REVIEW

Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence

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ABSTRACT
Review evidence for cannabinoids as adjunctive treatments for treatment-resistant epilepsy. Systematic search of Medline, Embase and PsycINFO was conducted in October 2017. Outcomes were: 50%+ seizure reduction, complete seizure freedom; improved quality of life (QoL). Tolerability/safety were assessed by study withdrawals, adverse events (AEs) and serious adverse events (SAEs). Analyses were conducted in Stata V.15.0. 36 studies were identified: 6 randomised controlled trials (RCTs), 30 observational studies. Mean age of participants was 16.1 years (range 0.5–55 years). Cannabidiol (CBD) 20 mg/kg/day was more effective than placebo at reducing seizure frequency by 50%+(relative risk (RR) 1.74, 95% CI 1.24 to 2.43, 2 RCTs, 291 patients, low Grades of Recommendation, Assessment, Development and Evaluation (GRADE) rating). The number needed to treat for one person using CBD to experience 50%+ seizure reduction was 8 (95% CI 6 to 17). CBD was more effective than placebo at achieving complete seizure freedom (RR 6.17, 95% CI 1.50 to 25.32, 3 RCTs, 306 patients, low GRADE rating), and improving QoL (RR 1.73, 95% CI 1.33 to 2.26), however increased risk of AEs (RR 1.24, 95% CI 1.13 to 1.36) and SAEs (RR 2.55, 95% CI 1.48 to 4.38). Pooled across 17 observational studies, 48.5% (95% CI 39.0% to 58.1%) of patients reported 50%+ reductions in seizures; in 14 observational studies 8.5% (95% CI 3.8% to 14.5%) were seizure-free. Twelve observational studies reported improved QoL (55.8%, 95% CI 40.5 to 70.6); 50.6% (95% CI 31.7 to 69.4) AEs and 2.2% (95% CI 0 to 7.9) SAEs. Pharmaceutical-grade CBD as adjuvant treatment in paediatric-onset drug-resistant epilepsy may reduce seizure frequency. Existing RCT evidence is mostly in paediatric samples with rare and severe epilepsy syndromes; RCTs examining other syndromes and cannabinoids are needed.

PROSPERO registration number CRD42017055412.

BACKGROUND
The International League Against Epilepsy (ILAE) defines epilepsy as a disease of the brain, diagnosis of which requires: (a) at least two unprovoked seizures occurring >24 hours apart; (b) one unprovoked seizure and a probability for further seizures of at least 60%, occurring over the next 10 years or (c) the diagnosis of an epilepsy syndrome.[1] Between 70% and 80% of patients with new-onset epilepsy achieve complete seizure control using antiepileptic drugs such as valproate or carbamazepine.[2] In 20%–30% who are drug-resistant,[3 4] there is great interest in investigating novel agents to reduce seizure frequency and severity. For the purposes of this review, the ILAE's definition of drug-resistant epilepsy—the failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs (AEDs) schedules (as either monotherapies or in combination) to achieve seizure freedom[5]—is used. For the 30% of patients who experience drug-resistant epilepsy, the efficacy of alternative and adjunctive therapies is likely to be of great interest.

Preclinical studies suggest that naturally occurring cannabinoids (phytocannabinoids) have anticonvulsant effects which are mediated by the endocannabinoid system.[6] Cannabidiol (CBD) and cannabidivarin have shown antiseizure effects in both in vivo and in vitro models. In contrast to tetrahydrocannabinol (THC), CBD does not produce euphoric or intrusive psychoactive side effects when used to treat seizures.[7] Cannabinoids have been proposed as an adjunctive treatment for epilepsy[7] and parents of children with epilepsy report using CBD products.[8–10] There are a number of phase III human trials underway of CBD as an adjunctive therapy for treatment resistant paediatric and adult epilepsies.[11 12]

Recently Israel, the Netherlands, Germany and Canada have legislated to allow the use of cannabinoids for medicinal purposes. In Australia, Federal and state legislation that allows doctors to prescribe cannabinoids is being implemented. Systematic reviews are required to synthesise the evidence for individual conditions for which cannabinoids may be used to inform clinical practice and patient guidance.

This review considers evidence on the safety and efficacy of cannabinoids as adjunctive treatments for drug-resistant epilepsy. As previous reviews noted a lack of controlled studies,[13 14] we synthesised evidence from randomised controlled trials (RCTs) and observational studies.

METHOD
This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (see PRISMA checklist in online supplementary materials 1). The search strategy and data extraction

Box 1

1. Cannabis or marijuana or cannabinoids or endocannabinoids or dronabinol or nabilone or marinol or levonantradol or tetrahydrocannabinol or cesamet or delta-9-THC or delta-9-tetrahydrocannabinol or nabiximols or sativex pr cannabidiol
2. Therapeutic use or drug therapy or analgesics
3. 1 and 2
4. (medical or medicinal) adj (mari?uana or cannab*) or 'medical mari?uana' or 'medicinal cannabis'
5. 3 or 4
6. Epilepsy
7. 5 and 6

process are briefly summarised here; methodology is detailed in full in the study protocol (Prospero registration number CRD42017055412; see online supplementary materials 2) Please note that there is considerable material documenting both the methods and the results of this review in the online supplementary materials, which we recommend reviewing.

Data sources and search strategy

To identify individual studies examining cannabinoids to treat epilepsy, the electronic databases Medline, Embase and PsycINFO, and the clinical trials registries: clinicaltrials.gov, the EU clinical trials register (www.clinicaltrialsregister.eu) and the Australian and New Zealand Clinical Trials Registry (ANZCTR, www.anzctr.org.au) were searched in October 2017 using terms shown in box 1 (corresponding subject headings in each database were used where specialised thesauri existed). We additionally searched reference lists of systematic reviews identified as relevant. Searches were limited to studies published from 1980 to 9 October 2017 on human subjects, in any language. The Medline search is provided in online supplementary materials 4.

Inclusion and exclusion criteria

Studies were included in the review if they administered plant-based and pharmaceutical cannabinoids to prevent or treat epilepsy and epileptic seizures in participants of any age, with any type of epilepsy or seizure. We included all experimental and epidemiological study designs including RCTs, non-RCTs, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case-control studies, analytical cross-sectional studies, self-report surveys and case reports.

Studies were excluded from the review if they were reviews of mechanisms of cannabinoid systems, commentary and review articles.

Study screening

Two reviewers independently examined titles and abstracts in the web-based systematic review program, Covidence.[15] Relevant articles were obtained in full, and assessed for inclusion independently by two reviewers. Inter-reviewer disagreement on inclusion was discussed with an aim to reach consensus. A third reviewer was consulted when consensus could not be reached by the two initial reviewers.

Outcomes

We considered primary and secondary outcomes suggested by the International League Against Epilepsy's Commission on Outcome Measurement.[16 17] The primary outcome was the proportion of patients who experienced a 50% or greater reduction in seizure frequency. Secondary outcomes included the proportion of patients achieving complete seizure freedom; quality of life indicators (including changes in mood, behaviour, sleep, attention, speech and cognitive, social and motor skills); withdrawal from the study (due to adverse events (AEs) or other reasons) and AEs.

Assessment of risk of bias

Methodological quality ratings for risk of bias in RCTs were determined using the Cochrane Collaboration risk of bias tool.[18] RCTs were judged to have an overall low risk of bias if they had six to eight risk domains rated as having a low risk of bias, unclear risk if four or more domains were judged as being unclear and high risk if three or more domains were judged as being high risk. Observational or case study reports were evaluated using risk of bias in non-randomised studies - of interventions (ROBINS-I) tool for assessing risk of bias in non-randomised studies of interventions.[19] Overall risk of bias was determined by the most serious risk of bias allocated to that study across the tool. Any disagreements were resolved through discussion, or with the input of a third reviewer.

Grading of evidence

An evidence grade was given to each reported study, based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool.[18] Randomised, double-blind placebo-controlled trials were considered to be of the highest quality, but ratings could be downgraded where there were instances of bias or poor design. Single case studies or self-report studies were considered to be of very low quality. We additionally conducted a GRADE assessment using GRADEPro (https://gradepro.org/) for each reported pooled estimate to evaluate the risk of bias, inconsistency, indirectness, imprecision and publication bias, resulting in an overall GRADE rating for each outcome. GRADE assessments were conducted independently by two reviewers with disagreements resolved via consensus with a third reviewer.

