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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

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, ≥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

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1 | INTRODUCTION

Epilepsy affects an estimated 50 million people worldwide[1]; of those, about one-third have a drug-resistant form[2] (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 review[10] 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, clinicians, and policy makers with up-to-date evidence to inform their decision making.

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

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, ≥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 tool[22]; 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 ClinicalTrial.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 series[33] (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).

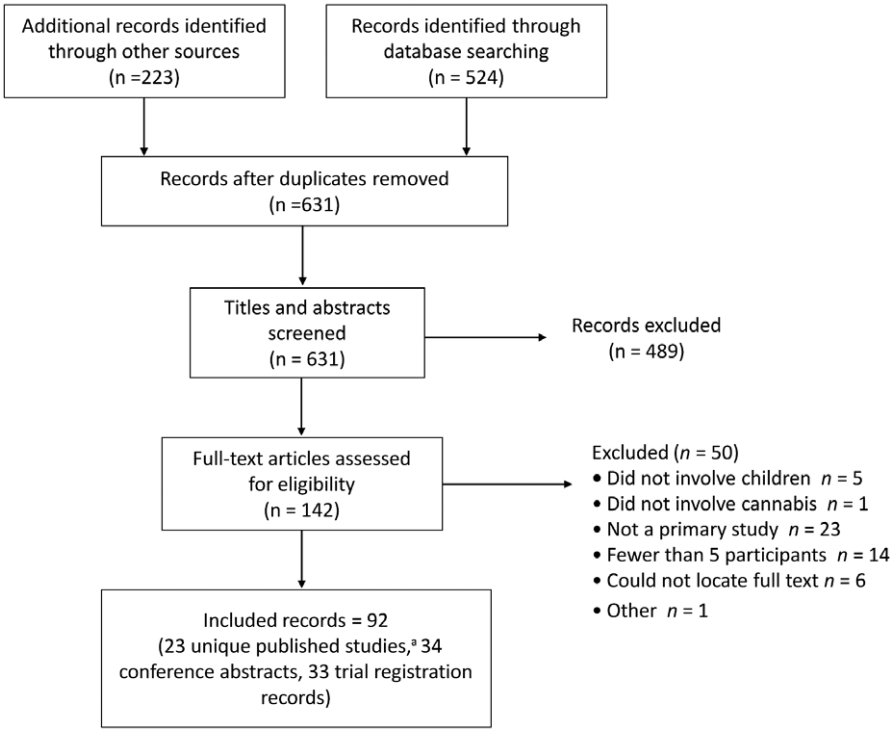


FIGURE 1 PRISMA flow diagram showing selection of studies. [a]There were 2 companion publications

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 study[14] 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 RCT[12] 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 e1204 (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), 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.

[a]Low risk of bias for each of allocation concealment, blinding, and outcome data reporting.

[b]Epidiolex (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) • 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)

AED, antiepileptic drug; BMI, body mass index; CBD, cannabidiol; IQR, interquartile range; NR, not reported; SD, standard deviation; VNS, vagus nerve stimulation.

[a]Unless otherwise stated.

TABLE 3 Evidence summary

	Randomized controlled trials					Nonrandomized studies				
Outcome	**Studies, k**	**Participants, n**	**Effect estimate (95% CI), cannabidiol vs placebo**	I^2	**GRADE assessment**	**Studies, n**	**Participants, n**	**Proportion exposed to a cannabis-based product (95% CI)[a]**	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%-11%)	72%	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%	Moderate	6	316	NA[c]	NA	Very low
Tonic–clonic seizure frequency	3	321	Median reduction in monthly seizures vs placebo: −27.5% (−38.7% to −16.3%)	0%	Moderate	2	95	NA[c]	NA	Very low
Treatment response[d]	1	171	RR = 1.76 (1.07-2.88), RD = 0.16 (0.03-0.29)	NA	Moderate	12	641	48% (39%-57%)	79%	Very low
Quality of life: child	3	516	Pooled mean difference: 0.6 (−2.6 to 3.9)[e]	0%	Moderate	1	48	Mean difference before–after: 8.12 (SD = 9.85)[e]	NA	Very low
Sleep disruption	3	516	Pooled mean difference: −0.3 (−0.8 to 0.2)[f]	0%	Moderate	0	NA	NA	NA	NA
Improved sleep	0	NA	NA	NA	NA	5	368	44% (15%-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%-7%)	6%	Very low
Status epilepticus	3	516	RR = 1.39 (0.55-3.47), RD = 0.01 (−0.02 to 0.03)	0%	Low	3	283	4% (0%-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%-2%)	0%	Very low

