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[Intervention Review]

Cannabinoids for epilepsy

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ABSTRACT

Background

Marijuana appears to have anti-epileptic effects in animals. It is not currently known if it is effective in patients with epilepsy. Some states in the United States of America have explicitly approved its use for epilepsy.

Objectives

To assess the efficacy of marijuana, or one of marijuana's constituents in the treatment of people with epilepsy.

Search methods

We searched the Cochrane Epilepsy Group Specialized Register (May 15, 2012), the Cochrane Central Register of Controlled Trials (CENTRAL issue 4 of 12, *The Cochrane Library* 2012),MEDLINE (PubMed, searched on May 15, 2012), ISI Web of Knowledge (May 15, 2012), CINAHL (EBSCOhost, May 15, 2012), and ClinicalTrials.gov (May 15, 2012). In addition, we included studies we personally knew about that were not found by the searches, as well as references in the identified studies.

Selection criteria

Randomized controlled trials (RCTs), whether blinded or not.

Data collection and analysis

Two authors independently selected trials for inclusion and extracted data. The primary outcome investigated was seizure freedom at one year or more, or three times the longest interseizure interval. Secondary outcomes included: responder rate at six months or more, objective quality of life data, and adverse events.

Main results

We found four randomized reports which included a total of 48 patients, each of which used cannabidiol as the treatment agent. One report was an abstract, and another was a letter to the editor. Anti-epileptic drugs were continued in all. Details of randomisation were not included in any study. There was no investigation of whether control and treatment groups were the same or different. All the reports were low quality.

The four reports only answered the secondary outcome about adverse effects. None of the patients in the treatment groups suffered adverse effects.

Authors' conclusions

No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. The dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients, for generally short periods of time, and so the safety of long term cannabidiol treatment cannot be reliably assessed.

PLAIN LANGUAGE SUMMARY

Cannabinoids for Epilepsy

Epilepsy is a disorder of recurrent unprovoked seizures. More than half of seizures can be controlled by anti-epileptic medications. For the remaining patients, they may wish to try other agents. Marijuana, or cannabinoids, may be one such agent. This review assesses the efficacy of marijuana, or cannabinoids, as a treatment for control of epilepsy. No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. Further trials are needed.

BACKGROUND

Description of the condition

Epilepsy is a common disorder of the human brain, accounting for approximately 1% of the global burden of disease (Murray 1994). It has an incidence of 33 to 57 per 100,000 person-years (Annegers 1999; MacDonald 2000; Olafsson 2005), with a lifetime risk of 1.3% to 4% (Hauser 1993; Juul-Jensen 1983).

In epilepsy, drug resistance is defined as failure to stop all seizures in a patient who has had adequate trials of at least two appropriate medications (Kwan 2010). Of those afflicted with epilepsy, about one-third will be drug-resistant (Kwan 2000; Mohanraj 2006); in these patients, the ability of current medications to stop all seizures is dismal (Kwan 2000; Mohanraj 2006). There is great interest in the development of new medications which may have anti-epileptic properties, particularly those agents that affect novel receptors, in the hope of helping those in whom current agents are ineffective.

Description of the intervention

The plant *Cannabis sativa*, commonly known as marijuana, is composed of more than 500 compounds, and new components continue to be discovered (Radwan 2009). Those that are unique to the cannabis plant are called cannabinoids. The principal active component of marijuana is the cannabinoid Δ^9-tetrahydrocannabinol (THC, dronabinol is a pure isomer of THC, which is the main isomer in cannabis) (Mechoulam 1970). Cannabinol is another cannabinoid which has some of the properties of THC, including the possible effect of preventing seizures (Howlett 2004). Cannabidiol is another cannabinoid that may be effective in reducing seizures (Mechoulom 2007). There is fairly extensive evidence in the animal literature that THC has weak anti-seizure properties (Razdan 1983). THC binds to the CB-1 receptor, which is found in the brain as well as peripherally (Matsuda 1990). Another receptor, CB-2, is found peripherally and functions in the immune system (Felder 1998; Munro 1993).

Marijuana has been used since the 19th century for patients with epilepsy. One patient from that time was described whose seizures stopped when marijuana was given and returned when marijuana use was ended (Gowers 1881). There have been other anecdotal reports of its efficacy in humans.