Data extraction

Data were extracted from studies using a standardised data extraction tool in Microsoft Office Excel 2016. The data extracted from studies included specific details about the intervention, populations, study methods and outcomes of significance to the review question and specific objectives. Data extraction tools were piloted and reviewed by the authors before being finalised (see online supplementary materials 5 for fields extracted).

During the review, clinical experts reviewed the extracted data and gave feedback on the need to define drug-resistant epilepsy, distinguishing between paediatric and adult epilepsies and distinguishing between AEs and serious adverse events (SAEs). Accordingly, we extracted whether studies identified their participants as having drug-resistant epilepsies, in line with the ILAE definition,[5] namely, the failure of two or more tolerated and appropriately chosen AEDs, used either in combination or as monotherapy, to achieve complete seizure freedom (see online supplementary materials 3 for a summary of this definition). Paediatric epilepsies were defined as those occurring in persons between the ages of 0 and 18 years. We also extracted concurrent AEDs reported by the participants.

All reported AEs, including SAEs and treatment-related adverse events (TSAEs) were included in the review. We extracted AEs as being 'serious' or 'treatment-related' based on authors' report.

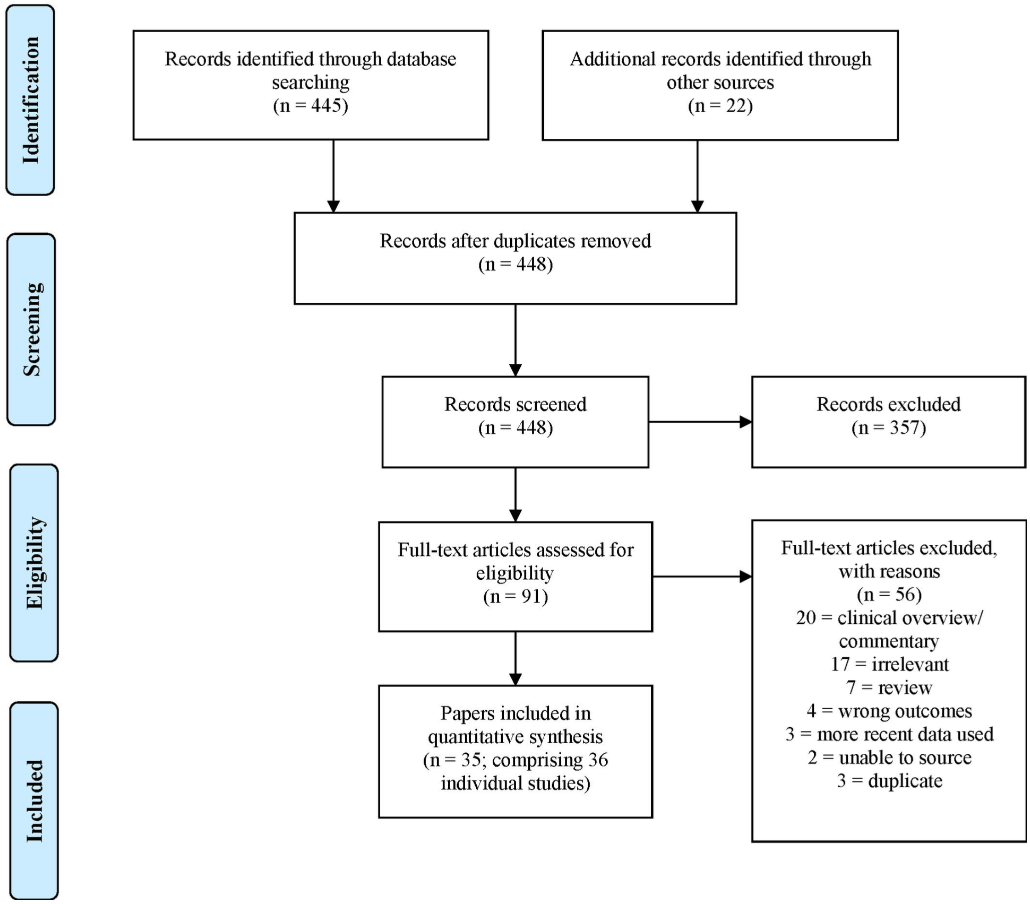

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

Where studies reported multiple points of follow-up data, we extracted the longest follow-up within each study.

Analysis

All analyses were conducted using Stata V.15.0.[20] We expected high levels of heterogeneity between studies due to differences in sociodemographic and clinical profiles, thus all outcomes were analysed using DerSimonian and Laird inverse-variance random effects meta-analysis.[21] For RCTs, the relative risk (RR) of participants in the treatment groups achieving study outcomes relative to participants in the comparison group were estimated using the '*metan*' command. For observational studies with no comparison group, the proportion of participants achieving study outcomes were pooled using the prevalence command, '*metaprop*' using the Freeman-Tukey double arcsine transformation to stabilise variances and prevent exclusion of studies where proportions approached 0 or 1.[20 22] For dichotomous outcomes from RCTs, we calculated numbers needed to treat (NNT) and numbers needed to harm (NNH) and their 95% CIs. We used pooled estimates of relative effect (ie, RRs) to take into account the event rate in control groups.[23] NNT was calculated for the outcomes 50% or greater reduction in seizures, complete seizure freedom and quality of life. NNH was calculated for all-cause AEs, SAEs, TSAEs and study withdrawals due to AEs.

Heterogeneity in all pooled estimates was summarised using the I^2 statistic and was described as being unimportant for values between 0% and 30%, moderate for 31%–60%, substantial for 61%–75% and considerable for 76%–100%.[18]

Where sufficient data were available, we conducted subgroup analyses on the basis of epilepsy type (such as Dravet or Lennox-Gastaut syndromes); sample age (paediatric vs adult or mixed aged samples) and overall risk of bias rating.

RESULTS

Searches identified 445 articles (see figure 1). An additional 11 poster abstracts were sourced through the American Epilepsy Society conference database[24] and the authors were contacted for further details. Three additional papers were published and identified through hand-search by the authors after the initial database search, and eight papers were identified via hand-searches of systematic review reference lists. After title and abstract screening, 91 articles were selected for full-text screening. Of these, 35 papers (comprising 36 individual studies) met criteria for inclusion in the review (table 1 and online supplementary materials 6, table A4; see online supplementary materials 9 for excluded studies). We additionally identified 10 ongoing studies that met inclusion criteria but for which results have not yet been published (see online supplementary materials 10).

Of the six randomised trials, four were parallel double-blind placebo-controlled trials,[25–28] one was a cross-over study[29] and one was a randomised placebo-controlled trial with limited details of blinding.[30] Of the 30 observational studies, 6 were open-label intervention trials,[11 12 31–34] 10 were case studies,[35–44] 8 were self-report surveys,[8 9 45–50] 5 were retrospective chart reviews[44 51–54] and the design of the remaining study was unclear.[55]

