] has been out of stock as well since legalization.” (Caregiver 19)

3.2.4 Affordability

Affordability in this context refers to the cost of cannabis products and parents’ ability and willingness to pay for them.

Medical cannabis was not considered affordable by most participants and was described as “costly,” “extremely expensive,” “prohibitive”, and “ridiculous.” Parents described spending up to CDN\$2000 per month out of pocket on medical cannabis for their child, which, for some families, resulted in financial stress and uncertainty:

“And I think after the third night where I didn't get any sleep, [father] just said ‘Put it on your credit card. Just get it done.’ [laughs] Like ‘Okay’ [laughs]. Right? I just needed someone to, you know, validate that I could spend hundreds of dollars that I didn't have.”
(Caregiver 14)

For some parents, the cost of cannabis affected their decision-making about whether to continue treatment, and some described not increasing their child’s cannabis dose to the recommended level owing to the cost:

“We have so many costs for [child], she's profoundly disabled. We have a lot of caregiving costs, a lot of equipment costs, a lot of secondary supplemental medication costs, so yeah, it's going to be... I don't know that we'll go that route, I don't know that we would bump up the dose. We'd be looking at five hundred and something a month, in addition to everything else. I think it's going to be prohibitive. It's going to be cost prohibitive to do that. And not just for a few months. If it's helpful we'd want to keep it going for long term...It's a lot of money on top of everything else, right? (Caregiver 18)

For others, the cost of cannabis factored into their decision-making about their employment status, with some questioning whether they could afford their child’s cannabis if one parent was to leave full-time employment.

The cost of medical cannabis was at least partially offset for some families by discounts offered by cannabis producers (e.g., through pediatric compassionate use programs). These discounts (ranging from 20% to almost 100%) had the potential to greatly reduce the out-of-pocket costs:

“...they're basically giving it away. Admittedly we're not on a high dose. But I think our dose, it would probably cost between \$100-\$200 a month. And we pay less than the postage. I think it was like \$2.50 or something like that... they're selling at a massive discount.”
(Caregiver 12)

Some parents, however, were concerned about what would happen when their child aged out of the pediatric discount program:

“So the cost right now is not that much of an issue. Now, once she hits 12 years old which is when their program ends ... she still has about 5 years, but its going to be very challenging. ... If we were only getting 30% off, then it would be extremely hard.” (Caregiver 3)

3.2.5. Appropriateness

This dimension broadly relates to the fit between the current model of medical cannabis access in Canada and the needs of families. Common themes raised by the participants were related to the current regulatory framework and the reimbursement of medical cannabis.

Regulatory framework: Several parents compared their experiences accessing medical cannabis before and after the introduction of cannabinoid oils to the medical system in mid-2016. Prior to that, some parents described converting dried cannabis to oil, which was labour intensive and expensive. As Caregiver 1 recalled, this period was marked by uncertainty and experimentation:

“So fast forward to mid 2014, I was able to access a prescription and get cannabis, albeit only dried form cannabis, because that was before the laws changed to allow for oil. I started becoming some kind of a mad scientist in my backyard and kitchen, creating oil... The bigger problems of course were figuring out and building the machinery needed to make oil, getting myself familiar with that process, and the dilution process, and the lab testing, and deciphering the results process...before you've done it, it's kind of a foreign language.”

Since regulatory changes in Canada in mid-2016, most parents no longer needed to prepare their own oils, although some continued to do so because of a desire for a product not commercially available (e.g., a specific CBD:THC ratio). The introduction of cannabinoid oils was described as making medical cannabis “*much easier*” and less expensive; however, clinicians generally advise against this practice owing to safety concerns.

Some parents expressed frustration that they were limited to purchasing from one licensed cannabis producer at a time:

“You're allowed one prescription per place, so we can't actually buy different strains from different places at the same time, you have to change your prescription every time if you want to do that. (Caregiver 19)

Parents felt that limiting in terms of trying new products for their children and in the event of a supply shortage. More education around this issue may be warranted, given that under the current regulations, medical cannabis authorizations may be split between multiple licensed producers (provided that the total amount of cannabis purchased stays under the authorized amount).

Reimbursement of medical cannabis: As described in Section 3.2.4, the cost of medical cannabis was prohibitive for some families. Parents expressed frustration that most antiepileptic drugs are reimbursed through either private or provincial insurance programs while medical cannabis is not.

“It's kind of frustrating as parents that there is an option out there that's not covered, but if we were ready to use clobazam or increase his stiripentol which, stiripentol especially costs thousands, that would be covered but this isn't. (Caregiver 2)

Although most parents interviewed had private insurance, none had coverage that included medical cannabis. Parents felt that if a doctor authorized cannabis use, it should be eligible for insurance coverage.

“I feel too though, insurance companies should be covering it. Because I don't know of any parents who would put their kids on this without having a medical condition. If it's been prescribed by a doctor, it should be covered. It's very frustrating that we still have to pay for it.” (Caregiver 10)

Parents were also frustrated that some insurance programs cover cannabis for other indications, but not for epilepsy:

“If they cover it for veterans they should cover it for kids who are having life-threatening seizures. If a neurologist says she thinks it's going to be helpful, how can they say no to that, right?” (Caregiver 18)

4. Discussion

“When you sit and watch your kid suffer and feel like you don't have any other medical options for them, it's pretty painful, you feel like you're failing your child when there's something out there that they need and might help them and you can't access it.” (Caregiver 17)

In the face of this unmet need, it is not surprising that parents of children with drug-resistant epilepsy wish to pursue medical cannabis. Yet, as described in this study, parents in Canada face many barriers when attempting to access medical cannabis for their children. In this qualitative study, we explored these barriers by use of a patient-centred access to care framework, focusing on five dimensions of access, namely approachability, acceptability, availability, affordability, and appropriateness. While participants described facing barriers related to each dimension, obtaining authorization (availability) and the cost of medical cannabis (affordability) represented important barriers expressed by the majority of parents.

Obtaining authorization for medical cannabis

In Canada, the first step to accessing the legal medical cannabis system is to obtain authorization from a health care provider, yet there are no regulations governing when it is appropriate for a physician to authorize medical cannabis [13]. In keeping with the experiences described by parents in this study, we recently found that some neurologists were unwilling (based on a lack of evidence and/or guidance) or unable (based on hospital or departmental policies) to authorize cannabis to children with drug-resistant epilepsy (Elliott et al. Unpublished results). Indeed, most parents described initially being met with resistance from their child's neurologist when they asked for medical cannabis authorization. An earlier study in Australia similarly noted that a lack of support and guidance from a child's health care provider was an important barrier to accessing medical cannabis for the treatment of epilepsy [6].

Ideally, care related to medical cannabis should be managed by health care providers who are knowledgeable and experienced in epilepsy care, antiseizure medications, and medical cannabis.[13] This recommendation from the Canadian Language Against Epilepsy stems from the potential for drug interactions between medical cannabis and commonly used antiepileptic drugs, which have been observed with both purified CBD [24] and cannabinoid oils [11,12]. However, about half of the parents interviewed for this study were unable to receive authorization from their child's neurologist, instead receiving authorization from another member of the child's care team (e.g., pediatrician) or from a cannabis clinic. For these patients, this resulted in a division of care, with antiepileptic medications being managed by the neurologist and cannabis being managed by another physician, which could lead to unsafe situations for the child [13].

The cost of medical cannabis

Medical cannabis is costly, with parents in this study spending up to \$2000 out of pocket each month on medical cannabis for their children. Although these costs were partially offset for some parents by discount programs, the cost of medical cannabis led to financial stress for many participants. Indeed,

some parents described incurring credit card debt or using Go Fund Me pages to pay for medical cannabis. Financial stress is common among parents of children with severe epilepsy [25], with parents frequently missing work, switching or quitting jobs, or losing a job because of their care-giving responsibilities [26,27]. The high cost of cannabis may add to this financial stress for some parents. Other studies have similarly identified the cost of cannabis as a barrier to treatment in epilepsy [6], and across other therapeutic purposes [14,28]. This barrier may disproportionately affect those in lower income groups[14] and may lead some patients to access cannabis through illegal channels instead of the medical system [29].

In Canada, cannabinoid oils are not reimbursed by any provincial or private insurance programs for the treatment of epilepsy [13]. Some private insurance companies have recently introduced coverage for medical cannabis [30]; however, epilepsy is not one of the approved indications. Parents in this study were frustrated that a treatment authorized by a health care provider is not eligible for insurance coverage. This was echoed in our previous study, in which neurologists described how parents were surprised to learn that medical cannabis is not eligible for insurance coverage (Elliott et al. Unpublished results). Further, some neurologists also expressed a belief that medical cannabis for epilepsy should be reimbursed by insurance programs, citing benefits to the health care system. This claim has not been tested [31], however, and will require formal consideration of the cost-effectiveness of cannabis-based products.

4.1 Limitations

In this study, we used qualitative methodology to provide an in-depth exploration of access to medical cannabis in Canada in the context of pediatric drug-resistant epilepsy. We recognize, however, that parents may have been motivated to participate in this study because of strong feelings about medical cannabis or as a type of advocacy. Notably, we interviewed only parents whose children had current or past use of medical cannabis, and we recognize that parents whose children have not used medical cannabis may have had different experiences, have different or more cautious

views about the potential benefits of cannabis for pediatric epilepsy, or faced additional barriers to access. Further, only those with authorization for medical cannabis use from a health care provider were eligible for participation in this study. Participants were recruited primarily from social media and by word of mouth, and we recognize that this may have excluded some participants.

Additionally, although we aimed to include participants from across Canada, the majority were from Ontario, and we acknowledge that experiences and perspectives may vary by region. We continued interviewing participants past saturation; however, some perspectives may have been missed.

4.2 Conclusion

Medical cannabis may address an unmet need among children with drug-resistant epilepsy. Despite perceiving medical cannabis as being an acceptable option, parents face important barriers when trying to access medical cannabis for their children. Strategies are needed to support parents who wish to pursue this treatment, including oversight by a health care provider with experience in epilepsy care, antiepileptic drugs, and medical cannabis.

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Appendix 1: Interview guide

- Question 1:** Can you tell me about when you first heard about cannabis as a potential treatment for epilepsy?
- Question 2:** How did you learn more about cannabis or get answers to your questions when you were considering giving it a try?
- Question 3:** Did you discuss cannabis with your child's health care providers?
- Question 4:** How did you decide whether or not to use cannabis for your child? What considerations were important to you in making the decision?
- Question 5:** From whom did you receive medical approval or authorization for cannabis use? Could you tell me about any problems you had in obtaining authorization?
- Question 6:** Before starting cannabis, what were your expectations about what would happen?
- Question 7:** Can you tell me about any concerns you had before starting cannabis?
- Question 8:** How often did you purchase cannabis? About how much money do you spend per month on cannabis for your child?
- Question 9:** Did you or do you have insurance coverage for your child's cannabis? If no, did you try to get it covered?
- Question 10:** How do you decide whether cannabis works for your child?
- Question 11:** Can you tell me about any problems that you've had related to the use of cannabis?
- Question 12:** Can you tell me about how your child's cannabis use has affected your relationships with others, starting with healthcare providers? What specific responses have you had?
- Question 13:** Can you tell me about any changes you've experienced with medical cannabis since the legalization of recreational cannabis in October 2018?
- Question 14:** Is there anything else that you would like to tell me about your experience with cannabis use for your child's epilepsy?

Chapter 6:

Discussion and Conclusion

6.1 Overview of Chapter 6

This thesis explored the use of medical cannabis in the treatment of pediatric drug-resistant epilepsy by use of a health technology assessment approach. Specifically, the safety and effectiveness of medical cannabis for pediatric epilepsy, including drug-resistant forms, was assessed via a living systematic review (**Chapter 3**), the cost-effectiveness of medical cannabis for drug-resistant pediatric epilepsy was assessed via systematic review and cost-utility analysis (**Chapter 4**), and the perspectives and experiences of key stakeholders (parents, neurologists) were explored via two qualitative studies (**Chapter 5**). Nine manuscripts were produced as part of this thesis; of these, five have been published and four have been submitted to peer-reviewed journals.

This final chapter serves as an overall discussion and conclusion for the thesis as a whole. (Each manuscript contained within Chapters 3–5 includes a discussion specific to that study.)

This chapter is intended to:

- Summarize the thesis rationale and objective (**Section 6.2**)
- Consider the implications of the thesis findings for clinical practice and health care policy (**Section 6.3**)
- Highlight the novelty of this thesis (**Section 6.4**), and describe its strengths and limitations (**Section 6.5**)
- Provide a brief introduction to ethical issues related to the use of medical cannabis in the treatment of pediatric drug-resistant epilepsy (**Section 6.6**).
- Provide suggestions for future research in this area (**Section 6.7**)

6.2 Summary of thesis rationale

The use of cannabis as a medicine dates back to at least 2700 BC,¹ and cannabis was described as a treatment for epilepsy as early as the mid-1800s in the medical literature.² However, owing to its illegal status in much of the world, the use of cannabis as a medicine received little clinical attention until the early 21st century. Among the general public and parents of children with epilepsy, interest in medical cannabis has grown exponentially since the early 2010s,³ owing largely to reports in the media of cases in which children's drug-resistant seizures were reduced or largely eliminated by treatment with cannabis.⁴ The clinical evidence base has also undergone important growth since that time, yet prior to this thesis there had been no comprehensive study of the use of cannabis as a treatment for pediatric drug-resistant epilepsy. As such, this thesis set out to provide usable evidence to clinicians, parents, and policy makers to inform their decisions about the use of medical cannabis in this population. To meet this aim, three research questions were addressed:

- Question 1:** What are the benefits and harms of medical cannabis for pediatric drug-resistant epilepsy?
- Question 2:** Is medical cannabis a cost-effective treatment for pediatric drug-resistant epilepsy compared to current therapeutic options?
- Question 3:** What are the perspectives of neurologists and parents about the use of medical cannabis for pediatric drug-resistant epilepsy?

6.3 Discussion of findings

The nine manuscripts that are included in this thesis included two protocols and seven result manuscripts distributed across three chapters (**Chapters 3–5**). The key findings from each chapter in relation to the three research questions are briefly summarized in Table 1. Following the table, the implications of the findings for clinical practice and health care policy are discussed.

Table 1: Summary of key findings from the thesis

Research question	Chapter	Key findings
<i>What are the benefits and harms of medical cannabis for pediatric drug-resistant epilepsy?</i>	Chapter 3 (Sections 3.1–3.3)	• 35 studies, including four RCTs, have assessed the benefits and harms of cannabis-based products for treatment of pediatric epilepsy; an additional 32 studies are registered in ClinicalTrials.gov • Cannabis-based products may be effective in reducing seizures among children with drug-resistant epilepsy; however, the certainty of the evidence is very low to moderate, and most of the evidence relates to purified CBD, which is not available in Canada • Only two studies have assessed cannabis-based products available in Canada*
<i>Is medical cannabis a cost-effective treatment for pediatric drug-resistant epilepsy compared to current therapeutic options?</i>	Chapter 4 (Sections 4.1–4.4)	• There have been no prior economic evaluations of cannabis-based products • Cannabinoid oil is cost-effective for the treatment of Dravet syndrome (compared with clobazam plus valproate) from the perspective of the Canadian public health care system, if a decision maker is willing to pay at least \$32,399 for each QALY gained • Cannabinoid oil is a more cost-effective choice than stiripentol, producing more QALYs at lower costs (dominant over stiripentol)
<i>What are the perspectives of neurologists and parents about the use of medical cannabis for pediatric drug-resistant epilepsy?</i>	Chapter 5 (Sections 5.1–5.2)	• Neurologists generally perceived medical cannabis as a viable option for children with drug-resistant epilepsy; however, important gaps in the evidence were identified, including a lack of long-term studies, knowledge about the effects of cannabinoids other than CBD, and an inability to predict which patients would benefit from medical cannabis • While some neurologists took on all aspects of the children’s care, including medical cannabis, others referred families to non-neurology health care professionals because of personal beliefs or institutional policies prohibiting authorization • Open communication with parents and families about medical cannabis is needed to ensure patient safety
		• Medical cannabis may address an unmet need for children with drug-resistant epilepsy, yet parents face many barriers in accessing it for their children • Most parents encountered resistance from their child’s neurologist about medical cannabis, and many received authorization from health care providers without training in neurology • Parents described being frustrated that medical cannabis is not reimbursed under private or public health care insurance programs
Note: CBD = cannabidiol, QALY = quality-adjusted life year, RCT = randomized controlled trial. *One study⁵ was identified as part of the living systematic review described in Chapter 3. A second study⁶ involving a cannabinoid oil available in Canada was identified in a review update performed after the final update included in this thesis.		

6.3.1 Implications for clinical practice

The evidence base related to the use of medical cannabis as a treatment for pediatric epilepsy has grown rapidly since the mid-2010s. As of May 2019, a total of 35 studies (including four randomized controlled trials [RCTs]) have been published that assess the benefits and harms of cannabis-based products in this population. The available data from the RCTs suggests that, among children with Dravet or Lennox-Gastaut syndrome, purified cannabidiol (CBD) probably reduces seizures compared with placebo. To date, seizure freedom has been assessed in one RCT⁷ involving 120 children with Dravet syndrome, with no statistically significant difference between placebo and CBD in terms of the number of children who became seizure free. However, the observed reduction in the number of seizures is likely a clinically meaningful finding. Similarly, no statistically significant difference was found in child quality of life after treatment with CBD compared with placebo across three RCTs involving 516 children with Dravet and Lennox-Gastaut syndromes.⁷⁻⁹ Improved quality of life has been reported, however, with the use of CBD relative to a before-treatment period in non-randomized studies^{10,11}; however, a lack of blinding and the absence of comparison groups makes the interpretation of these findings difficult. Further, there is uncertainty about the long-term effectiveness and harms associated with this treatment. (See Chapters 2 and 3 for description of these studies.)

The majority of the evidence available to date pertains to purified CBD (Epidiolex), which was recently approved by the US Food and Drug Administration¹² and the European Medicines Agency¹³ for the treatment of Dravet and Lennox-Gastaut syndromes. Epidiolex is not available in Canada, however, and, as of December 31, 2019, it has not been submitted for Health Canada review. Notably, Epidiolex differs from the cannabinoid oils available in Canada, in that the Canadian cannabinoid oils contain other cannabinoids in addition to CBD, in varying amounts depending on the product and supplier. Thus, the results of the RCTs described above do not necessarily apply to the Canadian context, an issue which was recently highlighted in the position statement from the

Canadian League Against Epilepsy (CLAE).¹⁴ Notably, in the study described in Chapter 5.1, several neurologists practicing in Canada described inferring the effectiveness and safety of Canadian cannabinoid oils based on the findings of studies involving Epidiolex, suggesting that additional education about cannabis is warranted.

To date, only two of the dozens of cannabinoid oils available to Canadian patients have been tested for effectiveness and/or safety in clinical studies. Both were small open-label prospective cohort studies involving children with Dravet syndrome¹⁵ or with either Dravet or Lennox-Gastaut syndrome.⁶ The interventions in the two studies differed, however, in terms of the ratio of CBD to THC in the cannabinoid oil. Both interventions are currently available through Health Canada-licensed producers, and both were associated with reduced seizure burden among study participants. Notably, adverse events were common in both studies, although most were transient and resolved with dosage reduction or reduction of concurrent antiepileptic drugs. Elevated hepatic aminotransferases levels were similarly common in both studies, indicating that liver function should be closely monitored for children using cannabinoid oils in conjunction with other drugs metabolized by the liver. (See Chapter 2 for a description of these studies.)

Most neurologists interviewed for the study described in Chapter 5.1 felt that a trial of medical cannabis was reasonable for children with drug-resistant epilepsy if other treatments had failed. Some participants felt that the evidence was sufficient for only Dravet and Lennox-Gastaut syndromes, although most were comfortable generalizing the evidence to other drug-resistant epilepsy syndromes. Notably, about half of the children of parents interviewed as part of the study described in Chapter 5.2 were authorized medical cannabis for the treatment of drug-resistant epilepsy syndromes other than Dravet and Lennox-Gastaut. At present, because Canadian cannabinoid oils are not subject to pre-market evaluation by Health Canada, they do not have an approved indication, and the determination of which children are suitable candidates for medical cannabis use is at the discretion of the authorizing physician. Several neurologists interviewed as part of the study

described Chapter 5.1 commented that it was difficult to predict which children would benefit from medical cannabis; this may be related to the heterogeneous nature of the epilepsy syndromes that make up “drug-resistant epilepsy.”

Most parents interviewed as part of the study described in Chapter 5.2 described purchasing cannabinoid oils directly from a Health-Canada licensed producer. However, some described purchasing dried cannabis and distilling their own oil (e.g., in a crock pot), which is permitted under the *Cannabis Act*. This practice was likely more common, however, prior to 2016 when cannabinoid oils were not available through the medical cannabis system. Clinicians should be aware that some parents may continue to distil their own oil because of a reluctance to change their child’s treatment regimen, and both clinicians and parents should be aware that the cannabinoid content of home-made oils will vary from batch to batch; further, home-made oils carry a risk of pesticide contamination.¹⁶ Some parents described having the contents of the oils tested; however, some noted that different laboratories had indicated different cannabinoid contents for samples from the same batch. Indeed, this anecdotal report has been confirmed in published studies of between-lab differences in cannabinoid content of the same product.¹⁷ In Canada, a total of 80 laboratories are authorized by Health Canada (as of December 31, 2019); however, Health Canada does not accredit laboratory testing methods or procedures.¹⁸

Additionally, some parents may be purchasing cannabinoid oils for their child outside of the medical system (e.g., from recreational distributors or from illicit suppliers). Obtaining cannabis outside the medical system carries additional risks, stemming primarily from the unknown composition and quality of the products, including the presence of pesticides^{16,19} and a lack of oversight by a health care provider. Additionally, product labels may not be accurate (or may not exist), and cannabinoid oils may contain either more or less cannabinoid than stated.²⁰ This is a particularly important issue for pediatric patients, as THC intoxication (inappropriate laughter, ataxia, reduced attention, and eye redness) and worsening of seizures has been reported among children with drug-resistant epilepsy

following administration of “CBD-enriched extracts,” although the children’s symptoms resolved after the extracts containing THC were replaced with purified CBD.²¹ It should be noted that parents who obtain(ed) cannabis outside the legal medical framework were not included in this thesis, in order to protect them from possible legal action. The University of Ottawa Research Ethics Board required that the study described in Chapter 5 include only parents who had obtained medical authorization for their child’s cannabis use.

Amendments to the Canadian *Cannabis Act* in mid-2019 have allowed the introduction of additional cannabis-based products (beyond oil and dried and fresh plant material) into the Canadian cannabis system (both recreational and medical); these products began appearing on the websites of licensed producers in early December 2019. These include, but are not limited to, cannabis edibles, extracts, and topicals. Although oil taken orally has traditionally been the preferred method of ingestion by medical users,^{16,22} these products will allow for more choice, and some may be attractive to parents of children with drug-resistant epilepsy. However, as with most of the available cannabinoid oils, the efficacy and safety of these products has not been evaluated, either by Health Canada or in clinical studies.

The availability of multiple cannabis-based products, as well as important differences between products, underscores the importance of open communication about medical cannabis between health care providers and parents. This was highlighted by the studies presented in Chapter 5, in which both neurologists and parents of children with drug-resistant epilepsy expressed a desire for open communication about medical cannabis. Although parents largely learned about medical cannabis from friends and family members, other parents, or the media, they described a desire for oversight and guidance from a neurologist, especially with respect to dosing. From the neurologists’ perspective, open communication with parents is required for the safety of the child. Neurologists described their concerns that some parents may be administering medical cannabis to their children without disclosing its use. Indeed, based on interviews conducted with parents as part of the study described in Chapter 5, this is a valid concern. In some cases, negative reactions from the child’s

neurologist about medical cannabis led parents to seek authorization from a health care provider at a cannabis clinic and to not inform the child's neurologist of the cannabis use. This can create a potentially unsafe situation for the child, as his or her neurologist is not able to monitor for drug-drug interactions or adjust the dose of other antiepileptic drugs in response to the cannabis use if needed. Although the prevalence of medical cannabis use among children with drug-resistant epilepsy is not known, medical cannabis use among children is not uncommon,²³ and neurologists are likely to encounter children using medical cannabis, even if they do not prescribe it themselves. As such, open discussions about medical cannabis, as well as other complementary and alternative treatments that a family may be trying, is necessary to prevent patient harm.

6.3.2 Considerations for Canadian policy makers

6.3.2.1 Reimbursement of cannabis-based products

Under the *Cannabis Act*, patients who receive authorization from a health care provider can purchase one of dozens of available medical cannabis products. However, these products can be expensive and are not covered by any public or private insurance program in Canada.¹⁴ In Chapter 5, parents of children with drug-resistant epilepsy described spending up to CDN\$2000 out of pocket per month on their children's cannabinoid oils. This was an important barrier to using medical cannabis for many parents, and most described being frustrated that medical cannabis is not eligible for insurance coverage while most other antiepileptic drugs are. However, there are important differences between how medical cannabis products and traditional pharmaceutical drugs are regulated (and hence reimbursed) in Canada.

Cannabis suppliers are licensed by Health Canada to cultivate, process and/or sell cannabis for medical purposes (licensed producers). However, these licenses centre mainly around manufacturing, security, and personnel, not the effectiveness and/or safety of the products. Notably, products designated as "Cannabis for Medical Purposes" (medical cannabis) are not subject to pre-market safety and efficacy review by Health Canada.²⁴ Further, these products are not issued a notice of

compliance (NOC) or a drug identification number (DIN). This is in contrast to “Health Products Containing Cannabis” (regulated under both the *Cannabis Act* and the *Food and Drug Act*), which are subject to pre-market safety and efficacy review by Health Canada and are issued a DIN and NOC.

Most of the Canadian products designated as “Cannabis for Medical Purposes” (e.g., cannabinoid oils) have not been tested for either effectiveness or safety, despite being used by patients for medical purposes with authorization from a health care provider required. There are two exceptions to this: two cannabinoid oils have been evaluated in small open-label single-group cohort studies.^{5,6} As described in the previous section, both were associated with reduced seizures in children with Dravet and Lennox-Gastaut syndromes, and adverse events were common but generally mild.

The cost-effectiveness of one of these oils (20:1 CBD:THC cannabinoid oil; CanniMed) was evaluated in Chapter 4. From the perspective of the Canadian public health care system, this oil was found to be a cost-effective treatment option compared to a regimen of clobazam and valproate for the treatment of Dravet syndrome, if a decision maker is willing to pay at least \$32,399 for each quality-adjusted life year (QALY) gained. Stiripentol, which is currently listed on several provincial formularies, was dominated by cannabinoid oil; that is, it was more costly and produced fewer QALYs, suggesting that it would not be the preferred treatment any willingness-to-pay threshold. Although there were limited data available for some model variables, a variety of sensitivity analyses were performed, and the findings were robust to all assumptions. Further, the 20:1 cannabinoid oil was cost-effective at all willingness-to-pay thresholds when a more broad societal perspective was adopted. Thus, there are opportunity costs associated with continuing to fund stiripentol when a more cost-effective option is available. That is, because health care resources are being spent in one way, they are not available to fund other drugs or technologies. When these health care resources are spent on a drug that produces fewer QALYs, this can lead to lower overall health of the population. Private insurance providers, which may reimburse stiripentol as well as other antiepileptic drugs, may also be

interested in these findings; however, they may be interested in different costs than those considered here (namely, costs related to absenteeism and drug costs but not those related to seizures).

Because the effectiveness of most other cannabinoid oils has not been tested, it is unclear whether these results are generalizable to other 20:1 cannabinoid oils, to oils with other CBD:THC ratios, or to patients with other types of drug-resistant epilepsy. In Chapter 5.2, some parents of children with drug-resistant epilepsy described achieving seizure control or reduction with one cannabinoid oil but not with others, suggesting that there may be differences in effectiveness between products; this could affect whether a specific oil is considered cost-effective. Further, the effectiveness data used in the cost-effectiveness evaluation were based on a very small number of children (seven) with Dravet syndrome or Lennox Gastaut syndrome who received the cannabinoid oil for a relatively short duration (up to seven months).

6.3.2.2 Amendments to the *Cannabis Act*

The *Cannabis Act* is set to be reviewed within the next 3 years. At that time, it is worth considering whether “Cannabis for Medical Purposes” should be reclassified as a Health Product and thus held to the same standards as both “Health Products Containing Cannabis” (e.g., nabiximols [Sativex] for treatment of multiple sclerosis, nabilone [Cesamet] for the treatment of nausea and vomiting associated with chemotherapy) and other prescription drugs. That is, policy makers should consider whether medical cannabis products (e.g., cannabinoid oils) should be subject to pre-market review of safety and efficacy by Health Canada. If medical cannabis products were brought under the Health Products umbrella, those that met the safety and efficacy standards would be issued a NOC and DIN and could be submitted to the Common Drug Review for review and listing recommendations for federal, provincial, and territorial public drug formularies. Further, these products would have an approved indication, which may improve the comfort of some health care providers in advising patients and caregivers about the use of these products. However, this would require a massive reorganization of the current medical cannabis framework. A full consideration of these issues would

require consultation with stakeholders including patients, health care providers, professional associations, and the cannabis industry.

6.3.2.3 Guidelines for professional associations

Authorization for medical cannabis use is commonly sought for children in Canada,²³ and, for parents of children with drug-resistant epilepsy, medical cannabis may be seen as a potential solution to an unmet health care need. As described in Chapter 5, neurologists are frequently asked to provide medical cannabis authorization for their pediatric patients, and some do not feel that there is adequate guidance on this topic. There are no approved indications for the use of medical cannabis in Canada, and health care providers must decide, in consultation with patients and/or their families, whether medical cannabis is an appropriate treatment. With the exception of the recent position statement by the Canadian League Against Epilepsy,¹⁴ most professional associations in Canada have been silent on the use of medical cannabis use by pediatric patients. However, neurologists interviewed as part of the study presented in Chapter 5 described a desire for guidance from associations such as these. The findings of this thesis, particularly those from Chapter 3 (benefits and harms of cannabis-based products in pediatric epilepsy) and Chapter 5 (stakeholder perspectives) will be of use to Canadian associations when they undertake updates of their policy documents. Notably, the Canadian Paediatric Society has indicated that an update of its 2016 statement²⁵ is forthcoming²⁶; the 2016 statement was released prior to the publication of most clinical studies related to the use of medical cannabis in the treatment of pediatric epilepsy.

6.4 Novelty of the thesis

This thesis represents the first comprehensive health technology assessment of medical cannabis for the treatment of pediatric drug-resistant epilepsy. Each chapter within the thesis makes a unique contribution to the literature, as summarized in Table 2. These findings represent an important contribution to the literature surrounding the use of medical cannabis for the treatment of drug-resistant epilepsy and will be useful for informing policies related to medical cannabis in Canada.

Table 2: Summary of key contributions of this thesis

Chapter	Area of contribution	Unique contribution
Chapter 3	Living systematic reviews	• When this project was conceived in early 2017, only four living systematic reviews had been published,^{27–30} and little methodological guidance was available • At the end of 2019, living systematic reviews are still relatively few, and most published to date have been undertaken by the Cochrane Living Evidence Network • A presentation about the considerations in undertaking a living systematic review was delivered at the 2019 CADTH Symposium (Appendix A)
	Effectiveness and safety of medical cannabis for pediatric drug-resistant epilepsy	• When this study was conceived, there had been one prior systematic review of medical cannabis for the treatment of epilepsy, published in 2014.³¹ This Cochrane review considered only evidence from RCTs and was performed prior to the publication of any RCTs involving children with epilepsy • While other systematic reviews of cannabis-based products for the treatment of epilepsy continue to be published,^{32–35} the review described in Chapter 3 is the only one to have an <i>a priori</i> defined update strategy and to have a stated intent of maintaining the currency of the review • Using living systematic review methodology, the evidence summary will continue to be kept up-to-date
Chapter 4	Economic evaluation of treatments for pediatric drug-resistant epilepsy	• Based on limitations identified in previously performed economic evaluations of treatments for pediatric drug-resistant epilepsy, a series of recommendations were proposed to improve the conduct and transparency of future economic evaluations in this area
	Cost-effectiveness of cannabinoid oil for Dravet syndrome	• The cost-utility analysis described in Chapter 4 represents the first economic evaluation of any medical cannabis product available in Canada for the treatment of any drug-resistant epilepsy syndrome
Chapter 5	Perspectives and experiences of neurologists with medical cannabis for pediatric drug-resistant epilepsy	• First in-depth exploration of the perspectives and experiences of neurologists related to the use of medical cannabis for treatment of pediatric drug-resistant epilepsy • Differences between clinical practice and the recommendations of the Canadian League Against Epilepsy were identified, including cannabis authorization and oversight being provided by health care practitioners without experience in epilepsy care • The impact of medical cannabis use by children with drug-resistant epilepsy on clinical practice was described
	Perspectives and experiences of parents of children with drug-resistant epilepsy who have used medical cannabis	• First study of the experiences and perspectives of parents of children with drug-resistant epilepsy with respect to accessing medical cannabis in Canada • Identified barriers to accessing medical cannabis in Canada, including difficulty finding a health care provider to provide authorization and the lack of affordability of medical cannabis for many families
Note: RCT = randomized controlled trial.		

6.5 Strengths and limitations

In this thesis, a health technology assessment was undertaken, guided by a framework developed by an international HTA agency.³⁶ The thesis addressed three primary aspects of HTA, namely a review of the benefits and safety, economic aspects, and stakeholder perspectives by use of differing, yet complementary, methodologies. Nine manuscripts were prepared as part of this thesis, and all have been published or submitted to peer-reviewed journals (Chapters 3–5). In this section, the strengths of each study are described (Table 3) followed by a discussion of the limitations that are common across studies.

Table 3: Strengths of the thesis

Chapter	Strengths
Chapter 3 (three published manuscripts)	• Comprehensive living systematic review of the published and grey literature, with a published protocol,³⁷ an explicit update plan, and an extensive search strategy developed by an experienced medical information specialist • Two family members of children with drug-resistant epilepsy and a pediatric neurologist were involved in selecting the outcomes for the review
Chapter 4 (two published manuscripts, two submitted manuscripts)	• Two comprehensive systematic reviews were undertaken to identify previous economic evaluations of medical cannabis, as well as decision models and inputs for a <i>de novo</i> cost-utility analysis • The review protocol was published,³⁸ and the search strategy was developed by an experienced medical information specialist • Canadian guidelines³⁹ were followed for the cost-effectiveness evaluation of cannabinoid oil
Chapter 5 (two submitted manuscripts)	• A pragmatic qualitative methodology (interpretive description) was followed as a guideline for the in-depth exploration of the perspectives of neurologists and parents of children with drug-resistant epilepsy about the use of medical cannabis

Despite the comprehensive and robust nature of this work, there are important limitations that bear consideration. In this section, these limitations are briefly described. (Note: The individual manuscripts presented in Chapters 3–5 each include a discussion of the limitations of importance to the individual studies; the focus here is on limitations that apply broadly across the thesis).

First, while the intent of this thesis was to provide information to aid in decision making about the use of medical cannabis for the treatment of pediatric drug-resistant epilepsy, it is important to note that the term “*drug-resistant epilepsy*” applies broadly across multiple types of epilepsy that may

have difference causes (e.g., structural, genetic, infectious).⁴⁰ The majority of the currently available clinical evidence, however, is related to specifically to two drug-resistant epilepsy syndromes: Dravet syndrome and Lennox-Gastaut syndrome. In particular, the four RCTs^{7-9,41} published to date have all involved children with these syndromes, as did the two studies^{5,6} involving cannabinoid oils available in Canada. Further, the cost-utility analysis presented in Chapter 4 relates to the use of cannabinoid oil in the treatment of Dravet syndrome. These considerations may limit the generalizability of the findings beyond these two syndromes.

Second, as described in Chapter 2, the cannabinoid oils available in Canada differ from those in other jurisdictions in important ways. Notably, the cannabinoid oils available in Canada contain THC and other cannabinoids as well as CBD. Purified CBD oil (Epidiolex), which is available in the US and Europe, does not contain THC or other cannabinoids beyond CBD. Further, there is a wide range of cannabinoid oils available in Canada, ranging from those high in CBD to those high in THC. As of December 31, 2019, a total of 61 cannabis producers in Canada have been licensed to sell cannabinoid oils to medical patients, and most carry multiple cannabinoid oils (e.g., with varying ratios of CBD to THC). However, only two of these oils have been evaluated in clinical trials. Thus, there is limited available information about the benefits and harms of the products available in Canada, which has implications for making decisions in practice. Further, the economic evaluation described in Chapter 4 is specific to one particular cannabinoid oil (CanniMed 20:1 Oil), and the findings do not necessarily apply to all cannabinoid oils produced in Canada or to those from other countries. This has implications for the use of these findings for making both clinical and policy decisions.

Finally, this thesis endeavored to include the perspectives of key stakeholders about the use of medical cannabis in the treatment of pediatric drug-resistant epilepsy (i.e., parents of children with drug-resistant epilepsy, neurologists who provide care for these children); however, there may be additional stakeholders who could provide insight into the use of medical cannabis. Notably, the

qualitative study described in Chapter 5 (Section 5.2) described barriers in accessing medical cannabis that were encountered by parents who had made the decision to use medical cannabis as a treatment for their children's epilepsy. However, parents whose children had not used medical cannabis may have experienced additional barriers that prevented cannabis authorization and/or use. Further, the interviews were conducted with the parents of the children, and the children may have different opinions or perspectives. Additionally, the qualitative study presented in Chapter 5 (Section 5.1) described the perspectives and experiences of neurologists; however, it became evident during the course of the study that some children received medical cannabis authorization from other health care providers, including physicians employed by cannabis clinics, as well as family physicians and pediatricians. Notably, in a 2017 survey, 38% of pediatricians reported having been asked to provide authorization in the past year,²³ although it is not known how many of these requests were related to drug-related epilepsy. Future studies involving additional stakeholder groups would further add to the knowledge base related to the use of medical cannabis.

6.6 Ethical issues related to medical cannabis in pediatric drug-resistant epilepsy

It has long been held that ethical issues should be considered as part of HTA,⁴² and some definitions of HTA include ethics as a key component.⁴³ Within the EUnetHTA Core Model, ethical analysis is intended to consider the “*prevalent social and moral norms and values relevant to the technology in question,*” with an aim of “*understanding the consequences of implementing or not implementing a technology.*”³⁶ Further, the Core Model differentiates between issues related to implementing (or not) the technology and issues related to the conduct of the HTA.³⁶ The process of fully assessing the ethical issues related to a health technology involves first identifying the ethical issues that are relevant to the technology and then completing an ethical analysis using structured methods to describe the relevant and potentially competing moral values; this analysis should consider the perspectives of all relevant stakeholders (e.g., patients, family members, health care providers, health insurers, industry).³⁶ A full analysis of the ethical issues related to the use of medical cannabis in the

treatment of pediatric drug-resistant epilepsy is beyond the scope of this thesis; however, these issues have been briefly explored in Table 4, in the context of the medical cannabis products available in Canada. The purpose of this section is to briefly introduce the ethical issues that may bear further consideration. These may include, but are not limited to, the balance between benefits and harms, autonomy, respect for persons, and justice and equity.³⁶ Further, the ethical issues related to performing the HTA are briefly considered.

Table 4: Ethical issues related to the use of Canadian medical cannabis products in the treatment of pediatric drug-resistant epilepsy

Ethical issue	Potentially relevant questions from the EUnetHTA Core Model ³⁶	Considerations
<i>Issues related to implementing the technology</i>		
Balance between benefits and harms	• What are the symptoms and the burden of disease or health condition for the patient? • What are the known and estimated benefits and harms for patients when implementing or not implementing the technology? • Are there any ethical obstacles for evidence generation regarding the benefits and harms of the intervention?	• There is no cure for drug-resistant epilepsy, which typically remains uncontrolled despite the use of multiple antiepileptic drugs • Epileptic seizures contribute to neurologic damage, cognitive impairment, an increased risk of status epilepticus and sudden unexpected death, and lower quality of life • Medical cannabis products in Canada do not undergo pre-market review by Health Canada, and the safety and effectiveness of most products has not been tested • Evidence from RCTs involving purified CBD does not necessarily apply to Canadian cannabinoid oils • Two small open-label cohort studies have suggested that cannabinoid oil may reduce seizures associated with Dravet and Lennox-Gastaut syndromes • There is limited evidence about the optimal dose, strain, or ratio of CBD to THC for treatment of drug-resistant epilepsy • Children with drug-resistant epilepsy may not be able to provide informed consent or assent to participate in clinical trials • Parents may not wish their child to be randomized to a control or placebo group because of the perception that their child requires medical cannabis
Autonomy	• Is the technology used for individuals that are especially vulnerable? • Does the implementation or use of the	• Children are considered a vulnerable group • Treatment decisions are typically made by a parent or adult caregiver. Children with

Ethical issue	Potentially relevant questions from the EUnetHTA Core Model ³⁶	Considerations
	technology affect the patient's capability and possibility to exercise autonomy? Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles?	drug-resistant epilepsy commonly have cognitive impairment that may further impede their ability to participate in treatment decisions - Medical cannabis may affect the patient–physician relationship if a parent wants to use medical cannabis but the health care provider is unwilling or unable to provide authorization - Health care providers are being asked to authorize use of a product that has not been evaluated by Health Canada for efficacy or safety; this may challenge health care providers' values and ethics
Respect for persons	- Does the implementation or use of the technology affect human dignity? - Does the implementation or use of the technology affect the patient's moral, religious or cultural integrity? - Does the technology invade the sphere of privacy of the patient/user?	- The child and/or family members may face stigma associated with medical cannabis use - Some family members may hold the belief that “drugs are bad”; this may result in these family members withdrawing from the child - Cannabis producers may collect health information about registered patients
Justice and Equity	- How does implementation or withdrawal of the technology affect the distribution of health care resources? - Are there factors that could prevent a group or person from gaining access to the technology?	- Authorizing medical cannabis use takes more time than writing a prescription for an antiepileptic drug - Health care providers may need to provide additional counseling and/or education to parents to dispel misinformation about medical cannabis - Health care may be managed by multiple care providers (e.g., authorization by a cannabis clinic); these providers may not have expertise and/or experience in providing epilepsy care - Parents may have to travel outside their community to find a health care provider willing to provide medical cannabis authorization - Because medical cannabis for pediatric epilepsy is not currently covered by provincial or private drug programs, it is only a treatment option for patients whose families can afford to pay out of pocket
Issues related to performing the HTA		
Ethical consequences of the HTA	- What are the ethical consequences of the choice of endpoints, cut-off values and comparators/controls in the assessment? - Are there any ethical problems related	- Endpoints of interest to families may not be measured in clinical trials (e.g., alertness) - The economic analysis assumed a social decision-making viewpoint; that is, that the aim of the decision maker is to maximize

Ethical issue	Potentially relevant questions from the EUnetHTA Core Model ³⁶	Considerations
	to the data or the assumptions in the economic evaluation? • What are the ethical consequences of conducting the technology assessment at this point of time?	population health • Cannabinoid oil is commonly used to treat drug-resistant epilepsy; change to the <i>Cannabis Act</i> or other policies may affect a large number of children
Note: CBD = cannabidiol, HTA = health technology assessment, RCT = randomized controlled trial, THC = tetrahydrocannabinol.		

6.7 Directions for further research

Based on the results of this thesis, as well as the limitations described in Section 6.5, four avenues of future research related pediatric drug-resistant epilepsy are proposed.