This review will assess the ingestion of marijuana, THC or synthetic cannabinoids (which must include cannabinol, but can include other agents such as cannabidiol) either orally or by inhalation for the treatment of seizures.

How the intervention might work

The possible mechanism of action of cannabinoids has not yet been fully elucidated. There are several theories, none of which provide a full explanation, however we provide two theories here that have been developed by others.

One of the most common kinds of epilepsy in adults arises from changes in the hippocampus. The hippocampus is involved in the transformation of short term memory into long term memory. One of the changes which occurs involves a neuronal subpopulation of the hippocampus called granule cells, which undergo aberrant synaptic reorganization, known as 'mossy fiber spouting'. Mossy fiber sprouting occurs in the human epileptic hippocampus even without hippocampal sclerosis (Sutula 1989). This fiber sprouting synapses with another type of cell called granule cells (Franck 1995). Animal models have shown that this then forms an excitatory feedback loop (Buckmaster 2002; Winokur 2004), which can be the underlying mechanism for seizures (Dudek 1997). In an animal model of seizures, endogenous release of cannabinoids with an excitotoxic agent led to worse and more deadly seizures in mutant mice without CB-1 receptors than in wild-type mice (Marsicano 2003), suggesting a protective effect of cannabinoids. In human hippocampus resected for epilepsy surgery, recordings of granule cells show a reduction of inhibition with a CB-1 agonist (Natasuka 2003). This is likely due to depolarization-induced inhibition of GABAergic cells (Wilson 2001). While this seeming contradiction has not been fully elucidated, one way to explain it would be to suggest that cannabinoids decrease inhibition of aberrant inhibitory cells. The existence of such aberrant inhibition is seen in epileptic rats (Buckmaster 1997).

Another possible mechanism for the protective effect of cannabinoids involves NMDA (N-methyl-D-aspartic acid) receptors. NMDA receptors are a glutamate receptor, which play a crucial role in learning and memory. A synthetic cannabinoid appears to block NMDA receptors in a rodent model, at a different site to other non-competitive NMDA antagonists (Feigenbaum 1989). This agent was shown to be effective at reducing NMDA-induced seizures in mice (Feigenbaum 1989).

Why it is important to do this review

Marijuana is currently licensed in 14 states in the United States for seizures or epilepsy (Hoffman 2010) although its use remains prohibited by federal law. Under the current regime, however, prosecutions have not been pursued following a presidential directive. Marijuana is also legal in Canada for use in epilepsy.

There is no agreement in Europe regarding the medical use of marijuana or THC. There appear to be wide differences in both the law and how the law in various countries is interpreted. According to the European Monitoring Centre for Drugs and Drug Addiction, there are five European countries where medical marijuana appears to be a legal option (EMCDDA 2002).

We wish to examine if there is enough efficacy and safety of cannabinoids in epilepsy through an examination of the medical evidence, to use it as a treatment for epilepsy.

OBJECTIVES

To assess the efficacy and safety of cannabinoids when used as monotherapy or add-on treatment for patients with epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies which examined the study objective and met the following criteria.

1. Randomized controlled trials (RCTs) with allocation concealment that are blinded (single- or double-blinded).
2. RCTs that are unblinded.

We excluded all other study designs, including cohort studies, case-control studies, outcomes research, case studies, case series and expert opinion.

Types of participants

People of any age or sex, with epilepsy of any type.

Types of interventions

Any type of marijuana, synthetic or natural THC, cannabinol, cannabidiol, or combinations that include these agents, for ingestion or inhalation for the control of seizures. We did not exclude trials that used other anti-epileptic medications.

If a trial compared one type of cannabinol to another; for example, THC versus a combination of THC and cannabidiol, we planned to included both arms.

Types of outcome measures

Primary outcomes

- The proportion of patients achieving seizure freedom.

We used the most current International League Against Epilepsy (ILAE) proposed definition of seizure freedom: no seizures of any type for either 12 months or three times the longest (pre-intervention) seizure-free interval, whichever is longest (Kwan 2010).

Secondary outcomes

- Responder rate (the proportion of patients who experienced a 50% or greater reduction in seizure frequency from baseline to maintenance period). We included any maintenance period of at least six months.
- Adverse events requiring either a medication change or emergency room visit (as a percentage).
- Quality of life outcomes measured with objective data.

Search methods for identification of studies

Electronic searches

We searched the following databases and imposed no language restrictions.