Table 1 Study-level summaries of included randomised controlled trials

Study	Design	Sample	Treatment	Pharma. grade	Outcomes measured	Results	Adverse events and serious adverse events	Bias assessment† /GRADE assessment
Ames and Crindland[30]	Randomised clinical trial	12 adults with frequent seizures not controlled by anticonvulsant therapy (drug-resistant epilepsy)	100 mg CBD or placebo sunflower oil 3 times a day for 1 week, then 2 times a day for 3 weeks	Not stated	Seizure reduction	- The trial was abandoned before the second stage of the trial could take place. No significant differences in seizure frequency were observed between groups.	Reported: drowsiness	Unclear risk/low
Cunha *et al*[25]	Randomised, double-blind, placebo-controlled trial	15 adults (mean age=24; range 14–49; 26.7% male) with secondary generalised epilepsy (drug-resistant epilepsy)	100 mg CBD or placebo glucose capsule, taken orally 2–3 times per day, for 8–18 weeks	Not stated	Reported seizure improvement; self-reported subjective improvement	- Four of seven (~57%) patients receiving CBD showed complete seizure freedom, compared with 1/8 (12.5%) placebo patients. - All 7 CBD patients showed some sort of improvement in seizure frequency, compared with only 2/8 (25%) placebo patients. - One CBD patient withdrew from the study, whereas two patient receiving placebo withdrew.	Somnolence (57.1%) Painful gastric sensation (14.3%)	High risk/moderate
Devinsky *et al*[26]	Randomised, double-blind, placebo-controlled trial	120 children and adolescents (mean age=9.8; range=2–18; 52% male) with Dravet syndrome (drug-resistant epilepsy)	20 mg/kg/day CBD or placebo, taken orally for 14 weeks, as an adjunctive treatment	Yes	Change in seizure frequency, caregiver global impression of change	- Three CBD patients achieved total seizure freedom during the test period, no placebo patients achieved seizure freedom (P=0.08). - Twenty-six CBD patients (~43%) had a >50% reduction in seizures, compared with 16 patients (~27%) in the placebo group. - Thirty-seven caregivers (~62%) judged their child's overall condition to be improved in the cannabidiol group, as compared with 20 (~34%) in the placebo group (P=0.02). - Nine CBD patients withdrew from the study, 8 of which were due to adverse events. In comparison, three placebo patients withdrew, with only one being due to adverse events.	Somnolence (36%) Diarrhoea (31%) Decreased appetite (28%) Fatigue (20%) Vomiting (15%) Fever (15%) Lethargy (13%) Upper respiratory tract infection (11%) Convulsion (11%) *Serious:* Elevated liver aminotransferase enzymes (20%) Status epilepticus (4.9%)	Low risk/high
GW Pharmaceuticals[27]	Randomised, double-blind, placebo-controlled trial	225 patients (mean age=16; range=2–55) with Lennox-Gastaut syndrome (drug-resistant epilepsy)	i) 10 mg/kg/day CBD for 14 weeks	Yes	Change in seizure frequency, change in QoL and caregiver global impression of change	- Patients randomised to 10 mg/kg/day of CBD achieved a median reduction in monthly drop seizures of 37%, in comparison with 17% in those patients in the placebo group (P=0.0016). - One patient receiving 10 mg/kg/day CBD withdrew due to adverse events, as did one placebo patient.	All cause (83.6%) *Serious:* All cause (17.8%)	Unclear risk/high
			ii) 20 mg/kg/day CBD for 14 weeks	Yes	Change in seizure frequency, change in QoL and caregiver global impression of change	- Patients taking 20 mg/kg/day of CBD showed a median reduction in monthly drop seizures of 42%, compared with 17% in the placebo group (P=0.0047). - Six patients receiving the higher dose (20 mg/kg/day) withdrew due to adverse events, compared with one placebo patient.	All cause (93.4%) *Serious:* All cause (17.1%)	
Thiele *et al*[28]	Randomised, double-blind, placebo-controlled study	171 patients (mean age=15.4; range=2–45; 51.5% male) with Lennox-Gastaut syndrome (drug-resistant epilepsy)	20 mg/kg/day CBD or placebo, taken daily for 14 weeks, as an adjunctive treatment	Yes	Change in seizure frequency, caregiver impression of overall improvement	- Five of 86 CBD patients achieved complete seizure freedom during the maintenance period, compared with none in the placebo group. - Thirty-eight patients (~44%) taking CBD had >50% decrease in seizures, compared with 20 (~24%) patients taking placebo. - Forty-two (~58%) CBD patients were reported (by either themselves or a caregiver) to have achieved an improvement in their overall condition, compared with 29 (~34%) placebo patients. - Fourteen CBD patients withdrew from the study, compared with just one patient given placebo.	Diarrhoea (18.6%) Somnolence (15.1%) Fever (12.8%) Decreased appetite (12.8%) Vomiting (10.5%) *Serious:* All cause (23.3%)	Unclear risk/high
Trembly and Sherman[29]	Double-blind, cross-over, placebo-controlled add-on trial	12 adults with incompletely controlled seizures (drug-resistant epilepsy)	100 mg CBD or placebo 3 times per day for 26 weeks	Not stated	Monthly seizure episodes	- Changes to seizure frequency were not statistically analysed, but authors report some reduction in seizure frequency for patients taking CBD.	None reported	Unclear risk/moderate

†Bias assessment based on risk of bias for randomised studies.
Studies are presented in alphabetical order; adverse events are reported for participants receiving cannabinoids and experienced by >10% of sample.
CBD, cannabidiol; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; Pharma. grade, pharmaceutical grade cannabinoid product; QoL, quality of life.

Characteristics of study participants

The RCTs included a total of 555 patients (range: 12–225), all of whom had drug-resistant epilepsy. The mean age of participants, where reported, was 16.3 years (range: 2.3–49) and the mean percentage of males was approximately 48.3% (range: 26.7%–52%). Two RCTs[27 28] examined Lennox-Gastaut syndrome, one[26] examined Dravet syndrome and the remaining studies[25 29 30] reported on 'mixed' epilepsy syndromes.

In comparison, the non-RCT studies included 2865 patients with drug-resistant epilepsy (range: 1–976), whom had a mean age of 15 years (range: 0.5–50). The percentage of males was approximately 48.6% (range: 0%–100%). Nine of the non-RCT studies examined Dravet syndrome either primarily or as a subgroup within a larger sample,[9 32 35 39 44 46 49 52 53] eight examined Lennox-Gastaut syndrome,[9 32 35 41 46 49 52 53] four studies examined Doose syndrome,[46 49 52 53] the remaining studies examined mixed epilepsy syndromes[8 9 11 12 31–35 37 38 40 42–54] and two studies[36 55] did not specify epilepsy subtype.

Cannabinoids used and features of treatment

The RCTs all studied CBD with a placebo comparator; CBD was an adjuvant treatment in all cases. The more recent studies that describe data based on participant weight[26–28] reported a CBD range of 2.5–20 mg/kg/day across a mean treatment length of 14 weeks. Earlier RCTs[25 29 30] reported using 100 mg of CBD administered 2–3 times per day for a treatment period between 8 and 26 weeks.

Cannabinoids used in the non-RCT studies varied, but CBD was most commonly used (n=15[9 11 12 31–35 37 41 43 45 46 49 52]); four studies examined a combined CBD:THC extract[39 44 54]; six examined cannabis sativa[8 36 40 47 48 50]; one examined dronabinol[38] and the remaining studies reported various other cannabinoid formulations. Cannabinoids were used as an adjuvant therapy, with a treatment range between 10 days and 7.5 years.

Risk of bias

Table 1 and online supplementary materials 6, table A4 include the quality assessment ratings for each of the included studies (see also online supplementary materials 6, figures A1 and A2). Of the six RCTs included in the review, only one was judged to be at a low risk of bias,[26] one study was judged to be high[25] and the remaining four were judged to have an unclear risk of bias[27–30] (see online supplementary materials 6, figures A1 and A2), primarily due to lack of detail.

Non-randomised trials were mostly judged to be at serious to critical risk of bias, particularly those with self-reported outcomes on self-selected participant samples (see online supplementary materials 6, figure A3). The lack of randomisation, blinding and control groups in these studies mean that their results can at most be indicators of clinical experience rather than evidence for the effectiveness of the product used. Methodological quality for these studies was typically graded as low or very low (see online supplementary materials 6, table A4 for full description of the studies).