First, an evaluation of the effectiveness and safety of medical cannabis products available in Canada is needed. Currently, products designated as “Cannabis for Medical Purposes” are not subject to pre-market review by Health Canada. As such, efficacy and safety has not been assessed for most of the currently available medical cannabis products in Canada. Thus, it is important that studies involving these products be conducted to establish patient safety and to help ensure that families are not spending their money on ineffective treatments. This is a complicated issue, however, given that, as of December 31, 2019, a total of 165 companies held a license to sell at least one form of cannabis for medical purposes to authorized patients (including 61 authorized to sell cannabinoid oils), and the products are not necessarily consistent across producers or between batches. This issue is further complicated by the rare nature some drug-resistant epilepsy syndromes, as well as the diverse causes of drug-resistant epilepsy. Notably, many drug-resistant epilepsy syndromes are caused by genetic mutations, and findings may not be generalizable across syndromes. As such, conducting appropriately powered RCTs of these products may not be feasible, and alternative study designs should be considered. These may include prospective or retrospective cohort studies or N-of-1 studies, as well as observational registries of patients using cannabis-based products. Any interventional studies involving cannabis-based products should be extended post-trial to include long-term follow-up, which could be embedded within such a registry. Notably, a medical cannabis

registry was in effect in Quebec (Quebec Cannabis Registry) from 2014 to 2018, enrolling 3004 patients;⁴⁴ however, this registry did not include children. A similar registry was launched in November 2019 in the UK (Project Twenty21⁴⁵) and is projected to include 20,000 patients by the end of 2021; however, it is unclear whether children will be included in this registry.

The second area for future research would be the development of a decision aid for use by parents of children with drug-resistant epilepsy who are considering medical cannabis for their child. Decision aids may help parents participate in shared decision making about medical cannabis by providing evidence-based information about the available treatment options and helping them to clarify their values and preferences related to the different options.⁴⁶ Based on interviews conducted as part of this thesis, education for parents about medical cannabis is important, given that most learn about medical cannabis from friends and family, social media, or the lay media, and misinformation is common. The development of a decision aid would require a needs assessment with both patients and health care providers, creating the decision aid with a steering group including clinical experts and patients/family members, designing a prototype, testing its usability and feasibility with patients/families and clinicians, and field testing.⁴⁷ Finally, the effectiveness of the decision aids could be evaluated in an RCT, involving random allocation of parents and/or health care providers to receive the decision aid or usual care/education (i.e., no decision aid). Additionally, as exemplified in Section 5.1, additional formal education for neurologists about medical cannabis is warranted. This could be provided, at least in part, by a decision aid for use by clinicians to support communication with parents about medical cannabis use for the treatment of pediatric epilepsy. Such instruments, ideally developed together so that they are in alignment with each other, could improve the provision of high-quality family-centered care, by more fully involving parents into treatment decisions.

Third, as described in Section 6.6, there are many ethical issues related to the use of medical cannabis as a treatment for pediatric epilepsy. These should be considered in a formal ethical analysis led by an ethics expert and involve the use of structured methods to “*expose the relevant, often competing,*

moral values in the HTA, and to weigh their relative merits.”³⁶ Such an analysis will be of use to those making recommendations about the use of medical cannabis (e.g., policy makers, guideline developers).

Finally, core outcome sets for pediatric drug-resistant epilepsy are needed. At present, there is no core outcome set for this population, and the clinical trials reviewed as part of this thesis used a variety of outcome measures to assess the benefits and harms of medical cannabis. The development of a core outcome set would support informed health care decision making, by improving the reliability of systematic reviews by reducing outcome reporting bias among the included studies.⁴⁸

6.8 Conclusion

This thesis explored the intended and unintended consequences of treating pediatric drug-resistant epilepsy with medical cannabis, with the aim of providing usable information to clinicians, parents, and policy makers. Given the increasing interest in the use of medical cannabis, both in the general population and among parents of children with drug-resistant epilepsy, this thesis makes an important contribution to the literature by offering insights into the effectiveness and safety of these products. While cannabis-based products may reduce seizures among children with drug-resistant epilepsy, there is considerable uncertainty in the evidence base and most evidence relates primarily to a purified CBD product that is not available in Canada. This thesis also investigated the cost-effectiveness of treatment strategies involving medical cannabis, finding that cannabinoid oil may be a cost-effective treatment for Dravet syndrome compared with other currently available options. Finally, this thesis explored, for the first time, the perspectives and experiences of parents and neurologists in Canada related to the use of medical cannabis. Notably, parents sought medical cannabis to fill an unmet need stemming from the failure of currently available antiepileptic drugs but encountered many barriers in trying to access cannabis for their children. Neurologists, while generally in favour of a trial of medical cannabis after the failure of other treatments, identified

important gaps in the evidence base, including the lack of long-term studies and a lack of evidence related to the effects of cannabinoids other than CBD. These findings will be use in the development and refinement of policies related to the use of medical cannabis, as well as to clinicians and parents making treatment decisions about the use of medical cannabis for children with drug-resistant epilepsy.

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APPENDICES

Appendix A

Abstracts accepted for oral presentation

Cannabis for the treatment of pediatric epilepsy:

The case for a living systematic review

Elliott J, DeJean D, Clifford T, Coyle D, Potter B, Skidmore B, Alexander C, Repetski A, McCoy B, Wells GA.

Presented at: Society for Medical Decision Making, 40th North American Meeting, Montreal, QC; October 2018.

Purpose: To provide an example of how living systematic review (LSR) methodology can be used to supply up-to-date information to support evidence-informed decision-making. LSRs are frequently updated and incorporate evidence as it become available, thus avoiding the limitation of traditional systematic reviews, which may quickly become out of date. Here we describe a LSR of the use of cannabis for the treatment of pediatric epilepsy, an area of active research.

Method: We searched the published and grey literature (April 25, 2018) for randomized controlled trials (RCTs) and non-randomized studies (NRS) evaluating the use of cannabis-based products to treat epilepsy in children (0–18 yr). The primary outcome was seizure freedom; secondary outcomes included seizure frequency and quality of life. Data were pooled by random-effects meta-analysis, and risk of bias was assessed. Going forward, the literature search will be updated every 6 months, and newly identified records will be screened for inclusion. There are 3 potential update scenarios: 1) no new evidence is located, 2) new evidence is located but is not sufficient to trigger an updated analysis, or 3) new evidence is located, and new analysis and dissemination to stakeholders is required.

Result: In total, 4 RCTs and 19 NRS met the inclusion criteria for the initial review. Data from the included RCTs suggest that cannabidiol is effective in reducing monthly seizure frequency (median difference compared with placebo –20%, 95% confidence interval [CI] –28% to –12%), although only about 5% (95% CI 0% to 10%) of children experience seizure freedom with cannabidiol

treatment, and there was no significant difference in quality of life. Most RCTs were at low ROB, while most NRS were at high risk of bias. We identified 34 eligible on-going clinical studies at varying stages of completion; the results from these studies will be included in subsequent updates of this LSR in order to provide up-to-date information to decision makers.

Conclusion: To date, few RCTs have evaluated the use of cannabis as a treatment for pediatric epilepsy, although there are many ongoing studies. This is an ideal topic for a LSR because it is a priority for decision-making, there is little certainty in the existing evidence base, and evidence is rapidly accumulating. Registration: PROSPERO no. CRD42018084755.

How living systematic reviews can support health care decision-making:

The case of cannabis for pediatric epilepsy

Elliott J. DeJean D, Clifford T, Coyle D, Potter B, Skidmore B, Alexander C, Repetski A, McCoy B, Wells GA.

Presented at: CADTH Symposium, Edmonton, AB; April 2019.

Systematic reviews can quickly become out of date with the publication of new studies. Living systematic review (LSR) methodology can be used to incorporate evidence as it becomes available, to better inform health care decision-making.

LSRs comprise a baseline systematic review, followed by updates at set intervals. We performed an initial review in April 2018, which will be updated at 6-month intervals. Eligible studies were randomized controlled trials (RCTs) and non-randomized studies (NRS) involving children with epilepsy administered any cannabis-based product. The primary outcome was seizure freedom; secondary outcomes included seizure frequency and quality of life. Data were pooled, and risk of bias was assessed.

In the baseline review, 23 eligible studies (4 RCTs, 19 NRS) were identified. Data from the RCTs suggests that cannabidiol reduces seizure frequency (median difference –20% [95% confidence interval –27% to –13%]) with no significant effect on seizure freedom (risk difference 5% [–1% to 11%]) or quality of life (mean difference 0.6 [–2.6 to 3.9]). Thirty-three on-going studies were identified, which will be incorporated in subsequent updates. At Symposium, we will present data from the baseline review and first update, as well as our experiences in conducting a LSR.

Maintaining up-to-date systematic reviews is important in evidence-based decision-making, especially in areas with rapidly accumulating evidence. Cannabis for pediatric epilepsy is an ideal topic for a LSR because it is a priority for decision-making, there is little certainty in the existing evidence base, and there are many ongoing studies. PROSPERO CRD42018084755.

Appendix B

Abstracts accepted for poster presentation

Cannabis for pediatric epilepsy: A living systematic review

Elliott J, DeJean D, Clifford T, Coyle D, Potter B, Skidmore B, Alexander C, Repetski A, McCoy B, Wells GA.

Presented at: Innovations in the Science of Cannabis, Michael DeGroote Centre for Medicinal Cannabis Research, Hamilton, ON; February 2018.

Introduction: Interest has been steadily growing in the use of cannabis as a treatment for pediatric epilepsy, due in part to media reports of successful cases in which children's seizures have responded to cannabis despite the failure of conventional antiepileptic medications. However, there are large discrepancies between the beliefs of health care professionals and the general public with respect to its effectiveness and safety. As part of a health technology assessment of the use of cannabis in pediatric epilepsy, we are undertaking a comprehensive living systematic review of the benefits and harms of cannabis in this population to inform decision-making by parents, clinicians, and policy makers.

Methods: We performed a systematic review of the published and grey literature to identify randomized controlled trials (RCTs), quasi-experimental studies, and observational studies that involved children (aged 0–18 years) with any form of epilepsy taking any form of cannabis. The outcomes for this review were selected in consultation with family members of children with epilepsy and a clinical expert. The *primary outcome* is seizure freedom, and *secondary outcomes* are seizure frequency, quality of life, quality and/or quantity of sleep, all-cause death, sudden unexpected death in epilepsy, status epilepticus, and visits to the emergency department. The search will be updated every 6 months to identify newly available studies that meet the inclusion criteria. This poster presents on seizure freedom among children with epilepsy who received any form of cannabis.

Results: In total, 15 unique published studies were included (1 RCT, 6 prospective cohort studies, 3 retrospective cohort studies, 4 cross-sectional surveys, 1 case series). An additional 37 records from

ClinicalTrials.gov were included, suggesting that additional studies will be forthcoming. Among published studies, 1 RCT and 11 non-randomized studies reported seizure freedom. In the double-blind placebo-controlled RCT, no children in the placebo arm ($n = 59$) became seizure free, while three children in the cannabis arm ($n = 61$) became seizure free. Among all studies, the proportion of children administered cannabis who became seizure free was between 1% and 16%, with significant differences between study types.

Conclusions: To date, relatively few studies have assessed the benefits and harms of cannabis in children with epilepsy. The use of cannabis appears to be associated with an increased proportion of children who become seizure free, although estimates vary depending on study type. Although preliminary, these findings will be of use to decision makers as they navigate this rapidly evolving area.

Cannabis-based products for the treatment of pediatric epilepsy: A systematic review

Elliott J, DeJean D, Clifford T, Coyle C, Potter B, Skidmore S, Alexander C, Repetski A, McCoy B, Wells GA.

Presented at: Canadian League Against Epilepsy 2019 Annual Scientific Meeting, Winnipeg, MB; September 2019.

Rationale: Interest in cannabis as a treatment for epilepsy has grown over the past decade, driven in part by media reports of children whose epilepsy has responded to cannabis. An up-to-date overview of the available evidence is needed to support clinical decision-making.

Methods: We performed a comprehensive systematic review of the literature by searching MEDLINE, Embase, PsycINFO, Cochrane Library, and grey literature (May 9, 2019). We included randomized controlled trials (RCTs) and non-randomized studies involving children with any type of epilepsy who were administered a cannabis-based product (e.g., cannabidiol). The primary outcome was seizure freedom; secondary outcomes included seizure frequency and quality of life. Data were pooled, and risk of bias was assessed. The search will be updated at 6-month intervals to identify new studies.

Results: Thirty-four studies (4 RCTs) were included. Most involved the use of Epidiolex (cannabidiol) administered to children with drug-resistant epilepsy syndromes. Data from RCTs suggest that cannabidiol reduces seizure frequency (median difference –20% [95% confidence interval –27% to –13%]) with no significant effect on seizure freedom (risk difference 5% [–1% to 11%]) or quality of life (mean difference 0.6 [–2.6 to 3.9]). In total, 35 ongoing studies are registered in ClinicalTrials.gov; results will be included in subsequent updates of this review as data become available.

Conclusion: Evidence from high-quality RCTs suggests that cannabidiol may reduce seizures among children with drug-resistant epilepsy. At this time, evidence is primarily limited to cannabidiol, and the findings should not be extended to all cannabis-based products.

Appendix C

Abstracts submitted for conference presentation

Does cannabidiol represent good value for money?

A cost-utility analysis of cannabidiol for Dravet syndrome

Elliott J. Clifford T, Potter B, McCoy B, Wells GA, Coyle DC.

Submitted to: CADTH Symposium, Toronto, ON; April 2020.

Background: Drug-resistant Dravet syndrome in children is associated with morbidity and high health care costs. Limited clinical evidence suggests that cannabidiol improves seizure control, yet is costly and not reimbursed by any provincial formularies. We assessed whether cannabidiol is cost-effective compared with other available treatments (stiripentol, clobazam plus valproate).

Methods: We performed a probabilistic cost-utility analysis by use of a Markov model with health states related to seizure frequency. Transition probabilities, drug efficacy, utilities, and costs were obtained from a review of the literature. Outcomes included quality-adjusted life years (QALYs) and total costs. The incremental cost-effectiveness ratio (ICER; costs per QALY) was calculated over a 13-year period (age 5–18 years); assumptions were tested in scenario analyses.

Results: From a Canadian health system perspective, cannabidiol resulted in a gain of 4.2 QALYs at an additional cost of CDN\$146,686 compared to clobazam/valproate (ICER: \$34,919). At a willingness-to-pay threshold of \$50,000, cannabidiol was the optimal treatment in 71% of replications. Stiripentol was dominated by cannabidiol, producing fewer QALYs at higher costs. From a societal perspective, cannabidiol dominated both stiripentol and clobazam/valproate, owing to lower productivity costs. These findings were robust to most assumptions.

Conclusion: Compared with clobazam/valproate, cannabidiol is cost-effective for the treatment of Dravet syndrome, if a decision maker is willing to pay at least \$34,919 for each QALY gained. Cannabidiol is a more cost-effective choice than stiripentol, which is currently listed on several provincial formularies. The opportunity costs of continuing to fund stiripentol but not cannabidiol should be considered.

Decision-making in the face of uncertainty: Experiences of neurologists and parents with medical cannabis for children with drug-resistant epilepsy

Elliott J. DeJean D, Potter B, Coyle D, Clifford T, McCoy B, Wells GA.

Submitted to: CADTH Symposium, Toronto, ON; April 2020.

Background: Interest in the use of medical cannabis as a treatment of drug-resistant epilepsy in children is increasing; however, there is little clinical evidence or guidance for its use.

Methods: We conducted semi-structured telephone interviews with 12 neurologists and 19 parents of children with drug-resistant epilepsy in Canada. We sought to understand neurologists' perspectives about medical cannabis and their decision-making about cannabis authorization, and we explored parents' decision-making about medical cannabis. We also aimed to understand barriers to accessing medical cannabis from the parents' perspective and barriers to authorizing from the neurologists' perspective. Data analysis was guided by thematic analysis.

Results: Both neurologists and parents generally perceived medical cannabis as a viable treatment option for children with drug-resistant epilepsy. Parents viewed cannabis as less harmful than antiepileptic drugs; however, most experienced difficulty in finding a health-care provider to authorize its use. Neurologists expressed concerns about the lack of long-term evidence but desired open communication with families about cannabis use and their treatment goals. Cost was a key consideration in the decision-making of both parents and neurologists and was an important barrier to access for some families.

Conclusion: Our findings highlight the diverse experiences of neurologists and parents in Canada with medical cannabis for pediatric epilepsy. Cost and finding a health care provider to provide authorization are important barriers to medical cannabis use. Additional education about medical cannabis for both neurologists and parents may be warranted, in order to better prepare both groups to have informed conversations about medical cannabis.

Appendix D

Living systematic review — UPDATE 1:

Cannabis-based products for pediatric epilepsy

APPENDIX OVERVIEW and CONNECTION TO THESIS

Appendix D presents the results of the first update of the living systematic review described in **Chapter 3**. In October 2018, the literature search was updated, reflecting the 6-month period after the initial literature search. At that time, an additional 7 non-randomized studies were identified. In this appendix, data from the newly identified studies were combined with those from the baseline review and an updated summary of the evidence is presented. The data contained within in this appendix were subsequently included in the manuscript presented in **Section 3.3**.

SUPPORTING MATERIAL

Supplementary file 1: Included and excluded records

Supplementary file 2: GRADE summary – UPDATE 1*

AUTHOR ROLES AND CONTRIBUTIONS

JE, TC, DC, BP, CA, AR, BM and GW designed the study. BS developed and executed the search strategy. JE and DD selected studies for inclusion and assessed risk of bias. JE extracted study data, which were checked by DD. JE and VS assessed the certainty of the evidence using GRADE criteria. JE analyzed the data and wrote the first draft, which was critically revised for intellectual content by all authors.

SUMMARY

Objective: To update the baseline systematic review to include newly available evidence, in order to provide an up-to-date summary of the benefits and harms of cannabis-based products for pediatric epilepsy.

Methods: We updated the baseline systematic review to include evidence made available in the 6-month period following the initial literature search (April 25, 2018 to October 25, 2018; Update 1). Randomized controlled trials and non-randomized studies involving children with epilepsy administered any type of cannabis-based product were eligible for inclusion. The primary outcome was seizure freedom; secondary outcomes were seizure frequency (total, $\geq 50\%$ reduction), quality of life, sleep, status epilepticus, death, gastrointestinal adverse events, and visits to the emergency room. Risk of bias was assessed for each newly included study, and data from studies identified in the baseline review and Update 1 were pooled. Using the GRADE criteria, we assessed the updated the certainty of evidence for each outcome.

Results: In this first update of the living systematic review, we identified 7 studies published between April and October 2018, as well as 2 newly registered clinical trials. All of the newly identified studies were non-randomized, and each was at high risk of bias. Findings from these studies were generally consistent with earlier findings, and the certainty of the evidence did not change for any outcome.

Significance: Living systematic reviews can provide up-to-date summaries of the evidence base that can be used to support informed decision-making. At the time of this update, data from 30 studies assessing the benefits and harms of cannabis-based treatments for pediatric epilepsy were available; evidence from additional ongoing studies will be incorporated in future updates as data become available.

PROSPERO: CRD42018084755

INTRODUCTION

The use of cannabis as a treatment for epilepsy in children is an important topic for health care decision making, receiving frequent media attention and interest among parents and health care providers. In April 2018, we initiated a living systematic review to summarize the current evidence supporting the use of cannabis-based products in this population. Specifically, we sought to identify and appraise studies that have assessed the benefits and harms of cannabis-based treatments in children with epilepsy.

Living systematic review methodology was chosen for this project because the use of cannabis for pediatric epilepsy is a priority for decision-making, there is little certainty in the existing evidence base, and there are many ongoing studies.¹ Unlike traditional systematic reviews, which may be updated infrequently or not at all, living systematic reviews are updated at set, *a priori* defined intervals, in order incorporate new evidence as it becomes available.¹

In the baseline review (April 2018), we identified 23 studies (4 randomized controlled trials [RCTs], 19 non-randomized studies [NRS]) that met the eligibility criteria.² Evidence from high-quality RCTs suggests that, among children with drug-resistant epilepsy, cannabidiol reduces seizure frequency and increases the number of children with at least a 50% reduction in seizures (treatment response), while increasing the risk of diarrhea. We found no statistically significant difference in seizure freedom, quality of life, sleep disruption, or vomiting between cannabidiol and placebo.² Among the NRS, seizure freedom was reported for up to 20% of children administered a cannabis-based product, with estimates of treatment response between 24% to 100% and improved quality of life reported in two small studies. Notably, all NRS were at high risk of bias, and the certainty of the evidence was very low for most outcomes.

In the baseline review, we identified an additional 33 trial registration records in ClinicalTrials.gov and 14 conference abstracts that did not correspond to published studies, indicating that this is an

area of active research. In order to incorporate newly published evidence, we updated the review in October 2018, 6 months after the initial literature search.

Objectives

1. To identify and appraise studies published in the 6-month interval (April–October 2018) following the baseline systematic review;
2. To integrate findings from the newly published studies with those from previously published studies, in order to provide a comprehensive, up-to-date summary of the evidence base.

METHODS

The methods for this review have been published³ and are presented in Chapter 3.1 and 3.2. Briefly, we systematically searched the published and grey literature for randomized and non-randomized studies involving children with any form of epilepsy who were administered any type of cannabis-based product. The literature search strategy has been published³ and is available in Chapter 3.1. The search was performed on October 25, 2018, and covered the 6-month interval following the baseline review search April 25, 2018. The eligibility of each identified record was evaluated by two independent reviewers by use of the following PICO criteria:

Population: Children (≤ 18 yr) with any type of epilepsy.

Intervention: Any type of cannabis-based product, including CBD, cannabitol, THC, or their combinations, administered by any route (e.g., oral, inhalation).

Comparators: Pharmacologic (i.e., antiepileptic drugs [AEDs]) and non-pharmacologic (e.g., diet therapy, vagus nerve stimulation, resective brain surgery) treatments, as well as placebo, usual care, or no treatment.

Outcomes: The primary outcome was seizure freedom. Secondary outcomes: seizure frequency (total, tonic-clonic, $\geq 50\%$ reduction from baseline), quality of life (child, caregiver), sleep, status epilepticus, death (all-cause, sudden unexpected death in epilepsy [SUDEP]),

gastrointestinal adverse events (vomiting, diarrhea), and visits to the emergency room. The outcomes were selected in consultation with two patient family representatives and a clinical expert.

Study designs: All study designs were eligible.

Data were extracted and risk of bias was assessed by one reviewer (J.E.) and checked for completeness and accuracy by a second reviewer (D.D). Descriptive summaries are provided for study selection, study and patient characteristics, and quality assessment. Data from RCTs were pooled by random-effects meta-analyses (RevMan v.5.3) or Comprehensive Meta-Analysis (v. 2.2.064) and are reported as relative risk (RR), risk difference (RD), mean difference (MDs), or median difference and 95% confidence intervals (CIs). Data from non-randomized studies are reported as the proportion of participants who experienced an outcome (pooled via *metaprop* command in STATA), and data are reported as percentage of those exposed (with 95% CIs). In cases where multiple time points were reported, data from the longest duration of follow-up were analyzed. Finally, we updated the GRADE assessment performed as part of the baseline review to include newly available evidence.

RESULTS

Study selection and characteristics

A total of 320 records were screened after removal of duplicates (Figure 1). Of these, 17 records met the eligibility criteria, corresponding to seven unique published studies^{4–10} (all non-randomized designs; Table 1), one study protocol,¹¹ seven conference abstracts,^{12–18} and two clinical trial registration records.^{19,20} The full list of included and excluded studies is available in Supplemental file 1. Of the included conference abstracts, three correspond to published studies,^{13,15,18} while four represent as yet unpublished studies (Table 2).^{12,14,16,17} Of the two newly identified clinical trial registration records, one corresponds to a randomized controlled trial,¹⁹ and one corresponds to a prospective single group cohort study²⁰ (Table 3).

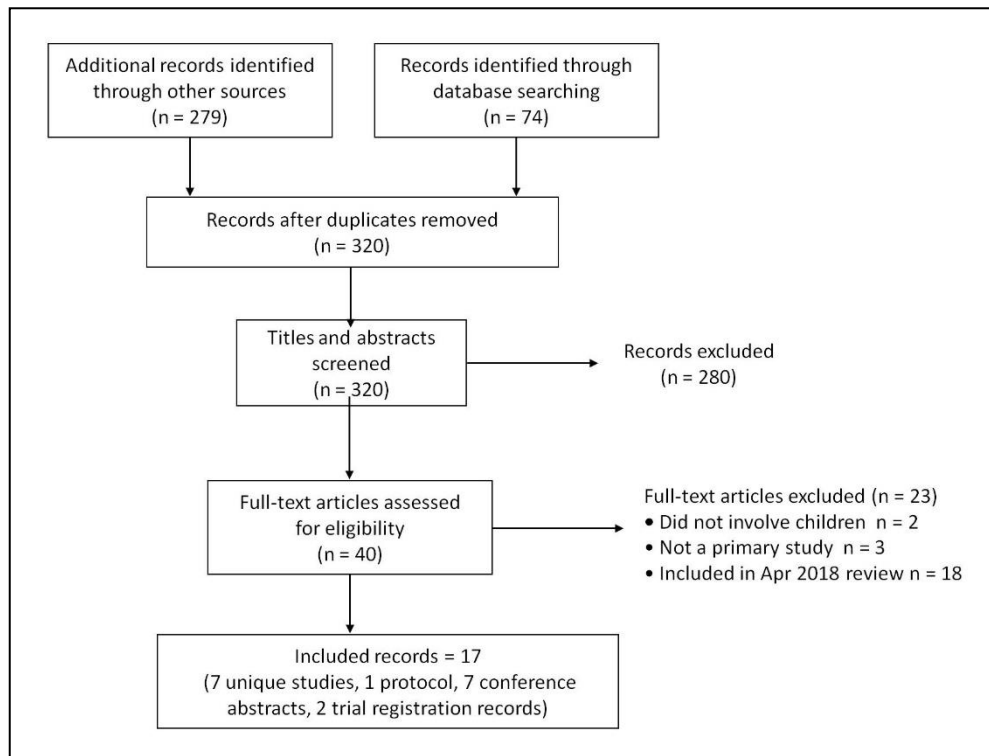


Figure 1: PRISMA flow diagram showing selection of studies

Of the seven newly published studies, six were single-group prospective cohort studies⁴⁻⁹ and one was a cross-sectional survey¹⁰ (Table 1). Suraev and colleagues¹⁰ reported parent's perceptions of the effectiveness and safety of different cannabis-based interventions and did not provide usable data toward this review. Additionally, one publication⁶ reported an additional analysis of a single-group prospective cohort study that had been included in the baseline review (Gaston 2017²¹; NCT02695537); however, the publication by Gaston 2017²¹ did not report any outcomes of interest. One additional study⁴ included in this update reports the pooled analysis of data from 25 expanded access programs in the US for 607 participants over a median treatment duration of 48 weeks; data from 11 of these sites for a shorter treatment duration (12 wk) were previously published and were included in the base review (Devinsky 2016²²). Similarly, the publication by Devinsky and colleagues (2018)⁸ represents a subgroup analysis of a patients included in the 2016 analysis by Devinsky and colleagues²² as well as patients enrolled after the cut-off for the analysis by Devinsky

2016. As such, Update 1 identified three new cohorts of participants^{5,7,9} and three cohorts^{4,6,8} that included at least some participants who had been enrolled in studies included in the baseline review.

In Update 1, the type of cannabis-based intervention was consistent across most included studies: all studies involved an oral solution involving cannabidiol, although the dose by patient weight varied across preparations (Table 1). One study involved a product containing both cannabidiol (100 mg/ml) and THC (2 mg/mL).⁵ This is consistent with the baseline review, in which most (68%) studies involved cannabidiol-based products. The treatment duration among studies included in Update 1 ranged from 12 to 146 weeks, while studies included in the baseline review ranged from 10 days to 57 months.

Table 1: Characteristics of studies identified in UPDATE 1

Author, yr, page no. (NCT no.)	Design features	Population	Inclusion criteria	Treatments (no. in group)	Duration of cannabis treatment	No. centres; country	Funding source	Risk of bias (primary reason)
Szaflarski 2018, p. 131 ⁶ (NCT02695537)	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	>1 yr to 19 yr, failure of ≥ 4 AEDs at an adequate dose, including ≥ 1 trial of 2 concomitant AEDs, stable VNS settings and ketogenic diet for ≥ 3 mo	Oral CBD solution, up to 50 mg/kg/d, given in 2 divided doses (70)*	48 wk	1 centre; US	State of Alabama GW Research Ltd.†	High (potential selection bias; unblinded outcome assessment; lack of a comparison group; outcomes not consistent with NCT record)
Szaflarski 2018, p. 1540 ⁴	Prospective, single-group, open-label cohort‡	Drug-resistant epilepsy	DRE, receiving stable doses of AEDs for ≥ 4 weeks before enrollment	Oral CBD solution, up to 50 mg/kg/d, given in 2 divided doses (607)	Median 48 weeks (range 2-146 weeks)	11 centres; US	Alabama General Funds; GW Research; New York State Department of Health; Epilepsy Foundation	High (potential selection bias; unblinded outcome assessment; lack of a comparison group)
McCoy 2018, p. 1077 ⁵ (NCT02983695)	Prospective, single-group, open-label cohort	Dravet syndrome	1–18 yr, Dravet syndrome with DRE, frequent motor seizures, stable AED therapy for 4 wk and stable KD/VNS settings for ≥ 3 mo	Oral solution (50:1 CBD:THC; TIL-150), up to 16 mg/kg/d CBD (0.32 mg/kg/d THC) (20)	20 wk	1 centre; Canada	Tilray, The Little Rocky Project	High (potential selection bias; small sample size; unblinded outcome assessment; lack of a comparison group)
Chen 2018, p. 217 ⁷	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	<18 years, DRE, $\geq$ seizure/d for ≥ 6 mo, ≥ 1 epilepsy-related hospital admissions, failure of ≥ 5 AEDs including a trial of a combination of 2 drugs	Oral CBD solution, up to 25 mg/kg/d, given in 2 divided doses (40)	12 wk	3 centres; Australia	NSW Government, GW Pharmaceuticals†	High (small sample size; unblinded outcome assessment; lack of a comparison group)
Freeman 2018, p. 228 ⁹	Prospective, single-group, open-label cohort	Drug-resistant epilepsy	Children with severe refractory epilepsy	Oral CBD solution, up to 20 mg/kg/d, given in 2 divided doses (20)	Up to 40 weeks; median 23 weeks	1 centre; Australia	NR	High (small sample size; lack of detail about methods [published as a research letter], potential selection bias; unblinded

Author, yr, page no. (NCT no.)	Design features	Population	Inclusion criteria	Treatments (no. in group)	Duration of cannabis treatment	No. centres; country	Funding source	Risk of bias (primary reason)
								outcome assessment; lack of a comparison group)
Devinsky 2018, p. 131 ⁸	Prospective, single-group, open-label cohort¶	CDKL deficiency, Aicardi, Dup15Q, Doose syndrome	Severe childhood-onset epilepsy (CDKL deficiency, Aicardi, Dup15Q, or Doose syndrome)	Oral CBD solution, up to 25 mg/kg/d or 50 mg/kg/d (depending on study centre), given in 2 divided doses (55)	48 wk (efficacy); up to 144 wk for safety	8 centres; US	GW Pharmaceuticals†	High (potential selection bias; small sample size for individual syndromes; unblinded outcome assessment; lack of a comparison group; publication bias [outcome listed in methods not reported in results])
Suraev 2018, p. 10154 ¹⁰	Cross-sectional	Children with epilepsy (72% with DRE)	Epilepsy, with or without current or prior use of medical cannabis Respondent: Parent or guardian Control: no cannabis use Online survey link distributed by Epilepsy Action Australia	41 families provided 61 cannabis samples; of these, 62% extracts were from medicinal suppliers, 15% were from a recreational “dealer”, 13% were made by the family, 9% were from online suppliers, 3% were from federal/state government schemes	NR	NA	The Lambert Initiative for Cannabinoid Therapeutics	NA (no reported outcomes of interest)
Reithmeier 2018, p. 221 ¹¹ (NCT03024827)	Protocol: open-label, dose-escalation phase 1 trial	Drug-resistant epilepsy	1–10 years with drug-resistant* epileptic encephalopathy	Oil-based extract of Cannabis sativa (CanniMed Therapeutics Inc.), 20:1 CBD:THC ratio (NR)	6 months	1; Canada	Non-industry**	NA (no reported outcomes of interest)

Note: AED = antiepileptic drugs, CBD = cannabidiol, DRE = drug-resistant epilepsy, KD = ketogenic diet, NA = not applicable, NR = not reported, THC = tetrahydrocannabinol, VNS = vagus nerve stimulation.

*Pediatric group; study also enrolled an additional 62 adults.

†Provided CBD solution (Epidiolex).

‡Pooled results from 25 US Expanded Access Programs (EAP); updated analysis of Devinsky 2016²², which included 11 EAP programs and 214 children.

¶Includes patients from Devinsky 2016²² with CDKL deficiency, Aicardi, Dup15Q, Doose syndrome, as well as additional patients enrolled after the cut-off for Devinsky 2016.

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Table 2: Conference abstracts identified in UPDATE 1

Author, yr (NCT no.)	Design features	Population	Treatment (no. in group)	Duration of treatment
MATCHED*				
Joshi 2018 ¹³	GWPCARE4 (matches to Thiele 2018 ²³ ; included in baseline review)	Lennox-Gastaut syndrome	Oral CBD, 20 mg/kg/d (86) Placebo (85)	14 wk
Wirrell 2018 ¹⁵	GWPCARE3 (matches to Devinsky 2018 ²⁴ ; included in baseline review); randomized controlled trial	Lennox-Gastaut syndrome	Oral CBD, 10 mg/kg/d (73) Oral CBD, 20 mg/kg/d (76) Placebo (76)	14 wk
Szaflarski 2018 ¹⁸	NCT0269553 (matches to Szaflarski 2018 ⁶ ; included in Update 1); open-label, single group prospective cohort study	Drug-resistant epilepsy	Oral CBD, up to 50 mg/kg/d (70)	48 wk
UNMATCHED				
Miller 2018 ¹⁷ (GWPCARE5; NCT02224573)	Open-label extension of NCT02091375 or NCT02224703	Drug-resistant epilepsy, aged 13–19 yr, mean 10 yr, 50% male	Oral CBD, 100 ng/ml, mean dose 21 mg/kg/d (264)	48 wk
Wirrell 2018 ¹⁴	Pooled data from GWPCARE3 (NCT02224560) and GWPCARE4 (NCT02224690)	Lennox-Gastaut syndrome; mean 15 yr (32% ≥ 18 yr)	Oral CBD, 10 mg/kg/d (73), 20 mg/kg/d (162) Placebo (161)	14 wk
Morrison 2018 ¹⁶	Pooled data from GWPCARE3 (NCT02224560) and GWPCARE4 (NCT02224690)	Lennox-Gastaut syndrome; age range 2.6–48 yr	Oral CBD, 10 mg/kg/d, 20 mg/kg/d Placebo (360 patients)	14 wk
Halford 2018 ¹² (GWPCARE5; NCT02224573)	Open-label extension of NCT02224560 or NCT02224690	Lennox-Gastaut syndrome; mean age 16 yr (33% ≥ 18 yr)	Oral CBD, 100 ng/ml, mean dose 23 mg/kg/d (366)	60 wk
Note: CBD = cannabidiol. *Records were matched to included published studies by study name, ClinicalTrials.gov record number, study authors, or description of the study population and results.				

Table 3: Trial registration records identified in UPDATE 1*

Registration number	Title	Sponsor	Population	Eligible ages, yr	Treatments	Design	Recruitment status	Primary completion date (estimated or actual)	Country
NCT03676049	Cannabidiol for drug resistant pediatric epilepsy	University of Mississippi Medical Centre	Drug-resistant epilepsy	5–19 years	CBD oral solution, up to 300 mg/d	Single group interventional	Available	NR	US
ACTRN12618001706268	A double-blind placebo-controlled study investigating the safety, tolerability, efficacy and pharmacokinetics of EP1, and enriched cannabidiol oil in children and adolescents with medication resistant refractory epilepsy	Cann Pharmaceutical Australia Limited	Drug-resistant epilepsy	2–18 years	Oral solution, CBD:THC 20:1 ratio	Randomized	Not yet recruiting	2022	Australia
Note: CBD = cannabidiol, NR = not reported, THC = tetrahydrocannabinol. *An additional 33 trial registration records were identified in the baseline review.									

Participant characteristics

The newly included studies⁴⁻⁹ involved 812 participants (range 20–607) with various types of drug-resistant epilepsy (Table 1). Four studies included participants with multiple forms of drug-resistant epilepsy,^{4,6,7,9} while one study focused Dravet syndrome⁵ and one focused on participants with CDKL deficiency, Aicardi, Dup15Q, and Doose syndrome.⁸ The range of mean ages of included participants, where available, was between 10 and 13 years (Table 4), which is comparable to studies included in the baseline review (range of means 7 to 14 years). Similar to studies in the baseline review, those included in Update 1 involved the addition of a cannabis-based product to an established regimen of antiepileptic therapies, with participants taking an average of four antiepileptic drugs during the study period.

Risk of bias

The overall risk of bias was considered to be high for each of the six non-randomized studies that provided data for Update 1, owing primarily to lack of a control group and lack of blinding (Table 1). Five⁴⁻⁸ of six studies reported support from a pharmaceutical company, ranging from supplying the intervention^{4,6-8} to collecting study data and supplying it to the authors for analysis⁸; the remaining study did not report the source of study funding.⁹ The high risk of bias among the studies included in Update 1 is consistent with the risk of bias among those included in the baseline review.

Table 4: Characteristics of participants included in studies identified in UPDATE 1

Author, yr	Treatments*	Age, yr, mean (range)†	Male, %	BMI or weight at baseline	No. of concomitant AEDs	No. previous AEDs	Other interventions
Szaflarski 2018, p. 131 ⁶ (NCT02695537)	CBD	10.1 (SD 4.9)	47%	NR	Mean 2.7 (SD 1.0)	Mean 8.2 (SD 2.8)	NR
Szaflarski 2018, p. 1540 ⁴	CBD	13.2 (0.4–62.1)	52%	NR	Median 3 (range 0–10)	NR	NR
McCoy 2018 ⁵ (NCT02983695)	CBD:THC 50:1	10.2 (2.1–17.8)	50%	Mean 19.2 (range 15.8–30.7)	Mean 2.9 (range 1–4)	NR	KD: 10% VNS: 20%
Chen 2018 ⁷	CBD	Median 8.5 (1.6–16.6)	55%	NR	Median 3 (range 1–5)	Median 9 (range 3–14)	KD: 48% VNS: 5% Surgical resection: 10% Corpus callosotomy: 7.5%
Freeman 2018 ⁹	CBD	Median 10 (2–17)	25%	NR	NR	NR	NR
Devinsky 2018 ⁸	CBD	32% aged < 5 yr; 60% aged 6–17 yr; 8% aged ≥ 18 yr	20%	NR	Range 0 to >4; 70% taking 2 or 3 AEDs	NR	NR
Note: AED = antiepileptic drug, CBD = cannabidiol, KD = ketogenic diet, NR = not reported, SD = standard deviation, THC = tetrahydrocannabinol, VNS = vagus nerve stimulation. *Described in Table 1. †Unless otherwise stated.							

Summary of results

Of the seven studies identified in Update 1, six reported at least one outcome of interest.⁴⁻⁹ For each outcome, we first summarize the evidence that had been available as of the baseline review (April 2018), then describe the newly available evidence made available between April and October 2018. This is followed by a summary of all available evidence up to October 2018, incorporating studies identified in both the baseline review and Update 1. The updated GRADE assessment is provided in Supplemental file 2.

Primary outcome: *Seizure freedom*

BASILINE REVIEW: Fifteen studies reported results related to seizure freedom after administration of a cannabis-based product, including one RCT²⁵ and 14 non-randomized studies (six prospective single-arm cohort studies,^{22,26-30} four retrospective single-arm cohort studies,³¹⁻³⁴ one comparative retrospective cohort study,³⁵ three cross-sectional studies³⁶⁻³⁸) (Table 5). In the RCT,²⁵ three children (5%; n = 61) with Dravet syndrome who received CBD experienced freedom from all seizures, while no children in the placebo group (n = 59) became seizure free during a 14-week treatment period (RD 5%, 95%CI -1% to 11%; low certainty). Among the NRS available at that time, the estimates of seizure freedom ranged from 1% to 20%, with a pooled proportion of 7% (95%CI 4% to 11%), with the highest estimates observed among cross-sectional studies (very low certainty).

UPDATE 1: Four prospective single-arm cohort studies⁴⁻⁷ reported results related to freedom from all seizure types after administration of a cannabis-based product (Table 5), with a pooled proportion of 8% (95%CI 3% to 12%); duration 12 to 96 weeks) (Figure 2).

EVIDENCE SUMMARY (as of October 2018): In total, 19 studies, including one RCT²⁵ and 18 non-randomized studies^{4-7,22,26-31,33-39} have reported seizure freedom (Table 5). The estimate of seizure freedom from RCTs remains unchanged from the baseline review, as does the pooled proportion of seizure freedom from non-randomized studies (7%, 95%CI 4% to 10%) (Figure 3). The

certainty of the evidence (based on GRADE criteria) related to seizure freedom with cannabis-based treatment remains unchanged from the baseline review (RCTs: low; NRS: very low; Supplemental file 2), although the uncertainty around the point estimate is reduced (i.e., more narrow 95% CI).

