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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 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.

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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

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 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.

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.

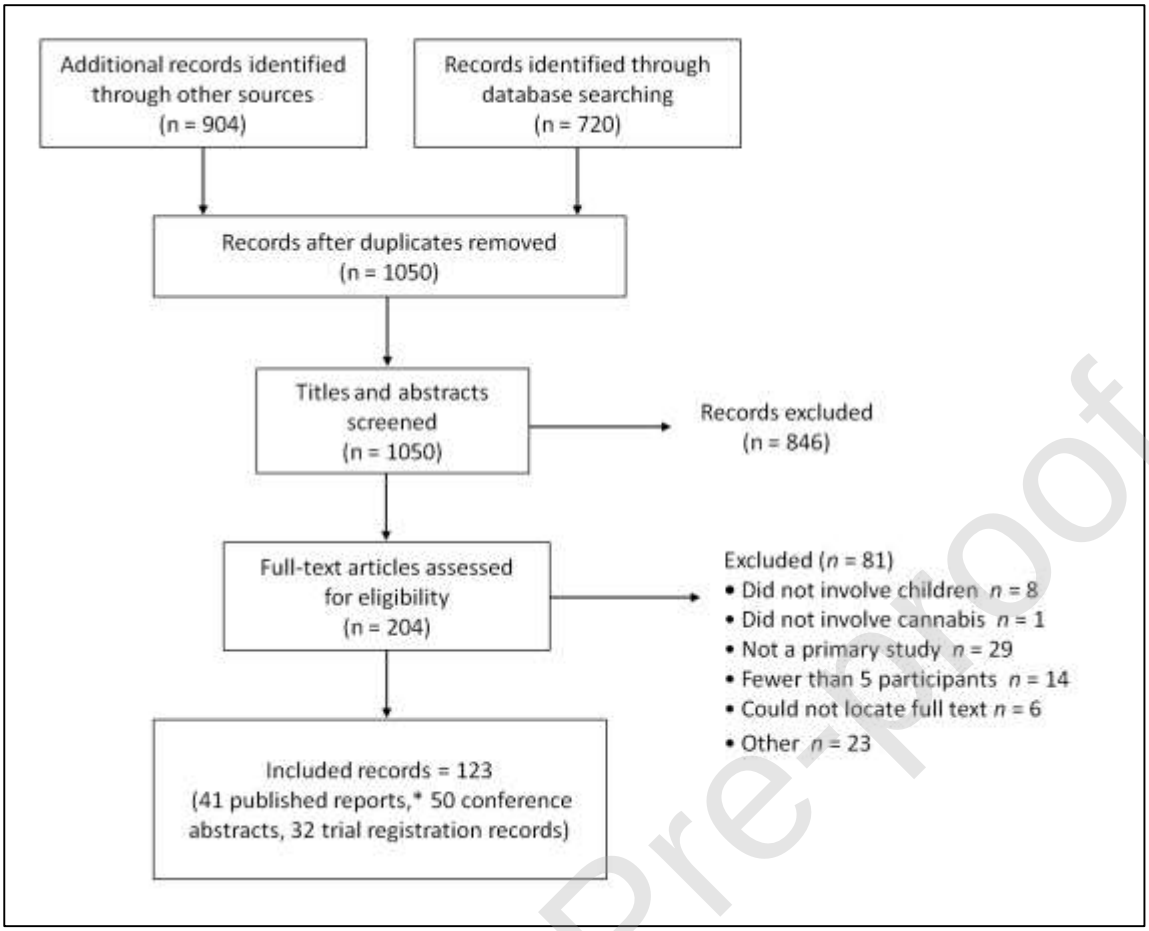

Figure 1: PRISMA flow diagram showing selection of studies. *Includes 35 unique studies (4 randomized controlled trials, 31 non-randomized studies) available as published studies or as clinical trial records with available data.

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 (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% 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 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).

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 (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 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 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).

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.

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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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.

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