Primary outcome: 50% reduction in seizure frequency

Nineteen studies reported the proportion of participants who experienced 50% or greater reductions in seizure frequency. This comprised 2 RCTs[26 28] and 17 observational studies, including 4 open-label trials,[11 31 34 37] 3 retrospective chart studies,[44 53 54] 3 self-report studies,[45 46 49] 3 case reports[39 43 44] and 4 studies of a general observational design.[12 32 52 55]

CBD was more likely to produce >50% reduction in seizures than placebo in two RCTs (RR 1.74, 95% CI 1.24 to 2.43, n=291 patients, mean age: 25.9 years, range: 10–45 years, I^2=0%; low GRADE rating; see table 2 and in online supplementary material 7.1, figure A4). We estimated that the NNT for one person to achieve a 50% reduction in seizures was 8 (95% CI 6 to 17). Estimates did not differ based on epilepsy type, sample age or study risk of bias rating (see online supplementary material 7.1, figure A5–A7). An estimated 48.5% of the 970 patients in 17 observational studies achieved a 50% or greater reduction in seizures (95% CI 39.0% to 58.1%, mean age: 8.8 years, range: 6 months to 46 years, considerable heterogeneity, I^2=79.5%; low GRADE rating; see table 2, supplementary material 8.1, figure B1). This estimate is comparable to, although larger than the proportion of responders in the two larger, high-quality RCTs (42.6%[26] and 44.2%[28]). Estimates did not differ by epilepsy type, sample age or study risk of bias (see online supplementary material 8.1, figures B2–B5). The pooled estimate for paediatric only samples (57.7%, 95% CI 39.0% to 75.6%) was somewhat higher than that for adult, or mixed adult and paediatric samples (36.2%, 95% CI 11.3% to 64.4%); however, these estimates fell within overlapping bounds of uncertainty (online supplementary material 8.1.2a, figure B4).

As noted in table 4, we conclude there is mixed quality evidence that there may be some treatment effect of CBD as an adjunctive therapy in achieving 50% or greater reduction in seizures. There is insufficient evidence from moderate-quality or high-quality studies to assess whether there is a treatment effect of *Cannabis sativa*, CBD:THC combinations or oral cannabis extracts.

Secondary outcome: complete seizure freedom

Seventeen studies reported rates of complete seizure freedom among individuals receiving cannabinoids as adjunctive treatments (see table 2 for full details). This comprised 3 RCTs[25 26 28] and 14 observational studies, including 4 self-report surveys,[9 45 46 49] 3 open-label trials,[11 31 37] 2 retrospective chart reviews,[44 54] 2 case studies[35 44] and 3 studies of a general observational design.[12 52 55]

Of the three RCTs that reported data on complete seizure freedom, one study involved only paediatric patients with Dravet syndrome (n=120),[26] one included both paediatric and adult patients with Lennox-Gastaut syndrome (n=171)[28] and one study involved only adult patients with secondary generalised epilepsy (n=15),[25] all of which were classified as drug-resistant. The pooled RR from these studies for CBD in achieving complete seizure freedom compared with placebo was 6.17 (95% CI 1.50 to 25.32, total n=306 participants, mean age: 16.4 years, range: 2.3–45.1 no heterogeneity, I^2=0%; low GRADE rating; see table 2 and online supplementary material 7.2, figure A8). We estimated that the NNT for one person to achieve complete seizure freedom was 171 (95% CI 155 to 339). There were no differences identified in the RR of complete seizure freedom based on epilepsy type, age group or study risk of bias (see online supplementary material 7.2, figures A9–A11); however, each subgroup only contained one study in these analyses.

The pooled prevalence of participants achieving complete seizure freedom in the 14 observational studies with no comparison group was 8.5% (95% CI 3.8% to 14.5%, n=944, mean age: 8.1, range 6 months to 46 years, substantial heterogeneity, I^2=77.3%; see online supplementary material 8.2, figure B6, low GRADE rating). This was higher than the proportion

Table 2 Meta-analysis of study outcomes of RCTs; non-randomised study pooled estimates as comparison

End points Subgroup analysis	#RCTs	#RCT participants	RCT pooled relative risk (95% CI)*	I^2	GRADE (RCTs)	#Non-RCTs	#Non-RCT participants	Non-RCT pooled estimate (95% CI)	I^2	GRADE (non-RCTs)
1. 50% or greater reduction in seizures	**2**	**291**	**1.74 (1.24 to 2.3)**	0.0	⊕⊕◯◯ LOW	17	970	48.5% (39.0 to 58.1)	78.2	⊕⊕◯◯ LOW
Age group										
Paediatric	1	120	1.57 (0.94 to 2.62)		⊕⊕◯◯ LOW	13	370	57.1% (39.2 to 74.4)	81.1	⊕⊕◯◯ LOW
Adult						2	7	24.6% (0.0 to 74.1)		⊕⊕◯◯ LOW
Paediatric and adult	**1**	**171**	**1.88 (1.24 to 2.43)**		⊕⊕◯◯ **LOW**	4	637	42.7% (38.7 to 46.8)	0.0	⊕⊕◯◯ LOW
Epilepsy type										
Dravet syndrome	1	120	1.57 (0.94 to 2.62)		⊕⊕◯◯ LOW	6	78	46.9% (16.1 to 78.7)	79.1	⊕⊕◯◯ LOW
Lennox-Gastaut syndrome	**1**	**171**	**1.88 (1.20 to 2.95)**		⊕⊕◯◯ **LOW**	4	59	63.8% (32.1 to 91.1)	67.0	⊕⊕◯◯ LOW
Secondary generalised epilepsy										
Doose syndrome						3	15	29.4% (0.0 to 73.9)		⊕⊕◯◯ LOW
Mixed epilepsy syndromes						7	580	46.9% (38.3 to 55.6)	64.0	⊕⊕◯◯ LOW
Tuberous sclerosis complex						1	18	22.2% (9.0 to 45.2)		⊕⊕◯◯ LOW
Febrile infection-related epilpesy syndrome						1	5	100.0% (56.6 to 100.0)		⊕⊕◯◯ LOW
Malignant migrating partial seizures						1	1	100.0% (20.7 to 100.0)		⊕⊕◯◯ LOW
2. Complete seizure freedom	**3**	**306**	**6.17 (1.50 to 25.32)**	**0.0%**	⊕⊕◯◯ **LOW**	14	944	8.5% (3.8 to 14.5)	77.3	⊕⊕◯◯ LOW
Age group										
Paediatric	1	120	6.77 (0.36 to 128.38)		⊕⊕◯◯ LOW	10	362	15.2% (5.2 to 28.0)	80.4	⊕⊕◯◯ LOW
Adult	1	15	4.57 (0.66 to 31.89)		⊕⊕◯◯ LOW					
Paediatric and adult	1	171	10.87 (0.61 to 193.64)		⊕⊕◯◯ LOW	4	582	5.5% (2.5 to 9.5)	59.6	⊕⊕◯◯ LOW
Epilepsy type										
Dravet syndrome	1	120	6.77 (0.36 to 128.38)		⊕⊕◯◯ LOW	3	48	6.3% (0.0 to 41.3)		⊕⊕◯◯ LOW
Lennox-Gastaut syndrome	1	171	10.87 (0.61 to 193.64)		⊕⊕◯◯ LOW	2	83	6.4% (1.7 to 13.0)		⊕⊕◯◯ LOW
Secondary generalised epilepsy	1	15	4.57 (0.66 to 31.89)]		⊕⊕◯◯ LOW					
Febrile infection-related epilepsy syndrome						1	8	25.0% (7.1 to 59.1)		⊕⊕◯◯ LOW
Mixed epilepsy syndromes						8	634	7.6% (2.7 to 14.1)	75.6	⊕⊕◯◯ LOW
Tuberous sclerosis complex						1	18	5.6% (1.0 to 25.8)		⊕⊕◯◯ LOW
3. Quality of life	**2**	**274**	**1.73 (1.33 to 2.26)**	**0.0**	⊕⊕◯◯ **LOW**	12	440	55.9% (40.5 to 70.6)	93.9	⊕◯◯◯ VERY LOW
Age group										
Paediatric	**1**	**118**	**1.79 (1.19 to 2.69)**		⊕⊕◯◯ **LOW**	8	292	30.1% (16.7 to 44.9)	88.9	⊕◯◯◯ VERY LOW
Adult						2	126	89.3% (75.5 to 98.3)	70.8	⊕◯◯◯ VERY LOW
Paediatric and adult	**1**	**156**	**1.69 (1.19 to 2.41)**		⊕⊕◯◯ **LOW**	2	13	89.9% (60.5 to 100.0)		⊕◯◯◯ VERY LOW
Epilepsy type *										
Dravet syndrome	**1**	**118**	**1.79 (1.19 to 2.69)**		⊕⊕◯◯ **LOW**	2	4	100.0% (84.3 to 100.0)	0.0	⊕◯◯◯ VERY LOW
Lennox-Gastaut syndrome	**1**	**156**	**1.69 (1.19 to 2.41)**		⊕⊕◯◯ **LOW**	1	1	100.0% (48.7 to 100.0)		⊕◯◯◯ VERY LOW
Mixed epilepsy syndromes						10	433	44.4% (29.6 to 59.5)	95.2	⊕◯◯◯ VERY LOW
Tuberous sclerosis complex						2	27	66.8% (47.1 to 84.2)		⊕◯◯◯ VERY LOW
Malignant migrating partial seizures						1	1	100.0% (21.3 to 100.0)		⊕◯◯◯ VERY LOW