Figure 2: Seizure freedom among non-randomized studies included in UPDATE 1

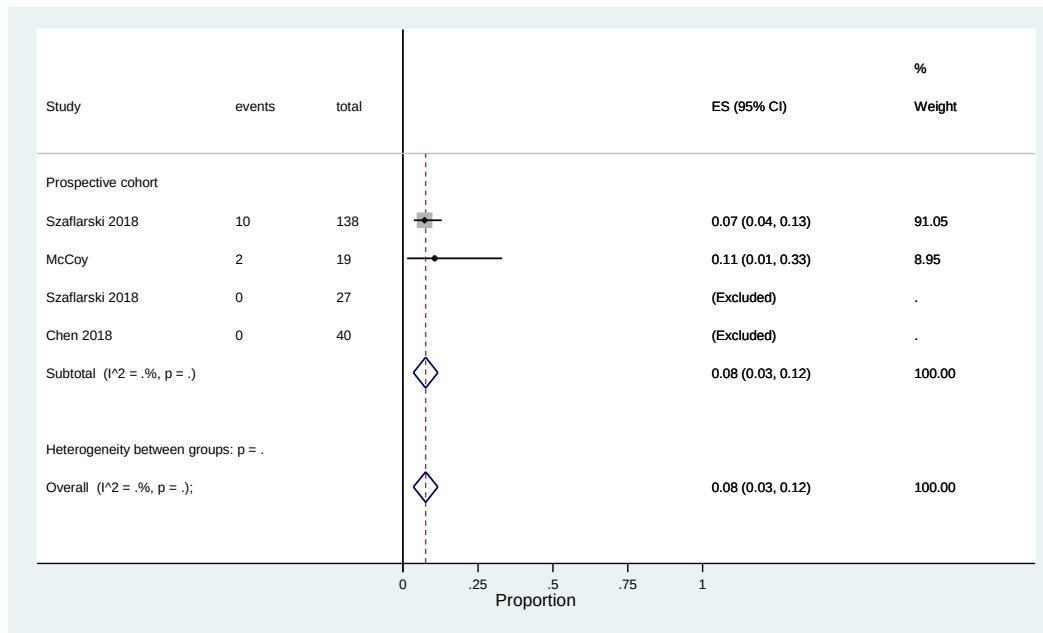


Figure 3: Seizure freedom among non-randomized studies — State of the evidence as of October 2018

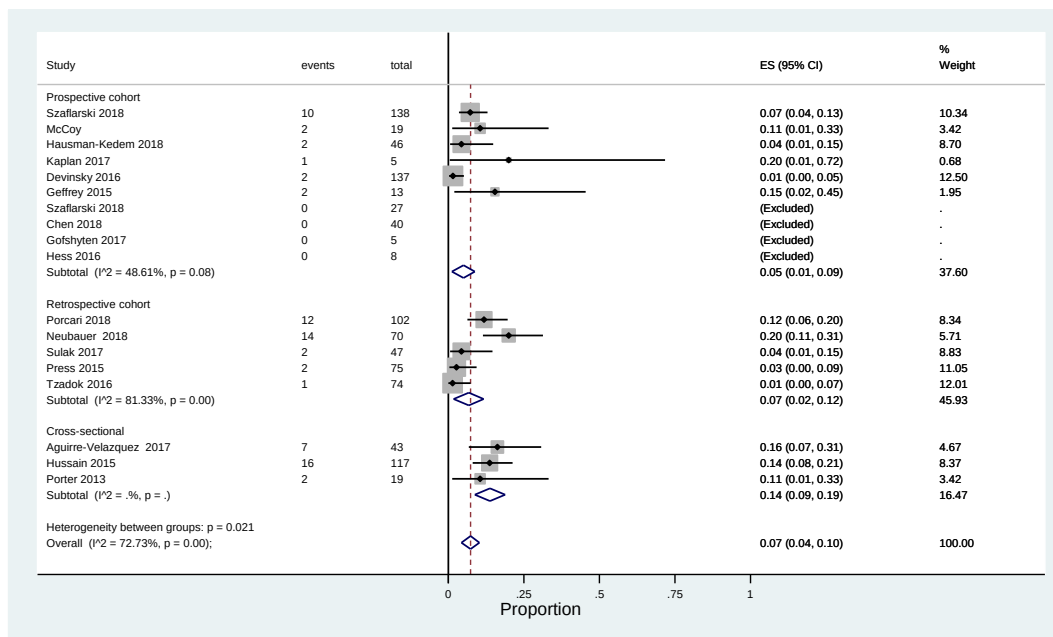


Table 5: Evidence summary — Seizure freedom (freedom from all seizure types)*

Author, yr	Study design	Population	Treatments†	Duration	No. events/no. in group (%)‡	
					Cannabis-based treatment	Control
UPDATE 1 (April–October 2018)						
Szaflarski 2018, p. 131 ⁶	Prospective single-group cohort	Drug-resistant epilepsy	CBD	• 12 wk • 24 wk • 48 wk	• 6/70 (9) • 4/43 (9) • 0/27 (0)	NA
Szaflarski 2018, p. 1540 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	CBD	• 12 wk • 24 wk • 48 wk • 72 wk • 96 wk	• 26/431 (6) • 25/412 (6) • 17/282 (6) • 16/197 (8) • 10/138 (7)	NA
McCoy 2018 ⁵	Prospective single-group cohort	Dravet syndrome	CBD:THC	20 wk	2/19 (11)	NA
Chen 2018 ⁷	Prospective single-group cohort	Drug-resistant epilepsy	CBD	12 wk	0/40 (0)	NA
BASELINE REVIEW (Up to April 2018)						
Devinsky 2017 ²⁵	RCT	Dravet syndrome	CBD Placebo	14 wk	3/61 (5)	0/59 (0)
Hausman-Kedem 2018 ²⁶	Prospective single-group cohort	Drug-resistant epilepsy	CBD:THC	Median (range): 18 (3–33) mo	2/46 (4)	NA
Devinsky 2016 ²²	Prospective single-group cohort	Drug-resistant epilepsy	CBD	12 wk	2/137 (1)	NA
Geffrey 2015 ²⁷	Prospective single-group cohort	Drug-resistant epilepsy taking CLO	CBD	8 wk	2/13 (15)	NA
Hess 2016 ²⁸	Prospective single-group cohort	Tuberous sclerosis complex	CBD	3 mo 12 mo	1/18 (0.6) 0/8 (0)	NA
Kaplan 2017 ²⁹	Prospective single-group cohort	Sturge-Weber syndrome	CBD	14 wk Most recent visit (6–82 wk)	0/5 (0) 1/5 (20)	NA
Gofshteyn 2017 ³⁰	Prospective single-group cohort	FIRES (acute)	CBD	4 wk	1/2 (50)	NA
		FIRES (chronic)		4 wk 48 wk	1/5 (20) 0/5 (0)	NA
Porcari 2018 ³⁵	Retrospective comparative cohort	Drug-resistant epilepsy	CBD CBD + CLO CLO	Mean (SD), yr 1.1 (0.8) 1.3 (1.0) 2.5 (1.9)	CBD: 7/48 (15) CBD+CLO: 5/54 (9)	CLO: 8/74 (11)
Neubauer 2018 ³¹	Retrospective single-group cohort	Drug-resistant epilepsy	CBD	Median (range): 14.0 (6–29) mo	14/70 (70)	NA
Tzadok 2016 ³³	Retrospective single-group cohort	Drug-resistant epilepsy	CBD	≥ 3 mo	1/74 (1)	NA
Press 2015 ³⁹	Retrospective single-group cohort	Drug-resistant epilepsy	Mixed cannabis-based treatments	Mean (range): 5.59 (1–24) mo	2/75 (3)	NA
Sulak 2017 ³⁴	Retrospective single-group cohort	Drug-resistant epilepsy¶	Mixed cannabis-based treatments	NR	2/47 (4)	NA

Author, yr	Study design	Population	Treatments†	Duration	No. events/no. in group (%)‡	
					Cannabis-based treatment	Control
Aguirre- Velazquez 2017 ³⁶	Cross-sectional	Drug-resistant epilepsy	Mixed cannabis-based treatments	<1 to 12 mo	7/43 (16)	NA
Hussain 2015 ³⁷	Cross-sectional	Drug-resistant epilepsy	Mixed cannabis-based treatments	Median (IQR): 6.8 (3.8–9.8) mo	16/117 (14)	NA
Porter 2013 ³⁸	Cross-sectional	Drug-resistant epilepsy	CBD	> 1 yr	2/19 (11)	NA
Note: CBD = cannabidiol, CI = confidence interval, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, NA = not applicable, RCT = randomized controlled trial, SD = standard deviation, THC = tetrahydrocannabinol. *Adapted from Elliott et al. 2019. ² †Treatments described in Table 1. ‡No. randomized for RCTs; otherwise, no. included in efficacy analysis. ¶Washington cohort						

Secondary outcomes

Seizure frequency

BASELINE REVIEW: Nine studies assessed the effect of cannabis-based products on seizure frequency, including three RCTs^{23–25} and six non-randomized studies (four single-group prospective cohort studies,^{22,27,28,30} one comparative retrospective cohort study,³⁵ one cross-sectional study⁴⁰). Among the RCTs, which all had a treatment duration of 14 weeks, the pooled median difference in monthly total seizure frequency between CBD and placebo was –19.8% (95%CI –27.0% to –12.6%; moderate certainty), while the difference between CBD and placebo was –26.7% (95%CI –38.8% to –14.8%; moderate certainty) for tonic-clonic seizures. Among the NRS, the reported reduction in total seizure frequency was between 30% and 90% (duration: 8 wk to > 16 mo; very low certainty), with reported reductions between 16% and 91% for tonic-clonic seizures (two studies; duration 12 wk to 12 mo; very low certainty) (Table 6).

UPDATE 1: Two prospective single-arm cohort studies^{4,6} assessed the effect of cannabis-based products on the total frequency of seizures (Table 6); none assessed changes in tonic-clonic seizures. Among children with drug-resistant epilepsy, Szaflarski and colleagues⁶ reported a 79% reduction in the median frequency of seizures after 48 weeks of cannabidiol treatment; reductions of 49% and

43% were reported at 12 and 24 weeks, respectively. In a pooled analysis of children with drug-resistant epilepsy enrolled in 25 expanded access programs, Szaflarski and colleagues⁴ similarly reported a 46%–53% reduction in the monthly frequency of seizures among participants who received cannabidiol for up to 96 weeks.

EVIDENCE SUMMARY (as of October 2018): In total, 11 studies, including three RCTs^{23–25} and eight non-randomized studies^{4,6,22,27,28,30,35,40} have assessed the effect of cannabis-based products on the frequency of total or tonic-clonic seizures (Table 6). The estimate of seizure reduction from RCTs remains unchanged from the baseline review (moderate certainty), while the reported reduction in seizures in the non-randomized studies remains between 30% and 90% (very low certainty). Compared with the earlier non-randomized studies, the newly published studies provide evidence over a longer treatment period (up to 96 weeks), suggesting that the effect of cannabidiol on the frequency of seizures may be relatively consistent over time.

Table 6: Evidence summary — Seizure frequency*

Author, yr	Study design	Population	Treatments† (no. in group)	Duration	Seizure frequency‡; median per month¶		Effect estimate
					Baseline	After treatment	
UPDATE 1 (April–October 2018)							
Szaflarski 2018, p. 131 ⁶	Prospective single-group cohort	Drug-resistant epilepsy	• CBD	• 12 wk (69) • 24 wk (43) • 48 wk (27)	Per 2 wk period: 44.8 (IQR: 10.2–232.2)	Per 2 wk period: • 12 wk: 23 (IQR: 45, 86.8) • 24 wk: 25.7 (3, 80.4) • 48 wk: 9.2 (4.5, 55)	Change in median seizure frequency per 2 wk period from baseline: • 12 wk: –49% • 24 wk: –43% • 48 wk: –79%
Szaflarski 2018, p. 1540 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	• CBD	• 12 wk (431) • 24 wk (412) • 48 wk (282) • 72 wk (197) • 96 wk (138)	72 (IQR: 22–196)	NR	Change in median monthly seizure frequency (90%CI) from baseline: • 12 wk: –48% (42%–56%) • 24 wk: –46% (40%–50%) • 48 wk: –47% (42%–56%) • 72 wk: –53% (47%–65%) • 96 wk: –49% (40%–61%)
BASELINE REVIEW (Up to April 2018)							
Devinsky 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo (76) • CBD 10 mg/kg/d (73) • CBD 20 mg/kg/d (76)	14 wk	180.6 (IQR: 90.4–431.3) 165.0 (81.3–359.0) 174.3 (82.7–392.4)	NR	Change in median monthly seizure frequency: • Placebo: –18.5% • CBD 10 mg/kg/d: –36.4% • CBD 20 mg/kg/d: –38.4% Median difference v. placebo (95%CI): • CBD: 10 mg/kg/d: –19.5% (–30.4% to –7.5%) • CBD 20 mg/kg/d: –18.8% (–31.8% to –4.4%)
Thiele 2018 ²³	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD 20 mg/kg/d (86)	14 wk	176.7 144.6	128.7 83.8	Change in median (IQR) monthly seizure frequency: • Placebo: –13.7% (–45.0% to 7.3%) • CBD 20 mg/kg/d: –41.2% (–62.9% to –13.0%) Median difference v. placebo (95%CI): –21.1% (–33.3% to –9.4%)
Devinsky	RCT	Dravet	• Placebo (59)	14 wk	41.5	31.1	Adjusted median change:

Author, yr	Study design	Population	Treatments† (no. in group)	Duration	Seizure frequency‡; median per month¶		Effect estimate
					Baseline	After treatment	
2017 ²⁵		syndrome	• CBD 20 mg/kg/d (61)		24.0	13.7	• Placebo: –9% • CBD: –28.6% Median difference v. placebo (95%CI): –19.2% (95%CI –39.25% to –1.17%)
Devinsky 2016 ²²	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD (137)	12 wk	60 (range: 22.0–131.8)	NR	Change in median (IQR) monthly seizure frequency from baseline: –34.6% (–66.7% to –9.8%)
Geffrey 2015 ²⁷	Prospective single-arm cohort	Drug-resistant epilepsy taking CLO	• CBD (13)	8 wk	NR	NR	Mean (SD) change in monthly seizures from baseline: –51% (56%)
Hess 2016 ²⁸	Prospective single-arm cohort	Tuberous sclerosis complex	• CBD (8)	3 mo	22.0 (IQR: 14.8–57.4) per wk	13.2 (IQR: 5.06–22.1) per wk	Change in median (IQR) weekly seizure frequency from baseline: –48.8% (–69.1% to –11.1%)
Gofshteyn 2017 ³⁰	Prospective single-arm cohort	FIRES (chronic)	• CBD (5)	48 wk	NR	NR	Change in mean (SD) monthly seizures from baseline: 4 wk: –90.94% (19.9%) 48 wk: –63.3% (29.3%)
Porcari 2018 ³⁵	Retrospective comparative cohort	Drug-resistant epilepsy	• CBD (48) • CBD + CLO (54) • CLO (74)	Mean (SD), yr 1.1 (0.8) 1.3 (1.0) 2.5 (1.9)	Mean (range): 89 (0–675) 372 (0.3–4680) 437 (0.2–10,800)	Mean (SE): 63 (21) 252 (88) 198 (58)	Change in seizures from baseline: • CBD alone: –30% • CBD + CLO: –33% • CLO: –55%
Suraev 2017 ⁴⁰	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products (51) • No cannabis (340)	Mean (SD): 15.75 (15.65) mo	Mean (SD) 12.8 (16.7) 30.6 (196.4)	Mean (SD) 2.5 (73.2) NA	Change in seizures from baseline with cannabis-based product: –80%
Note: CBD = cannabidiol, CI = confidence interval, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, NR = not reported, RCT = randomized controlled trial, SD = standard deviation, SE = standard error. *Adapted from Elliott et al. 2019.² †Treatments described in Table 1. No. randomized for RCTs; otherwise, no. included in efficacy analysis. ‡Total seizures, includes convulsive and non-convulsive seizures. ¶Unless otherwise stated.							

Treatment response

BASELINE REVIEW: Thirteen studies assessed treatment response (one RCT²³, 12 NRS [six prospective single-arm cohort studies,^{22,26–30} three retrospective single-arm cohort studies,^{31–33} one comparative retrospective cohort study,³⁵ two cross-sectional studies^{36,38}]) (Table 7). In the RCT, children with Lennox-Gastaut syndrome who received cannabidiol were more likely than those who received placebo to experience a treatment response (RR 1.76, 95%CI 1.07 to 2.88; moderate certainty; duration: 14 wk).²³ Among the non-randomized studies, between 24% and 100% experienced a treatment response (duration: 8 wk to 57 mo; very low certainty); the pooled estimate among prospective cohort studies was 44% (95%CI 36% to 53%).

UPDATE 1 (Apr–Oct 2018): Three prospective single-arm cohort studies^{4–6} assessed treatment response ($\geq 50\%$ reduction in seizure frequency from baseline) (Table 7). Among these prospective cohort studies, between 49% and 63% of participants who received cannabidiol experienced at least a 50% reduction in seizures, with a pooled estimate of 55% (95%CI 45% to 65%; duration 12–96 wk) (Figure 4).

EVIDENCE SUMMARY (as of October 2018): In total, 16 studies, including one RCT²³ and 15 non-randomized studies^{4–6,22,26–33,35,36,38} have assessed the effect of cannabis-based treatments on treatment response (Table 7). The estimate of treatment response from RCTs remains unchanged from the baseline review (RR 1.76, 95%CI 1.07 to 2.88; moderate certainty). Among the non-randomized studies, estimates of treatment response remain between 30% and 90%, and although the pooled proportion among prospective cohort studies increased to 50% (95%CI 43% to 58%) (Figure 5), the certainty of the evidence remains very low. Compared with the earlier non-randomized studies, newly published studies provide evidence over a longer treatment period (up to 96 weeks), suggesting that the effect of cannabidiol on the treatment response may be relatively consistent over time.

Table 7: Evidence summary — Treatment response (≥ 50% reduction in total seizures from baseline period)*

Author, yr	Study design	Population	Treatments†	Duration	No. events/no. randomized‡ (%)	
					Cannabis-based treatment	Control
UPDATE 1 (April–October 2018)						
Szaflarski 2018, p. 131 ⁶	Prospective single-group cohort	Drug-resistant epilepsy	• CBD	12 wk 24 wk 48 wk	42/69 (61) 21/43 (49) 17/27 (63)	NA
Szaflarski 2018, p. 1540 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	• CBD	12 wk 24 wk 48 wk 72 wk 96 wk	211/431 (49) 202/412 (48) 135/282 (48) 102/197 (52) 68/138 (49)	NA
McCoy 2018 ⁵	Prospective single-group cohort	Dravet syndrome	• CBD:THC	20 wk	12/19 (63)	NA
BASELINE REVIEW (Up to April 2018)						
Thiele 2018 ²³	RCT	Lennox-Gastaut syndrome	• Placebo • CBD	14 wk	32/86 (37)	18/85 (21)
Devinsky 2016 ²²	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD	12 wk	51/137 (37)	NA
Geffrey 2015 ²⁷	Prospective single-arm cohort	Drug-resistant epilepsy taking CLO	• CBD	8 wk	7/13 (54)	NA
Hess 2016 ²⁸	Prospective single-arm cohort	Tuberous sclerosis complex	• CBD	3 mo 12 mo	9/18 (50) 4/8 (50)	NA
Kaplan 2017 ²⁹	Prospective single-arm cohort	Sturge-Weber syndrome	• CBD	14 wk Last visit (6–82 wk)	2/4 (50) 3/5 (60)	NA
Gofshteyn 2017 ³⁰	Prospective single-arm cohort	FIRES (acute)	• CBD	4 wk 48 wk	1/2 (50) NR	NA
		FIRES (chronic)		4 wk 48 wk	5/5 (100) 5/5 (100)	NA
Hausman-Kedem 2018 ²⁶	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD:THC	Mean 15.6 mo	24/46 (52)	NA
Porcari 2018 ³⁵	Retrospective comparative cohort	Drug-resistant epilepsy	• CBD • CBD + CLO • CLO	Mean, yr: 1.1; 1.3; 2.5	CBD: 16/48 (33) CBD+CLO: 24/54 (44)	CLO: 28/74 (38)
Neubauer 2018 ³¹	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD	Median: 14.0 mo	32/70 (46)	NA
Tzadok 2016 ³³	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD-enriched cannabis oil	≥ 3 mo	38/74 (51)	NA
Treat 2017 ³²	Retrospective single-arm cohort	Drug-resistant epilepsy	• Mixed cannabis-based products	Mean (range): 11.7 (0.3–57) mo	29/119 (24)	NA
Aguirre-	Cross-sectional	Drug-resistant	• Mixed	<1 to 12 mo	29/43 (67)	NA

Author, yr	Study design	Population	Treatments†	Duration	No. events/no. randomized‡ (%)	
					Cannabis-based treatment	Control
Velazquez 2017 ³⁶		epilepsy	cannabis-based products			
Porter 2013 ³⁸	Cross-sectional	Drug-resistant epilepsy	• CBD	> 1 yr	13/19 (68)	NA

Note: CBD = cannabidiol, CLO = clobazam, FIRES = Febrile Infection-Related Epilepsy syndrome, NA = not applicable, NR = not reported, RCT = randomized controlled trial, THC = tetrahydrocannabinol.

*Adapted from Elliott et al. 2019.²

†Treatments described in Table 1.

‡No. randomized for RCTs; otherwise, no. in efficacy analysis.

Figure 4: Treatment response reported in non-randomized studies included in UPDATE 1

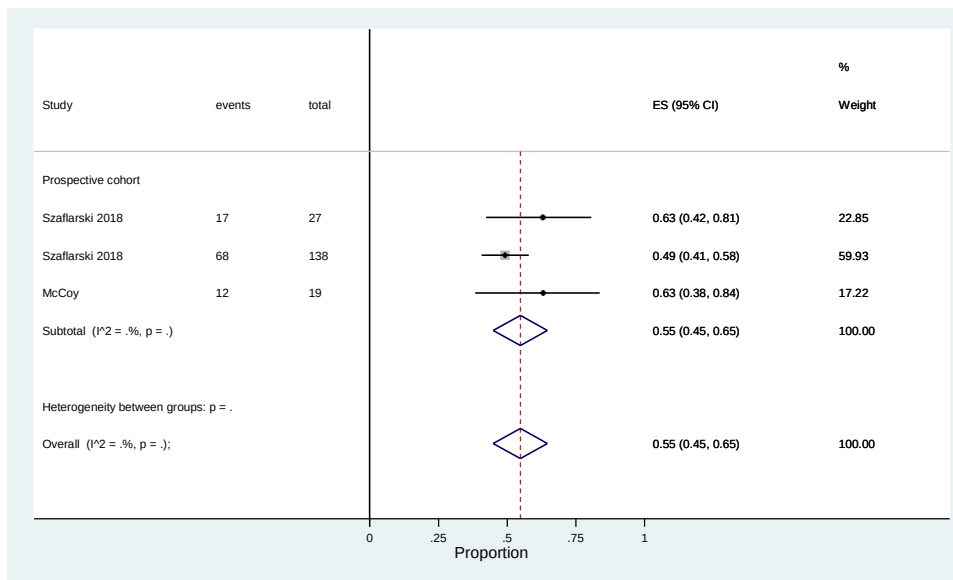
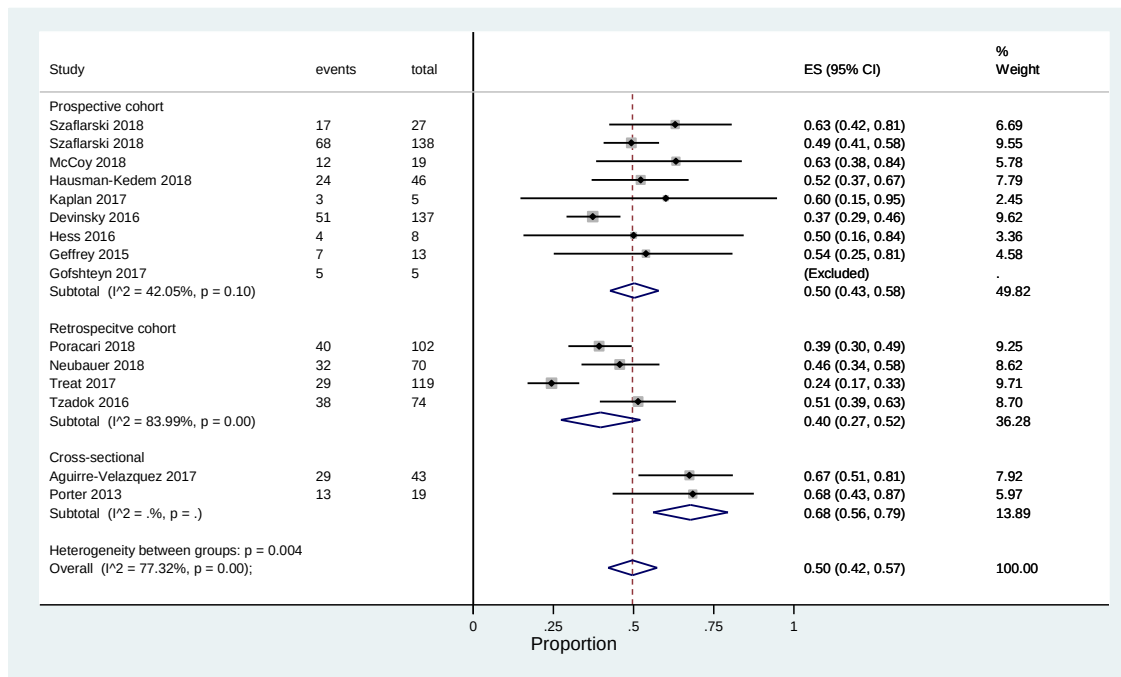


Figure 5: Treatment response reported in non-randomized studies — State of the evidence as of October 2018



Quality of life

BASELINE REVIEW: Quality of life was assessed in five studies (three RCTs,^{23–25} two prospective single-arm cohort studies^{29,41}) (Table 8). There was no statistically significant difference in overall score on the Quality of Life in Childhood Epilepsy scale between CBD and placebo groups in the RCTs over a 14-week treatment period (mean difference 0.6, 95%CI –2.6 to 3.9; moderate certainty). In the non-randomized studies, quality of life was reported to be significantly improved following treatment with cannabidiol compared to the baseline period (duration: 12 to 82 weeks; very low certainty).^{29,41} None of the included studies assessed caregiver quality of life.

UPDATE 1: One single-arm prospective cohort study⁵ assessed the effect of cannabidiol on quality of life in children with Dravet syndrome, reporting a statistically significant improvement on the Quality of Life in Childhood Epilepsy scale after treatment with cannabidiol compared to the baseline period (Table 8). None of the included studies assessed the impact of cannabis-based treatments on quality of life among adult caregivers.

EVIDENCE SUMMARY (as of October 2018): In total, quality of life has been assessed in six studies (three RCTs,^{23–25} three non-randomized studies^{5,29,41}) (Table 8). Evidence from the RCTs suggests that there is no statistically significant difference in response between cannabidiol and placebo (moderate certainty), while evidence from the non-randomized studies suggests that children administered cannabidiol may experience an improvement in quality of life relative to the pre-treatment period (very low certainty). To date, no studies have assessed quality of life among caregivers of children with epilepsy who received a cannabis-based product.

Table 8: Evidence summary — Quality of life (children)*

Author, yr.	Study design	Population	Treatments (no. in group)†	Duration	Quality of life; mean (SD)		Effect estimate
					Baseline	After treatment	
UPDATE 1 (April–October 2018)							
McCoy 2018 ⁵	Prospective single-group cohort	DS	• CBD:THC (19)	20 wk	39.60 (11.1)	46.02 (14.2)	Statistically significant improvement in quality in life after treatment (p = 0.045)‡
BASELINE REVIEW (Up to April 2018)							
Thiele 2018 ²³	RCT	LGS	• Placebo (85) • CBD (86)	14 wk	NR	NR	Adjusted¶ difference between groups after treatment: 3.7 (95% CI –3.3 to 10.7) ‡
Devinsky 2018 ²⁴	RCT	LGS	• Placebo (76)** • CBD 10 mg/kg/d (73) • CBD 20 mg/kg/d (76)	14 wk	NR	NR	Adjusted† mean difference (95%CI) between groups after treatment:‡ • 10 mg/kg/d v. placebo: 1.6 (–4.5 to 7.8) • 20 mg/kg/d v. placebo –5.1 (–11.4 to 1.2)
Devinsky 2017 ²⁵	RCT	DS	• Placebo (59) • CBD (61)	14 wk	NR	NR	Mean difference (95%CI) between groups after treatment: 1.5 (–3.8 to 6.8)‡
Rosenberg 2017 ⁴¹	Prospective single-group cohort	Drug-resistant epilepsy	• CBD (48)	12 wk	31.8 (7.8)	45.74 (8.50)	Mean (SD) difference before-after treatment: 8.12 (9.85); p < 0.001‡
Kaplan 2018 ²⁹	Prospective single-group cohort	Sturge-Weber syndrome	• CBD (5)	Up to 82 wk	NR	NR	"All subjects reported improvements in QoL for most of their time on CBD. All three subjects who have continued on CBD reported their QoL at last visit being “a lot better” since starting CBD."**
Note: CBD = cannabidiol, CI = confidence interval, DS = Dravet syndrome, LGS = Lennox-Gastaut syndrome, NR = not reported, QoL = quality of life, RCT = randomized controlled trial, SD = standard deviation, THC = tetrahydrocannabinol. *Adapted from Elliott et al. 2019.² †Treatments described in Table 1. No. randomized for RCTs unless otherwise stated; otherwise, no. included in efficacy analysis. ‡100-point Quality of Life in Childhood Epilepsy score; positive score favours CBD. ¶Adjusted for baseline score and age group **Analysis included 38 participants in the placebo group, 36 in 10 mg/kg/d group, and 33 in 20 mg/kg/d group. **Likert scale ranging from –3 to 3 (“A lot worse” to “A lot better”); no data reported.							

Sleep

BASELINE REVIEW: Twelve studies (three RCTs,^{23–25} nine NRS^{27–29,31,32,36–38,42}) reported changes in sleep (Table 9). Findings from the RCTs suggest that there is no statistically significant difference in sleep between children administered CBD or placebo (MD –0.3, 95%CI –0.8 to 0.2; moderate certainty). Among the non-randomized studies, both improved and impaired sleep was noted. Five studies reported improved sleep, with the highest proportion of improvement reported in cross-sectional studies (68%, 95%CI 46% to 90%) relative to retrospective cohort studies (8%, 95%CI 4% to 11%). Impaired sleep was reported in five non-randomized studies (four prospective cohort studies,^{27–29,42} one cross-sectional survey³⁶), affecting 4% (95%CI 0% to 7%) of children who received a cannabis-based product (very low certainty).

UPDATE 1: None of the newly included studies assessed the effect of cannabis-based treatments on sleep.

EVIDENCE SUMMARY (as of October 2018): There is no change to the evidence base for the effect of cannabis-based treatments on sleep as October 2018. Findings from RCTs suggest that there is no statistically significant effect of cannabidiol on sleep (moderate certainty), while both improved and impaired sleep has been reported in non-randomized studies (very low certainty)

Table 9: Evidence summary — Sleep*

Author, yr	Study design	Population	Treatments† (no.)	Duration	Reported finding
UPDATE 1 (April–October 2018)					
No new studies					
BASELINE REVIEW (Up to April 2018)					
Sleep Disruption Rating Scale score‡				Mean difference (95%CI) between groups after treatment	
Thiele 2018 ²³	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD (86)	14 wk	−0.2 (−1.1 to 0.7)¶
Devinsky 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo (76) • CBD 10 mg/kg/d (73) • CBD 20 mg/kg/d (76)	14 wk	• 10 mg/kg/d v. placebo: −0.8 (−1.7 to 0.1)¶ • 20 mg/kg/d v. placebo: −0.3 (−1.2 to 0.6)¶
Devinsky 2017 ²⁵	RCT	Dravet syndrome	• Placebo (59) • CBD (61)	14 wk	−0.4 (−1.5 to 0.7)**
Impaired sleep				Reported finding	
Thiele 2018 ²³	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD (86)	14 wk	Sleep apnea: 1 participant (1.2%) in the cannabidiol group; none reported in placebo group
INYS 2017 ⁴²	Prospective comparative cohort	Drug-resistant epilepsy	• CBD 10 mg/kg/d (20) • CBD 20 mg/kg/d (20) • CBD 40 mg/kg/d (21)	10 d††	Sleep apnea: 1 participant (4.8%) in the CBD 40 mg/kg/d group; none in the other dosage groups
Geffrey 2015 ²⁷	Prospective single-group cohort	Drug-resistant epilepsy taking CLO	• CBD (13)	8 wk	“Restless sleep” was reported for 1 participant (7.7%) who received CBD and CLO
Hess 2016 ²⁸	Prospective single-group cohort	Tuberous sclerosis complex	• CBD (18)	Up to 12 mo	“Poor sleep” was reported for 2 participants (11.1%) who received CBD
Kaplan 2017 ²⁹	Prospective single-group cohort	Sturge-Weber syndrome	• CBD (5)	Up to 82 wk	“Sleep difficulties” were reported for 1 participant (20%) who received CBD
Aguirre-Velazquez 2017 ³⁶	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (43)	Range <1 to 12 mo	“Broken sleep” was reported for 3 participants (7.0%) who received mixed cannabis-based products

Improved sleep					Reported finding
Neubauer 2018 ³¹	Single-arm retrospective cohort	Drug-resistant epilepsy	• CBD (70)	Median (range): 14.0 (6.0–29.3) mo	Better sleep was reported for 7 (10%) participants who received CBD
Treat 2017 ³²	Retrospective single-arm cohort	Drug-resistant epilepsy	• Mixed cannabis-based treatments (119)	Mean (range): 11.7 (0.3–57) mo	Better sleep was reported for 8 (6.7%) participants who received mixed cannabis-based products
Aguirre-Velazquez 2017 ³⁶	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (43)	Range <1 to 12 mo	“Improvement in sleep” was reported for 83% of participants who received mixed cannabis-based products
Hussain 2015 ³⁷	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based treatments (117)	Median (IQR): 6.8 (3.8–9.8) mo	“Improvement in sleep” was reported for 53% of participants who received mixed cannabis-based products
Porter 2013 ³⁸	Cross-sectional	Drug-resistant epilepsy	• CBD (19) • Stiripentol (22)	Range: 2 wk to > 1 yr	Better sleep was reported for 13 (68.4%) participants who received mixed cannabis-based products; better sleep was reported for 6 participants (27.3%) who received stiripentol
Note: CBD = cannabidiol, CI = confidence interval, CLO = clobazam, IQR = interquartile range, RCT = randomized controlled trial. *Adapted from Elliott et al. 2019.² †Treatments described in Table 1. No. randomized for RCTs; otherwise, no. included in analysis. ‡Sleep Disruption Rating Scale score, assessed on a numerical rating scale from 0 to 10, with higher scores indicating greater disruption. Negative mean difference favours cannabidiol. ¶Adjusted for baseline score and age group. **Adjusted; covariates not reported. ††Treatment for 10 days, followed by withdrawal period for up to 7 days. Participants who enrolled into a subsequent rollover study may not have had adverse event data collected after day 11.					

Status epilepticus

BASELINE REVIEW: Status epilepticus was reported in six studies, including three RCTs^{23–25} and three NRS (two prospective cohort studies,^{22,26} one retrospective cohort study³⁹) (Table 10). In the RCTs,^{23–25} the RR of status epilepticus was 1.39 (95%CI 0.55 to 3.47; low certainty) over a 14-week treatment duration). The pooled prevalence of status epilepticus among the non-randomized studies was 4% (95%CI 0% to 8%; duration: 12 wk to 33 mo; very low certainty).

UPDATE 1: Two single-group prospective cohort studies^{4,8} reported status epilepticus among participants who received cannabidiol (Table 10, Figure 6). Participants in both studies were enrolled in Expanded Access Programs in the US, and preliminary findings from these programs have previously been reported.²² As such, it is possible that at least some occurrences of status epilepticus have been previously reported, although the newly included publications reflect a longer treatment duration. Szaflarski and colleagues⁴ reported that 7% of participants with drug-resistant epilepsy who received cannabidiol experienced status epilepticus over a treatment duration of up to 146 weeks. Devinsky and colleagues⁸ focused on a subgroup of patients with CDKL deficiency, Aicardi, Dup15Q, Doose syndrome who received cannabidiol for up to 144 weeks, finding that 9% of participants experienced status epilepticus.

EVIDENCE SUMMARY (as of October 2018): In total, eight studies have reported the occurrence of status epilepticus among children administered cannabis-based treatments (Table 10). Evidence from RCTs suggests that there is no statistically significant difference in the risk of status epilepticus between cannabidiol and placebo, while evidence from non-randomized studies suggests that up to 9% of children administered cannabidiol may experience status epilepticus (Figure 7), although this may vary depending on specific epilepsy syndrome.

Table 10: Evidence summary — Status epilepticus*

Author, yr	Study design	Population	Duration	Treatment†	No. participants with status epilepticus /no. in group (%)
UPDATE 1 (April–October 2018)					
Szaflarski 2018, p. 1540 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	Median (range): 48 (2–146 wk)	• CBD	45/607 (7.4)
Devinsky 2018 ⁸	Prospective single-group cohort	CDKL deficiency, Aicardi, Dup15Q, Doose syndrome	Up to 144 wk	• CBD	5/55 (9)‡
BASELINE REVIEW (Up to April 2018)					
Thiele 2018 ²³	RCT	Lennox-Gastaut syndrome	14 wk	• Placebo • CBD	1/85 (1.2) 1/86 (1.2)
Devinsky 2018 ²⁴	RCT	Lennox-Gastaut syndrome	14 wk	• Placebo • CBD 10 mg/kg/d • CBD 20 mg/kg/d	3/76 (3.9) 7/67 (10.4) 4/82 (4.9)¶
Devinsky 2017 ²⁵	RCT	Dravet syndrome	14 wk	• Placebo • CBD	3/59 (5.1) 3/61 (4.9)
Devinsky 2016 ²²	Prospective single-arm cohort	Drug-resistant epilepsy	12 wk	• CBD	13/162 (8.0)
Hausman-Kedem 2018 ²⁶	Prospective single-arm cohort	Drug-resistant epilepsy	Median (range): 18 (3–33) mo	• CBD:THC	1/46 (2.2)
Press 2015 ³⁹	Retrospective single-arm cohort	Drug-resistant epilepsy	Mean (range): 5.59 (1–24) mo	• CBD, CBD + other oral cannabis extract, THCA only, or "other"	1/75 (1.3)
Note: CBD = cannabidiol, THCA = tetrahydrocannabinolic acid. *Adapted from Elliott et al. 2019.² †Treatments described in Table 1. No. randomized for RCTs; otherwise, no. included in safety analysis. ‡Includes patients from Devinsky 2016.²² ¶6 participants in the 10 mg/kg/d group received a dose above the target and were included in the 20 mg/kg/d group for the safety analysis.					

Figure 6: Status epilepticus reported in non-randomized studies included in UPDATE 1

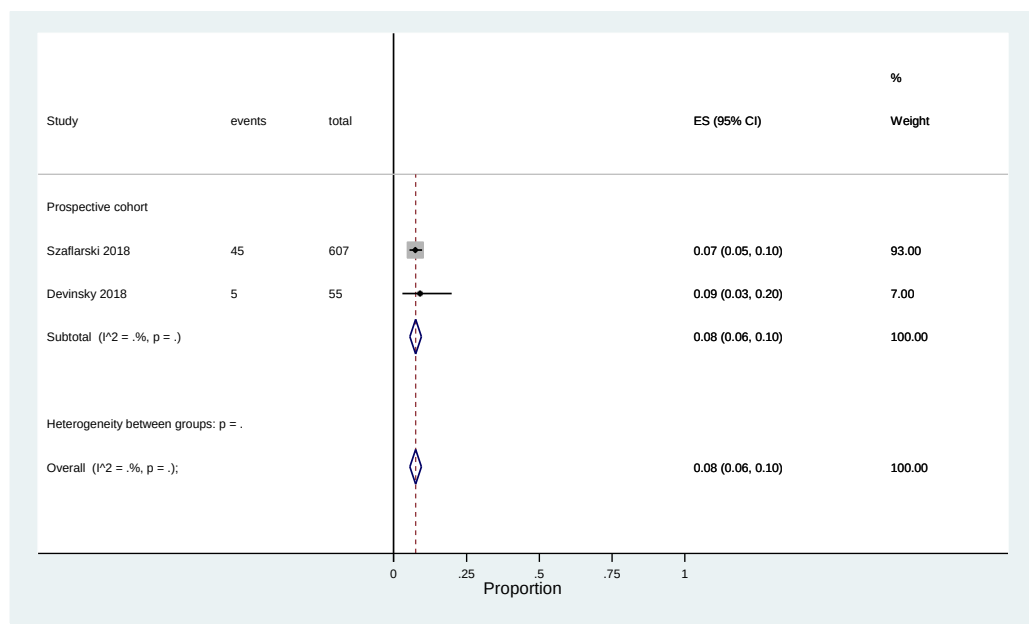
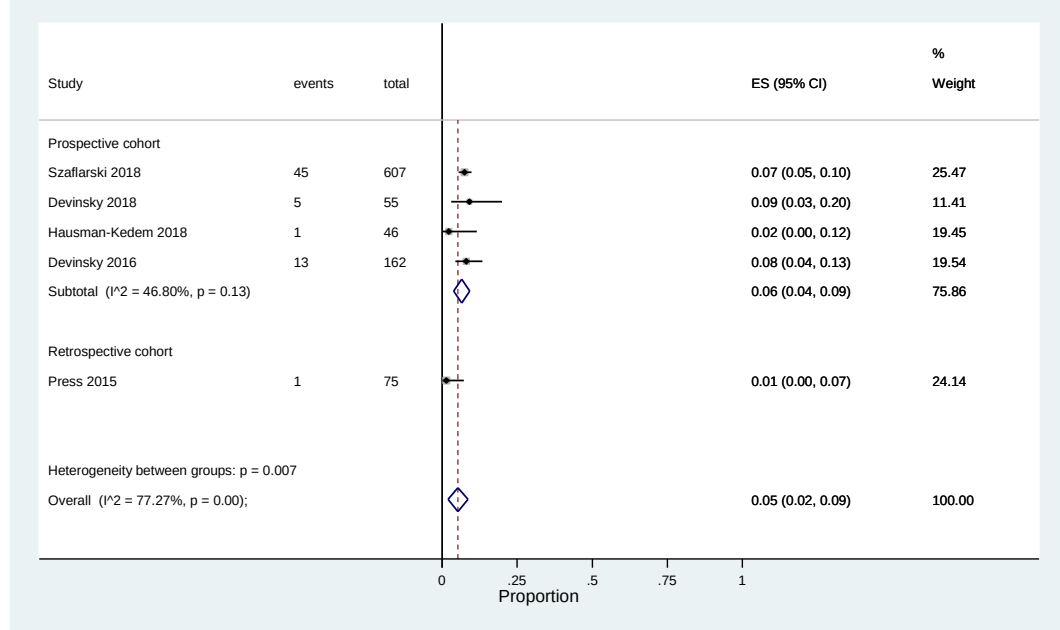


Figure 7: Status epilepticus reported in non-randomized studies — State of the evidence as of October 2018



Death

BASELINE REVIEW: As of April 2018, six studies (one RCT,²³ two prospective cohort studies,^{22,30} three retrospective cohort studies^{31,34,39}) had reported a total of seven deaths among children who received cannabis-based products (Table 11; very low certainty), and an additional three studies^{25,42,43} reported that no deaths had occurred during the treatment period. Of the seven deaths, two were attributed to SUDEP.

UPDATE 1: Two single-group prospective cohort studies^{4,5} reported a total of 13 deaths among children receiving cannabidiol; of these, three deaths were categorized as SUDEP (Table 11). Of the 12 deaths reported by Szaflarski and colleagues⁴ among 607 children enrolled in a US Expanded Access Program, one death (SUDEP) may have been previously reported in the publication by Devinsky and colleagues.²² In the Expanded Access Program, the incidence of death was 2%; this study represents the largest and longest study of cannabidiol in this population to date (up to 146 weeks).

EVIDENCE SUMMARY (as of October 2018): In total, 20 deaths, including five cases of SUDEP, have been reported among 1083 children with epilepsy who received a cannabis-based treatment (Table 11). Evidence from one RCT²³ suggests that there is no statistically significant difference in the risk of death between cannabidiol and placebo; however, this study was not powered to detect rare events and had a short treatment duration (14 weeks; low certainty of evidence). In the largest and longest study to date (up to 146 weeks), the incidence of death was 2%. Overall, the certainty of evidence from the non-randomized studies is very low (Supplemental File 2).

Table 11: Evidence summary — Death*

Author, yr†	Study design	Population	Duration	Treatment (no. in group)‡	Deaths	Reported cause of death
UPDATE 1 (April–October 2018)						
Szaflarski 2018, p. 1540 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	Median (range): 48 (2–146 wk)	• CBD (607)¶	12 deaths reported; one may have been previously reported in Devinsky 2016 ²²	2 deaths due to SUDEP (cause of 10 deaths NR); All deaths reported to be unrelated to study drug
McCoy 2018, p. 1077 ⁵	Prospective single-group cohort	Dravet syndrome	20 wk	• CBD:THC (20)	1 death reported	SUDEP (reported to be unrelated to study drug)
BASELINE REVIEW (Up to April 2018)						
Thiele 2018 ²³	RCT	Lennox-Gastaut syndrome	14 wk	• Placebo (85) • CBD (20 mg/kg/d) (86)	1 death reported in the CBD group; zero deaths in the placebo group	Respiratory failure (reported to be unrelated to study drug)
Devinsky 2016 ²²	Prospective single-arm cohort	Drug-resistant epilepsy	12 wk	• CBD (50 mg/kg/d) (214)	1 death reported	SUDEP (reported to be unrelated to the study drug)
Gofshteyn 2017 ³⁰	Prospective single-arm cohort	FIRES	48 wk	• CBD (up to 25 mg/kg/d) (acute: 2; chronic: 5)	1 death was reported in a child treated during the acute stage; no deaths in the chronic stage	Multi-organ failure (thought to be related to prolonged isoflurane exposure)
Press 2015 ³⁹	Retrospective, single-arm cohort	Drug-resistant epilepsy	Mean (range): 5.59 (1–24) mo	• CBD, CBD + other oral cannabis extract, THCA only, or "other" (75)	1 death reported	NR
Neubauer 2018 ³¹	Retrospective, single-arm cohort	Drug-resistant epilepsy	Median (range) 14.0 (6.0–29.3) mo	• CBD (up to 16 mg/kg/d) (70)	2 deaths reported	Multiple cavernomas (died suddenly during sleep; 1); bronchopneumonia (1)
Sulak 2017 ³⁴	Case series**	Drug-resistant epilepsy	NR	• THCA (2 mg/kg/d) (4‡)	1 death reported	SUDEP
Note: CBD = cannabidiol, FIRES = Febrile Infection-Related Epilepsy syndrome, NR = not reported, RCT = randomized controlled trial, SUDEP = sudden unexpected death in epilepsy, THCA = tetrahydrocannabinolic acid, THC = tetrahydrocannabinol. *Adapted from Elliott et al. 2019.² †An additional four studies^{8,25,42,43} reported that no deaths occurred during the study period. ‡Treatments described in Table 1. No. randomized for RCTs; otherwise, no. included in safety analysis. ¶Pooled results from 25 US Expanded Access Programs (EAP); updated analysis of Devinsky 2016²², which included 11 EAP programs and 214 children. **Case series of 4 children with epilepsy who received “herbal cannabinoid treatment.”						