- The Cochrane Epilepsy Group Specialized Register (15 May 2012), using the search terms "marijuana or cannabis or cannabinoids or tetrahydrocannabinol or cannabinol or dronabinol".
- The Cochrane Central Register of Controlled Trials (CENTRAL Issue 4 of 12, *The Cochrane Library* 2012), using the search strategy outlined in Appendix 1.
- MEDLINE (PubMed, searched 15 May 2012), using the search strategy outlined in Appendix 2.
- CINAHL (EBSCOhost, searched 15 May 2012) using the search strategy outlined in Appendix 3.
- ISI Web of Knowledge (searched 15 May 2012) using the search strategy outlined in Appendix 4.
- ClinicalTrials.gov (searched 15 May 2012) using the search terms set out in Appendix 5.

For any articles identified for full review, we used the related search criterion and also reviewed the first 25 related abstracts for possible inclusion.

Searching other resources

We contacted the manufacturers of cannabinol or THC, and experts in the field, for information about any unpublished or ongoing studies.

We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies.

Data collection and analysis

Selection of studies

Both review authors independently searched for trials and assessed them for inclusion. Any disagreements were resolved by mutual agreement.

Data extraction and management

Both review authors extracted data onto a data extraction form; any disagreements were resolved by mutual agreement.

The data form included:

- study design, including randomisation; blinding; allocation concealment; type of study;
- study size, including number of participants; type of epilepsy;
- type of intervention, including delivery system; dosage; frequency of use;
- outcomes, including number of drop outs; follow-up; responder rate; adverse effects; objective measures of quality of life; and
- ORBIT classification (Kirkham 2010).

We recorded the rawest form of the data, when possible.

Assessment of risk of bias in included studies

We assessed the risk of bias in the included studies using the Cochrane Collaboration's tool for assessing risk of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and contained in Review Manager 5.1 (RevMan 2011).

Measures of treatment effect

We measured the primary outcome as a continuous outcome.

We measured the secondary outcomes as continuous outcomes.

Unit of analysis issues

We do not expect any unit of analysis issues, except possibly for repeated measures. For measures that are repeated, we used the last recorded measurement, representing the longest follow-up after intervention.

Dealing with missing data

We planned to collect data missing from published studies, abstracts and posters by collecting data from unpublished sources which we hoped to obtain from the sponsors of clinical trials. We planned to undertake further sensitivity analysis to determine the effect of the addition of these data to the final results.

Missing data may be an important problem for this analysis, as we anticipated identifying some older studies which do not provide the same statistical information as present-day studies. If parts of the statistical analysis were missing, for example missing standard deviations, we planned to make an extension to the method of applying a sensible value to those studies (Song 1993).

We did not attempt to complete missing individual patient data.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of patient demographic factors (age, seizure type, number of anti-epileptic drugs taken at randomisation) included in the trials. We assessed statistical heterogeneity using the I^2 statistic, with a value of greater than 75% indicating significant heterogeneity (Higgins 2011).

Assessment of reporting biases

We used the ORBIT study classification scheme to classify trials and assign a risk of bias of the primary outcome to each classification (Kirkham 2010).

Data synthesis

If there is no statistical heterogeneity, we planned to carry out the analysis using a fixed-effect model. If there was significant heterogeneity, we planned to use a random-effects model. We planned to use a Bayesian model for combining the trials if there was significant heterogeneity in some trials and not in others (Prevost 2000).

We described quality of life outcomes narratively.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were planned unless, as above, there were some trials with significant heterogeneity and some trials without.

Sensitivity analysis

If there were at least two trials with missing data, we planned to perform a sensitivity analysis of any outcome that involves all the trials.

RESULTS

Description of studies

Results of the search

See: Characteristics of included studies; Characteristics of excluded studies.

From the formal search of the literature we found eight non-duplicate studies. After initial screening we were able to reject three of those. We also found one ongoing clinical trial. In addition, we identified another fifteen studies, which we either knew about or found in the references of the other studies. We reviewed all of the studies to assess whether they met the inclusion criteria for this review.

Of the fifteen studies either known, or found, by the review authors outside the formal search, four were reviews and another was a paper about illicit drug use in general, so it is not that surprising that we did not pick them up in the search. Another two were posters, one was the chapter of a book, and one was a paper awaiting publication on MEDLINE; such gray literature is not found in formal searching. Two older papers which were known to the authors spelled marijuana as "marihuana", and so we did not find them in the search.