*Significant results indicate a greater likelihood of the event in the intervention group relative to controls, and are highlighted bold.
GRADE, Grades of Recommendation, Assessment, Development and Evaluation; RCT, randomised controlled trial.

of participants who achieved complete seizure freedom in the two larger, high-quality RCTs (namely 4.9% and 5.8%). There were no significant differences in the proportion of participants achieving complete seizure freedom by epilepsy type, participant age or risk of bias (see online supplementary material 8.2, figures B7–B10). The pooled estimate for paediatric samples (14.3%, 95% CI 5.2% to 25.9%) was somewhat higher than that for adult or mixed adult and paediatric samples (4.3%, 95% CI 1.3% to 8.4%); however, these estimates fell within overlapping bounds of uncertainty (see online supplementary material 8.2.2a, figure B9).

As noted in table 4, we conclude that there is mixed quality evidence that the use of CBD as an adjunctive treatment may help achieve seizure freedom. There is insufficient evidence to assess whether CBD:THC combinations or oral cannabis extracts are effective.

Secondary outcome: quality of life

Fourteen studies (comprising 26 individual data points) evaluated the effects of cannabinoids on quality of life indicators. Two were RCTs,[26 28] and 12 were observational studies, of which 4 were retrospective chart reviews,[51–54] 4 were case study reports,[35 39 41 43] 2 were self-report surveys[48 49] and 2 were open-label trials.[12 32] Quality of life in the two RCTs[26 28] was measured by parent's/caregiver's global impression of change. Non-RCTs reported improvements in mood, social skills, cognitive skills, behaviour, alertness/attention, speech and language, sleep, appetite and motor skills and reductions in self-stimulation.

The pooled RR of parents/caregivers reporting that the patients' overall condition had improved (using the patient global impression of change measure) in those receiving CBD versus placebo of 1.73 (95% CI 1.33 to 2.26, n=274 patients, mean age: 12.6 years, range 2.3–45.1, no heterogeneity, I^2=0%; see table 2, online supplementary material 7.3, figure A12), and this did not differ on the basis of epilepsy type, sample age or study risk of bias (online supplementary material 7.3, figures A13–A15). The NNT for one person receiving CBD to experience an improvement in parental-reported quality of life was 5 (95% CI 4 to 9).

A pooled estimate from observational studies of the proportion of patients with improved quality of life when using cannabinoids was 55.8% (95% CI 40.5 to 70.6, n=440 patients, mean age: 12.7 years, range: 6 months to 50 years, considerable heterogeneity, I^2=93.9; see online supplementary material 8.3, figure B11). This included improvements in mood (95.9%, 95% CI 74.1 to 100), cognitive skills (76.1%, 95% CI 53.8 to 93.6), alertness (54.0%, 95% CI 28.3% to 78.9%) and sleep (50.9%, 95% CI 9.8% to 91.4%; see online supplementary figure B11). The proportion of participants reporting improvement in quality of life indicators was higher in samples with Dravet syndrome (100%, 95% CI 84.3% to 100%) compared with samples with mixed epilepsy syndromes (44.4%, 95% CI 29.6% to 59.5%); however, the studies comprising the Dravet syndrome subgroup were all case series (combined n=5 patients) in which every patient responded and thus this should be interpreted with great caution (online supplementary material 8.3.1, figure B12). Samples comprising adults only reported higher proportions of participants experiencing improved appetite, mood and sleep (89.3%, 95% CI 75.5% to 98.3%) compared with paediatric samples (30.1%, 95% CI 16.7% to 44.9%; see online supplementary material 8.3.2, figure B13). Studies rated as being at 'serious' risk of bias (the second highest risk rating) had lower overall proportions of participants reporting improvement in quality of life (16.6%, 95% CI 8.4% to 26.3%) compared with studies at 'critical risk' (the highest rating; 65.2%, 95% CI 34.5% to 91.3%) and studies where risk was unable to be determined due to lack of information (85.4%, 95% CI 67.5% to 98.0%; see online supplementary material 8.3.3, figure B14).

As noted in table 4, we conclude there is mixed quality evidence that CBD improved patient quality of life when used as an adjunctive treatment. There was very low-quality and low-quality evidence on the use of *Cannabis sativa*, oral THC, CBD:THC combinations and oral cannabis extracts. This was insufficient to assess their therapeutic usefulness.

Secondary outcome: study withdrawals

Withdrawals are used as an indicator of tolerability and effectiveness of a treatment. Twelve studies reported on patient withdrawal from treatment—four RCTs[25–28] and eight observational studies, including two open-label trials,[11 41] three retrospective chart reviews[44 53 54] and three studies of a general observational design.[12 52 55]

In RCTs, there was no difference in the likelihood of study withdrawal for any reason between patients given CBD and who received placebo (pooled RR 2.96, 95% CI 0.64 to 13.78, n=306 patients; mean age: 16.4 years, range: 2.3–49, moderate heterogeneity, I^2=52.2%; see table 3, online supplementary material 7.4, figure A16). This did not differ on the basis of epilepsy type, sample age or study risk of bias (see online supplementary material 7.4, figure A17–A19). Based on two RCTs,[26 27] patients receiving CBD were more likely to withdraw from the study due to experiencing AEs (pooled RR 4.87; 95% CI 1.10 to 21.68, n=345, mean age: 11.9, range: 2–55 years, no heterogeneity, I^2=0%; see online supplementary material 7.4.4, figure A20), with no difference based on epilepsy type, sample age or study risk of bias (see online supplementary material 7.4, figures 21–23). The NNH for one person to withdraw from CBD treatment due to AEs was 164 (95% CI 140 to 267).

A pooled estimate of the proportion of participants withdrawing from the study for any reason in four[11 52 53 55] non-RCTs was 28.0% (95% CI 5.2% to 59.5%, n=486, mean age: 8.7, range: 6 months to 32 years, considerable heterogeneity I^2=98.0%; see table 3, online supplementary material 8.4, figure B15). All samples comprised a mix of epilepsy subtypes (see online supplementary figure B16). Pooled estimates of withdrawal were higher for paediatric-only samples (47.9%; 95% CI 40.9% to 55.0%) compared with mixed paediatric and adult samples (15.2%; 95% CI 11.3% to 19.6%; see online supplementary material 8.4.1, figure B17). One study rated as critical risk of bias (the highest risk category)[53] had substantially higher proportions of participants reporting study withdrawal (70.6%, 95% CI 61.9% to 78.0%) than studies of lesser risk (see online supplementary material 8.4.2, figure B18). The pooled estimate for withdrawals from the study due to AEs in six studies[11 12 41 53–55] was 4.1% (95% CI 0.9% to 8.8%, substantial heterogeneity, I^2=72.3%, n=521, mean age: 10, range: 6 months to 32 years; see online supplementary material 8.4.3, figure B19), and did not differ based on epilepsy type, sample age or study risk of bias (see online supplementary material 8.4, figures B20–B22).

Study withdrawals were noted for patients receiving CBD and oral cannabis extracts (table 3). There is mixed quality evidence, including from two higher-quality RCTs that patients who received CBD were more likely to withdraw from treatment. There is insufficient evidence to draw any conclusions about withdrawals from oral cannabis extract treatment.