Gastrointestinal adverse events

BASELINE REVIEW: Gastrointestinal adverse events were reported in four RCTs^{23–25,43} and 11 non-randomized (six single-group prospective cohort studies,^{22,26,28–30,42} two retrospective cohort studies,^{32,33} three cross-sectional studies^{36–38}) (Table 12). In the RCTs, the pooled relative risk of any gastrointestinal event was 1.54 (95%CI 0.92 to 2.58), while the RR was 1.00 (95%CI 0.51 to 1.96) for vomiting and 2.25 (95%CI 1.38 to 3.68) for diarrhea (low certainty; duration: 3 to 14 wk). Among the non-randomized studies, 8% (95%CI 4% to 12%) of participants were reported to experience at least one of diarrhea or vomiting with cannabis-based treatments (very low certainty), with 5% (95%CI 2% to 8%) and 7% (95%CI 2% to 12%) of children administered a cannabis-based treatment reported to experience vomiting and diarrhea, respectively.

UPDATE 1: Gastrointestinal adverse events (diarrhea or vomiting) were reported in five single-group prospective studies^{4,5,7–9} (Table 12). Vomiting was experienced by between 3% and 25% of children who received cannabidiol (Figure 8), while diarrhea was experienced by between 5% to 32% of children (Figure 9). Overall, gastrointestinal adverse events were experienced by 35% (95%CI 29% to 42%) of participants who received cannabidiol (Figure 10).

EVIDENCE SUMMARY (as of October 2018):

Gastrointestinal adverse events have been reported in 20 studies, including four RCTs^{23–25,43} and 16 non-randomized studies. Evidence from the RCTs suggests that there is no overall difference in gastrointestinal adverse events between cannabidiol and placebo; however, there may be an increased risk of diarrhea with cannabidiol treatment (RR 2.25, 95%CI 1.38 to 3.68; low certainty). Estimates of gastrointestinal adverse events ranged between 2% and 60% of participants, with high heterogeneity between studies (Figure 11-13).

Table 12: Evidence summary — Gastrointestinal adverse events*

Author, yr	Study design	Population	Treatments (no. in group)†	Duration	% of participants	
					Vomiting	Diarrhea
UPDATE 1 (April–October 2018)						
Szaflarski 2018, p. 1540 ⁴	Prospective single-group cohort	Drug-resistant epilepsy	• CBD (607)	Median (range): 48 (2–146 wk)	3%	29%
McCoy 2018 ⁵	Prospective single-group cohort	Dravet syndrome	• CBD:THC (20)	20 wk	NR	31.6%
Chen 2018 ⁷	Prospective single-group cohort	Drug-resistant epilepsy	• CBD (40)	Up to 12 wk	17.5%	22.5%
Freeman 2018 ⁹	Prospective single-group cohort	Drug-resistant epilepsy	• CBD (20)	Up to 40 wk	25%	5%
Devinsky 2018 ⁸	Prospective single-group cohort	CDKL deficiency, Aicardi, Dup15Q, Doose syndrome	• CBD (55)	Up to 144 wk	18%	29%
BASELINE REVIEW (Up to April 2018)						
Thiele 2018 ²³	RCT	Lennox-Gastaut syndrome	• Placebo (85) • CBD (86)	14 wk	16% 10%	8% 19%
Devinsky 2018 ²⁴	RCT	Lennox-Gastaut syndrome	• Placebo (76) • CBD 10 mg/kg/d (67) • CBD 20 mg/kg/d (82)‡	14 wk	12% 6% 12%	8% 10% 15%
Devinsky 2018 ⁴³	RCT	Dravet syndrome	• Placebo (7) • CBD 5 mg/kg/d (10) • CBD 10 mg/kg/d (8) • CBD 20 mg/kg/d (9)	3 wk	0% 10% 13% 11%	NR
Devinsky 2017 ²⁵	RCT	Dravet syndrome	• Placebo (59) • CBD (61)	14 wk	5% 14.8%	10.2% 31.1%
Hausman-Kedem 2018 ²⁶	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD:THC (57)	Median (range): 18 (3–33) mo	8.8%	1.8%
INYS 2017 ⁴²	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD 10 mg/kg/d (20) • CBD 20 mg/kg/d (20) • CBD 40 mg/kg/d (21)	10 d¶	10% 5% 0%	5% 10% 33%
Kaplan 2017 ²⁹	Prospective single-arm cohort	Sturge-Weber syndrome	• CBD (5)	Up to 82 wk	40.0%	20.0%
Gofshteyn 2017 ³⁰	Prospective single-arm cohort	FIRES	• CBD (7)	48 wk	14.3%	NR
Devinsky 2016 ²²	Prospective single-arm cohort	Drug-resistant epilepsy	• CBD (162)	12 wk	NR	8.0%
Hess 2016 ²⁸	Prospective	Tuberous	• CBD (18)	12 mo	5.6%	22.2%

Author, yr	Study design	Population	Treatments (no. in group) [†]	Duration	% of participants	
					Vomiting	Diarrhea
	single-arm cohort	sclerosis complex				
Aguirre-Velazquez 2017 ³⁶	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products (43)	Up to 12 mo	NR	2.3%
Hussain 2015 ³⁷	Cross-sectional	Drug-resistant epilepsy	• Mixed cannabis-based products (117)	Median (IQR): 6.8 (3.8–9.8)	2.6%	NR
Porter 2013 ³⁸	Cross-sectional	Drug-resistant epilepsy	• Stiripentol (22) • CBD (19)	> 1 yr	9% 0%	NR
Tzadok 2016 ³³	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD-enriched cannabis oil, 1 to 20 mg/kg/d (20:1 CBD to THC ratio) (74)	≥ 3 mo	7%	
Treat 2017 ³²	Retrospective single-arm cohort	Drug-resistant epilepsy	• CBD, CBD + other oral cannabis extract, THCA only, or "other" (119)	Mean (range): 11.7 (0.3–57) mo	5%	

Note: CBD = cannabidiol, FIRES = Febrile Infection-Related Epilepsy syndrome, IQR = interquartile range, NR = not reported, RCT = randomized controlled trial, THCA = tetrahydrocannabinolic acid, THC = tetrahydrocannabinol.

*Adapted from Elliott et al. 2019.²

[†]Treatments described in Table 1. No. randomized for RCTs; otherwise, no. included in safety analysis.

[‡]6 participants in the 10 mg/kg/d group received a dose above the target and were included in the 20 mg/kg/d group for the safety analysis.

[¶]Treatment for 10 days, followed by withdrawal period for up to 7 days. Participants who enrolled into a subsequent rollover study may not have had adverse event data collected after day 11.

Figure 8: Pooled prevalence of vomiting reported among the non-randomized studies included in UPDATE 1

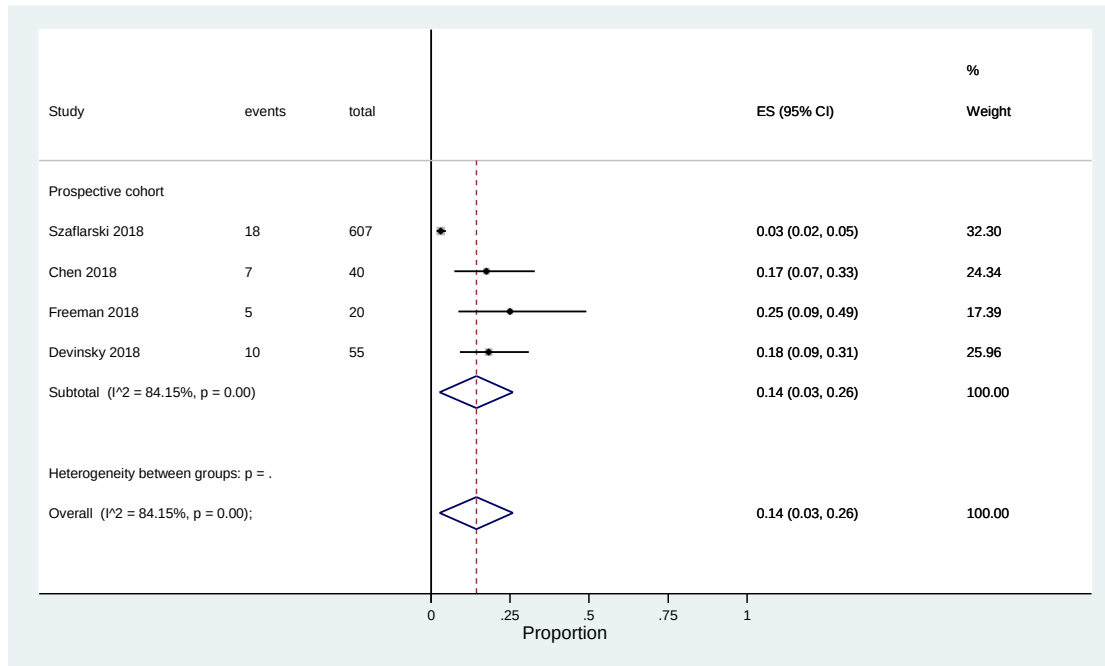


Figure 9: Pooled prevalence of diarrhea reported among the non-randomized studies included in UPDATE 1

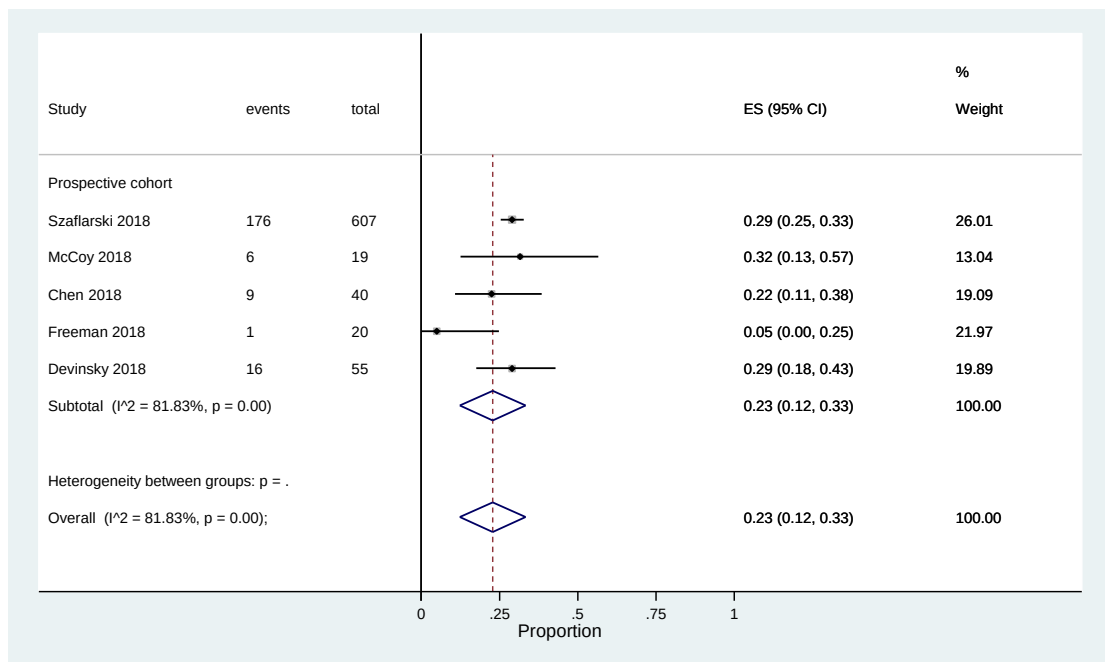


Figure 10: Pooled prevalence of any gastrointestinal adverse events (vomiting and/or diarrhea) reported among the non-randomized studies included in UPDATE 1

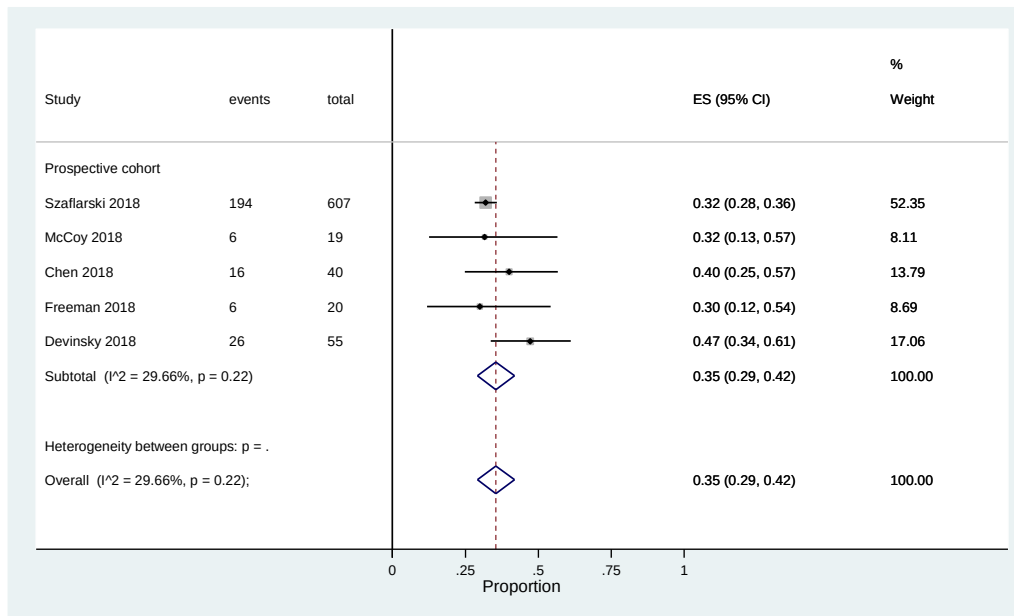


Figure 11: Pooled prevalence of vomiting reported among the non-randomized studies — State of the evidence as of October 2018

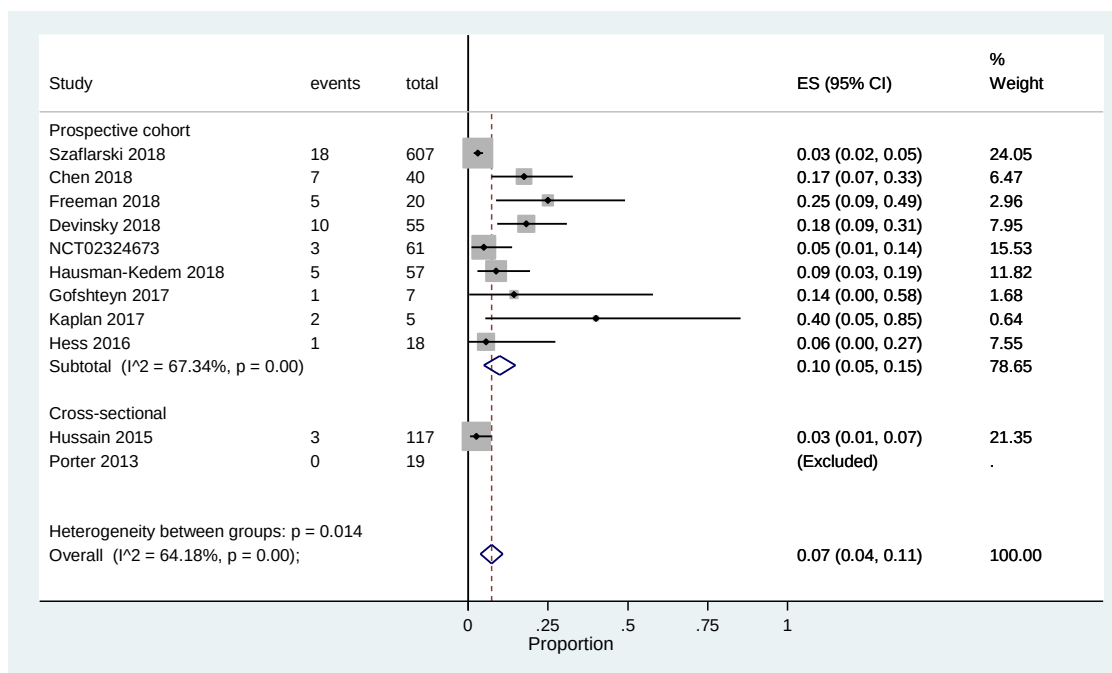


Figure 12: Pooled prevalence of diarrhea reported among the non-randomized studies — State of the evidence as of October 2018

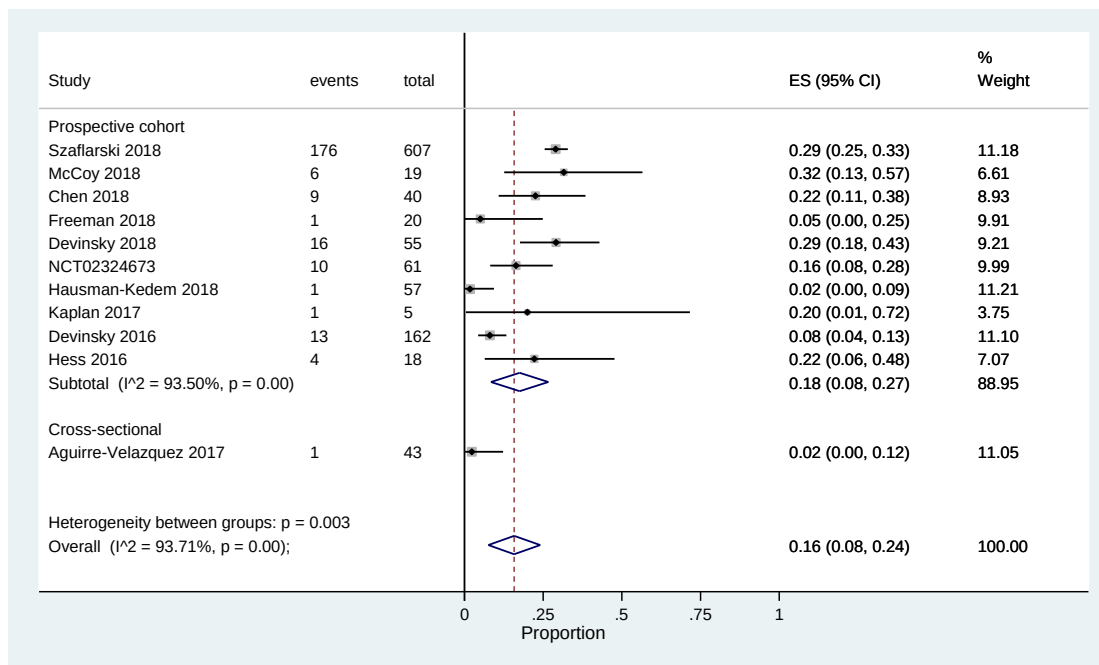
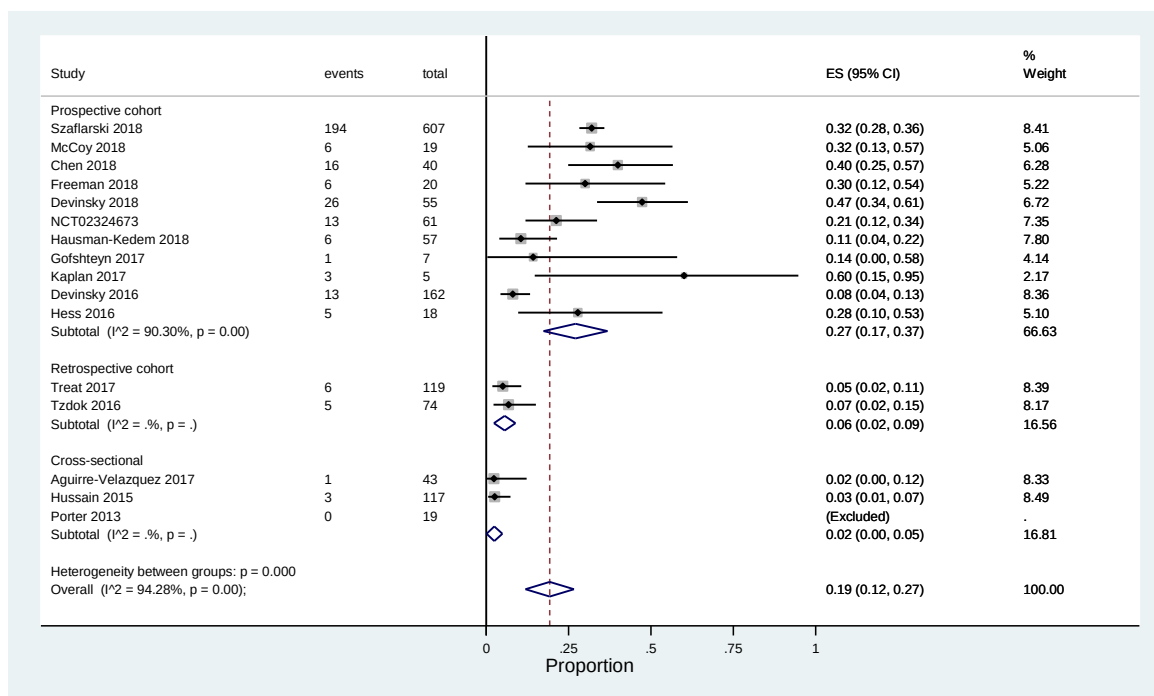


Figure 13: Pooled prevalence of any gastrointestinal adverse events (vomiting and/or diarrhea) reported among the non-randomized studies — State of the evidence as of October 2018



Visits to the emergency room

BASELINE REVIEW: No studies reported visits to the emergency department during the study period.

UPDATE 1: One study⁷ reported visits to the emergency room before and during cannabidiol treatment, finding no statistically significant difference in the number of visits per month between the two periods (Table 13).

EVIDENCE SUMMARY (as of October 2018): To date, visits to the ER have been reported by one non-randomized study⁷ (12 wk). Chen and colleagues reported no statistically significant difference in the monthly rate of visits per child before or during cannabis treatment; however, the duration of cannabidiol treatment was short, and the observation duration was different for the two periods (very low certainty of evidence).

Table 13: Evidence summary — visits to the emergency room

Author, yr	Study design	Population	Treatments (no. in group)*	Duration	Visits to the ER†; admissions per month per patient, mean (range)	
					Baseline‡	After treatment¶
UPDATE 1 (April–October 2018)						
Chen 2018 ⁷	Prospective single-group cohort	Drug- resistant epilepsy	• CBD (40)	12 wk	0.29 (0–1.25)	0.39 (0–2)**
BASELINE REVIEW (Up to April 2018)						
No studies						
Note: CBD = cannabidiol, ER = emergency room, CI = confidence interval, NR = not reported, SD = standard deviation. *Treatments described in full in Table 1. No. included in safety analysis. †Visits to the ER or admitted to hospital. ‡Visits per month over a 1-year period. ¶Visits per month over the 12-wk treatment period. **Not statistically significant different from the baseline rate.						

DISCUSSION

In the first update of this living systematic review, we identified seven studies that had been published in the six months following the initial review, bringing to 30 the total number of published studies assessing the benefits and harms of cannabis-based treatments for pediatric epilepsy. The findings of the newly included studies were generally consistent with the earlier studies, and the certainty of evidence did not change for any outcome. Importantly, 35 additional studies are registered in online clinical trial repositories, suggesting that additional evidence will be available for future updates of this review. Across outcomes, the current certainty of the evidence ranges from very low to moderate and may change as additional evidence becomes available.

Strengths and limitations

The protocol for this living systematic review was published *a priori*,³ and for this update, we followed the same methodology as used in the baseline review. The first update of this review shares several limitations in common with the baseline review:

1. Risk of bias: The studies included in Update 1 were all at high risk of at least one important source of bias (e.g., selection, performance, ascertainment) and the certainty of the evidence from such studies is very low. This is consistent with similarly designed studies included in the baseline review.
2. Heterogeneity (participants and interventions): Of the seven newly included studies, four included participants with multiple forms of drug-resistant epilepsy,^{4,6,7,9} and there may be differences in response across epilepsy syndromes. Similar to the baseline review, most newly included studies involved Epidiolex (6 studies), a pharmaceutical-grade CBD preparation. One study⁵ involved an oral cannabis-based treatment containing both CBD and THC (50:1 CBD:THC). Because CBD and THC bind to different receptors, it is possible that compounds containing both CBD and THC may have different biological effects compared to those containing CBD alone. The results from this study suggest that the CBD/THC product reduced seizures and improved quality of life among children with Dravet syndrome; however, the study was limited by a small sample size, short treatment

duration, and unblinded outcome assessment.⁵ Of the studies included in the baseline review, one involved a CBD/THC product (20:1 CBD:THC)²⁶; however, about 30% of participants were switched to an inhaled CBD-enriched cannabis product during the study, complicating the interpretation of findings. In total, more than half of the studies in the baseline review involved CBD alone, while others involved multiple cannabis-based products, which were often poorly described.

3. Heterogeneity (treatment duration): The treatment duration of studies included in Update 1 was variable, ranging from 12 to 146 weeks. Similarly, the duration of treatment was highly variable among studies in the baseline review (10 days to 57 months).

4. Background treatments: In most studies included in both Update 1 and the baseline review, cannabis-based products were added to an established regimen of antiepileptic therapies, including concomitant AEDs. The use of cannabis as a first-line treatment among children with newly diagnosed epilepsy has not been studied to date.

Conclusion

Update 1 of this living systematic review extends the evidence base six months after the baseline review, adding an additional seven published studies. Evidence published up to October 2018 suggests that CBD may be effective in reducing seizures among children with drug-resistant epilepsy. There is limited evidence suggesting that product containing CBD and THC may also be effective; however, the majority of evidence at this time pertains products including CBD alone. This is an active area of clinical research, and future updates will include additional evidence as it becomes available.

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3. Elliott J, DeJean D, Clifford T, et al. Cannabis for pediatric epilepsy: protocol for a living systematic review. *Syst Rev*. 2018;7:95.
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5. McCoy B, Wang L, Zak M, et al. A prospective open-label trial of a CBD/THC cannabis oil in Dravet syndrome. *Ann Clin Transl Neurol*. 2018;1-12.
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12. Halford J, Marsh E, Mazurkiewicz-Beldzinska M, et al. Long-term safety and efficacy of cannabidiol (CBD) in patients with Lennox-Gastaut Syndrome (LGS): Results from open-label extension trial (GWPCARE5). *Neurology*. 2018;Conference(15 Supplement 1).
13. Joshi C, Thiele E, Marsh E, et al. Treatment with cannabidiol (CBD) significantly reduces

- drop and total seizure frequency in Lennox-Gastaut Syndrome (LGS): Results of a multicenter, randomized, double-blind, placebo controlled trial (GWPCARE4). *Ann Neurol*. 2017;Conference(Supplement 21):S293.
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 16. Morrison G, Sardu ML, Rasmussen CH, Sommerville K, Roberts C, Blakey GE. Exposure-response analysis of cannabidiol (CBD) oral solution for the treatment of Lennox-Gastaut syndrome. *Neurology*. 2018;Conference(15 Supplement 1).
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Supplemental File 1: Included and excluded records

INCLUDED RECORDS (k = 17)

Published and grey literature reports (k = 8).

1. Szaflarski JP, Bebin EM, Cutter G, et al. Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. *Epilepsy Behav.* 2018;87:131-136.
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Conference abstracts (k = 7)

Matched* to an included published study.

Note: Abstracts were matched to published studies based on study name, registration number, authors, study and population characteristics or reported data.

1. Joshi C, Thiele E, Marsh E, et al. Treatment with cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a multicenter, randomized, double-blind, placebo controlled trial (GWPCARE4). *Ann Neurol.* 2017;Conference(Supplement 21):S293
2. Wirrell E, Devinsky O, Patel A, et al. Cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a dose ranging, multicenter, randomized, double blind, placebo controlled trial (GWPCARE3). *Ann Neurol.* 2017;Conference(Supplement 21):S279
3. Szaflarski J, Bebin E, Gaston T, et al. Response to pharmaceutical formulation of purified cannabidiol (CBD) in pediatric and adult patients with treatment-refractory epilepsy. *Neurology.* 2018;Conference(15 Supplement 1).

Unmatched (potentially unpublished studies)

1. Miller I, Devinsky O, Nabbout R, et al. Maintenance of long-term safety and efficacy of cannabidiol (CBD) treatment in Dravet syndrome (DS): Results of the open-label extension (OLE) trial (GWPCARE5). *Neurology*. 2018;Conference(15 Supplement 1)
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3. Morrison G, Sardu ML, Rasmussen CH, et al. Exposure-response analysis of cannabidiol (CBD) oral solution for the treatment of Lennox-Gastaut syndrome. *Neurology*. 2018;Conference(15 Supplement 1).
4. Halford H, Marsh E, Mazurkiewicz-Beldzinska M, et al. Long-term safety and efficacy of cannabidiol (CBD) in patients with Lennox-Gastaut syndrome (LGS): Results from open-label extension trial (GWPCARE5). *Neurology*. 2018;Conference(15 Supplement 1).

Registry records (k = 2)

1. Cannabidiol for drug resistant pediatric epilepsy. [http://ClinicalTrials.gov identifier: NCT03676049](http://ClinicalTrials.gov/identifier/NCT03676049). <https://clinicaltrials.gov/ct2/show/NCT03676049>
2. A double-blind placebo-controlled study investigating the safety, tolerability, efficacy and pharmacokinetics of EP1, and enriched cannabidiol oil in children and adolescents with medication resistant refractory epilepsy. ANZCTR identifier: ACTRN12618001706268. <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376037>

EXCLUDED RECORDS (k = 23)

Wrong population (k = 2)

1. Libzon S, Schleider LB, Saban N, et al. Medical cannabis for pediatric moderate to severe complex motor disorders. *J Child Neurol*. 2018;33:565.
2. Dahdah LS, Garcia IP. Medical marijuana-receptivity and knowledge in a cohort of Hispanic patients with epilepsy. *Neurology*. 2018;90(15 Supplement).

Not a primary study (k =3)

1. Suraev A, Lintzeris N, Stuart J, et al. Author Correction: Composition and Use of Cannabis Extracts for Childhood Epilepsy in the Australian Community. *Sci Rep*. 2018;8:11850.
2. Ostrovsky DA, Ehrlich A. Addition of cannabidiol to current antiepileptic therapy reduces drop seizures in children and adults with treatment-resistant Lennox-Gastaut syndrome. *Explore (NY)*. 2018;14:311-3.
3. Efron D, Freeman J. Medical cannabis for paediatric developmental-behavioural and psychiatric disorders. *J Paediatr Child Health*. 2018;54:715-7.

Other (k = 18)

1. Hausman-Kedem M, Menascu S, Kramer U. Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents — An observational, longitudinal study. *Brain Dev*. 2018; 40:544-51.
2. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Eng J Med*. 2018;378:1888-97.

3. A study to assess the efficacy, safety, and tolerability of cannabidiol oral solution with vigabatrin as initial therapy in participants with infantile spasms. [http://ClinicalTrials.gov identifier: NCT03421496](http://ClinicalTrials.gov/identifier:NCT03421496). <https://clinicaltrials.gov/show/nct03421496>.
4. Trial of cannabidiol (CBD; GWP42003-P) for infantile spasms (GWPCARE7). [http://ClinicalTrials.gov identifier: NCT02953548](http://ClinicalTrials.gov/identifier:NCT02953548). <https://clinicaltrials.gov/show/nct02953548>.
5. Phase 3 Trial of Cannabidiol (CBD; GWP42003-P) for infantile spasms: open-label extension phase (GWPCARE7). [http://ClinicalTrials.gov identifier: NCT02954887](http://ClinicalTrials.gov/identifier:NCT02954887). <https://clinicaltrials.gov/show/nct02954887>.
6. GWPCARE2 A study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome. [http://ClinicalTrials.gov identifier: NCT02224703](http://ClinicalTrials.gov/identifier:NCT02224703). <https://clinicaltrials.gov/show/nct02224703>
7. A study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults. [http://ClinicalTrials.gov identifier: NCT02224690](http://ClinicalTrials.gov/identifier:NCT02224690). <https://clinicaltrials.gov/show/nct02224690>
8. A study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults. [http://ClinicalTrials.gov identifier: NCT02224560](http://ClinicalTrials.gov/identifier:NCT02224560). <https://clinicaltrials.gov/show/nct02224560>
9. A dose-ranging pharmacokinetics and safety study of GWP42003-P in children with Dravet syndrome (GWPCARE1). [http://ClinicalTrials.gov identifier: NCT02091206](http://ClinicalTrials.gov/identifier:NCT02091206) <https://clinicaltrials.gov/show/nct02091206>
10. A double-blind, placebo-controlled two-part study to investigate the dose-ranging safety and pharmacokinetics, followed by the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome. EUCTR: 2014-000995-24-GB. <https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-000995-24/results>
11. Safety and tolerability of Epidiolex in patients (ages 1-19 years) with intractable epilepsy. [http://ClinicalTrials.gov identifier: NCT02695537](http://ClinicalTrials.gov/identifier:NCT02695537). <https://clinicaltrials.gov/ct2/show/NCT02695537>
12. Cannabidiol for pediatric epilepsy (compassionate use). [http://ClinicalTrials.gov identifier: NCT02556008](http://ClinicalTrials.gov/identifier:NCT02556008). <https://clinicaltrials.gov/ct2/show/NCT02556008>
13. A dose-ranging pharmacokinetics and safety study of GWP42003-P in children with Dravet syndrome (GWPCARE1). [http://ClinicalTrials.gov identifier: NCT02091206](http://ClinicalTrials.gov/identifier:NCT02091206)
14. Antiepileptic efficacy study of GWP42003-P in children and young adults with Dravet syndrome. [http://ClinicalTrials.gov identifier: NCT02091375](http://ClinicalTrials.gov/identifier:NCT02091375). <https://clinicaltrials.gov/ct2/show/NCT02091375>
15. Efficacy and safety of GWP42003-P for seizures associated with Lennox-Gastaut syndrome in children and adults (GWPCARE3). [http://ClinicalTrials.gov identifier: NCT02224560](http://ClinicalTrials.gov/identifier:NCT02224560). <https://clinicaltrials.gov/ct2/show/NCT02224560>
16. A study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults (GWPCARE4). [http://ClinicalTrials.gov identifier: NCT02224690](http://ClinicalTrials.gov/identifier:NCT02224690). <https://clinicaltrials.gov/ct2/show/NCT02224690>

17. Cannabidiol (CBD) to 27 patients (aged 2 years – 19 years) with drug resistant epilepsy.
<http://ClinicalTrials.gov> identifier: NCT02286986.
<https://clinicaltrials.gov/ct2/show/NCT02286986>
18. Cannabidiol oral solution in pediatric participants with treatment-resistant seizure disorders.
<http://ClinicalTrials.gov> identifier: NCT02324673.
<https://clinicaltrials.gov/ct2/show/NCT02324673>

Supplemental file 2: GRADE summary – UPDATE 1*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	standard care	Relative (95% CI)	Absolute (95% CI)		
Randomized controlled trials												
Seizure freedom (total seizures) (treatment duration: 14 weeks; number of patients with zero seizures during treatment)												
1	randomised trials	not serious	not serious	not serious	very serious ^{a,b,c}	none	3/61 (4.9%)	0/59 (0.0%)	RR 6.77 (0.36 to 128.38) ^d	—	⊕⊕○○ LOW	CRITICAL
Total seizure frequency (treatment duration: 14 weeks; median % reduction in monthly seizures from baseline)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	296	220	-	-19.8% (-27.0% to -12.6%)	⊕⊕⊕○ MODERATE	
Tonic-clonic seizure frequency (treatment duration: 14 weeks; median % reduction in monthly seizures from baseline)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	219	171	-	-26.7% (-38.6% to -14.6%)	⊕⊕⊕○ MODERATE	
Treatment response (treatment duration: 14 weeks; number of participants with at least a 50% reduction in total seizures from baseline)												
1	randomised trials	not serious	not serious	not serious	serious ^a	none	32/86 (37.2%)	18/85 (21.2%)	RR 1.76 (1.07 to 2.88)	161 more per 1,000 (from 15 more to 398 more)	⊕⊕⊕○ MODERATE	CRITICAL
Quality of life (child) (treatment duration: 14 weeks; Quality of Life in Childhood Epilepsy Scale, range: 0 to 100)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	296	220	-	MD 0.6 higher (2.6 lower to 3.9 higher)	⊕⊕⊕○ MODERATE	
Sleep disruption (treatment duration: 14 weeks; Sleep Disruption Rating Scale; range: 0 to 10)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	296	220	-	MD 0.3 lower (0.8 lower to 0.2 higher)	⊕⊕⊕○ MODERATE	
Status epilepticus (treatment duration: 12 weeks; number of children with status epilepticus during the treatment period)												
3	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	15/296 (5.1%)	7/220 (3.2%)	RR 1.39 (0.55 to 3.47)	12 more per 1,000 (from 14 fewer to 79 more)	⊕⊕○○ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	standard care	Relative (95% CI)	Absolute (95% CI)		
Death (treatment duration: 14 weeks; number of deaths during the treatment period)												
1	randomised trials	not serious	not serious	not serious	very serious ^{c,e}	none	1/86 (1.2%)	0/85 (0.0%)	not estimable		⊕⊕○○ LOW	
Gastrointestinal adverse events (treatment duration: 3 to 14 weeks; number of children with vomiting or diarrhea or both)												
4	randomised trials	not serious	serious ^f	not serious	serious ^{a,b}	none	89/323 (27.6%)	45/227 (19.8%)	RR 1.54 (0.92 to 2.58)	107 more per 1,000 (from 16 fewer to 313 more)	⊕⊕○○ LOW	CRITICAL
Observational studies												
Seizure freedom (total seizures) (treatment duration: 8 to 96 weeks; number of patients with zero seizures during treatment)												
18	observational studies	very serious ^g	serious ^h	serious ⁱ	not serious	none	The estimate of seizures freedom ranged from 1% to 29% (pooled proportion 7%, 95%CI 4% to 11%)			⊕○○○ VERY LOW	CRITICAL	
Total seizure frequency (treatment duration: range 12 weeks to 2.5 years; % reduction in seizures from baseline)												
8	observational studies	very serious ^j	very serious ^k	serious ⁱ	not serious	none	The reduction in total seizures among NRS with use of cannabis products between 30% and 90%; difference in reporting precluded pooling of effect estimates			⊕○○○ VERY LOW		
Tonic-clonic seizure frequency (treatment duration: 12 weeks to 12 months; % reduction in seizures from baseline)												
2	observational studies	very serious ^l	serious ^{k,m}	very serious ^{m,n}	serious ^e	none	Devinsky et al (2016) reported median frequency of monthly tonic-clonic seizures with any type of drug resistant epilepsy (−16%, 95%CI −60.1% to 35.3%, n=89) while Hess et al (2016) reported weekly reduction of tonic-clonic seizures: −91.4%, 95%CI −100 to −13.9%, n=6) in participants with tuberous sclerosis complex			-		
Treatment response (treatment duration: 8 wk to 96 wk; at least a 50% reduction in total seizures from baseline)												
15	observational studies	very serious ^o	very serious ^p	serious ⁱ	not serious	none	Range of reported treatment response: 30%–90%, with high heterogeneity precluding pooling. Among prospective cohort studies: 50% (95%CI 43% to 58%; 9 studies)			⊕○○○ VERY LOW		

Quality of life (child) (treatment duration: 12 to 82 weeks; assessed with: score from 0 to 100)											
3	observational studies	very serious ^q	serious ⁿ	serious ⁿ	very serious ^r	none	McCoy et al (2018) reported a statistically significant improvement in quality of life after treatment with a cannabis-based extract) Rosenberg et al (2017) reported a mean improvement of 8.12 points (SD 9.5; p<0.001) on the Quality of Life in Childhood Epilepsy scale after treatment with cannabidiol. Kaplan et al (2018) reported improved QoL for all participants, with no numerical data reported.	⊕○○○ VERY LOW			
Improved sleep (treatment duration: 2 weeks to 14 months; number of children with improved sleep)											
5	observational studies	very serious ^s	very serious	serious ⁱ	not serious	none	Pooled proportion of children who experienced an improvement in sleep (a) 8% (95%CI 4% to 11%) based on pooled analysis of 2 retrospective cohort study (b) 68% (95%CI 46% to 90%) based on pooled analysis of 3 cross-sectional surveys	⊕○○○ VERY LOW			
Impaired sleep (treatment duration: 10 days to 82 weeks; number of children with impaired sleep)											
5	observational studies	very serious ^t	not serious ^u	serious ⁱ	serious ^a	none	Pooled proportion of children with impaired sleep: 4% (95%CI 0% to 7%)	⊕○○○ VERY LOW			
Status epilepticus (treatment duration: 12 to 146 weeks; number of children with status epilepticus)											
5	observational studies	very serious ^v	not serious ^w	serious ⁱ	serious ^{a,c}	none	Pooled prevalence of status epilepticus: 5% (95% 2% to 9%), with high heterogeneity between studies	⊕○○○ VERY LOW			
Death (treatment duration: range 2 to 146 weeks; number of deaths)											
7	observational studies	very serious ^x	not serious ^k	serious ⁱ	very serious ^{a,c}	none	19 deaths from various causes (including 5 reports of SUDEP) were reported in 7 non-randomized studies(n = 997)	⊕○○○ VERY LOW			
Gastrointestinal adverse events (treatment duration: 10 days to 146 weeks; number of children with vomiting and/or diarrhea)											
16	observational studies	very serious ^y	serious ^z	serious ⁱ	not serious	none	Proportion of patients experienced at least one of vomiting or diarrhea: 19% (95%CI 12% to 27%), with high heterogeneity between studies and significant differences in estimates between study designs	⊕○○○ VERY LOW			
Quality of life (caregiver)											
0								not estimable		-	
Visits to the emergency department (treatment duration: 12 weeks; number of admissions per month per patient)											
1	Observational studies	Serious ^{aa}	Not serious	Not serious	serious ^e	none	One study reported no statistically significant difference in the monthly rate of ER visits or hospital admissions in the year before treatment compared with 12 weeks of cannabidiol treatment.	⊕○○○ VERY LOW			
Note: footnotes appear on next page											

Note: CI = confidence interval, RR = relative risk, MD = mean difference

*Adapted from Elliott et al. 2019.²

- a. Number of participants is less than the optimal information size
- b. 95%CI includes important benefits and harms
- c. Rare event; confidence intervals may be misleading because of fragility
- d. Risk difference: 5% (95% -1% to 11%)
- e. Small sample size
- f. Heterogeneity (I^2): 52%
- g. Mix of different observational study designs (10 prospective cohort studies, 5 retrospective cohort studies, 3 cross-sectional surveys); risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in intervention
- h. Heterogeneity (I^2): 73%
- i. Differences in patient populations, differences in exposure (type, dose of cannabis-based products), and differences in the duration of treatment across studies
- j. Mix of different observational study designs (1 comparative retrospective cohort, 7 single-group prospective cohorts, and 1 cross sectional study); risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in intervention
- k. Not pooled
- l. Two single-arm prospective cohort studies; risk of selection bias, unblinded outcome assessment, lack of a comparison group
- m. Considerable differences in point estimates and confidence intervals between the two studies, which involved different study populations
- n. Different patient populations, different duration of treatment across studies
- o. Mix of different observational designs (9 prospective cohort studies, 4 retrospective cohort studies, 2 cross-sectional studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention
- p. Heterogeneity (I^2) = 77%, with differences in effect estimates between study designs
- q. Three prospective single-group cohort studies; high risk of selection bias, unblinded outcome assessment, lack of a comparison group
- r. Numerical data only reported for two of three studies; small sample size; differences in intervention across studies.
- s. Mix of different observational designs (2 retrospective cohort studies, 3 cross-sectional studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention
- t. Mix of different observational designs (4 prospective cohort studies, 1 cross-sectional study); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention
- u. Heterogeneity (I^2) = 5.9%
- v. Mix of different observational designs (4 prospective cohort studies, 1 retrospective cohort study); high risk of selection bias, unblinded outcome assessment, lack of a comparison group
- w. Heterogeneity (I^2) = 77%
- x. Mix of different observational designs (4 prospective single-arm cohort studies, 3 retrospective single-arm cohort studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention
- y. Mix of different observational designs (11 prospective cohort studies, 2 retrospective cohort study, 3 cross-sectional studies); high risk of selection bias, unblinded outcome assessment, lack of a comparison group, variation in the intervention
- z. Heterogeneity (I^2) = 94%; Vomiting alone I^2 = 64%; Diarrhea alone: I^2 = 94%
- aa. Single study, high risk of bias; small sample size; unblinded outcome assessment; lack of a comparison group

Appendix E

Economic evaluation of stiripentol for Dravet syndrome:

A cost-utility analysis

APPENDIX OVERVIEW and CONNECTION TO THESIS

This appendix presents a cost-utility analysis developed as part of the candidate's PhD coursework; as such, it does not represent work done as part of the thesis objectives.