The clinical trial registered at www.ClinicalTrials.gov did not merit inclusion, since it was not about cannabis or cannabinoids. It was about the use of *Passiflora incarnata* in the treatment of partial epilepsy (NCT00982787) which is not the subject of this review.

Included studies

No studies assessed the primary outcome in this review; seizure freedom for twelve months or three times the longest seizure-free interval.

Four studies met all the inclusion criteria except the primary outcome; however, we have reviewed them here as all of them did include one of the secondary outcomes; adverse events.

In Cunha 1980, there were 15 patients with temporal lobe epilepsy with secondarily generalized seizures, with at least one generalized seizure weekly. These patients received 200 to 300 mg of cannabidiol daily or placebo. The patients received the medication for as long as four and-a-half months, and seizure frequency was reported. The patients tolerated cannabidiol without toxicity.

In Ames 1985, 12 patients institutionalized due to mental retardation with uncontrolled seizures were given three capsules of sunflower oil (as placebo) or sunflower oil and 100 mg of cannabidiol for the first week (as treatment). Thus, patients who were treated received 300 mg of cannabinol daily for the first week. During the next three weeks (weeks two to four), the patients were given two capsules, so for those in the treatment arm, they received 200 mg of cannabidiol daily. There were no differences in seizure frequency between the two groups, although no details were given. The only side effect was mild drowsiness.

In Mechoulam 1978, nine patients were randomized to either 200 mg of cannabidiol or placebo. Patients were treated with their habitual medication and either cannabidiol or placebo for three months. Two of four patients treated with cannabidiol achieved seizure freedom for the three months of treatment, and none of the five treated with placebo were described as experiencing improvement. No toxic effects were observed.

The fourth trial is an unpublished abstract from a conference, Trembly 1990. In this abstract, 12 patients were treated with a single-blind placebo for six months followed by double-blind 300 mg of cannabidiol or placebo in a cross-over trial lasting an additional 12 months. No statistics were performed, but a preliminary review suggested that there was some reduction in seizure frequency. Further information is provided by Consroe 1992. Here, they stated that 10 patients in the trial did not have changes in the seizure character or frequency, and did not suffer any side effects.

Excluded studies

There were sixteen excluded studies. Most were case reports and retrospective studies. Two were observational studies without controls. Two were review papers; one of the review papers

included additional information about Trembly 1990 which we included when describing the study.

Risk of bias in included studies

Allocation

None of the four studies reported on allocation, since none of them mentioned how the patients were randomized.

Blinding

Each of the four trials used placebo. Ames 1985 and Cunha 1980 specify that the placebo appeared identical to the experimental capsules. Ames 1985 and Mechoulam 1978 were reportedly double-blind studies. Ames 1985 used "arbitrary" allocation, and the people who measured effectiveness were not aware of which arm the patients were in. No details of the investigator-blinding were provided by Mechoulam 1978. Trembly 1990 was a partially single-blind and partially double-blind study, with no details of the investigator-blinding provided. Cunha 1980 was meant to be a single-blind study, but there is risk for unblinding of the participants of the study, as one patient was switched from the control to the experimental arm. No information was given except that such a switch occurred.

Incomplete outcome data

No study provided data for the primary outcome in this review. Of the secondary outcomes, data were only provided for safety. There was no mention of patients dropping out in any of the studies.

Selective reporting

There did not appear to be selective reporting in any of the four trials. There is a question about drop outs in Cunha 1980, because when the results are re-reported, the number of patients changes from 12 to 10, and that might possibly raise the question of selective reporting.

Since the primary outcome was not measured, for any of these studies, the ORBIT classification does not apply.

Other potential sources of bias

None of the studies have a table that compares baseline characteristics of the patients in the control versus the treatment group.

Effects of interventions

No information was given in any of the four included studies about the primary outcome: seizure freedom meeting the current ILAE definition. There was also no information in any of the four included studies about two of the secondary outcomes: responder rate lasting at least six months, or objective quality of life measures. There was reporting about one secondary outcome, adverse events: all four trials reported no toxic effects with treatment of 200 to 300 mg of cannabidiol however, one mentioned mild drowsiness (Ames 1985).