Table 3 Meta-analysis of study-reported tolerability and safety

End points Subgroup analysis	#RCTs	#RCT participants	RCT pooled relative risk (95% CI)*	I^2	GRADE (RCTs)	#Non-RCTs	#Non-RCT participants	Non-RCT pooled estimate (95% CI)†	I^2	GRADE (non-RCTs)
4. Withdrawals	3	306	2.96 (0.64 to 13.78)	55.2	⊕⊕◯◯ LOW	4	486	28.0% (5.2 to 59.5)	98.0	⊕◯◯◯ VERY LOW
Age group										
Paediatric	1	120	2.90 (0.83 to 10.20)		⊕⊕◯◯ LOW	2	194	47.9% (40.9 to 55.0)	0.0	⊕◯◯◯ **VERY LOW**
Adult	1	15	0.57 (0.06 to 5.03)		⊕⊕◯◯ LOW					
Paediatric and adult	**1**	**171**	**13.84 (1.86 to 102.91)**		⊕⊕◯◯ **LOW**	2	292	15.2% (11.3 to 19.6)	0.0	⊕◯◯◯ **VERY LOW**
Epilepsy type										
Dravet syndrome	1	120	2.90 (0.83 to 10.120)		⊕⊕◯◯ LOW					
Lennox-Gastaut syndrome	**1**	**171**	**13.84 (1.86 to 102.91)**		⊕⊕◯◯ **LOW**					
Secondary generalised epilepsy	1	15	0.57 (0.06 to 5.03)		⊕⊕◯◯ LOW					
5. Withdrawals due to adverse events	**3**	**345**	**4.87 (1.10 to 21.68)**	**0.0**	⊕⊕◯◯ **LOW**	6	521	4.1% (0.9 to 8.8)	72.3	⊕⊕◯◯ LOW
Age group										
Paediatric	1	120	7.74 (1.00 to 59.97)		⊕⊕◯◯ LOW	3	211	6.7 (2.2 to 12.9)	0.0	⊕⊕◯◯ LOW
Adult										
Paediatric and adult	2	225	2.88 (0.33 to 25.53)	0.0	⊕⊕◯◯ LOW	3	310	2.2% (0.0 to 6.8)	0.0	⊕⊕◯◯ LOW
Epilepsy type										
Dravet syndrome	1	120	7.74 (1.00 to 59.97)		⊕⊕◯◯ LOW					
Lennox-Gastaut syndrome	2	225	2.88 (0.33 to 25.53)		⊕⊕◯◯ LOW					
Mixed epilepsy syndromes						5	503	3.7% (0.7 to 8.4)	75.5	⊕⊕◯◯ LOW
Tuberous sclerosis complex						1	18	11.1% (3.1 to 32.8)		⊕⊕◯◯ LOW
6. Adverse events—all cause	**5**	**531**	**1.24 (1.13 to 1.36)**	**0.0**	⊕⊕◯◯ **LOW**	12	651	50.6% (31.7 to 69.4)	94.4	⊕◯◯◯ VERY LOW
Age group										
Paediatric	**1**	**120**	**1.25 (1.06 to 1.48)**		⊕⊕◯◯ **LOW**	8	353	47.7% (32.4 to 63.3)	82.7	⊕◯◯◯ **VERY LOW**
Adult	1	15	5.71 (0.86 to 37.91)		⊕⊕◯◯ LOW	3	132	27.6% (4.0 to 59.8)	0.0	⊕◯◯◯ **VERY LOW**
Paediatric and adult	**3**	**396**	**1.23 (1.10 to 1.38)**	**0.0**	⊕⊕◯◯ **LOW**	2	166	82.8% (75.6 to 89.1)	0.0	⊕◯◯◯ **VERY LOW**
Epilepsy type										
Dravet syndrome	**1**	**120**	**1.25 (1.06; to 1.48)**		⊕⊕◯◯ **LOW**	1	3	100.0% (43.9 to 100.0)		⊕⊕◯◯ LOW
Lennox-Gastaut syndrome	**3**	**396**	**1.23 (1.10 to 1.38)**	**0.0**	⊕⊕◯◯ **LOW**	1	1	100.0% (20.7 to 100.0)		⊕⊕◯◯ LOW
Secondary generalised epilepsy	1	15	5.71 (0.86 to 37.91)		⊕⊕◯◯ LOW					
Mixed epilepsy syndromes						4	216	74.3% (41.0 to 98.0)	89.1	⊕⊕◯◯ LOW
Tuberous sclerosis complex						1	18	66.7% (43.7 to 83.7)		⊕⊕◯◯ LOW
Specific event†										
Drowsiness	**3**	**306**	**2.53 (1.40 to 4.57)**	**7.0**	⊕⊕◯◯ **LOW**	15	897	22.6% (15.3 to 30.7)	84.4	⊕⊕◯◯ LOW
Diarrhoea	**2**	**291**	**2.63 (1.45 to 4.76)**	**0.0**	⊕⊕◯◯ **LOW**	9	209	11.3% (2.8 to 23.0)	85.2	⊕⊕◯◯ LOW
Vomiting	2	291	1.25 (0.28 to 5.49)	75.3	⊕⊕◯◯ LOW	7	333	2.6% (0.8 to 5.1)	0.0	⊕⊕◯◯ LOW
Fatigue	**1**	**120**	**5.80 (1.36 to 24.83)**		⊕⊕◯◯ **LOW**					
Fever	2	291	1.63 (0.83 to 3.21)	0.0	⊕⊕◯◯ LOW					
Upper respiratory tract infection	1	120	1.35 (0.46 to 4.03)		⊕⊕◯◯ LOW	4	108	2.1% (0.0 to 6.5)	0.0	⊕⊕◯◯ LOW
Change in appetite	2	291	5.46 (2.18 to 13.69)	0.0	⊕⊕◯◯ LOW	12	613	7.2% (3.1 to 12.5)	67.8	⊕⊕◯◯ LOW

Continued

Table 3 Continued

End points Subgroup analysis	#RCTs	#RCT participants	RCT pooled relative risk (95% CI)*	I^2	GRADE (RCTs)	#Non-RCTs	#Non-RCT participants	Non-RCT pooled estimate (95% CI)†	I^2	GRADE (non-RCTs)
Convulsion	1	120	2.26 (0.61 to 8.32)		⊕⊕◯◯ LOW	1	162	11.1% (7.1 to 16.9)		⊕⊕◯◯ LOW
Lethargy	1	120	2.58 (0.72 to 9.26)		⊕⊕◯◯ LOW	4	223	3.6% (0.6 to 8.3)	21.6	⊕⊕◯◯ LOW
Gastrointestinal symptoms	1	15	3.38 (0.16 to 71.67)		⊕⊕◯◯ LOW	3	268	6.9% (4.0 to 10.5)	0.0	⊕⊕◯◯ LOW
Ataxia						7	94	17.1% (1.1 to 41.7)	79.9	⊕⊕◯◯ LOW
Change in weight						5	340	5.7% (1.6 to 11.5)	79.7	⊕⊕◯◯ LOW
Confusion						2	135	0.6% (0.0 to 3.4)	0.0	⊕⊕◯◯ LOW
Insomnia						6	221	2.6% (0.8 to 5.1)	0.0	⊕⊕◯◯ LOW
7. Serious adverse events	**4**	**516**	**2.55 (1.48 to 4.38)**	**0.0**	**⊕⊕◯◯ LOW**	7	201	2.2% (0.0 to 7.9)	94.2	⊕⊕◯◯ LOW
Age group										
Paediatric	1	120	3.22 (0.93 to 11.14)		⊕⊕◯◯ LOW	5	179	3.9% (0.0 to 11.4)	64.9	⊕⊕◯◯ LOW
Adult										
Paediatric and adult	**3**	**396**	**2.40 (1.17 to 4.93)**	**29.6**	**⊕⊕◯◯ LOW**	2	22	0.0% (0.0 to 6.4)		⊕◯◯◯ VERY LOW
Epilepsy type										
Dravet syndrome	1	120	3.22 (0.93 to 11.14)		⊕⊕◯◯ LOW					
Lennox-Gastaut syndrome	**3**	**396**	**2.40 (1.17 to 4.93)**	**29.6**	**⊕⊕◯◯ LOW**					
Mixed epilepsy syndromes						6	183	2.7% (0.0 to 9.5)	56.1	⊕⊕◯◯ LOW
Tuberous sclerosis complex						1	18	0.0% (0.0 to 17.6)		⊕◯◯◯ VERY LOW
Treatment-related serious adverse events	**3**	**396**	**5.93 (1.38 to 25.46)**	**0.0**	**⊕⊕◯◯ LOW**	1	162	1.1% (0.6 to 1.8)		⊕⊕◯◯ LOW
Specific event†										
Status epilepticus	1	120	0.97 (0.20 to 4.60)		⊕⊕◯◯ LOW	1	162	5.6% (3.0 to 10.2)		⊕⊕◯◯ LOW
Elevated aminotransferase levels	**1**	**120**	**11.61 (1.56 to 86.48)**		**⊕⊕◯◯ LOW**					
Severe diarrhoea						1	162	1.9% (0.6 to 5.3)		⊕⊕◯◯ LOW
Appetite loss						1	162	0.6% (0.1 to 3.4)		⊕⊕◯◯ LOW
Death						1	162	0.6% (0.1 to 3.4)		⊕⊕◯◯ LOW