The manuscript contained within this appendix describes a *de novo* model developed by Jesse Elliott and Doug Coyle, with input from the other co-authors, in order to evaluate the cost-effectiveness of stiripentol for Dravet syndrome. This model was subsequently updated and adapted for use in **Chapter 4.4** to evaluate the cost-effectiveness of cannabinoid oil for treatment of Dravet syndrome.

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SUPPORTING MATERIAL

Supplementary file 1: CHEERS Checklist

Supplementary file 2: Technical Appendix

AUTHOR ROLES AND CONTRIBUTIONS:

JE, BM, GA, TC, and DC conceived the study. JE drafted the Markov model which was critically reviewed by DC. BM provided clinical input. JE drafted the manuscript, which was revised by all authors. All authors (JE, BM, GA, TC, and DC) provided comments on the draft and approved the version of the manuscript submitted for publication.

Economic evaluation of stiripentol for Dravet syndrome: A cost-utility analysis

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Conflicts of interest: Bláthnaid McCoy is principal investigator in a study of cannabinoids for Dravet syndrome. Tammy Clifford is employed by CADTH. She had no role in the review of stiripentol that was undertaken by the Common Drug Review. Jesse Elliott, George Wells, and Doug Coyle have no conflicts of interest to declare.

ABSTRACT

Background: Dravet syndrome is a catastrophic form of pediatric treatment-resistant epilepsy with few effective treatment options. Stiripentol is approved for use in Canada for treatment of Dravet syndrome, but the associated long-term costs and benefit have not been well studied and its cost-effectiveness is unclear.

Objective: The aim of this study was to evaluate the cost-effectiveness of stiripentol as an adjunctive treatment to clobazam and valproate for treatment of Dravet syndrome from the perspective of the Canadian public health care payer.

Methods: A cost-utility analysis was performed to estimate the costs and quality adjusted life years (QALYs) associated with adjunctive stiripentol treatment compared with clobazam and valproate alone in children with Dravet syndrome. Transition probabilities, drug efficacy, utility weights, and costs were obtained from a review of the literature. Probabilistic analyses were conducted using a Markov model with health states related to seizure frequency. A 10-year horizon was used. The incremental cost per QALY gained (ICER) for adjunctive use of stiripentol was calculated, and assumptions were explored in scenario analyses. All costs are expressed in 2017 Canadian Dollars.

Results: Compared with clobazam and valproate alone, the adjunctive use of stiripentol is associated with an ICER of \$151,310. At a willingness-to-pay threshold of \$50,000, the probability that stiripentol was the optimal treatment was 5.2%. The cost of stiripentol would need to be reduced by 61.4% for stiripentol to be cost effective.

Conclusion: From the perspective of the Canadian public health care payer, stiripentol is not cost-effective at its current price at a willingness-to-pay threshold of \$50,000. Funding stiripentol will be associated with important opportunity costs that bear consideration.

Key points for decision makers

1. Compared with clobazam and valproate alone, the adjunctive use of stiripentol in the treatment of Dravet syndrome is not cost-effective at a willingness-to-pay threshold of \$50,000
2. Decision makers should consider the opportunity cost of funding stiripentol for treatment of Dravet syndrome

1. Introduction

Dravet syndrome is a rare form of catastrophic childhood epilepsy that accounts for slightly more than one percent of childhood epilepsies [1], with an estimated incidence of 1 in 15,700.[2] Seizures typically begin before age one, with developmental delays becoming apparent during the child's second year [3]. Dravet syndrome is typically resistant to antiepileptic drugs, and polytherapy is often used in an attempt to control the multiple seizure types common to this syndrome [4]. Few clinical trials have evaluated the efficacy of antiepileptic drugs among patients with Dravet syndrome [5], and the long-term benefits, safety, and tolerability are largely unknown.

Stiripentol is a second-generation antiepileptic drug that has shown efficacy against tonic and tonic-clonic seizures in Dravet syndrome in two short-term randomized controlled trials [6,7]. In Canada, stiripentol is approved for use in conjunction with clobazam and valproate in patients with Dravet syndrome whose seizures are resistant to treatment with clobazam and valproate alone [8]. However, the cost-effectiveness of stiripentol has not been well characterized. A cost-utility analysis (CUA) by the manufacturer reported an incremental cost-effectiveness ratio (ICER) of \$50,122 for each quality-adjusted life year (QALY) gained with stiripentol treatment over a 5-year horizon [9]; however, the Common Drug Review noted several limitations with the analysis both in terms of methodology and in data assumptions [10]. A more robust and independent analysis is needed to provide an estimate of the costs and benefits of funding stiripentol for Dravet syndrome.

In the present study, we conducted a CUA to address the decision problem related to the cost-effectiveness of stiripentol for the treatment of Dravet syndrome. We evaluated the cost-effectiveness of stiripentol as an adjunctive treatment to clobazam and valproate in the treatment of patients with Dravet syndrome from the perspective of a Canadian public health care payer.

2. Methods

We performed a model-based CUA from the perspective of the Canadian health care system. As such, Canadian guidelines [10] were followed throughout. A pediatric neurologist with expertise in the treatment of children with Dravet syndrome in Canada (B.M.) verified the relevance of the model and model inputs to clinical practice. The CHEERS statement [11] was followed in the reporting of this cost-effectiveness analysis (Supplemental file 1).

2.1 Analytic framework

We developed a Markov model within Microsoft Excel to simulate the outcomes associated with stiripentol treatment. The model consists of 4 states related to the frequency of seizures relative to the baseline period: seizure free (SF; 100% reduction in seizures from baseline), not seizure free (NSF; 50%–99% reduction), not adequately controlled (NAC; 0%–49% reduction), and death (Figure 1). The structure of this model analysis was adapted from a model developed by the National Institute for Health and Care Excellence (NICE) for the economic evaluation of pediatric epilepsy treatments.[12] Patients were assumed to enter the model in the NAC state, consistent with previous treatment failure. After each 1-month cycle, patients could move between the SF, NSF, and NAC states dependent on the assigned transition probabilities; death was the final absorbing state. Patients who responded to stiripentol treatment (seizure free or 50–99% reduction in seizures) were assumed to continue stiripentol in subsequent cycles. Patients whose seizures did not respond to stiripentol could remain in the NAC state (0–49% reduction in seizures) for up to 6 cycles, after which time they were assumed to discontinue stiripentol and continue on clobazam and valproate alone. The time horizon for the analysis was 10 years.

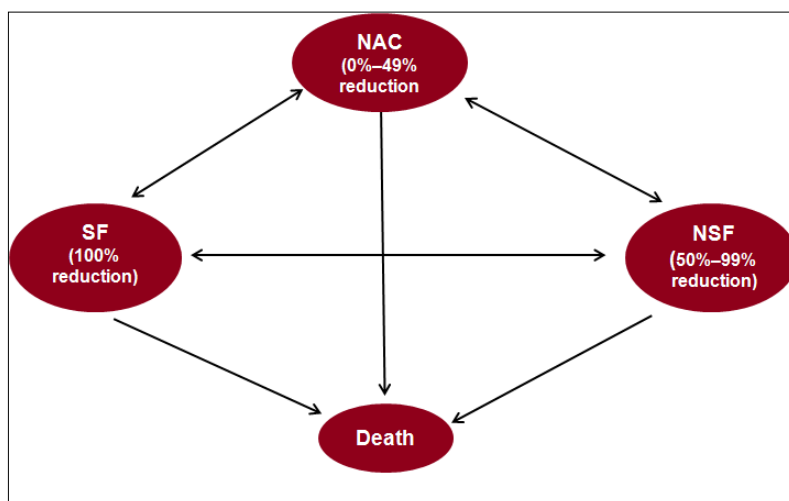


Figure 1: Schematic of Markov model showing movement of patients between states. Note: SF = seizure free (100% reduction in seizures from baseline), NSF = not seizure free (50%–99% reduction), NAC = not adequately controlled (0%–49% reduction).

Expected values for costs and QALYs were obtained through probabilistic analysis and were discounted at a rate of 1.5% per year, as per recent Canadian guidelines [10]. The Markov model was run for 5000 replications, with each model input parameter represented by a probability distribution (Table 1). Uncertainty around data was based on sampling error where available. For parameters for which uncertainty was not available, a conservative standard error of 25% of the mean was assumed. Costs and QALYs were estimated for each replication, and the ICER was calculated comparing the use of adjunctive stiripentol with clobazam and valproate alone.

2.2 Patient population

The target population was Canadian patients with Dravet syndrome that had not previously responded to concomitant treatment with clobazam and valproate. In the reference case, the typical patient was based on the STICLO France trial [6], a randomized controlled trial of stiripentol compared with placebo on a background of clobazam and valproate alone in children with Drave syndrome. The mean age in this group was 9.3 yr with a starting weight of 31 kg [6]. A 10-year analysis horizon was chosen such that patients would be considered adults at the end of the analysis.

2.3 Comparators

Stiripentol as an adjunctive to clobazam and valproate was compared to clobazam and valproate alone. In Canada, stiripentol is approved for the use in patients with Dravet syndrome whose seizures are not adequately controlled by clobazam and valproate. Patients were assumed to be taking the maximum recommended Health Canada-approved dose of each agent (stiripentol: 50 mg/kg/d; clobazam: 1 mg/kg/d up to a maximum of 40 mg/d; valproate: 60 mg/kg/d).

2.4 Model inputs

Data were required to inform the transition between model health states, mortality (sudden unexpected death in epilepsy [SUDEP] and non-SUDEP), the relative impact of treatment on seizure status, as well as utility values and costs related to each health state; these are described below and in Table 1. Additional information about key model parameters is available in Supplemental file 2.

2.4.1 Efficacy

The probability of transitioning between model states for patients taking clobazam and valproate alone were obtained by pooling data from the control arms of the STICLO randomized controlled trials, which involved the use of placebo on a background of clobazam and valproate.[6,7] Individual patient data for seizure frequency in patients taking stiripentol on a background of clobazam and valproate were obtained from a single-arm cohort study in Japan involving 24 patients taking stiripentol (50 mg/kg/d) for up to 56 weeks [13]. For each patient, the number of seizures experienced in a one-month period while taking stiripentol was compared to the number of seizures in the baseline period; these data were used to derive transition probabilities for each cycle. Uncertainty around probabilities was represented by Dirichlet distributions [14].

Table 1: Input parameters for the economic model

Parameter	Base estimate†	Probability distribution	Source
Patient weight	31 kg	Fixed	STICLO France [6]
Utilities*			
NAC	0.427	Normal (0.427, 0.03)	Verdian 2008 [17]
NSF	0.605	Normal (0.605, 0.03)	
SF	0.699	Normal (0.699, 0.03)	
Annual rates			
SUDEP	0.10	Gamma (10, 0.0009))	Cooper 2015 [15]
Non-SUDEP	0.007	Gamma (7,0.0009)	
Health care resource use			
Probability of resource use if SF			
Emergency department visit	0.02	Beta (7,343)	NICE [12]
Neurologist visit (initial)	0.85	Beta (23,4)	
Neurologist visit (follow-up)	0.85	Beta (23,4)	
General practitioner visit	0.36	Beta (10,17)	
Probability of resource use if NAC or NSF			
Emergency department visit	0.25	Beta (9,27)	NICE [12]
Neurologist visit (initial)	0.92	Beta (33,3)	
Neurologist visit (follow-up)	0.92	Beta (33,3)	
General practitioner visit	0.47	Beta (17,19)	
Hospital admission (non-SE)		Beta (9,27)	
Expected number of visits			
Emergency department visit	2	Gamma (16, 0.13)	NICE [12]
Neurologist visit (initial)	1	Gamma (16, 0.06)	
Neurologist visit (follow-up)	2	Gamma (64, 0.13)	
General practitioner visit	2	Gamma (16, 0.13)	
Admission (non-SE)	1	Gamma (16, 0.06)	
Land ambulance transfer to hospital	1	Gamma (1.58, 0.42)	Whittington 2018[21]
Costs			
Admission to hospital for status epilepticus	\$9024.96	Gamma (51.5, 171.8)	Ontario Case Costing Initiative
Admission to hospital (non-status epilepticus)	\$8439.48	Gamma (7.07, 1170.5)	
Land ambulance transfer to hospital	\$205	Fixed	Ontario Municipal Benchmarking Initiative [31]
Stiripentol	\$6.37 per 250 mg	Fixed	BC PharmaCare Formulary
Clobazam	\$0.1120 per 10 mg	Fixed	Ontario Drug Benefit Formulary
Valproate	\$0.1393 per 250 mg	Fixed	
Lorazepam	0.0713 per 2 mg	Fixed	
Emergency department visit	\$100.53	Fixed	Ontario Schedule of

Parameter	Base estimate†	Probability distribution	Source
Outpatient neurology visit, initial	\$81.16	Fixed	Benefits
Outpatient neurology visit, follow-up	\$63.96	Fixed	
General practitioner visit	\$79.52	Fixed	
Effectiveness			
Transition between states if on clobazam + valproate			STICLO France[6], STICLO Italy [7]
Remaining NAC	0.94	Beta (29, 2)	
NAC to NSF	0.06	Beta (2, 29)	
NAC to SF	0	Fixed	
Transition between states if on stiripentol	IPD	Dirichlet method	Inoue 2015[13]
Probability of status epileptics			
Clobazam + valproate	0.05	Beta (1, 19)	STICLO France[6]
Stiripentol	0.05	Beta (1, 21)	

Note: IPD = individual patient data, NAC = not adequately controlled, NICE = National Institute for Health and Care Excellence, NSF = not seizure free, SE = status epilepticus, SF = seizure free, SUDEP = sudden unexpected death in epilepsy.

*Cholsky decomposition ($\rho = 0.75$).

†Costs are valued in 2017 Canadian dollars.

Ontario Schedule of Benefits: www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/physserv_mn.html

British Columbia PharmaCare Formulary: <https://pharmacareformularysearch.gov.bc.ca/>

Ontario Drug Benefit Formulary: www.formulary.health.gov.on.ca/formulary/

Ontario Case Costing Initiative: <https://hsim.health.gov.on.ca/hdbportal/>

2.4.2 Mortality

Patients with Dravet syndrome are at risk of SUDEP as well as death from non-epileptic causes. The rates of SUDEP and non-SUDEP in Dravet syndrome were obtained from the available literature with uncertainty represented by Gamma distributions [15]. Rates were then converted to monthly probabilities [16]. We assumed that patients experiencing seizures (NAC or NSF states) were at risk of SUDEP and non-SUDEP, while seizure-free patients were assumed to be at risk of non-SUDEP only.

2.4.3 Adverse events

Patients with Dravet syndrome are at risk of status epilepticus, a prolonged seizure lasting for 30 minutes or longer or intermittent seizures totaling 30 min or more without regaining consciousness between seizures [3]. The probability of status epilepticus while on stiripentol and/or clobazam and valproate was obtained from the STICLO France trial [6] and represented by Beta distributions. No additional adverse events were considered in this analysis.

2.4.4 Utility values

A review of the literature found no published utility values specific to Dravet syndrome. Utility values from another severe form of pediatric epilepsy (Lennox-Gastaut syndrome) were used in the analysis [17] and represented by normal distributions. We incorporated correlation between utility values by use of the Cholesky decomposition matrix ($\rho = 0.75$) [18] and tested the impact of correlation in sensitivity analyses. All other parameters were assumed to be uncorrelated.

2.4.5 Cost variables

Costs associated with each medication, health care resource use, and managing status epilepticus were included in the model. Costs were converted to 2017 Canadian Dollars by use of the Bank of Canada's Inflation Calculator. The costs associated with diagnosis of Dravet syndrome were not included because we assumed that this cost would be incurred by all Dravet patients regardless of treatment strategy. We assumed that medication changes would be managed as part of routine clinic visits and that no additional costs would be associated with changing therapy.

Medication costs were obtained from provincial formularies (Table 1). Health care resource use by seizure status among patients with Dravet syndrome were not available at the time of this study. We assumed that resource use would be consistent with that described in the NICE cost-effectiveness analysis of treatments for pediatric epilepsy [12], based on an earlier study by Jacoby and colleagues [19]. Resource use included emergency department visits, general practitioner visits, and neurologist visits and varied by model state, with patients experiencing seizures having a greater probability of

resource use compared with those who are seizure free [12]. The expected number of visits was based on the NICE guidelines [12], and the unit cost of each resource was obtained from the Ontario Schedule of Benefits (www.health.gov.on.ca/en/pro/programs/ohip/sob/physsserv/physsserv_mn.html).

2.5 Scenario analyses

Scenario analyses were performed to test the impact of key model assumptions on the ICER, including revised input and structural assumptions. Specifically, we explored the impact of stiripentol price, dose of valproate, patient age, correlation between utility values, discount rate, and analysis horizon on the ICER.

3. RESULTS

3.1 Reference case

Over a 10-year horizon, the use of adjunctive stiripentol resulted in an increase in QALYs (0.60) at an additional cost of \$91,080 (Table 2). Drug costs were the most costly component of the costs of treatment, accounting for 72% of total costs. Other health care costs were lower for treatment with adjunctive stiripentol than without but this was substantially lower than the increased drug costs.

The adjunctive use of stiripentol was associated with an incremental cost of \$151,310 for each QALY gained. At a willingness to pay threshold of \$50,000, stiripentol was the optimal treatment in 5.2% of replications (Figure 2). At a willingness-to-pay threshold of \$100,000, stiripentol would be the optimal treatment in 20.7% of replications.

Table 2: Results of base case analysis

	Adjunctive stiripentol	Clobazam + valproate	Increment
QALYs	4.37	3.77	0.60
Drug costs (\$)	\$105,293	\$6,231	\$ 99,062
Other health care costs	\$ 41,183	\$49,165	-\$7,982
Total costs (\$)	\$146,477	\$55,397	\$ 91,080
Incremental cost per QALY gained (\$)			\$151,310

Results are based on probabilistic analysis and are discounted at 1.5% per annum.

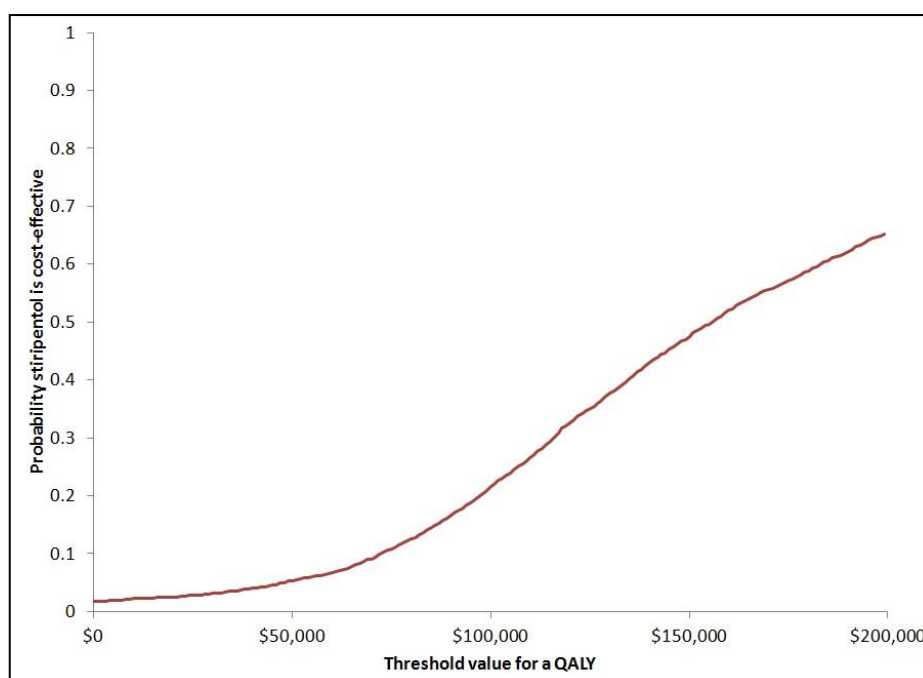


Figure 2: Cost-effectiveness acceptability curve: base case. Threshold values are given in 2017 Canadian dollars. QALY quality-adjusted life-year

3.2 Scenario analyses

We conducted several scenario analyses to test the impact of model assumptions; the results were robust to changes in most model assumptions (Table 3). Results varied by patient age, but not to the extent that the interpretation of the result would change. Results were very sensitive to the cost of

stiripentol. Stiripentol would be considered cost-effective at a willingness-to-pay threshold of \$50,000 if its price was reduced by 61.4%.

Table 3: Results of scenario analyses

Scenario	Incremental cost per QALY gained (\$)
Base case	151,310
Revised input assumptions	
Reduced price of STP	
10%	135,705
20%	119,036
40%	85,698
60%	52,360
80%	19,022
Valproate dose: 80 mg/kg/d	153,501
Patient age	
1 yr	56,076
5 yr	94,843
10 yr	168,000
15 yr	243,643
18 yr	261,081
Revised structural assumptions	
No correlation between utility values	155,491
Discount rate	
3%	152,121
0%	150,299
Horizon	
1 year	105,754
20 years	149,747

4 Discussion

Our results suggest that, from the perspective of the Canadian public health care payer, stiripentol is not cost-effective in the treatment of Dravet syndrome. Compared with the use of clobazam and valproate alone, the adjunctive use of stiripentol was associated with an incremental cost per QALY gained of \$151,310. The incremental costs were primarily due to the cost of stiripentol, with the costs of stiripentol accounting for 67% of the total costs. Thus, the results were sensitive to the cost of

stiripentol. A reduction in the cost of 61.4% would lead to stiripentol being considered cost-effective from the perspective of the health care system.

Children with epilepsy have higher health care-related costs than those without epilepsy, with effects lasting into adulthood [20]. The costs related to Dravet syndrome have not been extensively studied. A recent US survey of caregivers (n = 34) estimated the direct costs of caring for a child with Dravet syndrome to be USD\$27,276 (95% confidence interval: \$15,757 to \$41,904) per patient per year, with hospitalizations accounting for about 42% of costs; however, costs related to antiepileptic medications were not included in this analysis [21]. In an earlier single-centre retrospective study in Germany, the use of adjunctive stiripentol and clobazam by children with Dravet syndrome (n = 9) for a one-year period resulted in a 42.7% increase in total direct costs compared with one-year baseline period [22]. This increase was primarily owing to the cost of stiripentol, which accounted for 55.4% of the total direct costs [22]. This is consistent with our finding that 72% of the costs incurred over a 10-year period were due to the cost of stiripentol.

Despite the high health care costs associated with epilepsy and its treatment, there have been few economic evaluations of pharmacologic treatments for epilepsy [23], with fewer still focused on pediatric treatment-resistant epilepsy syndromes. The cost-effectiveness of stiripentol was previously assessed by the manufacturer [9], with a reported ICER of \$50,122 per QALY gained over a 5-year horizon compared with the use of clobazam and valproate alone. However, the time horizon, cycle length, patient weight, and assumptions related to the response rate within the comparator group were not consistent with clinical practice and available evidence. For example, the manufacturer's analysis assumed that patient weight was fixed, with no increase in weight over the five-year horizon [9]. This is an important consideration because the dosage of stiripentol is based on patient weight. In our analysis, patient weight was assumed to increase over time. Hence, cost effectiveness varied by the age of initiation of therapy.

In 2014, the Canadian Drug Expert Committee (CDEC) recommended listing stiripentol for use by patients with Dravet syndrome without adequate seizure control with clobazam and valproate alone, with the provision that the cost of stiripentol be reduced to an “acceptable level” [24]. Our analysis confirms that this recommendation was merited and suggests the necessary price reduction will be over 60%.

4.1 Strengths and limitations

Our analysis conformed with the recent Canadian guidelines for economic evaluations [10]. We estimated all outcomes through probabilistic analysis and adopted the perspective of a public health care payer with the objective of maximizing population health. Adoption of a wider societal perspective is not in keeping with the goal of maximizing population health; as it requires a willingness to accept lower population health for gains in other objectives such as productivity. In our study, we restricted quality of life gains to patients; future studies could include consideration of caregiver burden by incorporating the quality of life of caregivers into the analysis.

This study has limitations that require consideration. First, because Dravet syndrome is a rare condition, limited data were available for several model inputs, including utility values and health care resources utilization. Although resource utilization data have been published for Canadian patients with epilepsy [25], these data were not specific to children, treatment-resistant epilepsy, or reported by seizure status, each of which affect health resource utilization[12]. In discussion with a clinical expert, we assumed that resource use in Canada would be similar to that used by NICE [12]; future analyses should incorporate Canadian data as it becomes available.

Secondly, our analysis did not include adverse events beyond status epilepticus. The adverse effects associated with antiepileptic treatments are generally thought to disappear with either dose adjustment or withdrawal of treatment [12]. This is in keeping with cost-utility analyses used to inform NICE clinical practice guidelines [12].

Finally, we assumed that patients who discontinue stiripentol would return to treatment with clobazam and valproate alone. In clinical practice, however, such patients would likely initiate an alternative antiepileptic treatment with the aim of reducing seizure burden and maximizing quality of life. There is wide variation by jurisdiction in clinical practice surrounding antiepileptic treatments used in Dravet syndrome [26], which may limit the generalizability of our findings beyond the Canadian context.

It is not uncommon for treatments of rare disease to fail to meet conventional cost-effectiveness thresholds, and some authors argue that treatments for rare diseases should not be held to the same cost-effectiveness standards as drugs to treat common diseases [27,28]. However, although rare diseases are individually rare, together they affect millions of people, with the potential for important economic consequences [29]. As such, any funding decisions about treatments for rare diseases require consideration of opportunity cost, or the benefits forgone by funding one intervention over another [30].

5. Conclusion

In this analysis, we found that patients receiving stiripentol would gain 0.60 QALYs over a 10-year period over clobazam and valproate. Although this benefit may appear higher than with many other commonly funded treatments, our analysis suggests that given the high incremental costs, adjunctive treatment with stiripentol is not cost-effective from the perspective of the Canadian public health care payer. Stiripentol is currently funded in several Canadian provinces through special access programs. Although confidential agreements with manufacturers may have resulted in reduced prices, the price would need to be reduced by at least 60% to ensure that funding of stiripentol would not lead to a reduction in overall population health. Thus, the decision to cover stiripentol should be reconsidered in light of the likely high opportunity costs of this coverage.

Data Availability Statement: All data generated or analysed during this study are included in this published article (and its supplementary information files).

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Supplementary file 1: CHEERS Checklist

Section/item	Item No	Recommendation	Reported on page no.
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	5
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	5
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

Cont.

	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	6-7, Appendix 2
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6-7, Appendix 2
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Table 1
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	5, Fig. 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	5
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	5-8; Appendix 2
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2
Characterising	20a	<i>Single study-based economic evaluation:</i> Describe the effects	NA

uncertainty		of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Table 2, appendix 2
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	8
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	1
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	2

Supplementary file 2: Technical Appendix

Identification and Choice of Key Model Inputs

We performed a review of the published literature in PubMed to identify key model inputs (utilities, mortality, resource use, effectiveness). The choice of input parameters was based on identifying the most recent relevant and appropriate data from a Canadian context. All inputs were verified for clinical relevance by an experienced neurologist (B.M.).

Utilities. We searched for utility values related to the model states (seizure free, not seizure free, not adequately controlled) using keywords (“Dravet” or “severe myoclonic epilepsy in infancy” and “preference,” “utility,” “QALY,” or “quality adjusted life year”). No utility values for Dravet syndrome were located. We expanded the search to include other forms of pediatric treatment-resistant epilepsy. One conference abstract¹ was identified, which presented utility values for children with Lennox-Gastaut syndrome.

Verdian and colleagues¹ reported utility values for children with uncontrolled seizures (0.393), less than 50% reduction in seizures following treatment (0.461), reduction between 50% and 75% (0.605), and more than 75% reduction (0.699). In our model, we assumed that children who were seizure free (100% reduction) would have an equivalent utility to children with >75% reduction (0.699) in the Verdian study. Further, we assumed that children who were not seizure free (50%–99% reduction) would have a utility of 0.605, and that children with not adequately controlled seizures (<50% reduction) would have a utility of 0.427 (average of the values for uncontrolled disease and <50% reduction). These utilities have been used in a previous cost-utility analysis involving children with Dravet syndrome.²

Although not reported by Verdian and colleagues¹, we incorporated uncertainty around the utility values in the probabilistic analysis by assuming that the interquartile range for each utility value would be 0.25 to 0.75, and we calculated the standard deviation (SD) by use of the following

formula: $SD = (upper\ limit - lower\ limit)/1.35$. The SD was converted to standard error and incorporated into the model.

We assumed that the utility values were correlated ($\rho = 0.75$); correlation was incorporated via Cholesky decomposition matrix.³

Mortality. We searched using keywords (“Dravet” or “severe myoclonic epilepsy in infancy” and “death” “mortality,” or “sudden unexpected death in epilepsy”). We located one recent retrospective cohort study⁴ that provided the mortality rate and the rate of sudden unexpected death in epilepsy among children with Dravet Syndrome.

Resource use. We searched for resource use related to seizure frequency in children included in the model by use of keywords (“Dravet” or “severe myoclonic epilepsy in infancy” and “resource,” “cost,” or “service”). Because no relevant records were located, we expanded the search to include all types of pediatric treatment-resistant epilepsy and also searched more broadly using Google Scholar. We located the NICE clinical practice guidelines for epilepsy, which include cost-effectiveness analyses of treatments pediatric treatment resistant epilepsy.⁵ The NICE guidelines cited a 1998 study of resource use by children with epilepsy that reported use by seizure state, categorized as seizure free or not seizure free.⁶ Although this study was set in the United Kingdom, a clinical expert (B.M.) confirmed that the amount of services consumed would not be expected to be different in Canada. The Canadian unit cost for each resource was obtained from the Ontario Schedule of Benefits.

Effectiveness. We searched using keywords (“Dravet” or “severe myoclonic epilepsy in infancy” and “stiripentol” or “Diacomit” or “clobazam” or “valproate”). A 2015 Cochrane review⁷ of RCTs for the treatment of Dravet syndrome included 2 randomized controlled trials (RCTs)^{8,9} of stiripentol as an add-on to clobazam and valproate. Because these RCTs had a short duration (12 weeks), we further searched for non-randomized studies involving the use of stiripentol on a background of clobazam and valproate. We located one long-term prospective study¹⁰ of the effectiveness of

stiripentol in patients previously taking clobazam and valproate. This study provided individual patient data for the monthly frequency of seizures experienced by each patient in the cohort over a one-year period (n = 24 patients); specifically, the number of tonic or tonic-clonic seizures experienced by each patient during a baseline phase (before treatment) and during 11 subsequent 30-day periods were reported. We used these data to determine the probability of transition between seizure states, as described below.

We did not locate any long-term studies that assessed the effectiveness of clobazam and valproate in children with Dravet syndrome. As such, we used data from the clobazam + valproate arms of the two RCTs^{8,9} identified in the Cochrane review.⁷

Derivation of Transition Probabilities

Stiripentol

Inoue and colleagues¹⁰ reported individual patient data (number of seizures) for 24 patients before (4 weeks) and after initiation of stiripentol on a background of clobazam and valproate (eleven 30-day periods). For the first one-month period, we determined whether each patient was seizure free (100% reduction from baseline), not seizure free (50–99% reduction), or not adequately controlled (< 50% reduction) by comparing the number of seizures experienced in the baseline period to the number experienced in period 1. In each subsequent cycle, we determined if the patient had remained in his or her current state or moved to a different state based on the number of seizures experienced. Using these data, we created a series of gamma distributions to estimate the transition probabilities between states by use of the Dirichlet method.¹¹ For analyses with outcomes beyond 12 months, we assumed continuation of the transition probabilities from previous cycles, thus assuming no waning of treatment effect.

Clobazam + Valproate

The number of patients taking clobazam and valproate who achieved seizure free status or a more than 50% reduction in seizures were pooled from the clobazam + valproate arms of two 12-week RCTs.^{8,9} For example, one patient (of 20) achieved a 50–99% reduction in seizures in the STICLO France RCT,⁸ and one patient (of 11) achieved a 50–99% reduction in seizures in the STICLO Italy RCT⁹. Taken together, 2 of 31 patients achieved a 50–99% response to clobazam + valproate in these trials. In total, no patients in either trial achieved complete seizure freedom, and the remainder of patients (29/31) achieved a 0–50% response. We applied gamma distributions to these event rates to estimate the probability of being in each seizure state in the model (seizure free: 100% reduction; not adequately controlled: 50–99% reduction; not seizure free: 0–49% reduction). These transition probabilities were then applied for each cycle within the model.

Appendix references

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Appendix F

Ethics approval

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL**Numéro du dossier / Ethics File Number**

H-09-18-1083

Titre du projet / Project Title

Understanding caregivers' and clinicians' perspectives and experiences related to the use of cannabis for the treatment of drug-resistant epilepsy in children

Type de projet / Project Type

Thèse de doctorat / Doctoral thesis

Statut du projet / Project Status

Approuvé / Approved

Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)

23/11/2018

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Conditions spéciales ou commentaires / Special conditions or comments

Le Comité d'éthique de la recherche (CÉR) de l'Université d'Ottawa, opérant conformément à l'*Énoncé de politique des Trois conseils* (2014) et toutes autres lois et tous règlements applicables, a examiné et approuvé la demande d'éthique du projet de recherche ci-nommé.

L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales ou Commentaires". Le formulaire « Renouvellement ou Fermeture de Projet » doit être complété quatre semaines avant la date d'échéance indiquée ci-haut afin de demander un renouvellement de cette approbation éthique ou afin de fermer le dossier.

Toutes modifications apportées au projet doivent être approuvées par le CÉR avant leur mise en place, sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques du projet. Les chercheurs doivent aviser le CÉR dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou pouvant affecter considérablement le déroulement du projet, rapporter tout événement imprévu ou indésirable et soumettre toute nouvelle information pouvant nuire à la conduite du projet ou à la sécurité des participants.

The University of Ottawa Research Ethics Board, which operates in accordance with the *Tri-Council Policy Statement* (2014) and other applicable laws and regulations, has examined and approved the ethics application for the above-named research project.

Ethics approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special Conditions or Comments". The "Renewal/Project Closure" form must be completed four weeks before the above-referenced expiry date to request a renewal of this ethics approval or closure of the file.

Any changes made to the project must be approved by the REB before being implemented, except when necessary to remove participants from immediate endangerment or when the modification(s) only pertain to administrative or logistical components of the project. Investigators must also promptly alert the REB of any changes that increase the risk to participant(s), any changes that considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project or the safety of the participant(s).

Riana MARCOTTE

Responsable d'éthique en recherche / Protocol Officer

Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences sociales et humanités / Social Sciences and Humanities Research Ethics Board**

Appendix G

Published manuscripts

OVERVIEW

This appendix includes the PDFs of manuscripts published as part of this thesis. The citation for each PDF, as well as the permissions obtained, are provided below:

CHAPTER 3

Section 3.1

Elliott J, Clifford T, Coyle D, Potter B, McCoy B, Wells GA. Cannabis for pediatric epilepsy: Protocol for a living systematic review. *Systematic Reviews*. 2018;7:95.

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Section 3.2

Elliott J, DeJean D, Clifford T, Coyle D, Potter B, Skidmore B, Alexander C, Repetski A, Shukla V, McCoy B, Wells GA. Cannabis-based products for pediatric epilepsy: A systematic review. *Epilepsia*. 2019;60(1):6-19.

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Section 3.3

Elliott J, DeJean D, Clifford T, Coyle D, Potter B, Skidmore B, Alexander C, Repetski A, Shukla V, McCoy B, Wells GA. Cannabis-based products for pediatric epilepsy: An updated systematic review. *Seizure*. 2020;75:18-22.

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CHAPTER 4

Section 4.1

Elliott J, McCoy B, Clifford T, Potter B, Skidmore B, Wells GA, Coyle D. Cost-effectiveness of cannabinoids for pediatric drug-resistant epilepsy: Protocol for a systematic review of economic evaluations. *Systematic Reviews* 2019;8:75.

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Section 4.2

Elliott J, van Katwyk S, McCoy B, Clifford T, Potter B, Skidmore B, Wells GA, Coyle D. Decision models for assessing the cost-effectiveness of treatments for pediatric drug-resistant epilepsy: a systematic review of economic evaluations. *PharmacoEconomics* 2019; 37(10):1261-1276

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PROTOCOL

Open Access



Cannabis for pediatric epilepsy: protocol for a living systematic review

Jesse Elliott^{1,8*} , Deirdre DeJean², Tammy Clifford^{1,3}, Doug Coyle¹, Beth Potter¹, Becky Skidmore⁴, Christine Alexander⁴, Alexander E. Repetski⁵, Bláthnaid McCoy^{6,7} and George A. Wells^{1,8}

Abstract

Background: Pediatric epilepsy, including treatment-resistant forms, has a major effect on the quality of life, morbidity, and mortality of affected children. Interest has been growing in the use of medical cannabis as a treatment for pediatric epilepsy, yet there has been no comprehensive review of the benefits and harms of cannabis use in this population. In this systematic review, we will search for, synthesize, and assess the published and gray literature in order to provide usable and relevant information to parents, clinicians, and policy makers.

Methods: We will perform a living systematic review of studies involving the use of cannabis to treat pediatric epilepsy. We will search the published and gray literature for studies involving children with any type of epilepsy taking any form of cannabis. Studies will be selected for inclusion by two independent reviewers. The primary outcome is seizure freedom. Secondary outcomes are seizure frequency, quality of life (child, caregiver), quality and quantity of sleep, status epilepticus, tonic-clonic seizures, death (all-cause, sudden unexpected death in epilepsy), gastrointestinal adverse events (diarrhea, vomiting), and visits to the emergency room. The quality of each included study will be assessed. If data are sufficient in quantity and sufficiently similar, we will conduct pairwise random-effects meta-analysis. We will repeat the literature search every 6 months to identify studies published after the previous search date. Sequential meta-analysis will be performed as necessary to update the review findings.

Discussion: Our review aims to provide a comprehensive and up-to-date summary of the available evidence to inform decisions about the use of cannabis in children with treatment-resistant epilepsy. The results of this review will be of use to parents, clinicians, and policy makers as they navigate this rapidly evolving area.

Systematic review registration: PROSPERO [CRD42018084755](https://www.crd42018084755)

Keywords: Pediatric epilepsy, Cannabis, Cannabinoids, Cannabidiol, Seizure, Efficacy, Safety, Living systematic review, Meta-analysis

Background

Interest in the use of cannabis for pediatric epilepsy has grown over the last decade, driven in part by media reports of children whose treatment-resistant epilepsy has responded to cannabis [1]. The well-publicized case of Charlotte Figi, whose parents started her on medical cannabis at age 5, is not unique [2], and many parents of children with treatment-resistant epilepsy have reported turning to alternative treatments [3], both with and

without the aid of medical professionals. In particular, parents of children with treatment-resistant epilepsy (an inadequate response to two or more adequate trials of antiepileptic drugs [4]), which affects between 28 and 37% of people with epilepsy [5], have expressed great interest in the use of cannabis for the treatment of their children's epilepsy [3]. Indeed, pediatric treatment-resistant epilepsy has potentially catastrophic consequences, including cognitive delay, behavioral problems, autism, poor quality of life, and early death [6–9].

Despite the recorded medicinal use of cannabis dating back to the second century BCE [10], there has been relatively little research into its effectiveness or safety, likely owing to its illegal status in many jurisdictions. In

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adults, cannabis has been reported to be effective in the treatment of nausea and vomiting due to chemotherapy, chronic pain, spasticity associated with multiple sclerosis, sleep disorders, and Tourette syndrome, with inconclusive evidence for its use in appetite stimulation in patients with HIV/AIDS, anxiety disorders, and glaucoma [11]. There is relatively little clinical evidence to support the use of cannabis in the treatment of pediatric epilepsy, and there are large discrepancies between the beliefs of health care professionals and the general public with respect to its effectiveness and safety [12]. A 2014 Cochrane review of the use of cannabinoids for the treatment of epilepsy included four small low-quality randomized controlled trials (RCTs), none of which involved children [13]. At the time of this review, the authors concluded that there was insufficient evidence to make reliable conclusions about the efficacy or long-term safety of cannabinoids for the treatment of epilepsy [13]. However, the evidence base in this area is changing rapidly, and recently published studies have suggested a beneficial effect of cannabis in this population [14, 15], although the mechanisms underlying this response are not clear [16].

The use of cannabis in the treatment of pediatric epilepsy is an ideal topic for a living systematic review because it is a priority for decision-making, there is little certainty in the existing evidence base, and there is rapidly accumulating evidence [17]. Living systematic reviews are a relatively new approach to continually updating systematic reviews, with new evidence being incorporated as it becomes available [17]. Unlike traditional systematic review updates, which may be undertaken infrequently, living systematic reviewers search for new studies at a priori-defined intervals and follow a set protocol for determining whether updated analysis and publication are warranted. At present, 37 studies involving the use of various forms of cannabis for the treatment of pediatric epilepsy are registered in ClinicalTrials.gov, suggesting that there will be an abundance of new data in the coming years.

In this living systematic review, we will comprehensively search the published and gray literature for studies that have evaluated the benefits and harms of cannabis for pediatric epilepsy. The results of our review will be of use to parents, clinicians, and policy makers in making treatment decisions for children with epilepsy.

Methods/design

This systematic review protocol has been submitted to PROSPERO (CRD42018084755) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (Additional file 1) [18].

Patient involvement

Two family members of children with epilepsy were involved in selecting the outcome measures for inclusion

in this systematic review and are co-authors of this protocol (CA, AR).

Search strategy

A search of the published and gray literature will be performed by an experienced medical information specialist to identify studies involving the use of cannabis for the treatment of pediatric epilepsy. The search strategy was developed in consultation with an experienced medical information specialist and the research team (Additional file 2). The search will be peer-reviewed by another librarian by use of the Peer Review of Electronic Search Strategies (PRESS) checklist [19]. Using the OVID platform, we will search Ovid MEDLINE®, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase Classic + Embase, and PsycINFO. We will also search the Cochrane Library on Wiley. The search strategies will use a combination of controlled vocabulary (e.g., “Epilepsy”, “Cannabinoids”, “Medical Marijuana”) and keywords (e.g., “seizure”, “cannabis”, “THC”). Vocabulary and syntax will be adjusted across databases. No date or language restrictions will be imposed. Gray literature will be searched by use of CADTH’s Gray Matters Light [20], Google Scholar, the clinical trials registries ClinicalTrials.gov, and the ICTRP Search Portal of the World Health Organization.

Eligibility criteria

Studies will be eligible for inclusion if they meet the population, intervention, comparator, and study design criteria described below. Studies will not be selected based on reported outcomes.

Population

The population includes children (aged 18 years or younger) with any form of epilepsy. Studies that report mixed populations of children and adults will be included if they report data separately for participants aged less than 19 years or if, based on descriptive statistics, we can determine that at least 60% of patients are aged less than 19 years.

Intervention

The intervention is any type of cannabis (synthetic or natural), cannabinal, cannabidiol [CBD], tetrahydrocannabinol [THC], or combinations of these agents. The intervention may be administered by any route (e.g., oral, inhalation), include any strain of cannabis, and any ratio of THC to CBD.

Comparators

Eligible comparators include pharmacologic and non-pharmacologic treatments for epilepsy, including anti-epileptic drugs, diet therapy, vagus nerve stimulation,

and resective brain surgery. Comparators may also include placebo, usual care, or no treatment.