(Continues)

TABLE 3 (Continued)

Outcome	Randomized controlled trials					Nonrandomized studies				
	Studies, k	Participants, n	Effect estimate (95% CI), cannabidiol vs placebo	I^2	GRADE assessment	Studies, n	Participants, n	Proportion exposed to a cannabis-based product (95% CI)[a]	I^2	GRADE assessment
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%)	69%	Very low

AE, adverse event; CBD, cannabidiol; CI, confidence interval; NA, not applicable; RD, risk difference; RR, relative risk; SD, standard deviation.

[a]Unless otherwise stated.

[b]None of the included studies assessed caregiver quality of life or visits to the emergency department.

[c]Data reported in a variety of ways precluded pooling; see Appendices S9 and S10.

[d]≥50% reduction in seizure frequency relative to baseline period.

[e]Quality of Life in Childhood Epilepsy scale.

[f]Assessed by use of the Sleep Disruption Rating Scale (negative value favors CBD).

one cross-sectional study[39]; 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 al[13] 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 colleagues[44] 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 RCT[30] 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.

TABLE 4 GRADE evidence profile for critical outcomes

Certainty Assessment							No. of events/No. of patients		Effect		
Studies, k	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	Standard care	Relative (95% CI)	Absolute (95% CI)	Certainty
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

The full GRADE assessment of all outcomes is reported in Appendix S8.

CBD, cannabidiol; CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

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

[b]95% CI includes important benefits and harms.

[c]Rare event; CIs may be misleading because of fragility.

[d]Risk difference: 5% (95% −1% to 11%).

[e]Heterogeneity (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 survey[11]), 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 study[46]; 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 colleagues[30] 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-desmethylclobazam 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 CYP34A and CYP2C19, which are involved in the clearance of N-desmethylclobazam, 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-desmethylclobazam 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 review[49] 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 colleagues[49] 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 colleagues[49] 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 Stockings[49] review and our analysis. Stockings and colleagues[49] 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 review[49] 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 studies[52] 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 NRS 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 epilepsy[43]; 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 ≥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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REFERENCES

1. World Health Organization. Epilepsy. 2018. Available at: http://www.who.int/mediacentre/factsheets/fs999/en/. Accessed February 18, 2018.
2. Téllez-Zenteno JF, Hernández-Ronquillo L, Buckley S, Zahagun R, Rizvi S. A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy. Epilepsia. 2014;55 :829–34.
3. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE commission on therapeutic strategies. Epilepsia. 2010;51:1069–77.
4. Howard MA, Baraban SC. Catastrophic epilepsies of childhood. Annu Rev Neurosci. 2017;40:149–66.
5. Begley CE, Durgin TL. The direct cost of epilepsy in the United States: a systematic review of estimates. Epilepsia. 2015;56:1376–87.
6. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav. 2013;29:574–7.
7. Perucca E. Cannabinoids in the treatment of epilepsy: hard evidence at last? J Epilepsy Res. 2017;7:61–76.
8. O'Connell BK, Gloss D, Devinsk O. Cannabinoids in treatment-resistant epilepsy: a review. Epilepsy Behav. 2016;70:341–8.
9. Mathern GW, Beninsig L, Nehlig A. Fewer specialists support using medical marijuana and CBD in treating epilepsy patients compared with other medical professionals and patients: result of Epilepsia's survey. Epilepsia. 2015;56:1–6.
10. Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev. 2014;3:CD009270.
11. 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;2017:1–5.
12. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med. 2017;376:2011.
13. 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.
14. 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.
15. 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.
16. US Food and Drug Administration. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm611046.htm. Accessed June 27, 2018.
17. Murad M, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evid Based Med. 2016;21:125–6.
18. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
19. Elliott J, DeJean D, Clifford T, et al. Cannabis for pediatric epilepsy: protocol for a living systematic review. Syst Rev. 2018;7:95.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62:1006–12.
21. CADTH. Grey matters light. Available at: https://www.cadth.ca/resources/finding-evidence/grey-matters. Accessed January 16, 2018.
22. Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JP, Green S, eds. *Cochrane handbook for systematic reviews of interventions*. Chichester, UK: Wiley-Blackwell; 2008:187–242.