*Significant results indicate a greater likelihood of the event in the intervention group relative to controls, and are highlighted bold.
†See online supplementary materials for full list of reported adverse events.
GRADE, Grades of Recommendation, Assessment, Development and Evaluation; RCT, randomised controlled trial.

Secondary outcome: AEs

Sixteen studies reported AEs, 4 were RCTs[25–28] and 12 were non-RCTs,[11 12 31 32 35 45 48 49 51–54] including 3 self-report surveys,[45 48 49] 3 retrospective chart reviews,[51 53 54] 2 open-label trials,[11 31] 1 case study[35] and 3 were a general observational design.[12 32 52]

A meta-analysis of 516 patients in three RCTs[26–28] found that patients who received CBD had a small but significant increase in the risk of experiencing any AE compared with those who received placebo (pooled RR 1.24, 95% CI 1.13 to 1.36, mean age: 13.7, range: 2–55 years, no heterogeneity, I^2=0%; see table 3, online supplementary material 7.5, figure A24), with no difference based on epilepsy type, sample age or study risk of bias (see online supplementary material 7.5, figures A25–A27). Specific AEs for which participants receiving CBD were at increased risk included drowsiness (RR 2.53, 95% CI 1.40 to 4.57), diarrhoea (RR 2.63, 95% CI 1.45 to 4.76), fatigue (RR 5.80, 95% CI 1.36 to 24.83) and changes in appetite (RR 5.46, 95% CI 2.18 to 13.69; see online supplementary material 7.5.4, figure A28). The NNH for one person receiving CBD to experience any AE was 3 (95% CI 3 to 6).

Pooled estimates of 651 patients in 12 non-RCTs were that 50.6% of patients experienced any AE (95% CI 31.7% to 69.4%, mean age: 12.6, range: 6 months to 50 years, considerable heterogeneity, I^2=94.4%; see online supplementary material 8.5, figure B23). This did not differ based on epilepsy type. Mixed paediatric and adult samples had significantly higher proportions of participants reporting any AE (82.8%, 95% CI 75.6% to 89.1%) compared with adult-only and paediatric-only studies (see online supplementary material 8.5.2, figure B25), and studies at critical risk of bias (the highest risk level) had significantly smaller proportions (27.0%, 95% CI 14.2% to 41.9%) than studies at lesser risk (see online supplementary material 8.5.3, figure B26). The most common specific AEs included drowsiness (22.6%, 95% CI 15.3% to 30.7%), ataxia (17.1%, 95% CI 1.1% to 41.7%) and diarrhoea (11.3%, 95% CI 2.8% to 23.0%; see online supplementary material 8.5.4, figure B27).

Three RCTs[26–28] found that patients in the CBD treatment groups were more likely to experience any SAE event than patients in placebo conditions (pooled RR 2.55, 95% CI 1.48 to 4.38, n=516, mean age: 14.3, range: 2–55, no heterogeneity I^2=0.4%, low GRADE rating; see online supplementary material 7.6, figure A29), with no difference based on epilepsy type, sample age or study risk of bias (see online supplementary material 7.6, figures A30–A32). Specific SAEs recorded included status epilepticus and elevated aminotransferase levels (see online supplementary material 7.6.4, figure A33) The NNH for one person using CBD to experience any SAE was calculated to be 23 (95% CI 18 to 40).

Patients receiving CBD also had increased odds of experiencing TSAEs (RR 5.93, 95% CI 1.38 to 25.46, n=396, mean age: 15.8, range: 2–55 years, no heterogeneity, I^2=0%, low GRADE rating; see online supplementary material 7.6.6, figure A34), with no difference based on epilepsy type, sample age or study risk of bias. The NNH for one person to experience a TSAE was 191 (95% CI 167 to 529).

In the five non-RCT studies[12 32 33 45 52] with 201 patients, the pooled estimate of patients experiencing any SAE were 2.2% (95% CI 0% to 7.9%, mean age: 9.1 years, range: 6 months to 31 years, moderate heterogeneity, I^2=52.5%, low GRADE rating) (see online supplementary material 8.6, figure B28). The percentage of participants experiencing SAEs did not differ by epilepsy type or sample age; however, studies at critical risk of bias (the highest risk level) had lower rates of SAEs than studies at lesser risk (see online supplementary material 8.6, figure B29–B31). SAEs included pneumonia and thrombophlebitis; however, these were reported in only one study[33] (see online supplementary material 8.6.4, figure B32). Only one observational study reported TSAEs,[11] with 1.1% (95% CI 0.6% to 1.8%) of participants reporting this outcome (n=162, mean age: 10.5, range: 0.9 to 2.62 years, unimportant heterogeneity, I^2=22.5%, very low GRADE rating). Specific TSAEs included status epilepticus, convulsion, hepatoxicity, pneumonia and death in one case (see online supplementary material 8.6.5, figure B33).

There is mixed quality evidence, including from three moderate-quality to high-quality RCTs, that patients receiving CBD are more likely to experience mild-to-moderate AEs (see table 4). There is insufficient evidence to draw any conclusions on whether patients receiving *Cannabis sativa*, oral THC and oral cannabis extracts were more likely to experience AEs.

Discussion

We synthesised available evidence on the safety and efficacy of cannabinoids as an adjunctive treatment to conventional AEDs in treating drug-resistant epilepsy. In many cases, there was qualitative evidence that cannabinoids reduced seizure frequency in some patients, improved other aspects of the patients' quality of life and were generally well tolerated with mild-to-moderate AEs. We can be much more confident about this statement in the case of children than adults, because the recent, larger, well-conducted RCTs were performed in children and adolescents.

In studies where there was greater experimental control over the type and dosage of cannabinoid used, there was evidence that adjuvant use of CBD reduced the frequency of seizures, particularly in treatment-resistant children and adolescents, and that patients were more likely to achieve complete seizure freedom. There was a suggestion that the benefits of adding CBD may be greater when patients were also using clobazam.[11 12] However because clobazam and CBD are both metabolised in the cytochrome P450 pathway, the pharmacokinetic interactions of these two drugs still need to be fully determined.[56] Further randomised, double-blind studies with a placebo or active control are needed to strengthen this conclusion.

Non-RCT evidence was consistent with RCT evidence that suggested cannabinoids may reduce the frequency of seizures. In most of these studies, cannabinoid products and dosages were less well-controlled, and outcomes were based on self-report (often by parents). These studies provide lower quality evidence compared with RCTs due to the potential for selection bias in the study populations, and other weaknesses in study design. There was also some evidence that studies at very high risk of bias had higher reported proportions of participants reporting reductions in seizures and lower proportions reporting AEs. In RCTs, and most of the non-RCTs, cannabinoids were used as an adjunctive therapy rather than as a standalone intervention, so at present there is little evidence to support any recommendation that cannabinoids can be recommended as a replacement for current standard AEDs.