Outcomes

The primary outcome is seizure freedom. Secondary outcomes are seizure frequency, quality of life (child, caregiver), improvement or worsening of sleep, status epilepticus, tonic-clonic seizures, death (all-cause, sudden unexpected death in epilepsy), gastrointestinal adverse events (diarrhea, vomiting), and visits to the emergency room. Study eligibility will not be evaluated based on reported outcomes.

Study designs

Eligible study designs are RCTs (including cross-over and N-of-1 trials), quasi-randomized controlled trials, controlled before-after, non-randomized controlled trials, historically or concurrently controlled cohort series [prospective or retrospective], case-control studies, uncontrolled cohort studies, case series involving at least five patients, and cross-sectional studies. Conference abstracts and clinical trial registrations will be eligible for inclusion.

Screening and selection procedure

Two independent reviewers will screen the title and abstract of each identified record and assess the eligibility against the above criteria. The full text of any record deemed potentially relevant by at least one reviewer will be examined in detail and evaluated for eligibility by two independent reviewers. Disagreements on eligibility will be resolved by discussion. Studies will not be excluded based on treatment duration, and no language exclusions will be applied. All screening and data extraction will be performed using standardized and piloted forms in Distiller SR (Evidence Partners).

Data extraction

Data will be extracted by one reviewer and checked for accuracy by a second reviewer. Data to be extracted includes study characteristics (e.g., first author, year of publication, study design, country of study), participant characteristics (e.g., age, sex, epilepsy syndrome, ethnicity, comedications, comorbidities), intervention and comparator details (e.g., type of treatment, dose, route of administration, duration), and outcome data at the longest duration of follow-up. Event counts will be extracted for dichotomous outcomes (seizure freedom, improvement or worsening of sleep, status epilepticus, deaths, diarrhea, vomiting, visits to the emergency room). Data for continuous outcomes (seizure frequency, quality of life, quality and/or quantity of sleep) will be extracted as mean or median change from baseline or difference between groups after treatment. If available, the number of participants who achieve at least a 50% reduction in seizures from

baseline will be extracted. Estimates of variability (e.g., standard deviation, standard error, 95% confidence intervals) will be extracted. First-period data as well as end-of-study effects will be extracted from cross-over studies. Additional information will be extracted, including the number of cases and controls (case-control studies), adjusted odds ratios, relative risk or hazard ratios, and 95% confidence intervals, as reported by the study authors. No data will be extracted from studies that do not present study-specific data (e.g., odds ratios, 95% confidence intervals) or provide sufficient information for calculation of an outcome measure (event counts and denominators).

Quality and risk of bias assessment

The quality of included studies that report at least one outcome of interest will be assessed by use of the Cochrane Collaboration's Risk of Bias tool for RCTs [21]. The Institute of Health Economics Quality Appraisal Checklist for Case Series Studies [22], or SIGN50 [23] will be used for other study designs as appropriate. Other quality assessment tools will be identified as needed depending on the designs of the included studies. Quality will be assessed by two independent reviewers, and disagreements will be resolved by discussion.

Data synthesis

First, we will provide a descriptive summary of study selection, study and patient characteristics, and the results of the quality assessment.

Second, we will assess whether the data are sufficient in quantity and sufficiently homogeneous to be pooled via random-effects meta-analyses (i.e., minimal clinical, methodological, statistical heterogeneity). We will assess clinical heterogeneity by examining the patient characteristics of the included studies and methodological heterogeneity by assessing the study characteristics. Statistical heterogeneity will be assessed by use of the I^2 statistic. If substantial heterogeneity is present ($I^2 > 75\%$), we will explore this by subgroup analyses. At I^2 values above 75%, pooled data will not be reported, and descriptive summaries of the study-level findings will be presented. The primary analysis will involve data from RCTs involving children (at least 80% of participants aged less than 19 years) with any type of epilepsy, and data from other study designs will be evaluated in secondary analyses if deemed appropriate. Other secondary analyses will involve (a) studies including participants with treatment-resistant epilepsy or (b) studies in which at least 60% of the population is aged less than 19 years. If data are sufficient and sufficiently similar, meta-analysis will be performed by use of RevMan (v.5.3; Cochrane Collaboration). If there are insufficient data for meta-analysis, we will report descriptive

summaries for each outcome. The findings of conference abstracts will be summarized descriptively.

Additional analyses

If sufficient data are available, sensitivity analyses will be performed to test the robustness of the estimates. For example, we will look at the impact of excluding studies with high risk of bias or poor methodological quality. We will also assess the impact of comedications; study location; and cannabis strain, dose, level of THC, or ratio of THC to CBD; or route of administration, depending on data availability. Subgroup analyses will investigate the effect of epilepsy syndrome (e.g., Dravet syndrome, Lennox-Gastaut syndrome), age, and sex. Publication bias will be assessed by visual inspection of funnel plots for outcomes that have data from at least ten studies [24].

Quality of the evidence

The quality of the evidence will be assessed for each outcome by use of the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group method [25].

Update plan

In keeping with current recommendations for the conduct of living systematic reviews [17], the literature search will be repeated at regular a priori-defined intervals to identify newly available studies. Published and gray literature searches will be updated every 6 months, and any records identified after the date of the last update will be screened for inclusion as described above. This frequency of updating was chosen to maximize the visibility of new information for decision-makers but to minimize the resources required [17]. There are three potential update scenarios: (1) no new evidence is located, (2) new evidence is located but is not sufficient to trigger updated analysis and publication, or (3) new evidence is located and new analysis and dissemination is required [17]. If new studies that meet the eligibility requirements are located, the reviewer team will decide, in consultation with a clinical expert (BM), whether updated analyses are required, with consideration of balancing the needs of decision-makers with the available resources [17]. If required, meta-analyses will be updated by use of trial sequential analyses (type I error, 0.05; power, 80%; assumed effect size, moderate Cohen's effect size [0.5 standard deviations]) for living systematic reviews [26].

Discussion

Pediatric epilepsy has a major impact on the quality of life for patients and their families. Interest in the use of cannabis as a treatment for pediatric epilepsy and, in particular, for treatment-resistant epilepsy has grown over the last decade, driven in part by media reports of children whose treatment-resistant epilepsy has responded

to cannabis after the failure of conventional treatments [1]. This living systematic review will provide a comprehensive summary of the current evidence for the use of cannabis for the treatment of pediatric epilepsy and will incorporate new evidence as it becomes available. The results will be of use to decision-makers, including parents of affected children, clinicians, and policy makers.

Additional files

Additional file 1: PRISMA-P checklist. (DOC 97 kb)

Additional file 2: Search strategy. (DOCX 18 kb)

Abbreviations

CBD: Cannabidiol; RCT: Randomized controlled trial; THC: Tetrahydrocannabinol

Funding

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Authors' contributions

JE, TC, DC, BP, and GW conceived the study. BS designed and will execute the search strategy. JE drafted the protocol, which was revised by all authors. BM provided clinical input, while CA and AR provided patient and family perspectives. JE and DD will select the studies for inclusion and perform the data extraction. All authors have approved the version of the manuscript submitted for publication.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Bláthnaid McCoy is the principal investigator in a study of cannabinoids for Dravet syndrome. Alexander Repetski is a director of communications at a licensed cannabis producer. The authors declare that they have no competing interests.

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FULL-LENGTH ORIGINAL RESEARCH

Cannabis-based products for pediatric epilepsy: A systematic review

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Summary

Objective: To assess the benefits and harms of cannabis-based products for pediatric epilepsy.

Methods: We identified in this living systematic review randomized controlled trials (RCTs) and nonrandomized studies (NRSs) involving children with epilepsy treated with cannabis-based products. We searched MEDLINE, Embase, PsycINFO, Cochrane Library, and gray literature (April 25, 2018). The primary outcome was seizure freedom; secondary outcomes were seizure frequency (total, $\geq 50\%$ reduction), quality of life, sleep, status epilepticus, death, gastrointestinal adverse events, and visits to the emergency room. Data were pooled by random-effects meta-analysis. Risk of bias was assessed for each study, and GRADE was used to assess the quality of evidence for each outcome.

Results: Four RCTs and 19 NRSs were included, primarily involving cannabidiol. All RCTs were at low risk of bias, whereas all NRSs were at high risk. Among RCTs, there was no statistically significant difference between cannabidiol and placebo in seizure freedom (relative risk [RR] = 6.77, 95% confidence interval [CI] = 0.36-128.38; 1 RCT), quality of life (mean difference = 0.6, 95% CI = -2.6 to 3.9; 3 RCTs), sleep disruption (mean difference = -0.3, 95% CI = -0.8 to 0.2; 3 RCTs), or vomiting (RR = 1.00, 95% CI = 0.51-1.96; 4 RCTs). There was a statistically significant reduction in the median frequency of monthly seizures with cannabidiol compared with placebo (-19.8%, 95% CI = -27.0% to -12.6%; 3 RCTs) and an increase in the number of participants with at least a 50% reduction in seizures (RR = 1.76, 95% CI = 1.07-2.88; 1 RCT) and diarrhea (RR = 2.25, 95% CI = 1.38-3.68; 3 RCTs). Death and status epilepticus were infrequently reported.

Significance: Evidence from high-quality RCTs suggests that cannabidiol probably reduces seizures among children with drug-resistant epilepsy (moderate certainty). At this time, the evidence base is primarily limited to cannabidiol, and these findings should not be extended to all cannabis-based products.

KEYWORDS

cannabidiol, cannabis, efficacy, pediatric drug-resistant epilepsy, safety, seizure, systematic review

1 | INTRODUCTION

Epilepsy affects an estimated 50 million people worldwide¹; of those, about one-third have a drug-resistant form² (failure of two or more adequate trials of antiepileptic drugs [AEDs]³). Consequences of drug-resistant epilepsy (DRE) during childhood are catastrophic, with frequent seizures impairing neurological and cognitive development, impacting quality of life,⁴ and contributing high costs to the health care system.⁵ Although AEDs are the mainstay of treatment, these are often ineffective at reducing seizures and are associated with multiple adverse events.⁶

Interest has been steadily growing in the use of cannabis-based treatments for pediatric epilepsy,⁷ partly owing to media reports of successful cases.⁸ Nine-delta-tetrahydrocannabinol (THC) and cannabidiol (CBD) have received the greatest attention as potential antiepileptic agents. In practice, the psychoactive properties of THC may limit its potential as an antiepileptic treatment, especially in children. In contrast, CBD has little psychoactive effect and, in animal models, is protective against multiple seizure types.⁷ However, until recently there had been relatively little clinical research into the effectiveness and safety of cannabis-based treatments for epilepsy, and there are large discrepancies between the beliefs of neurologists and the general public as to whether there is sufficient evidence of effectiveness and safety.⁹ A 2014 Cochrane review¹⁰ included four randomized controlled trials (RCTs) that assessed the use of cannabinoids in adults with epilepsy, reporting that no reliable conclusions could be made about its efficacy and safety.¹⁰ However, recent RCTs and nonrandomized studies (NRSs) have suggested a beneficial effect of CBD in the treatment epilepsy in children,^{11–15} and the US Food and Drug Administration recently approved the first cannabis-based product (Epidiolex; GW Pharmaceuticals), a pharmaceutical-grade cannabidiol extract, for the treatment of Dravet and Lennox-Gastaut syndromes.¹⁶

In the present study, we performed a systematic review to identify studies involving the use of cannabis and cannabis-based products as treatment for pediatric epilepsy. Systematic review methodology provides a lens through which the evidence from various types of studies can be viewed and compared, to assess their quality and applicability to stakeholders (eg, caregivers, clinicians, policymakers).¹⁷

1.1 | Objective and significance

The aim of this study is to provide an up-to-date comprehensive summary of the evidence assessing the use of cannabis-based treatments for epilepsy in children. Because the evidence base is rapidly changing, living systematic review methodology will be used to provide parents,

Key Points

- Few RCTs have assessed the use of cannabis-based treatments for pediatric epilepsy
- Evidence from short-duration high-quality RCTs suggests that cannabidiol may be effective in reducing seizures among children with drug-resistant epilepsy
- All available evidence from RCTs is related to one pharmaceutical cannabidiol product and should not be extended to all cannabis-based products

clinicians, and policy makers with up-to-date evidence to inform their decision making.

2 | MATERIALS AND METHODS

The systematic review protocol was developed using guidance from the PRISMA-P statement,¹⁸ registered in PROSPERO (CRD42018084755), and published.¹⁹ Two family members (C.A., A.E.R.) of children with epilepsy and a pediatric neurologist (B.M.) with experience caring for children with DRE were involved in protocol development. Screening and data extraction were performed using Distiller SR (Evidence Partners). This report follows the PRISMA guidelines (Appendix S1).²⁰

2.1 | Eligibility criteria

We included RCTs and NRSs examining the use of cannabis as a treatment for any type of epilepsy in children (≤ 18 years). Interventions included any type of cannabis-based product, including CBD, cannabinol, THC, or their combinations, administered by any route (eg, oral, inhalation). Eligible comparators included pharmacologic (ie, AEDs) and nonpharmacologic (eg, diet therapy, vagus nerve stimulation, resective brain surgery) treatments, as well as placebo, usual care, or no treatment.

2.2 | Outcomes

The outcomes were chosen in consultation with a practicing neurologist (B.M.) and two patient family representatives (C.A., A.E.R.). The primary outcome was seizure freedom. Secondary outcomes were seizure frequency (total, tonic-clonic, $\geq 50\%$ reduction from baseline), quality of life (child, caregiver), sleep, status epilepticus, death (all-cause, sudden unexpected death in epilepsy), gastrointestinal adverse events (vomiting, diarrhea), and visits to the

emergency room. Quality of life could be measured by any instrument designed to assess quality of life in children or their adult caregivers. Impact on sleep could be assessed by use of an instrument or reported as the number of children who experienced a sleep improvement or impairment. Studies were not selected for inclusion based on reported outcomes.

2.3 | Search strategy, screening, data extraction

We searched Ovid MEDLINE, Embase, PsycINFO on Ovid, and the Cochrane Library on Wiley from inception to April 25, 2018, with no language or date restrictions (Appendix S2). Gray literature was identified using CADTH's Grey Matters Light,²¹ Google Scholar, ClinicalTrials.gov, and the ICTRP Search Portal. Two independent reviewers (J.E., D.D.) screened the title and abstract of each record and the full text of any record deemed potentially relevant. Data were extracted from primary reports and companion publications by one reviewer and checked for completeness and accuracy by a second reviewer. Disagreements were resolved by discussion.

2.4 | Risk of bias and quality of the evidence

Risk of bias (RoB) was assessed by two reviewers (J.E., D.D.) for each study that reported at least one outcome of interest. For RCTs, bias was assessed by use of the Cochrane Collaboration's RoB tool²²; to be considered at overall low RoB, a study must have been at low risk for each of the following domains: allocation concealment, blinding (participants, outcome assessors, investigators) for subjective outcomes, and incomplete outcome data. The potential for bias in NRS was assessed by use of the SIGN50 Checklist (comparative cohort studies),²³ the National Institutes of Health Quality Assessment Tool for Before–After (Pre–Post) Studies With No Control Group (single-arm cohort studies),²⁴ and the Joanna-Briggs Institute Checklist for Analytic Cross Sectional Studies.²⁵ To facilitate comparison across tools, we judged overall RoB according to the most serious risk across all domains, regardless of assessment tool. Two independent reviewers (J.E., V.S.) assessed the quality/certainty of the evidence for each outcome by use of the GRADE method.²⁶ Disagreements were resolved by discussion.

2.5 | Data synthesis

The full analysis plan is available.¹⁹ Descriptive summaries are provided for study selection, study and patient characteristics, and quality assessment. Data from RCTs were pooled by random-effects meta-analyses by use of RevMan

(v5.3; Cochrane Collaboration) or Comprehensive Meta-Analysis (v2.2.064; Biostat) and reported as relative risk (RR), risk difference, mean difference, or median difference and 95% confidence intervals (CIs). For NRSs, the proportion of participants who experienced an outcome was pooled by use of the *metaprop* command in STATA using the Freeman-Tukey double arcsine transformation,²⁷ and the data are reported as percentage of those exposed and 95% CIs. Where multiple time points were reported, data from the longest duration of follow-up were analyzed. Clinical and statistical heterogeneity were investigated by examining study and patient characteristics and the I^2 statistic, respectively. I^2 values above 75% were considered to represent substantial heterogeneity.

3 | RESULTS

3.1 | Study selection and characteristics

In total, 631 records were screened after removing duplicates (Figure 1). Subsequently, 142 records were screened in full-text format, with 92 records meeting the eligibility criteria (Appendix S3). Of these, 25 records corresponded to 23 unique published studies (four RCTs,^{12,28–30} 19 NRSs^{11,13–15,31–45}). An additional 33 records corresponded to trial registration records in ClinicalTrials.gov without reported results, and 34 corresponded to conference abstracts. See Appendix S4 for a full list of excluded studies.

The four RCTs^{12,28–30} included a total of 550 participants (range = 34–225) with either Dravet^{12,28} or Lennox-Gastaut^{29,30} syndrome (Table 1) randomized to placebo or oral CBD (5–20 mg/kg/d) for up to 14 weeks. The mean age in each study was between 7 and 16 years, with an approximately equal number of male and female children taking multiple AEDs at baseline (Table 2). The baseline frequency of total seizures was variable across RCTs (Table 2).

Of the 19 NRSs, two were comparative cohort studies (one prospective, one retrospective),^{31,35} 12 were single-arm cohort studies (eight prospective, four retrospective),^{13–15,32,34,37,38,40–44} four were cross-sectional surveys,^{11,36,39,45} and one was a case series³³ (Appendix S5). In total, the NRSs involved 1,115 participants (range = 5–214) with variable baseline seizure frequency, and variable treatment durations (10 days to 57 months). Fourteen NRSs included participants with multiple forms of DRE (Appendix S5),^{11,13–15,31,34–42} whereas some studies focused on specific syndromes, including Dravet syndrome,¹² tuberous sclerosis complex (TSC),⁴⁴ Sturge-Weber syndrome,³² and febrile infection-related epilepsy.⁴³ The range of mean ages of included participants, where available, was between 7 and 14 years (Appendix S6).

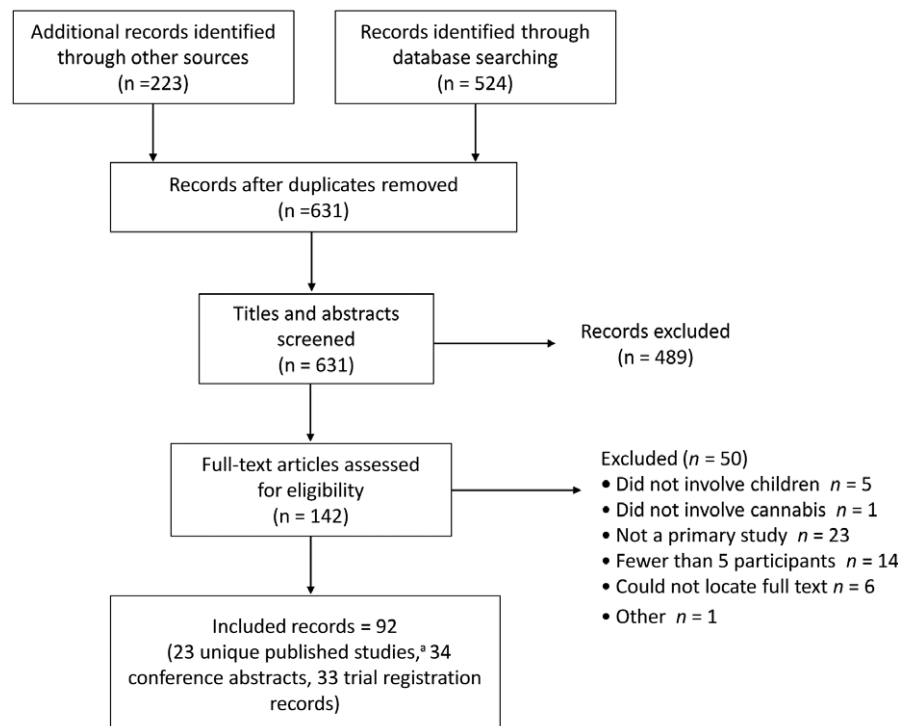


FIGURE 1 PRISMA flow diagram showing selection of studies. ^aThere were 2 companion publications

The types of cannabis-based interventions varied among studies, although more than half involved CBD (68%). Not all interventions were well described, and some included “artisanal” products,³⁸ products from illicit cannabis suppliers,³⁹ or homemade extracts.¹¹ Most cannabis-based products were administered orally, although one study¹⁴ involved use of inhaled cannabis by some participants.

3.2 | Risk of bias

All four RCTs were at overall low RoB (Appendix S7); however, selective outcome reporting was a potential concern in three RCTs,^{12,29,30} with discrepancies noted between the protocol or ClinicalTrials.gov record and the published report.

The overall RoB was considered high for all NRSs, owing to at least one of the following: lack of a control group, lack of blinding and subjective outcomes, self-selection or unclear selection of participants, inconsistency in interventions across participants, or a lack of detail about the interventions (Appendix S5).

3.3 | Summary of results

In total, four RCTs^{12,28–30} and 17 NRSs^{11,13–15,31,32,34–40,42–45} reported at least one outcome of interest and form the evidence base for this review. The evidence summary, including GRADE assessment, is shown in Table 3 and 4. The full GRADE assessment is provided in Appendix S8.

3.4 | Primary outcome

3.4.1 | Seizure freedom

Fifteen studies reported results related to freedom from all seizure types after administration of a cannabis-based product (Appendix S8), including one RCT¹² and 14 NRSs (six prospective single-arm cohort studies,^{13,14,32,42–44} four retrospective single-arm cohort studies,^{15,34,38,40} one comparative retrospective cohort study,³⁵ three cross-sectional studies^{11,36,45}).

Among children with Dravet syndrome who received CBD in one RCT,¹² 5% (3/61) experienced freedom from all seizures, whereas no children in the placebo group ($n = 59$) became seizure-free during a 14-week treatment period (risk difference = 5%, 95% CI = −1% to 11%; low GRADE certainty). Among the NRSs, estimates of seizure freedom ranged from 1% to 20% (pooled proportion = 7%, 95% CI = 4%–11%, duration = 8 weeks to 33 months), with the highest estimates observed among cross-sectional studies (very low certainty; Appendix S9).

3.5 | Secondary outcomes

3.5.1 | Seizure frequency

Nine studies assessed the effect of cannabis-based products on seizure frequency, including three RCTs^{12,29,30} and six NRSs (four single-arm prospective cohort studies,^{13,42–44} one comparative retrospective cohort study,³⁵

TABLE 1 Characteristics of included randomized controlled trials

Author, year, page (NCT Record)	Design features	Population	Inclusion criteria	Treatments (randomized, n)	Duration	Centers, n; country	Funding source	Risk of bias ^a
Devinsky 2018, p 1204 (NCT02091206; GWPCARE1 part A) ²⁸	Double-blind, placebo controlled RCT	Dravet syndrome	4–10 y, taking ≥ 1 AED and experiencing <4 convulsive seizures during a 4-wk baseline period, stable medications or interventions (inc. ketogenic diet and VNS) for 4 wk	- Oral cannabidiol solution,^b 5 mg/kg/d (10), 10 mg/kg/d (8), 20 mg/kg/d (9); given in 2 divided doses - Placebo (7)	3-wk treatment, 10-day taper, 4-wk follow-up	12 centers; USA, UK	GW Research	Low
Devinsky 2017, p 2011 (NCT02091375; GWPCARE1 part B) ¹²	Double-blind, placebo controlled RCT	Dravet syndrome	2–18 y, taking ≥ 1 AED, ≥ 4 convulsive seizures during the 28-day baseline period, stable medications or interventions (inc. ketogenic diet and VNS) for 4 wk	- Oral cannabidiol solution,^b up to 20 mg/kg/d (61); given in 2 divided doses - Placebo (59)	14-wk treatment period (2 wk escalation, 12 wk maintenance), 10-day taper, 4-wk follow-up	23 centers; USA and Europe	GW Pharmaceuticals	Low
Devinsky 2018, p 1888 (NCT02224560; GWPCARE3) ²⁹	Double-blind, placebo controlled RCT	Lennox-Gastaut syndrome	2–55 y, with an electroencephalogram that showed a pattern of slow spike-and-wave complexes and ≥ 2 types of generalized seizures, inc. drop seizures, for ≥ 6 mo, with use of 1–4 AEDs and ≥ 2 drop seizures per wk during the 28-d baseline period	- Oral cannabidiol solution,^b 10 mg/kg/d (73), 20 mg/kg/d (76); given in 2 divided doses - Placebo (76)	14 wk (2 wk escalation, 12 wk treatment), 4-wk follow-up	30 centers; USA, Spain, UK, France	GW Pharmaceuticals	Low
Thiele 2018, p 1085 (NCT02224690; GWPCARE4) ³⁰	Double-blind, placebo controlled RCT	Lennox-Gastaut syndrome	2–55 y, >1 type of generalized seizure, inc. drop seizures, for at least 6 mo; taking 1–4 AEDs, and ≥ 2 drop seizures per wk during the 4-wk baseline period; stable medications or interventions (inc. ketogenic diet and VNS) for 4 wk	- Oral cannabidiol solution,^b 20 mg/kg/d (86); given in 2 divided doses - Placebo (85)	14 wk (2 wk escalation, 12 wk treatment), 4-wk taper period, 4-wk follow-up	24 centers; USA, The Netherlands, Poland	GW Pharmaceuticals	Low

AED, antiepileptic drug; inc., including; NCT, National Clinical Trial; RCT, randomized controlled trial; VNS, vagus nerve stimulation.

^aLow risk of bias for each of allocation concealment, blinding, and outcome data reporting.^bEpidiolex (GW Pharmaceuticals).

TABLE 2 Characteristics of participants in the included randomized controlled trials

Author, year, page	Treatments (randomized, n)	Baseline total seizure frequency, mo, median (IQR)	Age, y, mean (SD)	Male, n (%)	BMI or weight, mean (SD)	Concomitant AEDs, n, mean (SD) ^a	Previous AEDs, n, mean (SD) ^a	Ketogenic diet, n (%)	VNS, n (%)
Devinsky 2018, p e1204 ²⁸	• Placebo (7)	NR	7.0 (0.9),	5 (71),	BMI:	2.1 (0.9),	NR	0,	0,
	• CBD 5 mg/kg/d (10)		7.2 (1.9),	5 (50),	18.7 (4.0),	2.6 (1.1),		1 (10),	1 (10),
	• CBD 10 mg/kg/d (8)		7.4 (2.1),	3 (38),	18.9 (4.4),	2.8 (0.5),		2 (25),	0,
	• CBD 20 mg/kg/d (9)		8.7 (1.8)	3 (33)	16.1 (1.5), 16.1 (2.3); weight: NR	2.8 (0.8)		3 (33)	1 (11)
Devinsky 2017, p 2011 ¹²	• Placebo (59)	41.5 (NR),	9.8 (4.8),	27 (46),	BMI:	2.9 (1.0),	4.6 (3.3),	4 (7),	9 (15),
	• CBD 20 mg/kg/d (61)	24.0 (NR)	9.7 (4.7)	35 (47)	19.1 (4.7), 18.3 (4.5); weight: NR	3.0 (1.1)	4.6 (4.3)	6 (10)	6 (10)
Devinsky 2018, p 1888 ²⁹	• Placebo (76)	180.6 (90.4-431.3),	15.3 (9.3),	44 (58),	NR	Median (range):	Median (range):	6 (8),	21 (28),
	• CBD 10 mg/kg/d (73)	165.0 (81.3-359.0),	15.4 (9.5),	40 (55),		3 (1-5),	(range):	6 (8),	15 (21),
	• CBD 20 mg/kg/d (76)	174.3 (82.7-392.4)	16.0 (10.8)	45 (59)		3 (1-5),	6 (1-22),	6 (8)	17 (22)
Thiele 2018, p 1085 ³⁰	• Placebo (85)	176.7 (68.6-359.5),	15.3 (9.8),	43 (51),	NR	3 (0-5)	6 (0-21),		
	• CBD 20 mg/kg/d (86)	144.6 (72.0-385.7)	15.5 (8.7)	45 (52)		Median (IQR): 3 (1-4), 3 (1-5)	Median (IQR): 6 (0-28), 6 (1-18)	10 (12), 4 (5)	25 (29), 26 (30)

AED, antiepileptic drug; BMI, body mass index; CBD, cannabidiol; IQR, interquartile range; NR, not reported; SD, standard deviation; VNS, vagus nerve stimulation.

^aUnless otherwise stated.

TABLE 3 Evidence summary

Outcome	Randomized controlled trials				Nonrandomized studies			
	Studies, k	Participants, n	Effect estimate (95% CI), cannabidiol vs placebo	<i>I</i> ² assessment	Studies, n	Participants, n	Proportion exposed to a cannabis-based product (95% CI) ^a	GRADE assessment
Primary outcome								
Seizure freedom	1	120	RR = 6.77 (0.36 to 128.38), RD = 0.05 (−0.01 to 0.11)	NA	14	761	7% (4%–11%)	Very low
Secondary outcomes ^b								
Total seizure frequency	3	516	Median reduction in monthly seizures vs placebo: −19.8% (−27.0% to −12.6%)	0%	6	316	NA ^c	Very low
Tonic-clonic seizure frequency	3	321	Median reduction in monthly seizures vs placebo: −27.5% (−38.7% to −16.3%)	0%	2	95	NA ^c	Very low
Treatment response ^d	1	171	RR = 1.76 (1.07–2.88), RD = 0.16 (0.03–0.29)	NA	12	641	48% (39%–57%)	Very low
Quality of life: child	3	516	Pooled mean difference: 0.6 (−2.6 to 3.9) ^e	0%	1	48	Mean difference before–after: 8.12 (SD = 9.85) ^e	Very low
Sleep disruption	3	516	Pooled mean difference: −0.3 (−0.8 to 0.2) ^f	0%	0	NA	NA	NA
Improved sleep	0	NA	NA	NA	5	368	44% (15%–72%)	Very low
Impaired sleep	1	171	Sleep apnea reported for 1 participant (1.2%) in the CBD group; none in the placebo group	NA	5	140	4% (0%–7%)	Very low
Status epilepticus	3	516	RR = 1.39 (0.55–3.47), RD = 0.01 (−0.02 to 0.03)	0%	3	283	4% (0%–8%)	Very low
Death	1	171	1 death reported in the CBD group (n = 86); zero deaths in the placebo group (n = 85)	NA	5	314	1% (0%–2%)	Very low

(Continues)

TABLE 3 (Continued)

Outcome	Randomized controlled trials				Nonrandomized studies			
	Studies, k	Participants, n	Effect estimate (95% CI), cannabidiol vs placebo	<i>I</i> ²	GRADE assessment	Studies, n	Participants, n	Proportion exposed to a cannabis-based product (95% CI) ^a
Gastrointestinal AEs	4	550	RR = 1.54 (0.92-2.58), RD = 0.12 (−0.01 to 0.24)	52%	Low	11	682	8% (4%-12%)
								<i>I</i> ² 69%
								GRADE assessment Very low

AE, adverse event; CBD, cannabidiol; CI, confidence interval; NA, not applicable; RD, risk difference; RR, relative risk; SD, standard deviation.

^aUnless otherwise stated.

^bNone of the included studies assessed caregiver quality of life or visits to the emergency department.

^cData reported in a variety of ways precluded pooling; see Appendices S9 and S10.

^d≥50% reduction in seizure frequency relative to baseline period.

^eQuality of Life in Childhood Epilepsy scale.

^fAssessed by use of the Sleep Disruption Rating Scale (negative value favors CBD).

one cross-sectional study³⁹; Appendix S10). Among the RCTs, the pooled median difference in monthly seizure frequency between CBD and placebo was −19.8% (95% CI = −27.0% to −12.6%; moderate certainty; 14 weeks). Among the NRSs, the reported reduction in total seizures with use of a cannabis-based product was between 30% and 90% (duration = 8 weeks to >16 months; very low certainty).

Five studies reported the effect of cannabis-based products on the frequency of tonic-clonic seizures (three RCTs,^{12,29,30} two prospective single-arm cohorts^{13,44}; Appendix S11). The pooled median difference in monthly seizure frequency between CBD and placebo in the RCTs was −26.7% (95% CI = −38.8% to −14.8%; moderate certainty; duration = 14 weeks). Among the NRSs, Devinsky et al¹³ reported a non-statistically significant reduction in the median frequency of monthly tonic-clonic seizures with CBD among 89 children with any type of DRE (−16%, 95% CI = −60.1% to 35.3%; duration = 12 weeks), whereas Hess and colleagues⁴⁴ reported a significant median reduction in weekly tonic-clonic seizures (−91.4%, 95% CI = −100% to −13.9%; duration = 12 months) among 6 children with TSC (very low certainty).

Thirteen studies assessed treatment response (≥50% reduction in seizure frequency from baseline), including one RCT³⁰ and 12 NRSs (six prospective single-arm cohort studies,^{13,14,32,42–44} three retrospective single-arm cohort studies,^{15,34,40} one comparative retrospective cohort study,³⁵ two cross-sectional studies^{11,36}; Appendix S12). Among children with Lennox-Gastaut syndrome in one RCT, 37% (23/86) of children randomized to CBD had a 50% or greater reduction in seizure frequency, compared with 21% (18/85) of children randomized to placebo (RR = 1.76, 95% CI = 1.07-2.88; moderate certainty; duration = 14 weeks).³⁰ Among NRSs, estimates of treatment response ranged from 24% to 100% (duration = 8 weeks to 57 months; very low certainty).

3.5.2 | Quality of life

Five studies (three RCTs,^{12,29,30} two prospective single-arm cohort studies^{13,46}) assessed quality of life among children (Appendix S13). In the RCTs, there was no statistically significant difference in overall score on the Quality of Life in Childhood Epilepsy scale between CBD and placebo groups (mean difference = 0.6, 95% CI = −2.6 to 3.9; moderate certainty; duration = 14 weeks). Both single-arm cohort studies reported statistically significant improvements in quality of life relative to the baseline period after treatment with CBD (duration = 12-82 weeks; very low certainty).^{32,37}

None of the included studies assessed caregiver quality of life.

Certainty Assessment			No. of events/No. of patients			Effect	
Studies, k	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Seizure freedom (total seizures; treatment duration = 14 wk; number of patients with zero seizures during treatment)							
1	RCTs	Not serious	Not serious	Not serious	Very serious ^{a,b,c}	None	3/61 (4.9%) 0/59 (0.0%) RR = 6.77 (0.36-128.38) ^d — ⊕⊕○○ Low
Treatment response (treatment duration = 14 wk; number of participants with at least a 50% reduction in total seizures from baseline)							
1	RCTs	Not serious	Not serious	Not serious	Serious ^a	None	32/86 (37.2%) 18/85 (21.2%) RR = 1.76 (1.07-2.88) 161 more per 1000 (from 15 more to 398 more) ⊕⊕⊕○ Moderate
Gastrointestinal adverse events (treatment duration = 3-14 wk; number of children with vomiting or diarrhea or both)							
4	RCTs	Not serious	Serious ^e	Not serious	Serious ^{a,b}	None	89/323 (27.6%) 45/227 (19.8%) RR = 1.54 (0.92-2.58) 107 more per 1000 (from 16 fewer to 313 more) ⊕⊕⊕○ Low

^eHeterogeneity (I^2): 52%.

3.5.3 | Sleep

Twelve studies (three RCTs,^{12,29,30} nine NRS^{11,31,32,34,36,40,42,44,45}) reported changes in sleep, including improvement or impairment, after administration of a cannabis-based product (Appendix S14). In the RCTs, there was no statistically significant difference in Sleep Disruption Rating scale score between CBD and placebo (mean difference = -0.3, 95% CI = -0.8 to 0.2; moderate certainty; duration = 14 weeks). One child (1.2%) with Lennox-Gastaut syndrome who received CBD was reported to have ongoing treatment-related sleep apnea at the end of the trial.³⁰ Sleep apnea was also reported in one NRS,³¹ with one child (4.8%) who received 40 mg/kg/d CBD experiencing sleep apnea.

Improved sleep was reported in five NRSs (two retrospective cohort studies,^{34,40} three cross-sectional studies^{11,36,45}; duration = 2 weeks to 57 months), with a higher proportion reported in cross-sectional studies (68%, 95% CI = 46%-90%) compared with retrospective cohort studies (8%, 95% CI = 4%-11%; very low certainty; Appendix S14). Impaired sleep was reported in five NRSs (four prospective cohort studies,^{31,32,42,44} one cross-sectional survey¹¹), affecting 4% (95% CI = 0%-7%) of children who received a cannabis-based product (duration = 10 days to 82 weeks; very low certainty).

3.5.4 | Status epilepticus

Status epilepticus was reported in six studies, including three RCTs^{12,29,30} and three NRSs (two prospective cohort studies,^{13,14} one retrospective cohort study⁴⁶; Appendix S15). In the RCTs,^{12,29,30} the RR of status epilepticus was 1.39 (95% CI = 0.55-3.47; low certainty; duration = 14 weeks). Among the NRSs, the pooled prevalence of status epilepticus was 4% (95% CI = 0%-8%; duration = 12 weeks to 33 months; very low certainty).

3.5.5 | Death

Deaths were reported among children who received a cannabis-based product in six studies (one RCT,³⁰ two prospective cohort studies,^{13,43} three retrospective cohort studies^{34,38,46}; Appendix S16); an additional three studies^{12,28,31} reported that no deaths had occurred during the treatment period). Thiele and colleagues³⁰ reported the death of one participant with Lennox-Gastaut syndrome who received CBD (20 mg/kg/d; n = 86) during their 14-week RCT; the death was attributed to respiratory failure and deemed by study authors to be unrelated to treatment. No deaths were reported in the placebo group (n = 85; low certainty). An additional six deaths from various causes (including two reports of sudden unexpected death in

epilepsy) were reported in five NRS^{13,34,38,43,46} (n = 313; duration = 1-29 months; very low certainty).

3.5.6 | Gastrointestinal adverse events

Diarrhea or vomiting was reported in four RCTs^{12,28-30} and nine NRSs (six prospective cohort studies,^{13,14,31,32,43,44} three cross-sectional studies^{11,36,45}; Appendix S17). An additional two NRSs^{15,40} reported gastrointestinal events without specifying the specific adverse events. In the RCTs, the pooled RR was 1.54 (95% CI = 0.92-2.58) for any gastrointestinal adverse event, 1.00 (95% CI = 0.51-1.96) for vomiting, and 2.25 (95% CI = 1.38-3.68) for diarrhea (low certainty; duration = 3 to 14 weeks).

Among the NRSs, the pooled proportion of participants who experienced at least one of vomiting or diarrhea was 8% (95% CI = 4%-12%; very low certainty; Appendix S17). A similar proportion of children were reported to have had vomiting (5%, 95% CI = 2%-8%) and diarrhea (7%, 95% CI = 2%-12%). The estimated incidence of both outcomes was highest for prospective cohort studies (vomiting: 7%, 95% CI = 3%-11%; diarrhea: 9%, 95% CI = 3%-16%), whereas estimates were considerably lower for cross-sectional studies (vomiting: 3%, 95% CI = 1%-7%; diarrhea: 2%, 95% CI = 0%-12%; duration = 10 days to 57 months).

3.5.7 | Visits to the emergency room

No studies reported visits to the emergency room during the study period.

3.6 | Sensitivity analyses

3.6.1 | Type of cannabis-based product

To date, all RCTs involved oral CBD (5-20 mg/kg/d). Similarly, most of the NRSs (68%) involved CBD. Although some NRSs involved the use of non-CBD-based treatments, such studies typically included use of more than one product of varying composition (Appendix S5), precluding assessment of the effect of individual formulations. Data were insufficient to assess the impact of cannabis strain, level of THC, or THC:CBD ratio.

3.6.2 | Comedications

Two NRSs^{35,42} assessed the effect of concomitant CBD and clobazam. Among children with DRE taking CBD and clobazam, the level of clobazam increased by 60% after 4 weeks of treatment, whereas N-desmethyloclobazam levels increased by 500% (n = 13).⁴² Nine of these children (69%) experienced ≥50% reduction in seizures from

baseline, with a mean reduction of 51% in seizure frequency; two children (15%) became seizure-free. The authors noted that the observed adverse events were similar to those seen in patients with high clobazam doses (eg, drowsiness) and were alleviated by clobazam dose reduction.⁴² A similar proportion of children were reported to have experienced seizure freedom when administered various artisanal CBD products in addition to clobazam (9%); seizure freedom was reported for 14% of children who received CBD alone and 11% who received clobazam alone.³⁵ A higher proportion of children taking concomitant CBD and clobazam experienced seizure freedom (44%), compared with either alone (CBD: 33%; clobazam: 38%).³⁵

3.7 | Subgroup analyses

Few studies have assessed cannabis-based treatments in specific epilepsy syndromes, with the exception of four RCTs involving participants with Dravet syndrome^{12,28} or Lennox-Gastaut syndrome^{29,30} and three NRSs involving participants with TSC,⁴⁴ Sturge-Weber syndrome,³² or febrile infection-related epilepsy.⁴³ In general, available evidence suggests that CBD reduces seizure frequency across epilepsy syndromes (Appendix S18); however, these findings are predominately based on small open-label studies at high RoB, and no data are available for other cannabis-based products. No data were available to assess the outcomes among different age groups or by sex.

3.8 | Ongoing studies

We identified 33 yet-unpublished studies registered in ClinicalTrials.gov, in varying stages of completion (Appendix S19). An additional 34 conference abstracts were identified, of which 14 represent potentially unpublished studies (Appendix S20).

4 | DISCUSSION

Despite recorded medical use of cannabis dating back to the 2nd century BCE,⁴⁷ until recently there had been few clinical studies of its effectiveness and safety, especially among children. However, the past few years have seen a sharp increase in the number of clinical studies involving cannabis for pediatric epilepsy. We undertook this systematic review to provide an up-to-date, comprehensive summary of the available evidence to support decision making by parents, clinicians, and policy makers.

The evidence from four recently published high-quality RCTs suggests that CBD probably reduces seizures in children with DRE, without a corresponding increase in seizure freedom or quality of life (moderate to low certainty of

evidence). In particular, all of the included RCTs involve the use of Epidiolex, and the findings should not be extrapolated to other preparations. The effects of CBD and other cannabis-based products on other outcomes are less clear, and our understanding of the potential benefits and harms in this population will be refined as data from ongoing studies become available. In particular, there is currently limited clinical information about the benefits and harms of cannabis-based products with high THC content.

The use of clobazam by children with DRE is common; in the included RCTs, up to 66% of children received clobazam in addition to CBD.^{12,28–30} Cannabidiol is an inhibitor of multiple CYP enzymes, notably CYP3A4 and CYP2C19, which are involved in the clearance of N-desmethyclobazam, the active metabolite of clobazam.⁴⁸ As such, inhibition of CYP enzymes by CBD has the potential to increase the serum concentration of clobazam and other AEDs. Elevated clobazam and N-desmethyclobazam levels have been reported among children with DRE who received both CBD and clobazam,^{28,42} which may have implications for both efficacy and safety. A higher rate of seizure freedom has been reported among children who received concomitant CBD and clobazam than either agent alone,³⁵ and increased somnolence has been noted among children who received both CBD and clobazam compared to those who received clobazam alone.¹² Others have noted that the adverse events observed among children taking both CBD and clobazam are similar to those seen at high clobazam doses, and that reduction of clobazam may be sufficient to alleviate adverse events.⁴²

A previous systematic review⁴⁹ involving children and adults with epilepsy similarly found that CBD was more effective than placebo at improving treatment response and reducing seizure frequency. In contrast with our findings, Stockings and colleagues⁴⁹ reported that CBD increased seizure freedom and improved quality of life. These apparent discrepancies are likely related to methodological differences. In their analysis of seizure freedom, Stockings and colleagues⁴⁹ combined estimates of freedom from all seizures with freedom from drop or convulsive seizures, whereas our assessment included only studies that reported freedom from all seizures. Although we found no statistically significant difference between groups, this finding was based on one RCT, and the publication of additional studies assessing freedom from all seizures will help to clarify whether there is a beneficial effect of CBD.