23. Scottish Intercollegiate Guidelines Network. Critical appraisal notes and checklists—methodology checklist 3: cohort studies. 2012. Available at: http://www.sign.ac.uk/checklists-and-notes.html. Accessed June 5, 2018.
24. National Heart Lung and Blood Institute. Quality assessment tool for before-after (pre-post) studies with no control group. Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed May 10, 2018.
25. Moola S, Munn Z, Aromataris E, et al. Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, eds. *Joanna Briggs Institute reviewer's manual*, Chapter 7. Adelaide, Australia: Joanna Briggs Institute; 2017. Available at: https://reviewersmanual.joannabriggs.org/.
26. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64:383–94.
27. Nyaga VN, Arbyn M, Aerts M. Metaprop: a STATA command to perform meta-analysis of binomial data. Arch Public Heal. 2014;72:1–10.
28. Devinsky O, Patel AD, Thiele EA, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology. 2018;90:e1204.
29. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med. 2018;378:1888–97.
30. 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. Lancet. 2018;391:1085.
31. INSYS Therapeutics. Cannabidiol oral solution in pediatric participants with treatment-resistant seizure disorders. ClinicalTrials.gov. 2017. Available at: https://clinicaltrials.gov/show/NCT02324673. Accessed April 28, 2018.
32. Kaplan EH, Offermann EA, Sievers JW, Comi AM. Cannabidiol treatment for refractory seizures in Sturge-Weber syndrome. Pediatr Neurol. 2017;71:18.
33. Lorenz R. On the application of cannabis in paediatrics and epileptology. Neuroendocr Lett. 2004;25:40.
34. Neubauer D, Perković Benedik M, Osredkar D. Cannabidiol for treatment of refractory childhood epilepsies: experience from a single tertiary epilepsy center in Slovenia. Epilepsy Behav. 2018;81:79–85.
35. 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;80:240–6.
36. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav. 2013;29:574.
37. Rosenberg EC, Louik J, Conway E, Devinsky O, Friedman D. Quality of life in childhood epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. Epilepsia. 2017;58:e96.
38. Sulak D, Saneto R, Goldstein B. The current status of artisanal cannabis for the treatment of epilepsy in the United States. Epilepsy Behav. 2017;70:328–33.
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;58:123.
41. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP, Program UABCBD. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia. 2017;58:1586.
42. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015;56:1246–51.
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;32:35.
44. Hess EJ, Moody KA, Geffrey AL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia. 2016;57:1617.
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;47:138–41.
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;45:1323–31.
49. Stockings E, Zagic 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;89:741–53.
50. Sabaz M, Cairns DR, Lawson JA, Nheu N, Bleasel AF, Bye AM. Validation of a new quality of life measure for children with epilepsy. Epilepsia. 2000;41:765–74.
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;20:1245–51.
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;108:1685–93.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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