Limitations

There are still few well-controlled, randomised and placebo-controlled studies on CBD in drug-resistant epilepsy.[57] Most studies in this review were observational and used self-report data, raising concerns about possible patient selection and self-reporting bias. This concern especially applies to self-report

Table 4 An overview of the research evidence on cannabis and cannabinoids in the treatment of epilepsy

	50% reduction in seizures n=19 studies (2 RCTs)	Complete seizure freedom n=17 studies (3 RCTs)	Quality of life n=14 studies (2 RCTs)	Withdrawals n=12 studies (4 RCTs)	Adverse events n=16 studies (4 RCTs)
Cannabis sativa/extract	Two studies (no RCT)	No studies	Two studies (no RCT)	No studies	Two studies (no RCT)
Findings	Positive effect		Positive effect		AEs reported by 13%
Evidence GRADE	⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk		Critical risk		Critical risk
Conclusion	Insufficient evidence		Insufficient evidence		Insufficient evidence
CBD	11 studies (2 RCT)	13 studies (3 RCT)	9 studies (2 RCT)	8 studies (3 RCT)	11 studies (4 RCT)
Findings	Small effect	Positive effect	Positive effect	Patients more likely to withdraw from CBD	AEs reported by 11%–100%
Evidence GRADE	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW
Risk of bias	Low to serious risk	Low to critical risk	Low to critical risk	Low to critical risk	Low to critical risk
Conclusion	Some evidence of effect	Some evidence of effect	Some evidence of effect	Greater likelihood of withdrawal	Mild-to-moderate AEs likely
Oral THC	No studies	No studies	No studies	No studies	One study (no RCT)
Findings					AEs reported by 12.5%
Evidence GRADE					⊕◯◯◯ VERY LOW
Risk of bias					No information
Conclusion					Insufficient evidence
CBD:THC	Five studies (no RCTs)	Three studies (no RCTs)	Two studies (no RCT)	Two studies (no RCT)	Two studies (no RCT)
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 14%	AEs reported by 42%
Evidence GRADE	⊕⊕◯◯ LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk	Serious to critical risk	Serious risk	Serious risk	Serious to critical risk
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence
Oral cannabis extracts	One study (no RCT)	One study (no RCT)	One study (no RCT)	One study (no RCT)	No studies
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 15%	
Evidence GRADE	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	
Risk of bias	Critical risk	Serious risk	Serious risk	Serious risk	
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	

Risk of bias=low to high in randomised trials; low to critical risk in non-randomised studies, no information where information not available.
GRADE ratings: high: we are very confident that the true effect lies close to that of the estimate of the effect; moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
CBD, cannabidiol; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; RCT, randomised controlled trial; THC, tetrahydrocannabinol,.

surveys of parents, most of whom were self-selected and so may only include the most satisfied users of cannabinoids. They are unlikely to have included patients who had negative experiences or received no benefits from using cannabinoids.

The fact that more patients withdrew or experienced AEs when receiving CBD than placebo indicates the need for clinicians and patients to weigh the risks and benefits of adding CBD to other AED treatment. The most commonly experienced AEs in patients receiving CBD (drowsiness and dizziness) are similar to those reported from approved AEDs such as gabapentin and levetiracetam, and occur at similar rates.[58 59]

Small numbers of patients (8%–12%) in two RCTs experienced TSAEs.[26 28] Studies are needed to assess whether the rate of these SAEs is similar to that experienced by patients receiving approved AEDs. Incidence rates of SAEs with clobazam, a common epilepsy treatment[60 61] are similar to the profiles of cannabinoid SAEs. If cannabinoids are more effective when combined with clobazam,[11] the possibility of increased rates of SAEs will need to be considered.

Safety issues need to be highlighted when discussing the results of poorly controlled studies of cannabinoids in epilepsy. In clinical trials and non-experimental clinical studies, doctors and other healthcare professionals can monitor patients and intervene if they experience AEs. When patients use 'artisanal' cannabis products, there is much less control over dosages and purity of the product, and so more variability in dosing. For example, in one study, dosages of CBD reported by parents ranged from 0.5 to 28.6 mg/kg/day, and THC dosages ranged from 0 to 0.8 mg/kg/day.[49] Well-controlled and well-regulated therapeutic trials are essential to specify the doses required to produce therapeutic effects with a minimum of AEs. We identified an additional 10 studies that met inclusion criteria but for which results were not yet posted. As these results become available, we hope to see these included in updated reviews[13] in order to improve recommendations on the use of cannabinoids for treatment-resistant epilepsy.

Conclusions

Few high-quality RCTs have been conducted to date, and those that currently exist have tested CBD in paediatric samples with rare and serious forms of drug-resistant epilepsy. Of these existing studies, a reasonable proportion of patients experienced a decrease in seizure frequency when using pharmaceutical grade CBD products in addition to AEDs; however, minor AEs were likely and complete seizure freedom was unlikely. The timely completion and publication of RCTs will provide a better basis for assessing the benefits and risks of cannabinoid products to control epilepsy.

These results will also provide a better basis for a more rational and informed clinical use of cannabis-based products and cannabinoids to treat drug-resistant epilepsy.

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Contributors MW, SN and LD devised the search strategy and data extraction tool, and ES and MW ran the literature searches. ES, DZ, GC and MW screened studies for inclusion, and extracted study data. DZ and GC conducted GRADE assessments, and ES resolved conflicts. ES conducted the data analysis. ES, GC, DZ, MW, WDH and LD wrote the manuscript, and SN, GKH and MF provided substantial comments on iterations of the draft. All authors approved the final version for submission.

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Competing interests SN, MF and LD have all been investigators on untied investigator-driven educational grants funded by Reckitt Benckiser. MF and LD have received an untied educational grant from Mundipharma for postmarketing surveillance studies of Reformulated OxyContin. SN, MF and LD have been investigators on untied investigator-driven educational grants funded by Indivior. WDH provided evidence to parliamentary committees on medical uses of cannabis in Australia and the UK, and is on the Australian Advisory Council on the Medicinal Use of Cannabis. MW, WDH, MF and LD have previously published manuscripts on the topic of therapeutic use of cannabis.

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JOURNAL OF NEUROLOGY NEUROSURGERY & PSYCHIATRY

Cannabis compound may help curb frequency of epileptic seizures

But evidence to date confined to kids/teens and rare and serious forms of the condition

A naturally occurring compound found in cannabis may help to curb the frequency of epileptic seizures, suggests a review of the available evidence, published online in the ***Journal of Neurology Neurosurgery & Psychiatry.***

But the evidence to date is confined to the treatment of children and teens whose epilepsy does not respond to conventional drugs, and rare and serious forms of the condition, caution the researchers.

Between 70 and 80 percent of people newly diagnosed with epilepsy manage to control their seizures completely using conventional drugs such as valproate and carbamazepine, but that still leaves up to a third whose condition is unresponsive to these treatments.

Preliminary research suggests that naturally occurring compounds found in cannabis (cannabinoids) may dampen down convulsions. And one of these cannabinoids, cannabidiol or CBD for short, seems to show promise for curbing seizures.

To explore this in more depth, the researchers trawled research databases for relevant published and unpublished studies looking at the potential impact of cannabinoids as an add-on to usual treatment on epilepsy seizures, and published up to October 2017.

Out of an initial haul of 91 studies they found six clinical trials (555 patients) and 30 observational studies (2865 patients) that were eligible for inclusion in their review.

All the participants, whose average age was 16, had rare forms of epilepsy that had not responded to usual treatment.

Pooled analysis of the clinical trial data showed that CBD was more effective than a dummy (placebo) drug at cutting seizure frequency by 50 percent or more, and improving quality of life.

CBD was also more effective than placebo at eradicating seizures altogether, although this was still rare.

But the risk of side effects (dizziness and drowsiness), although small, was significant--24 percent higher--while that of serious side effects was twice as high among those taking cannabidiol.

Pooled data from 17 of the observational studies showed that seizure frequency dropped by at least 50 percent in just under half of the patients and disappeared completely in nearly one in 10 (8.5%) in eight of these studies.Quality of life improved in half of the patients in 12 of the studies.

“Pharmaceutical grade CBD as adjuvant treatment in paediatric onset drug resistant epilepsy may reduce seizure frequency,” conclude the researchers. “Existing [randomised controlled trial] evidence is mostly in paediatric samples with rare and severe epilepsy syndromes; [randomised controlled trials] examining other syndromes and cannabinoids are needed.”

Notes for editors

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