DISCUSSION

Four studies met the inclusion criteria for this review. None of the four studies provided information to address the primary outcome of this review; seizure freedom of 12 months or three times the longest interseizure interval. Of the secondary outcomes, the only one that could be answered was that there were no significant side effects in any of the patients studied, except one study (Ames 1985), which reported mild drowsiness.

One of the major weaknesses of the present review is the fact that it is possible that there are other studies which may not have been included in this review. While we either knew of, or found, an additional fifteen studies, which we considered for inclusion, there may be others we do not know about.

Summary of main results

No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. The dose of 200 to 300 mg daily of cannabidiol may be safe, although the number of patients treated at this dose is small, and except for one study, the treatment was only during a short period of time.

Overall completeness and applicability of evidence

The evidence from the four trials is far from complete. These are four very small randomized trials of low quality, and none of them measure freedom at 12 months or three times the greatest interseizure period, or even responder rate at six months.

Quality of the evidence

Under contemporary standards, all four trials are low quality, and have to be at high risk for bias. The largest study was of 15 patients. One of the studies was an abstract that had additional details in the chapter of a book, and another was a letter to the editor.

Potential biases in the review process

The formal search process missed more than half of the articles that we considered for inclusion. It is possible that there are other articles of which the authors are unaware, or are not included in the reference lists of the included studies.

Agreements and disagreements with other studies or reviews

There have been no recent reviews of this topic.

AUTHORS' CONCLUSIONS

Implications for practice

No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy.

There is an insufficient body of evidence to recommend using marijuana to treat epilepsy. The dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients, for generally short periods of time, and so no conclusions can be drawn about the safety of long term cannabidiol treatment.

Implications for research

There is a body of animal research that suggests that it might be useful to evaluate the efficacy of cannabinoids for treatment of epilepsy in humans. None of the existing clinical research is of sufficient quality or size to answer this question. If the question were to be addressed, there would need to be a series of properly designed, high quality, and adequately powered trials.

ACKNOWLEDGEMENTS

None.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by year of study]

Mechoulam 1978

Methods	Controlled trial of 9 individuals with uncontrolled temporal lobe epilepsy who had failed treatment with multiple medications were randomized into two groups
Participants	Four people with uncontrolled epilepsy were treated with cannabidiol (Group I), and five people with uncontrolled epilepsy were treated with placebo (Group II). Groups I and II were not compared. Baseline seizure frequency was not reported
Interventions	Group I received 200 mg cannabidiol daily for three months. Group II received placebo for the same time. Both groups received anticonvulsants. No information is given as to clinic visits for either group
Outcomes	At three months, two of the Group I patients were seizure-free for the entire three months, one showed partial improvement, and one did now show any improvement. No definition of improvement was given. No toxic effects were observed. None of the placebo patients showed improvement
Notes	It was not specified if the doses of anticonvulsants at baseline were allowed to be varied during the three-month trial There was no power calculation and the sample size was very small. There is no statistical analysis

Risk of bias

Bias	Authors' judgement	Support for judgement

Mechoulam 1978 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The authors state this is a double-blind trial, but do not provide other information to make this judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	High risk	There was no comparison between Group I and Group II to determine if their baseline characteristics were similar
Orbit classification	Low risk	Not applicable

Cunha 1980

Methods	Controlled trial of 15 epileptic patients, with a documented EEG (electroencephalogram) showing a temporal lobe irritative activity, and who were having at least one generalized convulsion weekly, for a period of at least one year. These patients were randomized into two groups
Participants	Seven patients were treated with cannabidiol (Group I) and eight patients served as controls (Group II). One patient was transferred to the treatment group after one month. The baseline characteristics of the groups were not compared. An intention-to-treat analysis was not performed
Interventions	Both groups had two weeks to determine the baseline seizure frequency. Group I received 200 to 300 mg of cannabidiol daily for between three and 18 weeks. Group II received placebo
Outcomes	There were weekly visits at the hospital; there was no predetermined time for outcome determination. At the time of last clinical evaluation, one placebo patient was seizure-free, and four treatment patients were seizure-free
Notes	While not explicitly mentioned, based on their table IV, it seems that practitioners were allowed to increase the dosage from 200 to 300 mg daily of cannabidiol. It does not mention if there were any increases in the number of tablets of placebo. There was no power calculation and the sample size was very small

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias)	Unclear risk	Patients were allowed an increase in the dosage of cannabidiol from 2 to 3 tablets, and one patient was transferred from the control to treatment group.