Similarly, methodological differences may be responsible for the discrepant findings in quality of life between the Stockings⁴⁹ review and our analysis. Stockings and colleagues⁴⁹ assessed quality of life by use of the Caregiver Global Impression of Change score, which assesses whether, in the caregiver's opinion, the child's overall condition has improved. In our review, we used the Quality of

Life in Childhood Epilepsy score, which has been validated for use by parents of children with DRE to assess health-related quality of life and is sensitive to seizure severity and medication effects.⁵⁰

Parents of children with DRE have reported that “unacceptable AED side effects” and the belief that cannabis-based products are “more natural” and more effective are motivating factors for their willingness to enroll their child in a trial of cannabinoids for epilepsy.³⁹ However, a previous review⁴⁹ reported an increased risk of adverse events and serious adverse events among children and adults who received CBD compared with placebo, and we found that the risk of diarrhea was significantly higher among children who received CBD. As such, the decision to administer CBD or other cannabis-based products should be based on shared decision making between parents and health care providers, with consideration of both the potential benefits and harms.

4.1 | Strengths and limitations

The protocol for this review was published *a priori*,¹⁹ and we followed rigorous systematic review methodology. To ensure the relevance of our findings to decision making, two family members of children with epilepsy and a pediatric neurologist were collaborators on this project. Because there is little certainty in the evidence base, and because there are a number of ongoing studies, this review will be updated at 6-month intervals to include new evidence as it becomes available, and updates will be posted online at cannabisandepilepsy.blogspot.com.

Several limitations should be considered. First, most included NRSs were at high risk of at least one important source of bias (eg, selection, performance, ascertainment) and the certainty of the evidence from such studies is very low owing to the high risk of bias. Although NRSs may be important sources of evidence for understanding of real-world effectiveness and informing health care decision making,⁵¹ such biases affect the ability to evaluate effectiveness and safety. However, the findings were generally consistent between the included RCTs and NRSs, although the magnitude of treatment benefit was often greater among NRSs. This was expected, given the high rate of placebo response in pediatric epilepsy studies⁵² combined with the use of subjective outcomes and a lack of blinding. In the placebo arm of the included RCTs, the percentage reduction in seizures was between 9% and 18.5% and the responder rate was 21% (Appendix S10, Appendix S12), which is consistent with the reported placebo responder rate of 19.7% from a pooled analysis of double-blind RCTs involving children with refractory epilepsy.⁵² Given this high responder rate among participants who received

placebo in the RCTs, in the NRS involving only one treatment arm, it is difficult to separate the effect of the cannabis-based intervention from a possible placebo response.

Second, there was considerable heterogeneity in terms of the interventions and duration of treatment. All included RCTs involved Epidiolex, a pharmaceutical-grade CBD preparation recently approved by the US Food and Drug Administration for Dravet and Lennox-Gastaut syndromes.¹⁶ Whether the observed effects extend to other cannabis-based products is unknown. Similarly, almost half of the NRSs involved Epidiolex, whereas others involved multiple cannabis-based products, which were often poorly described. All included RCTs had relatively short treatment durations (up to 14 weeks); thus, it is not clear whether the observed effects are sustained over a longer duration. Although the NRSs involved up to 57 months of treatment, the available data did not allow for an assessment of maintenance of effect.

Third, the effects of cannabis-based products on individual epilepsy syndromes are currently limited and are primarily related to Dravet^{12,28} and Lennox-Gastaut syndromes.^{29,30} Evidence from NRSs suggests that CBD may also be effective in TSC,⁴⁴ Sturge-Weber syndrome,³² and febrile infection-related epilepsy⁴³; however, these studies were based on few participants and were subject to important biases.

Fourth, in most studies, cannabis-based products were added to an established regimen of antiepileptic therapies, including concomitant AEDs, in children with DRE. As such, whether cannabis-based products are effective as first-line therapy for newly diagnosed epilepsy is unknown. Additionally, although some studies required that the type and dose of AEDs be held constant, AED treatments were more fluid in other studies, particularly retrospective studies, with additional interventions added or removed during the treatment period, potentially confounding the results.³⁵ Interactions between some AEDs (eg, clobazam) and CBD have been suggested,⁴² although this has yet to be investigated in well-controlled long-term studies.

Fifth, although seizure freedom, the primary outcome of this review, was identified by family members and a practicing neurologist as being of utmost importance, it may not be an attainable outcome for children with DRE. In this population, a reduced burden of seizures and the avoidance of status epilepticus may be more realistic goals, with a 50% reduction in seizures being a desirable outcome. As such, it is not unsurprising that a small proportion of children with Dravet syndrome experienced seizure freedom with CBD treatment.¹² However, the observed reduction in seizure frequency and increased number of children with Dravet or Lennox-Gastaut syndrome with $\geq 50\%$ reduction in seizures is a clinically important finding.

5 | CONCLUSION

Evidence from recent high-quality RCTs suggests that CBD is effective in reducing seizure burden among children with drug-resistant Dravet and Lennox-Gastaut syndromes (moderate certainty); however, few children experienced complete seizure freedom. Although the evidence is currently limited, children with other DRE syndromes may experience similar benefit. These findings should not be extended to all cannabis-based products, especially those of unknown composition.

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DISCLOSURE OF CONFLICTS OF INTEREST

B.M. is principal investigator in a study of cannabinoids for Dravet syndrome. A.E.R. is director of communications at a licensed cannabis producer. The other authors have no conflicts of interest to report. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

J.E., T.C., D.C., B.K.P., C.A., A.E.R., B.M., and G.A.W. designed the study. B.S. developed and executed the search strategy. J.E. and D.D. selected studies for inclusion and extracted data. J.E. analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication.

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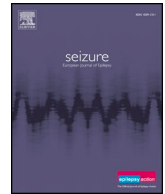
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Review

Cannabis-based products for pediatric epilepsy: An updated systematic review



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ABSTRACT

Purpose: To provide an up-to-date summary of the benefits and harms of cannabis-based products for epilepsy in children.

Methods: We updated our earlier systematic review, by searching for studies published up to May 2019. We included randomized controlled trials (RCTs) and non-randomized studies (NRS) involving cannabis-based products administered to children with epilepsy. Outcomes were seizure freedom, seizure frequency, quality of life, sleep, status epilepticus, death, gastrointestinal adverse events, and emergency room visits.

Results: Thirty-five studies, including four RCTs, have assessed the benefits and harms of cannabis-based products in pediatric epilepsy (12 since April 2018). All involved cannabis-based products as adjunctive treatment, and most involved cannabidiol. In the RCTs, there was no statistically significant difference between cannabidiol and placebo for seizure freedom (relative risk 6.77, 95 % confidence interval [CI] 0.36–128.38), quality of life (mean difference [MD] 0.6, 95 %CI –2.6 to 3.9), or sleep disruption (MD –0.3, 95 %CI –0.8 to 0.2). Data from both RCTs and NRS suggest that cannabidiol reduces seizure frequency and increases treatment response; however, there is an increased risk of gastrointestinal adverse events.

Conclusion: Newly available evidence supports earlier findings that cannabidiol probably reduces the frequency of seizures among children with drug-resistant epilepsy.

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1. Introduction

Interest in cannabis for treatment of pediatric epilepsy has grown over the last decade, [1] and the number of studies assessing its benefits and harms has grown in parallel. In 2018, we initiated a living systematic review (LSR) of cannabis-based products for pediatric epilepsy [2]. LSRs search for newly available studies at *a priori*-defined intervals, allowing evidence to be incorporated into the review shortly after it becomes available. [3] In the first iteration (“baseline review”) [2], we identified 23 studies, the findings of which supported a beneficial role

for cannabis-based products, particularly cannabidiol (CBD), in reducing seizures among children with drug-resistant epilepsy. At that time, we also identified 33 ongoing studies, signalling that the evidence base would continue to evolve.

In this updated review, we incorporated studies published in the year following the baseline review, thus providing an up-to-date overview of the evidence base.

Abbreviations: CBD, cannabidiol, LSR living systematic review; NRS, non-randomized study; RCT, randomized controlled trial; QoL, quality of life; SUDEP, sudden unexpected death in epilepsy; ER, emergency room; ROB, risk of bias; RR, relative risk; RD, risk difference; MD, mean difference; CI, confidence interval

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2. Methods

The protocol [4] and baseline review [2] have been published and PRISMA guidelines were followed [5]. The baseline review encompassed studies published up to April 2018; the present update is current to May 9, 2019. Briefly, we searched Ovid MEDLINE, Embase, PsycINFO, and the Cochrane Library (Appendix 1), as well as ClinicalTrials.gov and ICTRP Search Portal. Two independent reviewers (J.E., D.D.) selected randomized controlled trials (RCTs) and non-randomized studies (NRS) involving children with epilepsy who were administered a cannabis-based product, compared to pharmacologic treatment (i.e., antiepileptic drugs), non-pharmacologic treatment (e.g., diet therapy, vagus nerve stimulation), placebo, usual care, or no treatment. The primary outcome was seizure freedom; secondary outcomes were seizure frequency (total, tonic-clonic, ≥ 50 % reduction from baseline), quality of life (QoL), sleep, status epilepticus, death, gastrointestinal adverse events (vomiting, diarrhea), and emergency room (ER) visits. Risk of bias (RoB) and certainty of the evidence was assessed (GRADE criteria) [6]. Data from RCTs were pooled by random-effects meta-analyses and are reported as relative risk (RR), risk difference (RD), mean difference (MDs), or median difference with 95 % confidence intervals (CIs). Data from NRS are reported as the percentage of participants who experienced an outcome. Data were not pooled if there was substantial clinical or statistical heterogeneity (i.e., $I^2 > 75$ %). Data from the longest duration of follow-up were analyzed.

3. Results

Thirty-five studies have assessed the benefits and harms of cannabis-

based treatments in children with epilepsy (4 RCTs [7–10]; 31 NRS [11,12,21–30], [13,31–40], [14,41–46], [15–20]; Fig. 1, Appendix 2). This reflects a 52 % increase since April 2018. Most studies involved purified CBD products (63 %); of those, 77 % involved Epidiolex (Greenwich Biosciences; Appendix 3). Few studies involved products containing both CBD and delta-9-tetrahydrocannabinol (THC) (e.g., CBD:THC cannabis oil), [11,28,37] while others involved products from illicit cannabis suppliers [19], home-made extracts, [46] or “artisanal” products. [20] All studies involved cannabis added to an established regimen of antiepileptic therapies; no studies involved first-line treatment. Treatment duration ranged from 10 days to 146 weeks (RCTs up to 14 wk). All RCTs involved children with Dravet or Lennox-Gastaut syndrome (LGS), while NRS enrolled a wider range of drug-resistant epilepsy syndromes and participant characteristics (Appendix 4). All RCTs were considered low RoB; NRS were at high RoB, owing primarily to lack of a control group and unblinded outcome assessment (Appendix 6). In the following sections, data are summarized for all participants; data pertaining specifically to Dravet and LGS are presented in Appendix 7.

3.1. Seizure freedom

Twenty-three studies (one RCT, [7] 22 NRS [11,13,28,31,33,35–39,43,44,15,45,46,17,20,21,24–27],) have reported seizure freedom with cannabis treatment; an additional 3 studies reported that no children became seizure free (Table 1, Appendix 8). Among children with Dravet syndrome (61) who received CBD in one 14-wk RCT, [7] 5 % became seizure free, compared with none in the placebo group ($n = 59$; RD 5 %, 95 %CI –1 % to 11 %; low certainty).

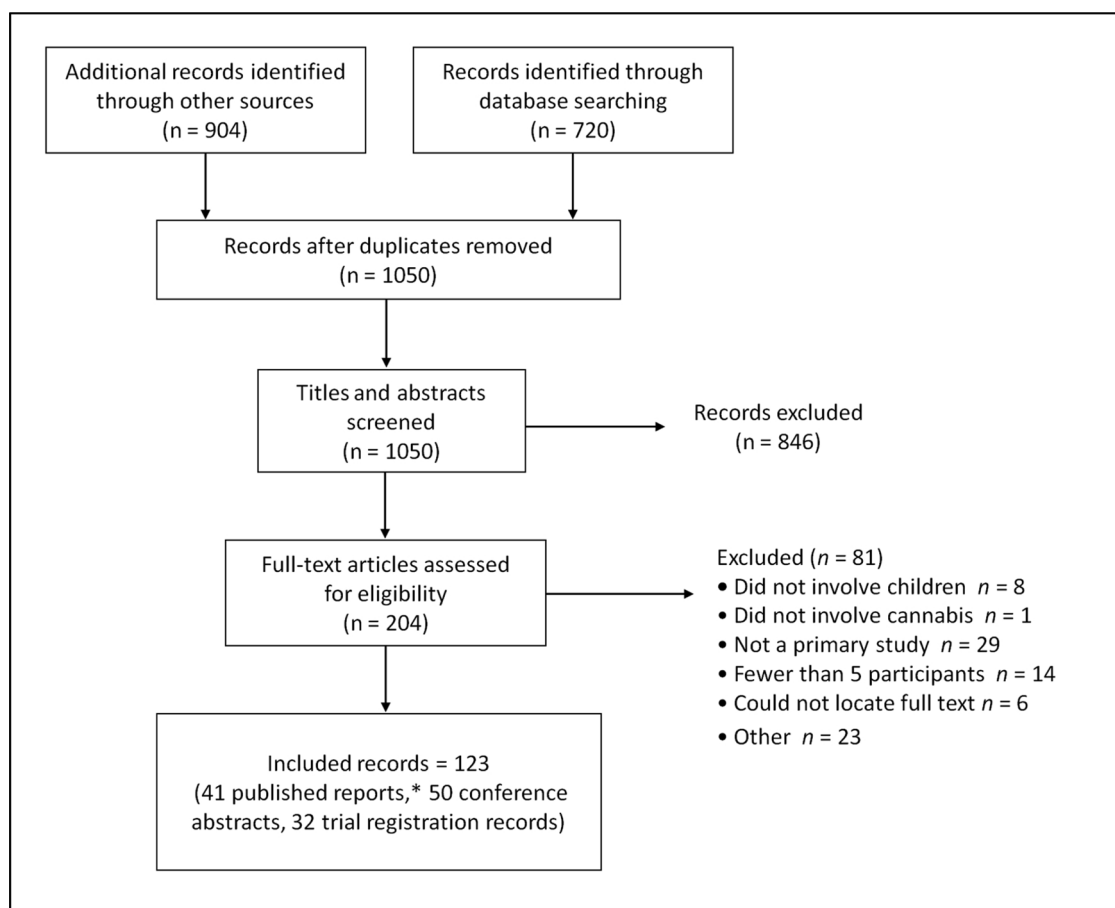


Fig. 1. PRISMA flow diagram showing selection of studies. *Includes 35 unique studies (4 randomized controlled trials, 31 non-randomized studies) available as published studies or as clinical trial records with available data.

Table 1
Evidence summary.^{a, *}

Outcome	Randomized controlled trials			Non-randomized studies						
	No. of studies	No. of participants	Effect estimate (95 %CI), cannabidiol v. placebo	I ²	GRADE assessment	No. of studies	No. of participants	Proportion of those exposed to a cannabis-based product (95 %CI) ^b	I ²	GRADE assessment
Primary outcome										
Seizure freedom	1	120	RR 6.77 (0.36–128.38), RD 0.05 (–0.01 to 0.11)	NA	Low	23	1488	8 % (5%–10%)	70 %	Very low
Secondary outcomes										
Total seizure frequency	3	516	Median reduction in monthly seizures v. placebo: –19.8 % (–27.0 % to –12.6 %)	0 %	Moderate	11	1914	NA ^f	NA	Very low
Tonic-clonic seizure frequency	3	321	Median reduction in monthly seizures v. placebo: –27.5 % (–38.7 % to –16.3 %)	0 %	Moderate	2	95	NA ^f	NA	Very low
Treatment response ^c	1	171	RR 1.76 (1.07–2.88), RD 0.16 (0.03 to 0.29)	NA	Moderate	18	1164	Prospective cohorts: 48 % (41%–56%)	71 %	Very low
Quality of life: Child	3	516	Pooled mean difference 0.6 (–2.6 to 3.9) ^d	0 %	Moderate	3	72	NA ^f (each study reported QoL improvement after treatment)	NA	Very low
Sleep disruption	3	516	Pooled mean difference –0.3 (–0.8 to 0.2) ^e	0 %	Moderate	0	NA	NA	NA	NA
Improved sleep	0	NA	NA	NA	NA	6	381	NA ^g	NA	Very low
Impaired sleep	1	171	Sleep apnea reported for 1 participant (1.2 %) in the CBD group; none in the placebo group	NA	NA	6	166	3 % (1%–6%)	0 %	Very low
Status epilepticus	3	516	RR 1.39 (0.55–3.47), RD 0.01 (–0.02 to 0.03)	0 %	Low	8	1601	7 % (4%–9%)	74 %	Very low
Death	1	171	1 death reported in the CBD group (n = 86); zero deaths in the placebo group (n = 85)	NA	Low	9	1623	1 % (1%–2%)	0 %	Very low
Gastrointestinal AEs	4	550	RR 1.54 (0.92–2.58)	52 %	Low	19	2079	NA ^g	NA	Very low
Vomiting	4	550	RR 1.00 (0.51–1.96)	34 %	NA	14	1662	NA ^g	NA	NA
Diarrhea	3	516	RR 2.25 (1.38–3.68)	0 %	NA	14	1743	NA ^g	NA	NA
ER visits	0	NA	NA	NA	NA	2	64	NA ^f	NA	Very low

Note: AE = adverse event, CBD = cannabidiol, CI = confidence interval, ER = emergency room, NA = not applicable, QoL = quality of life, RD = risk difference, RR = relative risk.
^a Adapted from Elliott et al. 2019.

^b Unless otherwise stated.

^c ≥ 50 % reduction in seizure frequency relative to baseline period.

^d Quality of Life in Childhood Epilepsy scale.

^e Assessed by use of the Sleep Disruption Rating Scale (negative value favours CBD).

^f Data reported in a variety of ways precluded pooling; see Appendices for full details.

^g High heterogeneity precluded pooling.

Among NRS, 8 % (95 %CI 5%–10%) became seizure free with cannabis treatment (duration: 14 d to 53 mo; very low certainty).

3.2. Seizure frequency

Fourteen studies (three RCTs, [7,9,10] 11 NRS [13,15,44,17,19,26,32,36,38,39,43]) assessed seizure frequency (Appendix 9). Total monthly seizures were reduced by CBD compared to placebo in the RCTs (median reduction 19.8 %, 95 %CI 27.0%–12.6 %; duration: 14 wk; moderate certainty), as well as by cannabis-based products in the NRS (30%–90%; duration: 11 d to 96 wk duration; very low certainty). Data from NRS suggest that the effects are maintained through at least 48 weeks of treatment in some children [13,15,17,43].

3.3. Quality of life

Six studies (three RCTs, [7,9,10] three NRS [23,28,31]) assessed the impact of cannabis-based products on childhood QoL (Appendix 10); no studies have assessed the effect on caregivers. Evidence from three 14-wk RCTs involving children with Dravet and LGS [7,9,10], suggests no statistically significant effect of CBD on QoL (MD 0.6, 95 %CI –2.6 to 3.9; moderate certainty); however, data from NRS [23,28,31] suggest an improvement relative to before cannabis treatment (very low certainty).

3.4. Sleep

Fourteen studies (3 RCTs, [7,9,10] 11 NRS [12,21,46,22,25,27,31,32,35,36,39]) reported changes in sleep with cannabis-based products (Appendix 11). Among children with Dravet or LGS in three 14-wk RCTs [7,9,10], there was no statistically significant difference in sleep between CBD and placebo (MD –0.3, 95 %CI –0.8 to 0.2; moderate certainty). Improved sleep was reported in six NRS [12,22,25,27,35,46], with a higher proportion reported in cross-sectional studies [22,25,35,46] (74 %, 95 %CI 54%–94%) compared with retrospective cohort studies (8 %, 95 %CI 4%–11%) (duration: 2 wk to 57 mo; very low certainty). Impaired sleep was reported in six NRS [21,31,32,36,39,46] affecting 3 % (95 %CI 1%–6%) of children who received a cannabis-based product (duration: 10 d to 53 mo; very low certainty).

3.5. Status epilepticus

Status epilepticus was reported in eleven studies (three RCTs, [7,9,10] eight NRS [13,17,21,24,37,42–44]) among children who received a cannabis-based product (Appendix 12). In the RCTs, there was no statistically significant difference in the frequency of status epilepticus among children with Dravet or LGS who received CBD or placebo for 14 weeks [7,9,10] (RR 1.39, 95 %CI 0.55–3.47; low certainty). Among NRS, 7 % (95 %CI 4%–9%) of children who received a cannabis-based product experienced status epilepticus, with higher rates reported among children with Dravet [43] or LGS [13] who received more than 20 mg/kg/d of CBD compared to 20 mg/kg/d (median duration: 263, 274 d).

3.6. Death

Twenty-six deaths, including seven owing to sudden unexpected death in epilepsy, have been reported among 1713 children who received a cannabis-based treatment (Appendix 13) in 10 studies (one RCT, [10] nine NRS [13,17,20,24,27,28,38,43,44]). Most deaths were reported as having been unrelated to treatment.

3.7. Gastrointestinal adverse events

Gastrointestinal adverse events were commonly reported among

children who received a cannabis-based product (4 RCTs, [7–10] 19 NRS [11,12,36–38,41–46], [13,17,21,25,28,31,32,35]; Appendix 14). Risk of diarrhea was higher among those who received CBD compared to placebo (RR 2.25, 95 %CI 1.38–3.68; low certainty) despite no overall significant difference in gastrointestinal adverse events. In the NRS, gastrointestinal adverse events have been reported for 2 %–60 % of participants who received a cannabis-based product (vomiting: 3 %–40 %; diarrhea: 2 %–35 %), with high heterogeneity between studies.

3.8. ER visits

Two NRS have assessed ER visits (Appendix 15). [21,45] Chen and colleagues [45] reported no statistically significant difference in the monthly rate of visits per child before or during cannabis treatment (12-wk treatment). Sands and colleagues [21] reported that, of children who had an ER visit during the 6-month baseline period, all had fewer visits during the treatment period (4–53 mo).

4. Discussion

This updated review incorporating studies published up to May 2019, reflecting a 52 % increase in the evidence base in the previous year. This is an active area of research, and clinicians require up-to-date evidence summaries on which to base treatment decisions. The findings of newly available studies were consistent with earlier studies, although the certainty of evidence did not change for any outcome, and no new RCTs were published during the update period. We identified an additional 32 clinical studies that have yet to report results (Appendix 16), including six RCTs, suggesting that further evidence will be available for future updates of this LSR. Because the certainty of the evidence is currently low for most outcomes, additional evidence may change the effect estimates and give clinicians more confidence in the effects of cannabis-based treatments in this population. Importantly, ongoing studies may provide data for longer treatment durations, helping us to better understand the long-term effects of cannabis-based products.

4.1. Limitations

First, most available evidence is from NRS, all of which are at risk of important sources of bias, primarily related to study design (e.g., lack of a comparison group, unblinded outcome assessment), and the certainty of the evidence from such studies is very low. Second, most studies have involved Epidiolex (purified pharmaceutical-grade CBD), and may not be generalizable to other cannabis-based products (e.g. CBD-THC cannabis oil). Third, most studies have involved participants with Dravet or LGS, and less is known about the effects on other epilepsy syndromes. Fourth, the treatment duration of the included studies was variable, ranging from 10 days to 146 weeks, with evidence from RCTs available only up to 14 weeks of treatment. The long-term effects of these products have not been evaluated in long-term randomized studies.

4.2. Conclusion

Newly available studies support CBD as an effective treatment option for reducing the frequency of seizures among children with drug-resistant epilepsy. Products containing both CBD and THC may also be effective; however, most available evidence pertains to pharmaceutical-grade CBD alone. This is an active area of research, and future updates will include additional evidence as it becomes available.

Author's contributions

JE, TC, DC, BP, CA, AR, BM and GW designed the study. BS developed and executed the search strategy. JE and DD selected studies for inclusion and extracted data. JE analyzed the data and wrote the

first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication.

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Declaration of Competing Interest

Bláthnaid McCoy is principal investigator in a study of cannabinoids for Dravet syndrome. Alexander Repetski is director of communications at a licensed cannabis producer. Deirdre DeJean is an employee of CADTH; this work was unrelated to her employment and was not funded by CADTH. The remaining authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.seizure.2019.12.006>.

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PROTOCOL

Open Access



Cost-effectiveness of cannabinoids for pediatric drug-resistant epilepsy: protocol for a systematic review of economic evaluations

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Abstract

Background: Drug-resistant epilepsy negatively impacts the quality of life and is associated with increased morbidity and mortality and high costs to the healthcare system. Cannabis-based treatments may be effective in reducing seizures in this population, but whether they are cost-effective is unclear. In this systematic review, we will search for cost-effectiveness analyses involving the treatment of pediatric drug-resistant epilepsy with cannabis-based products to inform decision-making by public healthcare payers about reimbursement of such products. We will also search for cost-effectiveness analyses of other pharmacologic treatments for pediatric drug-resistant epilepsy, as well as estimates of healthcare resource use, costs, and utilities, for use in a subsequent cost-utility analysis to address this decision problem.

Methods: We will search the published and gray literature for economic evaluations of cannabis-based products and other pharmacologic treatments for pediatric drug-resistant epilepsy, as well as resource utilization and utility studies. Two independent reviewers will screen the title and abstract of each identified record and the full-text version of any study deemed potentially relevant. Study and population characteristics, the incremental cost-effectiveness ratio (ICER), as well as total costs and benefits, will be extracted, and quality will be assessed by use of the Drummond and CHEERS checklists; context-specific issues will also be considered. From model-based cost-utility and cost-effectiveness analyses, we will extract and summarize the model structure, including health states, time horizon, and cycle length. From resource utilization studies, we will extract data about the frequency of resource use (e.g., neurology visits, emergency department visits, admissions to hospital). From utility studies, we will extract the utility for each health state, the source of the preferences (e.g., child, parent, patient, general public), and the method of elicitation.

Discussion: Drug-resistant epilepsy in children is associated with important costs to the healthcare system, and decision-makers require high-quality evidence on which to base reimbursement decisions. The results of this review will be useful to both decision-makers considering the decision problem of whether to reimburse cannabis-based products through public formularies and to analysts conducting studies in this area.

Systematic review registration: PROSPERO no.: [CRD42018099591](https://www.crd42018099591).

Keywords: Cannabis, Cannabidiol, Cost-effectiveness, Pediatric drug-resistant epilepsy, Resource use, Costs, Benefits, Utilities

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Background

Drug-resistant epilepsy (inadequate response to two or more trials of appropriate antiepileptic drugs [1]) affects between 28% and 37% of people with epilepsy [2] and can have profound consequences for affected children and their families, with affected children at increased risk of severe morbidity (e.g., cognitive delay, behavioral problems, autism) and mortality [3]. Pediatric epilepsy is associated with increased contacts with the healthcare system, including neurologist visits, visits to the emergency department, and admissions to hospitals [4, 5], and children with uncontrolled seizures use more health resources than children with controlled seizures, with costs correlated with epilepsy severity [4, 6]. Taken together, resource use by children with epilepsy contributes major costs to the healthcare system [6, 7].

Drug-resistant epilepsy comprises multiple types of pediatric epilepsies, frequently with underlying genetic causes (e.g., Dravet syndrome, Lennox-Gastaut syndrome, West syndrome) [3]. Pediatric epilepsy may also be caused by structural or metabolic (e.g., structural abnormality or chronic metabolic condition) or unknown causes [3]. Because of this variation, and variation in seizure types, there is no standard of care for treatment of pediatric drug-resistant epilepsy, with treatment dependent on the nature of a child's individual disease, which drugs are available in a given jurisdiction, and local practice [8]. Individual antiepileptic drugs may benefit only small groups of patients because of the rare nature of some epilepsy syndromes, and some antiepileptic drugs have designated orphan drug status (e.g., stiripentol for Dravet syndrome [9]). In addition to pharmacologic treatments (i.e., antiepileptic drugs), other treatment options include non-pharmacologic interventions (e.g., surgery to resect the seizure focus, vagus nerve stimulation, deep brain stimulation therapy, ketogenic diet therapy) [3], with increasing interest in the use of alternative therapies, including cannabinoids [10, 11].

Interest in the use of cannabis for the treatment of pediatric epilepsy has increased over the last decade, with recent clinical studies suggesting that cannabidiol, one of two main cannabinoids in cannabis, reduces seizure burden in some epilepsy syndromes [12, 13]. The first pharmaceutical-grade cannabidiol product intended to treat Dravet syndrome and Lennox-Gastaut syndrome was recently approved by the US Food and Drug Administration [14], and it is expected that public payers will soon be faced with decisions as to whether to include such products on their formularies. Economic evaluations can provide important information to decision-makers as they make such reimbursement and funding decisions [15]. As such, the objective of this systematic review is to provide a comprehensive overview

of the cost-effectiveness of cannabis-based treatments for pediatric drug-resistant epilepsy and to search for inputs for a de novo cost-utility analysis to address this decision problem in the Canadian context.

Research aims

There are three aims of this study:

1. Identify and assess the applicability of existing economic evaluations of cannabis-based products for the treatment of pediatric drug-resistant epilepsy;
2. Identify and assess the suitability of existing models that have been used in the economic evaluation of other pharmacologic treatments in this population;
3. Identify model inputs (e.g., resource use, utilities) from existing economic evaluations of pharmacologic treatments or from stand-alone studies in this population.

The findings of aims 2 and 3 will be used to inform a de novo cost-utility analysis intended to address the decision problem of whether Canadian public healthcare payers should reimburse cannabis-based products for the treatment of drug-resistant epilepsy in children with Dravet syndrome.

Methods

This systematic review protocol has been registered in PROSPERO (CRD42018099591) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (Additional file 1) [16]. All screening and data extraction will be performed by the use of standardized and piloted forms in Distiller SR (evidence partners).

Search strategy

The search strategy was developed in consultation with an experienced medical information specialist and the research team (Additional file 2). The search was peer-reviewed by another senior librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist prior to execution [17]. Databases to be searched include Ovid MEDLINE In-Process and Other Non-Indexed Citations and Ovid MEDLINE and Embase Classic+Embase. The Cochrane Library (HTA database, NHSEED, DSR, DARE, and CENTRAL), Wiley version, will also be searched. The search strategies will be adjusted to the individual database and will include a combination of controlled vocabulary (e.g., Medical Subject Headings) and keywords; no date restrictions will be applied. Gray literature searches will be undertaken using the relevant economic websites and databases listed in Gray Matters [18].

Eligibility criteria

We will include studies that meet the criteria described below. Conference abstracts and non-English language records will be excluded; however, studies performed in Canada but reported in French will be eligible. Studies that report mixed populations of children and adults will be included if they report data separately for participants aged less than 19 years or if, based on descriptive statistics, we can determine that most patients (i.e., > 80%) are aged less than 19 years.

A) *Research aim 1*

Population: Children (aged less than 19 years) with any form of drug-resistant epilepsy (inadequate response to two or more trials of appropriate antiepileptic drugs [1]).

Intervention: Any type of cannabis or cannabis-based product, cannabitol, cannabidiol (CBD), tetrahydrocannabinol (THC), or combinations of these agents, administered by any route (e.g., oral, inhalation), involving any strain of cannabis and any ratio of THC to CBD.

Comparator: Pharmacologic (i.e., antiepileptic drugs) or non-pharmacologic treatments (i.e., ketogenic diet, epilepsy surgery, vagus nerve stimulation) for pediatric drug-resistant epilepsy.

Study designs: Full economic evaluations (i.e., cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-minimization analysis) and health technology assessments that include a full economic evaluation. Both trial-based and model-based economic evaluations will be eligible for inclusion.

B) *Research aim 2*

Population: Children with any form of drug-resistant epilepsy [1].

Interventions and comparators: Pharmacologic treatments for pediatric drug-resistant epilepsy compared with other pharmacologic or non-pharmacologic treatments. **Study designs:** Full economic evaluations and health technology assessments that involve model-based cost-utility or cost-effectiveness evaluations.

C) *Research aim 3*

Population: Children with any form of drug-resistant epilepsy (resource utilization, utility, productivity studies) or adult caregivers of children with drug-resistant epilepsy (utility, productivity studies).

Study designs: Resource utilization studies involving at least five children, utility studies, productivity studies; full economic evaluations identified as part of Aim 1 or 2.

Screening and study selection

Two independent reviewers will screen the title and abstract of each identified record and the full-text version of any study deemed potentially relevant, with disagreements resolved by discussion.

Outcomes

Research aim 1: Total and incremental costs; direct, indirect (i.e., productivity costs), and drug-related costs; total and incremental quality-adjusted life years (QALYs); and incremental cost-effectiveness ratios (ICERs).

Research aim 2: Model structure (e.g., description of the included health states, horizon, cycle length), model inputs (e.g., resource use [e.g., number of neurologist visits, admission to hospital, visits to the emergency department] and utility values).

Research aim 3: Resource use, costs, and utility values, and by seizure status (e.g., controlled or uncontrolled seizures). From resource utilization studies, the number of resource units used (e.g., number of hospital admissions) will be extracted from all studies; associated costs will be extracted only from studies performed in Canada. Depending on the perspective, costs may include those incurred by the payer (e.g., costs to the healthcare system) or to society (e.g., costs to patients and caregivers, productivity costs). Productivity costs may include lost productivity, lost leisure time, and lost income by caregivers of affected children, as well as productivity losses by children with drug-resistant epilepsy. Utilities may be related to either affected children or their caregivers.

Data extraction

Data will be extracted by one reviewer, and the completeness and accuracy verified by a second reviewer. We will extract study characteristics (e.g., study design, location, decision problem, perspective [i.e., patient, hospital, healthcare, society], funding source), as well as population characteristics (e.g., epilepsy syndrome, age, comorbidities, setting or context) and details about the interventions and comparators. Details about the model structure, including health states, time horizon, and cycle length, will be extracted from model-based cost-effectiveness and cost-utility analyses, as well as model inputs, including resource use and utilities. From utility studies, we will extract the utility value for each health state, as well as details about the source of the utilities (e.g., population characteristics, setting), method of elicitation (e.g., time trade-off, standard gamble, preference-based multi-attribute classification system), and description of the health state. From resource utilization studies, we will extract details about the source of the resource use (e.g., population characteristics, setting, number of participants), and study design, along with the frequency of use of each type of reported service.

Quality and risk of bias assessment

We will evaluate the quality of the included economic evaluations by use of the 10-item Drummond checklist [19] and the CHEERS statement [20]. We will also evaluate whether the economic evaluations adequately considered context-specific issues, which may influence the ability of an evaluation to address the decision problem. For example, this may include how the evaluations accounted for changes to treatment regimens or patient weight gain during the analysis horizon. Each study will be appraised independently by two reviewers, with conflicts resolved by discussion.

Synthesis

The extracted data, including study and patient characteristics and study quality, will be summarized descriptively. Depending on the study type, model characteristics, resource use, costs, QALYs, and cost-effectiveness results (e.g., ICER) will be summarized. To facilitate comparison between studies, all costs will be reported in 2018 Canadian dollars. First, if necessary, costs will be converted to Canadian Dollars using purchasing power parity for the year of each study and then adjusted to 2018 based on the Bank of Canada Inflation calculator. Where possible, data will be reported separately by drug-resistant epilepsy syndrome and by seizure status (e.g., controlled, uncontrolled).

Discussion

Epilepsy is a major public health concern, affecting about 50 million people worldwide [21]. Because drug-resistant epilepsy is associated with important costs to the healthcare system [6, 7], it is crucial that the cost-effectiveness of new and existing treatments be evaluated using the best available evidence. This review will provide a comprehensive overview of the cost-effectiveness of current pharmacologic treatments, including cannabis-based treatments, for drug-resistant epilepsy in children, and will serve to inform the subsequent development of a de novo cost-effectiveness analyses in this population.

Additional files

Additional file 1: PRISMA-P checklist. (PDF 136 kb)

Additional file 2: Search strategy. (PDF 129 kb)

Abbreviations

CBD: Cannabidiol; ICER: Incremental cost-effectiveness ratios; QALY: Quality-adjusted life year; THC: Tetrahydrocannabinol

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Availability of data and materials

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Authors' contributions

JE and DC designed the study. BS designed and will execute the search strategy. JE drafted the protocol, which was revised by all the authors. All authors approved the version of the manuscript submitted for publication.

Ethics approval and consent to participate

Not applicable.

Competing interests

Bláthnaid McCoy is the principal investigator of a study assessing the use of cannabidiol for treatment of Dravet syndrome in children. The rest of the authors declared that they have no competing interests.

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Decision Models for Assessing the Cost Effectiveness of Treatments for Pediatric Drug-Resistant Epilepsy: A Systematic Review of Economic Evaluations

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Abstract

Background Drug-resistant epilepsy affects about one-third of children with epilepsy and is associated with high costs to the healthcare system, yet the cost effectiveness of most treatments is unclear. Use of cannabis-based products for epilepsy is increasing, and the cost effectiveness of such strategies relative to conventional pharmacologic treatments must be considered.

Objective The objective of this systematic review was to identify economic evaluations of cannabis-based treatments for pediatric drug-resistant epilepsy. We also sought to identify and appraise decision models that have been used in economic evaluations of pharmacologic treatments (i.e., antiepileptic drugs) in this population.

Methods Electronic searches of MEDLINE, EMBASE, and the Cochrane library, as well as a targeted grey literature search, were undertaken (11 June 2018). Model-based full economic evaluations involving cannabis-based treatments or pharmacologic treatments for drug-resistant epilepsy in children were eligible for inclusion. Two independent reviewers selected studies for inclusion, and study quality was assessed by use of the Drummond and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklists. Study findings, as well as model characteristics, are narratively summarized.

Results Nine economic evaluations involving children with drug-resistant epilepsy were identified; however, none involved cannabis-based treatments. All studies involved pharmacologic treatments compared with other pharmacologic treatments or non-pharmacologic treatments (i.e., ketogenic diet, epilepsy surgery, vagus nerve stimulation). Few studies have assessed the cost effectiveness of pharmacologic treatments in specific drug-resistant epilepsy syndromes, including Dravet and Lennox-Gastaut syndromes. Five included studies involved use of Markov models with a similar structure (i.e., health states based on seizure frequency relative to baseline). There was a wide range of methodological quality, and few studies fully addressed context-specific issues such as weight gain and treatment switching.

Conclusion Whether cannabis-based treatments for pediatric drug-resistant epilepsy represent good value for money has yet to be investigated. Economic evaluations of such treatments are needed and should address issues of particular importance in pediatric epilepsy, including weight gain over time, switching or discontinuation of treatments, effectiveness of interventions and comparators, and long-term effectiveness beyond the duration of available clinical studies.

PROSPERO Registration CRD42018099591.

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Key Points

The cost effectiveness of cannabis-based treatments for pediatric drug-resistant epilepsy has yet to be evaluated.

Few studies have evaluated the cost effectiveness of pharmacologic treatments for pediatric drug-resistant epilepsy.

The quality of existing cost-effectiveness evaluations in this area is variable, and few studies have addressed context-specific issues such as weight gain and treatment switching.

Extended author information available on the last page of the article

1 Introduction

Epilepsy is a chronic neurologic disorder that affects about 50 million people worldwide [1]. The goal of epilepsy treatment is to reduce seizures and improve quality of life with minimal adverse effects [2]. Although most people with epilepsy respond well to pharmacologic treatments, about one-third have a drug-resistant form [3] (failure of two or more adequate trials of antiepileptic drugs [AEDs] [4]). The consequences of drug-resistant epilepsy, especially among children, are severe, including cognitive delay, behavioral problems, autism, poor quality of life, and an increased risk of death [5–7]. Children with drug-resistant epilepsy use more healthcare resources than those whose seizures are controlled [8, 9], contributing high costs to the healthcare system [10, 11].

There are multiple types of drug-resistant epilepsy, e.g., Dravet syndrome and Lennox-Gastaut syndrome, each with individual seizure profiles. As such, there is no one standard of care [12], and treatment options include both pharmacologic (e.g., AEDs) and non-pharmacologic interventions (e.g., epilepsy surgery, ketogenic diet [KD], vagus nerve stimulation [VNS]). Parents of children with epilepsy also report use of complementary and alternative medicines [13], including cannabis-based treatments, after failure of conventional AEDs to control seizures [14], and recent clinical studies suggest that some cannabis-based treatments may reduce seizures among children with drug-resistant epilepsy [15–18].

In this systematic review, we sought to identify and appraise economic evaluations of cannabis-based treatments for drug-resistant epilepsy in children. We also sought to identify decision models that have been used in economic evaluations of pharmacologic treatments in this population, in order to inform the development of a de novo cost-utility analysis of cannabis-based treatments for Dravet syndrome.

2 Methods

The systematic review protocol was registered in PROSPERO (registration no. CRD42018099591) and published [19]. The focus of this paper is economic evaluations of cannabis-based products and decision models that have been used to evaluate the cost effectiveness of pharmacologic treatments for drug-resistant epilepsy in children. This report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Electronic Supplementary Material [ESM] Appendix 1) [20]. All screening and data extraction were performed using DistillerSR (Evidence Partners, Ottawa, ONT, Canada).

2.1 Eligibility Criteria

We included studies that met the criteria outlined in Sects. 2.1.1–2.1.4.

2.1.1 Population

Children aged less than 19 years with drug-resistant epilepsy, according to the International League Against Epilepsy (ILAE) definition (failure of two or more adequate trials of AEDs), were included [4]. Because few studies reported use of a definition of drug-resistant epilepsy, we also included those that described the target population as having “resistant”, “refractory”, or “intractable” epilepsy, focused on specific drug-resistant epilepsy syndromes (e.g., Dravet syndrome, Lennox Gastaut syndrome), or involved interventions intended to treat drug-resistant epilepsy (i.e., KD, epilepsy surgery, VNS).

2.1.2 Interventions and Comparators

We included studies involving any form of cannabis-based treatment (e.g., cannabidiol) compared with any pharmacologic (i.e., AEDs) or non-pharmacologic treatment (i.e., KD, epilepsy surgery, VNS) intended to treat drug-resistant epilepsy. In order to appraise decision models that have been used in this population, we also included studies that compared pharmacologic treatments with other pharmacologic treatments or non-pharmacologic treatments. Economic evaluations that compared non-pharmacologic interventions with other non-pharmacologic interventions were beyond the scope of this review.

2.1.3 Outcomes

Outcomes of interest were total and incremental costs, including direct, indirect (i.e., productivity costs), and drug-related costs; total and incremental quality-adjusted life-years (QALYs); and incremental cost-effectiveness ratios (ICERs). Additionally, outcomes of interest from Markov model-based analyses were model structure (e.g., description of the included health states, horizon, cycle length) and model inputs (i.e., resource use [e.g., number of neurologist visits, admission to hospital, visits to the emergency department], utility values).

2.1.4 Study Designs

We included model-based full economic evaluations (i.e., cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-minimization analysis) and health technology assessments that include a full economic evaluation

involving a decision model. Stand-alone resource utilization and utility studies were not included in this analysis.

2.2 Search Strategy and Study Selection

Using the OVID platform, we searched Ovid MEDLINE, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, EMBASE Classic and EMBASE, as well as the Cochrane Library on Wiley, from inception to 11 June 2018. Search strategies were adjusted across databases and used a combination of controlled vocabulary (e.g., “Epilepsy,” “Costs and Cost Analysis,” “Quality of Life”) and keywords (e.g., “seizure,” “cost,” “QALY”). The strategy (ESM Appendix 2) was peer-reviewed by use of the Peer Review of Electronic Search Strategies (PRESS) Checklist [21]. A targeted grey literature search was performed by searching relevant economic websites and databases included in the Canadian Agency for Drugs and Technologies in Health’s (CADTH) Grey Matters [22]. The title and abstract of each identified record were screened by two independent reviewers (JE, SVK), and the full text of any record deemed potentially relevant was examined in duplicate (JE, DC). We excluded conference abstracts and non-English-language records. Disagreements were resolved by discussion.

2.3 Risk of Bias and Quality of the Evidence

Two independent reviewers (JE, DC) evaluated the quality of included economic evaluations by use of the ten-item Drummond checklist [22] and the 24-item Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [23]. For both checklists, items were graded as ‘yes,’ ‘no,’ or ‘not applicable.’ The Drummond checklist assesses whether appropriate methodology was used in the conduct of the economic evaluation and evaluates the validity of the results, while the CHEERS checklist focuses on issues related to reporting. Because a study authored by JE and DC was among the included studies, a third reviewer (SVK) evaluated the quality of this study. Disagreements were resolved by discussion.

Both the CHEERS and Drummond checklists are generic instruments and may not identify context-specific issues that are important to specific decision problems [24]. We identified an additional five issues pertinent to economic evaluations in pediatric drug-resistant epilepsy: first, we considered whether weight gain had been incorporated into the decision model, if appropriate (i.e., time horizon longer than 1 year). Given that pharmacologic treatments are frequently dosed based on patient weight, and that a child’s weight may increase considerably over the analysis horizon, failure to consider weight gain may be a source of bias. Second, we considered whether discontinuation or switching

of treatments was addressed. Changing treatments is common among children with drug-resistant epilepsy, with new treatments added or current treatments discontinued in an attempt to control seizures. Third, we considered whether the assumptions made about effectiveness were unbiased across all study treatments. Fourth, we assessed whether all relevant clinical data were incorporated into the model. Finally, we assessed assumptions made about the effectiveness beyond the duration of existing clinical studies.

2.4 Data Extraction and Synthesis

Study data were extracted by one author (JE) and verified for completeness and accuracy by a second reviewer (DC), with disagreements resolved by discussion. We extracted study characteristics, including design, location, modeling method (i.e., decision tree or Markov model), and intervention/comparator details. Study findings (e.g., ICERs) as well as study and population characteristics, model inputs, and quality are summarized descriptively. To facilitate comparison between studies, all costs are expressed in 2018 Canadian dollars (\$Can) (\$Can1 = \$US0.7721, €0.6538). If necessary, costs were converted to Canadian dollars using purchasing power parity for the year of the study and then adjusted to 2018 based on the Bank of Canada Inflation calculator. Data are reported separately by drug-resistant epilepsy syndrome, where available.

3 Results

3.1 Search Results

The literature search yielded 7460 unique records (Fig. 1). Of these, 463 were reviewed for eligibility in full-text format. Ten economic evaluations met the inclusion criteria (ESM Appendix 3); however, it was unclear whether one study [25] was a model- or trial-based evaluation and it was not included in the evidence summary. Thus, the evidence base for this review comprised nine full economic evaluations based on decision models involving treatments for drug-resistant epilepsy in children [26–34]. No studies assessed the cost effectiveness of cannabis-based treatments for pediatric drug-resistant epilepsy.

3.2 General Characteristics of Included Studies

Each of the nine included economic evaluations evaluated the cost effectiveness of pharmacologic treatments for drug-resistant epilepsy compared with other pharmacologic treatments (four studies [26, 28, 30, 33]) or with VNS, KD, or epilepsy surgery (one study [29]) (Table 1). In the remaining four studies [27, 31, 32, 34], pharmacologic treatments were

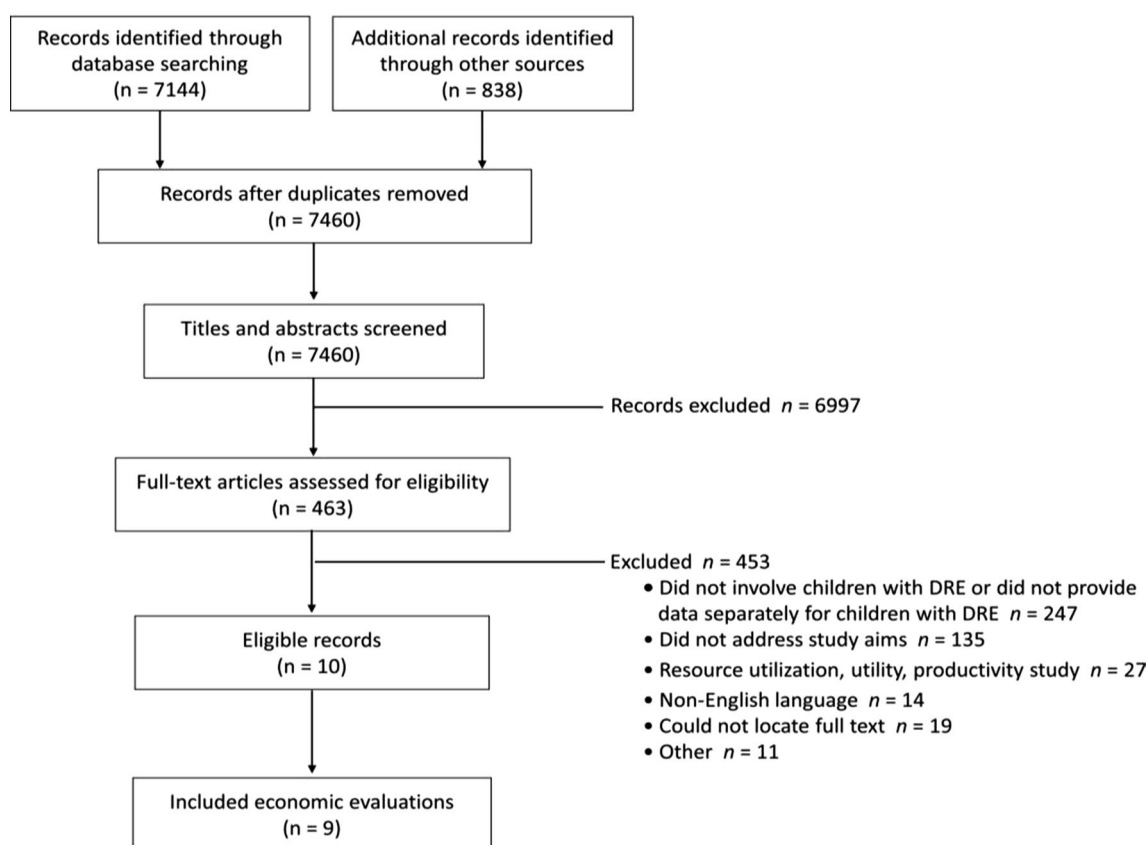


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing study selection. *DRE* drug-resistant epilepsy

grouped as ‘care as usual’ or ‘medical management’; the pharmacologic treatments included in these ‘usual care’ regimens were not well-described (e.g., did not specify which AEDs were involved in the treatments). The included studies comprised five cost-utility analyses [27–29, 32, 33], assessing costs per QALY gained, while four studies [26, 30, 31, 34] assessed cost effectiveness by use of alternative health outcomes, with one study each assessing health gains as percentage of successfully treated patients (defined as > 50% seizure reduction) [26], percentage of patients with seizures controlled (not defined) [30], percentage of seizures reduced compared with baseline [34], or seizure freedom [31].

Four studies targeted specific patient populations, including Dravet syndrome (one study [28]), Lennox Gastaut syndrome (two studies [26, 33]), and tuberous sclerosis complex (TSC; one study [29]), while the remaining studies targeted drug-resistant epilepsy in general [27, 30–32, 34]. The studies were conducted between 1999 and 2018, and the majority were performed in Canada (four studies [27, 28, 31, 34]) and the UK (two studies [26, 33]), with one study each from the USA [29], Iran [30], and The Netherlands [32]. Most studies were undertaken from the perspective of the healthcare system (seven studies [26–29, 32–34]). One study [31] adopted

a government perspective; however, the costs included were related to a societal perspective (direct costs, parent productivity loss, social or community living costs). Finally, the perspective of one study was described as “patient” but was limited to drug-related costs (drug-budget perspective) [30]. Five economic evaluations involved a Markov model [26–28, 32, 33], while the remainder involved a decision tree [29–31, 34]. Of the studies that involved a decision tree, two compared pharmacologic treatment to epilepsy surgery [31, 34], one compared pharmacologic treatment (carbamazepine) to KD, VNS, or epilepsy surgery [29], and one compared various pharmacologic treatments over a 3-month horizon [30]. Two studies assessed outcomes in terms of seizure reductions through the Engel criteria [29, 34], whilst another dichotomized the outcomes as seizure control or no control [30]. For the other study using a decision tree, it was not possible to determine the outcomes modeled [31]. The included economic evaluations were primarily funded by non-industry sources or had no funding (five studies [27–30, 32]; 56%), while two studies (22%) reported industry funding [26, 33] and two (22%) did not report the funding source [31, 34].

Table 1 Characteristics of the included studies

Study, year	Population	Study design	Perspective	Location	Funding	Modelling method	Analysis horizon	Intervention and comparators
Elliott et al. 2018 [28]	Dravet syndrome	CUA	Healthcare system	Canada	None	Markov model	10 years	1. Adjunctive stiripentol 2. Clobazam + valproate
Fallah et al. 2016 [29]	DRE secondary to TSC	CUA	Healthcare system	US	None	Decision tree	5 years	1. Carbamazepine 2. Ketogenic diet 3. Vagus nerve stimulation 4. Epilepsy surgery
de Kinderen et al. 2015 [32]	DRE	CUA	Healthcare system	The Netherlands	The Netherlands Organization for Health Research and Development	Markov model	12 months; 5 years	1. Ketogenic diet 2. Vagus nerve stimulation 3. Care as usual
Bowen et al. 2012 [27]	DRE	CUA	Healthcare system	Canada	Ontario Ministry of Health and Long-Term Care	Markov model	20 years	1. Surgery ^a 2. Medical management
Gharibnaseri et al. 2012 [30]	DRE	CEA	Drug budget	Iran	Tehran University of Medical Sciences	Decision tree	3 months	1. Conventional AEDs ^b 2. Newer AEDs ^b
Widjaja et al. 2011 [34]	DRE	CEA	Healthcare system	Canada	NR	Decision tree	1 year	1. Surgery 2. Medical management
Benedict et al. 2010 [26]	Lennox-Gastaut syndrome	CEA	Healthcare system	UK	Eisai Ltd.	Markov model	3 years	1. Rufinamide 2. Topiramate 3. Lamotrigine 4. Standard treatment
Verdian and Yi, 2010 [33]	Lennox-Gastaut syndrome	CUA	Healthcare system	UK	Eisai Ltd.	Markov model	3 years	1. Rufinamide 2. Topiramate 3. Lamotrigine 4. Standard treatment
Keene and Ventureyra, 1999 [31]	DRE	CEA	Societal	Canada	NR	Decision tree	25 years	1. Epilepsy surgery 2. Medical management

AEDs antiepileptic drugs, CEA cost-effectiveness analysis, CUA cost-utility analysis, DRE drug-resistant epilepsy, NR not reported, TSC tumor sclerosis complex

^aCost effectiveness of surgery vs. medical management among children considered eligible for surgery. Additional analyses addressed cost effectiveness of referral for epilepsy surgery, which was outside the scope of the current review

^bConventional AEDs: carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate; newer AEDs: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin, zonisamide

3.3 Critical Appraisal

There was a wide range in the methodologic and reporting quality of the included studies, ranging from 4 to 10 points on the Drummond checklist (of 10 points; Fig. 2) and 7 to 22

points on the CHEERS checklist (of 24 points; ESM Appendix 4). In general, most studies (> 75%) specified the decision problem, target population, and adopted perspective, and described the decision model and assumptions; however, few provided sufficient description of the competing

interventions (44%) or established the effectiveness of the interventions (33%). Overall, few studies (33%) fully reported model inputs, and only two studies (22%) reported efforts to validate model structure and/or inputs [28, 32]. Among the included cost-utility analyses, few studies (40%) described the population and methods used to elicit preferences for the health states. Although most authors addressed the limitations of their analyses, few addressed issues of concern such as generalizability of the findings to other jurisdictions or across epilepsy syndromes.

Most of the included studies performed sensitivity analyses; however, the type and parameters tested varied across studies (Table 2). All studies assessed the impact of at least one alternative model input, including costs, utilities, and/or effectiveness estimates, through deterministic or probabilistic sensitivity analyses or scenario analyses; fewer studies assessed the impact of alternative structural assumptions [26–28, 31, 33].

3.3.1 Context-Specific Issues

Weight Gain Of the included studies, only one considered the impact of increasing patient weight on the ICER. In sensitivity analyses, Elliott et al. [28] varied the starting age of the patient cohort, incorporating child weight by use of the World Health Organization's weight-for-age 50th percentile value [35]. The remaining studies assumed a fixed weight over the analysis horizon or did not report assumptions about patient weight. Although the dose of AEDs may not be adjusted at every clinical encounter, over time the weight-based dose would be expected to increase as a child ages and increases in weight. Among the decision models included in this review, the analysis horizon ranged from

3 to 20 years, and the failure to consider weight gain may underestimate total drug costs, especially for studies with a horizon longer than 10 years.

Treatment Discontinuation or Switching Four studies addressed switching treatments during the analysis horizon [26, 28, 32, 33], while the remaining studies assumed that no changes occurred [29, 30, 34] or did not report whether changes were permitted [27, 31]. Elliott et al. [28] assumed that patients with Dravet syndrome whose seizures did not respond to adjunctive stiripentol treatment within the first 6 months of treatment would discontinue stiripentol and continue on clobazam and valproate alone. Similarly, both Benedict et al. [26] and Verdian and Yi [33] assumed that patients with Lennox-Gastaut syndrome whose seizures were not adequately controlled by rufinamide, topiramate, or lamotrigine would switch to “standard treatment” (the patients' AEDs taken at baseline) [26] or to the mix of AEDs used in the placebo arm of a clinical trial [33]; in both cases, the specific AEDs that made up the standard treatment arm were not described. Finally, de Kinderen et al. [32] assumed that patients who withdrew from the KD would return to a normal diet, while patients with a VNS could have it switched off or removed; however, no changes were made to AED treatments in the “care as usual” group.

Among studies that did not permit switching between treatments, Gharibnaseri et al. [30] considered remaining on a treatment regimen for the 3 months' duration of the analysis as part of their effectiveness outcome, while Widjaja et al. [34] assumed that medication type and dose would remain constant for the first year following epilepsy surgery; whether patients in the medical management arm could switch AEDs was not reported. Finally, Fallah et al. [29] assumed that patients would stay on a chosen treatment for the 5-year study duration.

Effectiveness of Usual Care In six studies [26, 27, 31–34], pharmacologic treatments were included as “usual care”, “standard treatment”, or “medical management” without detailed description of the AEDs included in the treatment regimens, and one study [30] compared individual “newer” AEDs to older AEDs as a group (including carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, and valproate). Two studies [30, 34] derived effectiveness estimates from retrospective reviews of clinical data at single centers, while two studies [26, 32] derived estimates of the effectiveness of usual pharmacologic care from the control arms of RCTs. Other studies assumed that patients in the medical treatment arm would not improve (i.e., continue to have inadequately controlled seizures) [27], assumed a “spontaneous remission rate” of 10% [31], or did not describe assumptions related to the efficacy of standard medical care [33].

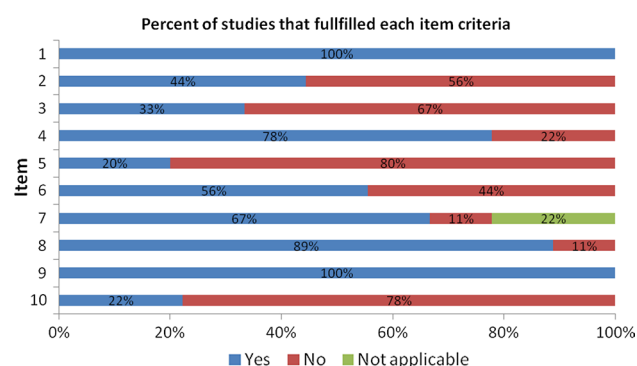


Fig. 2 Methodological quality of the included economic evaluations, evaluated by use of the Drummond checklist. Items: (1) well-defined question; (2) well-described competing alternatives; (3) established effectiveness; (4) important and relevant costs and consequences identified; (5) measurement accurately performed; (6) costs and consequences valued credibility; (7) discounting; (8) incremental analysis performed; (9) allowance made for uncertainty; and (10) all items of concern to users discussed

Table 2 Sensitivity analysis descriptions

Study, year	Reference case modelling method	Type of sensitivity analysis	Parameters for sensitivity analyses
Elliott et al. 2018 [28]	Markov model; probabilistic	Scenario analyses; probabilistic	Drug costs, dose Patient age Correlation between utility values Discount rate Analysis horizon
Fallah et al. 2016 [29]	Decision tree; deterministic	Probabilistic sensitivity analysis; one-way sensitivity analysis; two-way sensitivity analysis	Probabilistic sensitivity analysis Drug costs Effectiveness estimates Utilities One-way sensitivity analysis Costs Effectiveness outcomes Utilities Two-way sensitivity analysis Cost of VNS implantation and battery replacement
Benedict et al. 2010 [26]	Markov model; probabilistic	One-way sensitivity analysis	Analysis horizon Hospitalization rate for drop seizures Discount rate
Verdian and Yi, 2010 [33]	Markov model; deterministic	Probabilistic sensitivity analysis; one-way sensitivity analysis; scenario analysis	Probabilistic sensitivity analysis Model parameters One-way sensitivity analysis Uncertainty of model parameters Scenario analysis Drug unit costs Discount rates Analysis horizon
Gharibnaseri et al. 2012 [30]	Decision tree; deterministic	Scenario analysis	Drug costs Effectiveness endpoint
de Kinderen et al. 2015 [32]	Markov model; probabilistic	Probabilistic sensitivity analysis; deterministic sensitivity analysis	Probabilistic sensitivity analysis Costs Utilities Transition probabilities Deterministic sensitivity analysis KD costs
Widjaja et al. 2011 [34]	Decision tree; deterministic	One-way sensitivity analysis; probabilistic sensitivity analysis	One-way sensitivity analyses Effectiveness estimates Treatment costs AEs associated with surgical treatment Probabilistic sensitivity analysis Model parameters
Keene and Ventureyra, 1999 [31]	Decision tree; deterministic	Scenario analysis, one-way sensitivity analysis	Discount rates Effectiveness estimates Employment rates Surgical costs Post-surgery use of antiepileptic medications
Bowen et al. 2012 [27]	Markov model; deterministic	One-way sensitivity analysis	Analysis horizons Discount rate Utility values

AEs adverse events, *KD* ketogenic diet, *VNS* vagus nerve stimulation

The comparators in two studies were specific AED regimens [28, 29]. Elliott et al. [28] compared adjunctive stiripentol to a regimen of clobazam and valproate alone in children with Dravet syndrome, while Fallah et al. [29]

compared carbamazepine to KD, VNS, or epilepsy surgery in children with TSC. Elliott et al. [28] estimated the effectiveness of clobazam and valproate from a pooled analysis of the control arms of two RCTs [36, 37], while the

effectiveness estimate for carbamazepine used by Fallah et al. [29] was derived from a retrospective review of clinical data for children with TSC at a single center [38].

Clinical Effectiveness In general, meta-analyses of randomized controlled trials (RCTs) involving head-to-head comparisons of the competing interventions are considered to provide the highest level of evidence to inform decision models [39]. However, because of the rare nature of some drug-resistant epilepsy syndromes, and because few RCTs have been performed in some populations [40], we considered the source of data used to derive effectiveness estimates and how studies addressed a lack of RCTs, if applicable. Of the nine included studies, three used data derived from RCTs to inform their model [26, 32, 33], either by pairwise [32] or indirect treatment comparison pooling [26, 33]. One study [28] derived effectiveness estimates by use of individual patient data from a multicenter, prospective observational cohort [41], despite the availability of RCT data, due to a longer follow-up duration in the observational study than in the RCTs. Three studies [27, 30, 34] used data from retrospective observational studies, due to a lack of RCTs for the model comparators, while two studies [29, 31] did not provide sufficient information about the source of the effectiveness data.

Long-Term Clinical Effectiveness Among seven of the included decision models [26–29, 31–33], the analysis horizon was longer than the duration of the studies used to estimate effectiveness. As such, assumptions were required about the continuation of effect beyond the available data. Four studies [26, 28, 29, 33] assumed that the effectiveness (i.e., transition probabilities) would be consistent beyond the observed duration, assuming no waning of treatment effect. In contrast, one study [32] assumed that there would be no change to seizure status after the first 24 months of treatment, such that a patient in the seizure-free state would remain in that state for the remainder of the 5-year horizon. One study [27] assumed that all patients in the medical management arm would remain drug refractory (i.e., no improvement) over the entire 20-year horizon, while patients in the other comparator arms would continue to move through model states based on transition probabilities from the first year of treatment. One study [31] did not report assumptions about maintenance of effect beyond the available data, despite a 25-year horizon.

3.4 Decision Model Characteristics

Of the included studies, five involved use of a Markov model (Table 3) [26–28, 32, 33]. Each model involved three health states related to the frequency of seizures relative to a baseline period; death was the final absorbing state in each model. Each model included a state in which patients

experienced no improvement (one study [27]) or limited improvement (< 50% reduction in seizures; four studies [26, 28, 32, 33]). The models used in three studies [26, 27, 32] included a seizure-free state, while two studies [26, 33] used a > 75% seizure reduction as the state with greatest improvement. Most models involved a 3-month cycle (three studies [26, 32, 33]), while one study used a 1-month [28] and another a 1-year cycle [27]. No study justified the chosen cycle length. The analysis horizon ranged from 12 months to 20 years, and most studies provided justification for the chosen time horizon based on the availability of data (three studies [26, 32, 33]) or transition to adult care (one study [28]). Four studies [26–28, 33] tested the impact of alternative horizons in sensitivity analyses.

3.5 Decision Model Inputs

3.5.1 Costs

Each study included at least some costs directly related to the provision of healthcare (Table 4). One study included only drug costs in their evaluation [30], without consideration of other costs or resources that may differ between competing treatments, while one study [32] assumed that drug costs would be equivalent between competing treatments (pharmacologic treatment alone or in combination with KD or VNS), thus omitting drug costs from their analysis. Most studies included costs related to visits to a neurologist or epileptologist (78%), while fewer studies included visits to a primary care physician (33%) or emergency department (33%) (Table 4). Admission to hospital or an intensive care unit was included in 56% and 22% of analyses, respectively; one study [28] included costs related to ambulance transfer to hospital. Nursing-related costs were included in 44% of studies, although additional studies may have captured nursing costs as part of hospital-related costs. Diagnostic procedures were included in 22% of studies, and professional services (e.g., learning disability specialist, clinical psychologist) were included in 33% of studies.

One study [31] included indirect costs as part of their analysis, which was described as a governmental perspective but was more broad, including parental productivity losses as well as costs related to social or community living. No studies included costs related to patient productivity losses, either as losses during childhood or future losses during adulthood.

3.5.2 Utility Values

The cost-utility analyses included in this review [27–29, 32, 33] used health state utility values derived from three studies, reported in three conference abstracts [42–44] and one full publication [45]. Of these, two studies [42, 43,

Table 3 Structure of Markov models

Study, year	Time horizon	Cycle length	Discount rate	Health states
Elliott et al. 2018 [28]	10 years	1 month	Costs and benefits: 1.5%	0–49% reduction of seizures from baseline 50–99% reduction Seizure free Death
de Kinderen et al. 2015 [32]	12 months; 5 years	3 months	Costs: 4%; benefits: 1.5%	< 50% seizure reduction ≥ 50% seizure reduction Seizure free Death
Bowen et al. 2012 [27] ^a	20 years	1 year	Costs and benefits: 5%	No improvement Seizure reduction Seizure free Death
Benedict et al. 2010 [26]	3 years	3 months	Costs: 3.5%; benefits not discounted	< 50% seizure reduction from baseline 50–75% reduction > 75% reduction Death
Verdian and Yi, 2010 [33]	3 years	3 months	Costs and benefits: 3.5%	< 50% seizure reduction 50% to < 75% reduction 75% reduction from baseline Death

^aStarting at the point of epilepsy surgery**Table 4** Direct and indirect costs included in the economic evaluations

Cost category	Proportion of studies [% (no. of studies/total studies)]	References
<i>Direct costs</i>		
Drug costs	89 (8/9)	[26–31, 33, 34]
Non-pharmacologic intervention costs ^a	56 (5/9)	[27, 29, 31, 32, 34]
Hospitalization	56 (5/9)	[27, 28, 32–34]
Intensive care unit	22 (2/9)	[26, 33]
Emergency department visits	33 (3/9)	[28, 33, 34]
Ambulance transfer visits	11 (1/9)	[28]
General practitioner or pediatrician visits	33 (3/9)	[26, 28, 33]
Neurologist or pediatric epileptologist visits	78 (7/9)	[26–29, 32–34]
Nursing ^b	44 (4/9)	[26, 32–34]
Diagnostic procedures	22 (2/9)	[33, 34]
Professional services ^c	33 (3/9)	[26, 33, 34]
<i>Indirect costs</i>		
Productivity (parental)	11 (1/9)	[31]
Social or community living	11 (1/9)	[31]

^aIncluding costs of epilepsy surgery, vagus nerve stimulation (insertion and/or battery replacement, removal), ketogenic diet (may include vitamin supplements, keto sticks), follow-up after surgery^bEpilepsy nurse or not specified^cIncluding occupational therapy, psychotherapy, respite care, home care, learning disability specialist, psychiatry clinics, clinical psychologist, professional services type not specified

[45] assessed utilities among adults with epilepsy: in one study [45], patients in each health state (ranging from “sub-optimal” seizure control to seizure free) were asked how much time they would be willing to give up to live their remaining years in “excellent health,” while one study [42,

43] assessed EQ-5D scores among adults with recurrent seizures after 6 months of adjunctive AED treatment. One study [44] assessed preferences for states related to Lennox-Gastaut syndrome, elicited by time trade-off from members of the general population. None of the included cost-utility

analyses considered health effects on caregivers or other family members.

3.6 Study Findings

3.6.1 Cannabis-Based Treatments

No completed economic evaluations of cannabis-based treatments for pediatric drug-resistant epilepsy were located. We identified one in-progress cost-effectiveness analysis of cannabidiol for seizures associated with Dravet and Lennox Gastaut syndromes; no results are available at this time [46].

3.6.2 Pharmacologic Treatments

Nine studies of pharmacologic treatments for pediatric drug-resistant epilepsy were included in this review. The main outcomes, costs, and ICERs are summarized in Table 5. We summarize the findings separately by epilepsy syndrome, where possible.

Dravet Syndrome One study [28] assessed the cost effectiveness of adjunctive stiripentol compared with clobazam and valproate in children with Dravet syndrome whose seizures had not previously responded to clobazam and valproate. From the perspective of the Canadian public healthcare system, adjunctive use of stiripentol was both more effective and more costly than use of clobazam and valproate alone, resulting in an incremental cost of \$Can154,336 per QALY gained with stiripentol treatment.

Lennox-Gastaut Syndrome Two studies [26, 33] assessed the cost effectiveness of adjunctive rufinamide, topiramate, or lamotrigine compared with standard treatment with older AEDs among children with Lennox-Gastaut syndrome from the perspective of the UK healthcare system. For treatment of drop seizures, Benedict et al. [26] estimated that rufinamide, topiramate, and lamotrigine were each less costly and more effective than standard therapy with older AEDs. Compared with topiramate, rufinamide was associated with an ICER of \$Can132 for each 1% increase in successfully treated patients (drop seizures reduced by at least 50%), while lamotrigine and standard treatment were dominated. For total seizures, standard treatment and topiramate were dominated by lamotrigine, and rufinamide was associated with an ICER of \$Can5526 for each 1% increase in successfully treated patients. Similarly, Verdian and Yi [33] estimated that the addition of rufinamide to a background of standard AEDs would be more costly than the addition of either topiramate or lamotrigine, with an estimated ICER of \$Can52,955 compared with topiramate and \$Can399,214 compared with lamotrigine per QALY gained.

Tuberous Sclerosis Complex One study [29] assessed the cost effectiveness of adjunctive carbamazepine, KD, VNS implantation, and resective surgery for the treatment of drug-resistant epilepsy in children with TSC whose seizures had not responded to two previous AEDs. Compared to adding carbamazepine, KD and VNS implantation were both more costly and less effective (dominated), while resective surgery was associated with an incremental cost of \$Can369,712 per QALY gained.

Unspecified Types of Drug-Resistant Epilepsy Five studies assessed the cost effectiveness of treatments for drug-resistant epilepsy in children without specifying a specific syndrome [27, 30–32, 34]. One study [30] compared the addition of newer AEDs (gabapentin, levetiracetam, lamotrigine, oxcarbazepine, topiramate, vigabatrin, zonisamide) to a regimen including older AEDs (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate), considering only costs related to AEDs: lamotrigine, oxcarbazepine, topiramate, and vigabatrin were associated with ICERs of \$Can744, \$Can898, \$Can2458, and \$Can5123 per patient with controlled seizures, respectively; while gabapentin, levetiracetam and zonisamide were dominated by conventional AEDs.

The remaining four studies [27, 31, 32, 34] included pharmacologic treatments as comparators to KD, VNS implantation, or surgery (Table 1); each of these studies grouped pharmacologic treatments as “medical management” or “care as usual” without fully describing the AED regimens used. Among these studies, pharmacologic treatment was less effective and less costly than surgery [27, 34], KD [32], and VNS [32]. Compared with medical management, surgery was associated with an ICER of \$Can432 per 1% reduction in seizures [34], and KD and VNS were associated with an ICER of \$Can517,306 and \$Can955,979, respectively, per QALY gained [32] (Table 6). One study, undertaken from a government perspective, reported that surgery was less costly and more “cost-efficient” than pharmacologic treatment; however, effectiveness data and the ICER were not reported [31].

4 Discussion

The first objective of this review was to identify economic evaluations of cannabis-based treatments for drug-resistant epilepsy in children; however, no such completed studies were located. One ongoing health technology assessment of cannabidiol for the treatment of Lennox-Gastaut and Dravet syndromes was located, with results expected in late 2019 [46]. A 2018 systematic review of cannabis-based treatments for chronic illnesses in adults similarly found no economic evaluations of such treatments for epilepsy [47].

Table 5 Results of included cost-effectiveness and cost-utility analyses (costs in 2018 Canadian dollars^a)

Study, year	Total (incremental) benefits	Total (incremental) costs (\$Can)	Total (incremental) drug-related costs (\$Can)	Incremental cost-effectiveness results (\$Can)
<i>Dravet syndrome</i>				
Elliott et al. 2018 [28]	<i>QALYs</i> Clobazam + valproate: 3.77 (REF) Stiripentol: 4.37 (0.60)	Clobazam + valproate: 56,504 (REF) Stiripentol: 149,406 (92,902)	Clobazam + valproate: \$Can6356 (REF) Stiripentol: 107,399 (101,043)	<i>Incremental cost per QALY gained with stiripentol</i> 154,336
<i>Tuberous sclerosis complex</i>				
Fallah et al. 2016 [29]	<i>QALYs</i> Carbamazepine: 4.14 (REF) KD: 3.60 (−0.54) VNS: 3.89 (−0.25) Surgery: 4.38 (0.25)	Carbamazepine: 9050 (REF) KD: 18,544 (9494) VNS: 69,914 (60,864) Surgery: 101,108 (92,058)	NR	<i>Incremental cost per QALY gained</i> KD: dominated VNS: dominated Surgery: 369,712
<i>Lennox-Gastaut syndrome</i>				
Benedict et al. 2010 [26]	<i>% of patients successfully treated (at least 50% reduction)</i> Drop seizures: Topiramate: 7.2% (NR) Lamotrigine: 5.2% (NR) Rufinamide: 11.3% (NR) Standard therapy: 3.3% (NR) Total seizures Lamotrigine: 6.9% (NR) Standard therapy: 2.3% (NR) Topiramate: 5.6% (NR) Rufinamide: 7.7% (NR)	Drop seizures: Topiramate: 130,318 (NR) Lamotrigine: 130,953 (NR) Rufinamide: 130,978 (NR) Standard therapy: 132,140 (NR) Total seizures: Lamotrigine: 95,216 (NR) Standard therapy: 98,561 (NR) Topiramate: 99,052 (NR) Rufinamide: 99,748 (NR)	NR	<i>Incremental cost per 1% increase in successfully treated patients</i> Drop seizures: Topiramate: REF Lamotrigine: dominated Rufinamide: 132 Standard therapy: dominated Total seizures: Lamotrigine: REF Standard therapy: dominated Topiramate: dominated Rufinamide: 5526
Verdian and Yi 2010 [33]	<i>QALYs</i> Rufinamide: 1.44 Topiramate: 1.36 Lamotrigine: 1.42 <i>Incremental QALYs for rufinamide</i> Vs. topiramate: 0.079 Vs. lamotrigine: 0.021	Rufinamide: 64,439 Topiramate: 60,231 Lamotrigine: 56,165 <i>Incremental costs for rufinamide</i> Vs. topiramate: 1632 Vs. lamotrigine: 3209	Rufinamide: 16,579 (NR) Topiramate: 10,290 (NR) Lamotrigine: 7018 (NR)	<i>Incremental cost per QALY gained for rufinamide</i> Vs. topiramate: 52,955 Vs. lamotrigine: 399,214
<i>Drug-resistant epilepsy; type not specified</i>				
de Kinderen et al. 2015 [32]	<i>QALYs</i> 12 months: KD: 0.693 (NR) VNS: 0.688 (NR) CAU: 0.662 (NR) 5 years: KD: 3.338 (NR) VNS: 3.395 (NR) CAU: 3.153 (NR)	12 months: KD: 20,931 (NR) VNS: 29,708 (NR) CAU: 4930 (NR) 5 years: KD: 46,131 (NR) VNS: 47,095 (NR) CAU: 22,412 (NR)	NA ^b	12 months: KD: dominant over VNS KD vs. CAU: 517,306 VNS vs. CAU: 955,979 5 years: KD vs. VNS: 16,967 KD vs. CAU: 128,283 VNS vs. CAU: 102,133
Gharibnaseri et al. 2012 [30]	<i>Proportion of patients with seizures controlled</i> Conventional AEDs: NR (REF) Gabapentin: NR (−0.52) Lamotrigine: NR (0.13) Levetiracetam: NR (−0.52) Oxcarbazepine: NR (0.15) Topiramate: NR (0.36) Vigabatrin: NR (0.15) Zonisamide: NR (−0.52)	Conventional AEDs: NR (REF) Gabapentin: NR (179) Lamotrigine: NR (97) Levetiracetam: NR (203) Oxcarbazepine: NR (135) Topiramate: NR (885) Vigabatrin: NR (768) Zonisamide: NR (169)	NR	<i>Incremental cost per patient with seizures controlled, vs. conventional AEDs</i> Gabapentin: dominated Lamotrigine: 744 Levetiracetam: dominated Oxcarbazepine: 898 Topiramate: 2458 Vigabatrin: 5123 Zonisamide: dominated

Table 5 (continued)

Study, year	Total (incremental) benefits	Total (incremental) costs (\$Can)	Total (incremental) drug-related costs (\$Can)	Incremental cost-effectiveness results (\$Can)
Bowen et al. 2012 [27]	<i>QALYs</i> Medical management: NR (REF) Surgery: NR (0.892)	Medical management: NR (REF) Surgery: NR (−1967)	NR	Surgery was dominant over medical management
Widjaja et al. 2011 [34]	% seizure reduction Surgery: 76.53% (NR) Medical treatment: 34.33% (NR)	Surgery: 35,877 (NR) Medical treatment: 17,649 (NR)	Surgery: 2162 (NR) Medical treatment: 2007 (NR)	Incremental cost per 1% seizure reduction gained with surgery 432
Keene and Ventureyra, 1999 [31]	NR	Surgery: 14,235,807 Medical: 18,568,446	NR	NR

\$Can Canadian dollars, AEDs antiepileptic drugs, CAU care as usual, KD ketogenic diet, NR not reported, QALY quality-adjusted life-year, REF reference group, VNS vagus nerve stimulation

^a\$Can1 = \$US0.7721, €0.6538

^bCost of AEDs was assumed to be equal for all three comparators

Our second objective was to identify and appraise decision models that had been used in full economic evaluations of pharmacologic treatments for children with drug-resistant epilepsy in order to inform a subsequent de novo cost-utility analysis. Our findings highlight a lack of studies in this population, with a total of nine eligible studies, including two in Lennox-Gastaut syndrome [26, 33] and one each in Dravet syndrome [28] and TSC [29]. Because of important differences in patient populations, modelling approaches and assumptions, and study comparators, it is difficult to compare cost effectiveness across studies and interventions. Furthermore, we observed wide variation in the quality of published economic evaluations in this clinical area; decision makers should consider the study quality and its relevance to clinical practice in their jurisdiction when evaluating whether an intervention is cost effective.

There were important differences in methodologies among the included studies, including the modeling approach used (i.e., decision tree, Markov model), model assumptions, and included costs. However, among studies that involved use of a Markov model, the health states were relatively consistent, despite differences in cycle length and analysis horizons. Few studies considered issues specific to pediatric epilepsy, including weight gain and changing treatments during the analysis horizon. As well, although most studies were undertaken from a healthcare perspective, the resources included varied widely between studies. Most included visits to a neurologist or epileptologist (78%); however, few studies included visits to a general practitioner, emergency department, or admission to hospital (33–56%). This is an important consideration because costs related to hospitalization account for a large portion of direct costs in some drug-resistant epilepsy syndromes and may vary

depending on intervention [48]; as such, a failure to include such costs may introduce bias into the economic evaluation. Recent studies have reported costs associated with some drug-resistant epilepsy syndromes, including Dravet syndrome [49, 50], which may help to inform future economic evaluations in this population.

Healthcare decision makers will soon be faced with the decision of whether to reimburse cannabis-based products through public formularies. The first pharmaceutical-grade cannabidiol product, Epidiolex® (GW Pharmaceuticals, Cambridge, UK), recently received approval from the US Food and Drug Administration (FDA) [51], and cannabis producers in other jurisdictions have developed high-concentration cannabidiol products that have shown promise in clinical studies [52]. In order to evaluate whether such interventions represent good value for money compared to currently available treatments, it is imperative that both the costs and benefits of both the new interventions as well as the currently existing treatments are considered. In our review, we found that cost effectiveness has been evaluated for few of the currently available pharmacologic treatments for drug-resistant epilepsy in children, despite being listed on public formularies. This finding is consistent with a 2017 systematic review [53], which identified few economic evaluations of treatments drug-resistant epilepsy in children.

Drug-resistant epilepsy affects an estimated 16 million people worldwide. Despite this, some drug-resistant epilepsy syndromes are individually rare (e.g., Dravet syndrome, Lennox-Gastaut syndrome), and there are limited clinical trials to support the efficacy of most treatments, especially among children [54, 55]. Some authors have argued that treatments for rare diseases should not be held to the same standards as drugs to treat common diseases, instead following the

Table 6 Recommendations for model-based economic evaluations of treatments for pediatric drug-resistant epilepsy

Element	Issue	Recommendation
<i>General</i>		
Population	Drug-resistant epilepsy comprises multiple individual epilepsy syndromes, and there may be heterogeneity across syndromes (e.g., natural history, response to interventions)	The target population should be specified. Studies that target a broad population of ‘drug-resistant epilepsy’ should explore heterogeneity through stratified analyses. Generalizability of findings across epilepsy syndromes should be addressed as a study limitation, if appropriate
Comparators	The choice of comparator may vary by drug-resistant epilepsy syndrome and may depend on jurisdiction	Study comparators should be described in sufficient detail (e.g., specific AEDs and doses) such that decision makers can evaluate the relevance of comparators to clinical care in their jurisdiction
Modelling	Assumptions made during model development may impact the cost-effectiveness ratio	The model should be consistent with the current clinical understanding of the target condition, and model assumptions should be clearly stated and justified. During the model design phase, analysts should consult with a clinical expert with experience caring for children with drug-resistant epilepsy
Measurement and valuation of health	Health state utility values should reflect the model health states for the target population. Sources of utilities may include affected children, adult caregivers, clinical experts, or the general public	The source of preferences should be clearly stated and justified for the chosen utility values. Alternate sources of utilities should be tested in scenario analyses, if available
Resource use and costs	All relevant resources and associated costs should be considered; choice of resources and costs may depend on perspective and jurisdiction	Analysts should consult with a clinical expert in their jurisdiction to ensure that all relevant resources have been considered. If appropriate given the choice of perspective, analysts should consider both the impacts on the productivity of adult caregivers and affected children
<i>Context-specific issues</i>		
Weight gain	Drug dosages are frequently based on patient weight; failure to consider weight gain may underestimate drug costs	For studies with an analysis horizon longer than 1 year, patient weight gain should be considered. This may be most relevant for studies involving young children and those with uncontrolled seizures
Treatment discontinuation/switching	Patients with drug-resistant epilepsy whose seizures do not respond to treatment may discontinue the intervention or switch to an alternative treatment	Medication switches should be considered, including any costs associated with switching. The duration of treatment before discontinuation or switching should be specified and justified
Effectiveness of usual care	‘Usual care’ may vary by jurisdiction and epilepsy syndrome, and insufficient description of usual care as a comparator does not allow decision makers to assess relevance to their jurisdiction	The interventions that comprise ‘usual care’ should be explicitly described. Any assumptions about the effectiveness of usual care should be justified
Clinical effectiveness	There may be limited information about the clinical effectiveness of interventions for drug-resistant epilepsy, owing to the rarity of some individual syndromes	Choice of data should be based on fitness for purpose, credibility, and consistency; use of a hierarchy [39] may be useful in selecting data
Long-term effectiveness	Decision analyses with a long-term horizon may require assumptions about the maintenance of effect beyond the duration of treatment reported in available clinical studies	Assumptions about the effectiveness of interventions beyond the duration of clinical observation should be explicitly reported
<i>AEDs antiepileptic drugs</i>		

rule of rescue without consideration of the cost per benefit gained [56]. However, a recent survey found that Canadians place more value on drug effectiveness and safety, as well as the ability to improve quality and quantity of life, than rarity of the target condition [57]. Because of this, as well as high opportunity costs, drugs to treat rare diseases, including drug-resistant epilepsy syndromes, should be rigorously evaluated and must show good value for money through cost-effectiveness evaluations. In Table 6, we provide recommendations for future economic evaluations in this area.

4.1 Strengths and Limitations

We undertook a systematic review of the published and grey literature to identify relevant economic evaluations, and the protocol was registered a priori. However, several limitations should be considered. First, the review was limited to studies reported in English, which may have excluded relevant studies. Second, because we sought to identify and appraise decision models that had been used to evaluate the cost effectiveness of pharmacologic treatments for drug-resistant epilepsy, we excluded trial-based economic evaluations. Although RCTs provide important information that can be used in the context of a decision model, trial-based economic evaluations are unlikely to include all relevant comparators, have a short analysis horizon, and include costs not relevant to clinical practice [58]. Third, the included studies were of variable quality, and few adequately considered context-specific issues, which may bias their findings. Finally, the generalizability of the findings from most of the included studies is limited, because most did not specify a specific epilepsy syndrome. Drug-resistant epilepsy is a heterogeneous population, defined based on response to AEDs [4], not on clinical characteristics or seizure profile. Similarly, about half of the reviewed studies included pharmacologic treatments as ‘care as usual’ or ‘medical treatment’ without adequately describing the treatment regimen. However, the decision models used in such studies are likely to be generalizable across epilepsy syndromes, with inputs tailored to the specific populations and interventions of interest.

5 Conclusion

Although cannabis-based treatments may be effective in reducing seizures associated with drug-resistant epilepsy, the cost effectiveness of such treatments relative to other currently available treatments has yet to be investigated. Few economic evaluations of treatments for drug-resistant epilepsy have been conducted, and this review highlights areas where additional research is needed. Future studies will be improved by addressing issues of particular importance in economic evaluations of pediatric epilepsy.

Compliance with Ethical Standards

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Conflict of interest Bláthnaid McCoy is principal investigator in a study of cannabinoids for Dravet syndrome. Jesse Elliott, Sasha van Katwyk, Tammy Clifford, Beth Potter, Becky Skidmore, George Wells, and Doug Coyle have no conflicts of interest to declare.

Author contributions JE, TC, DC, BP, BM, GW, and DC designed the study. BS developed and executed the search strategy. JE, SVK, and DC selected studies for inclusion and extracted data. JE analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All of the authors contributed to the conception and planning of the study, the analysis and/or interpretation of the data, drafting and critical revision of the manuscript, and approved the final version submitted for publication.

Data Availability Statement All data generated or analyzed during this study are included in this published article (and its supplementary information files [Electronic Supplementary Material]).

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