Cunha 1980 *(Continued)*

All outcomes		This increase may have unblinded the patients so treated. Also, this changing suggests that the investigators were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No time for outcome given in trial
Selective reporting (reporting bias)	Low risk	All patients were evaluated weekly
Other bias	High risk	There was no comparison between Group I and Group II to determine if their baseline characteristics were similar
Orbit classification	Low risk	Not applicable

Ames 1985

Methods	Controlled trial of 12 institutionalized, mentally retarded patients with frequent seizures who were not controlled on conventional anticonvulsant therapy. These patients were "arbitrarily" divided into two groups; it is unclear if they were randomized. They recorded seizures and measured side effects
Participants	The abstract does not state if the patients were evenly split between the two groups. One group received cannabidiol (Group I), and the other group received placebo (Group II). These patients were segregated to one ward and observed with experienced nursing staff. The baseline characteristics of the groups were not compared
Interventions	One group was treated with 300 mg cannabidiol daily for the first week and then 200 mg daily for the next three weeks (Group I), and the other was treated with placebo (Group II)
Outcomes	There was found to be no statistically significant difference in seizure frequency between the two groups. Presumably, this occurred at the end of the four weeks, but this is not explicitly indicated. They state there were "no immediate side effects except for mild drowsiness"
Notes	This is a letter to the editor, and lacks a lot of details. There was no power calculation and the sample size was very small

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	One of the experimenters was not blinded. Charts submitted to the unblinded experimenter to analyze the data
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	No information given

Ames 1985 *(Continued)*

Other bias	High risk	There was no comparison between Group I and Group II to determine if their baseline characteristics were similar
Orbit classification	Low risk	Not applicable

Trembly 1990

Methods	This is a randomized trial where there were two groups in a cross-over design. There were 12 patients with incompletely controlled epilepsy which was reported in an abstract (Trembly 1990). That study was summarized in a book chapter two years later by others, who report only 10 patients were part of the study (Consroe 1992).
Participants	The patients were incompletely controlled epileptic adults. See below for further details
Interventions	Each patient served as his own control. There was a three-month period where the patients received only their outpatient anti-epileptics. This was followed by six months of all patients receiving placebo, which was not blinded to investigators. Patients' anti-epileptic medications were allowed to be changed during this period, but not afterwards. This was followed by randomization to control and cannabidiol 100 mg given three times a day, for six months. Afterwards, patients on placebo received treatment, and patients receiving treatment received placebo, for six months. Both groups, then had a three-month period without either placebo or treatment
Outcomes	The abstract (Trembly 1990) did not report statistical analysis of the trial outcomes/main effects, only safety (lab tests) and verbal statements about "no discernable effect" on MMPI (Minnesota Multiphasic Personality Inventory), Beck depression inventory, trail making test, and finger tapping test. Consroe's book chapter in 1992 states that Trembly reported that there were "no effects on seizure pattern, character or frequency"
Notes	We attempted to contact authors for additional information. Trembly's group was no longer at the original institution and could not be located. Consroe was emailed, and he did respond. We could not resolve the discrepancy between the book chapter and the abstract. The book chapter had a different sample size, and additional reported outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not specified
Allocation concealment (selection bias)	Unclear risk	Information not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single-blind for first part of study. The second part was double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not specified
Selective reporting (reporting bias)	Unclear risk	Information not specified

Trembly 1990 *(Continued)*

Other bias	High risk	Unclear why the information from original abstract is different than information contained in Consroe 1992. This discrepancy is not talked about in Consroe 1992.
Orbit classification	Low risk	Not applicable

Characteristics of excluded studies [ordered by year of study]

Study	Reason for exclusion
Davis 1949	This study is of five institutionalized children who received two homologs of THC. Two responded to the first homolog. One more responded to the second homolog, but another's seizures worsened. Response was not quantified. The time of treatment was seven weeks. Since there was no control group, this is an observational study, and was excluded. It did not have the primary outcome.
Keeler 1967	A 29-year-old with generalized tonic clonic (GTC) seizures with EEG findings consistent with that, had been seizure-free for six months after stopping his two anti-epileptic medications. On the same time period when he started using marijuana regularly, he had a recurrence of 3 GTCs. This was a case report, and so was excluded.
Perez-Reyes 1974	A patient with epilepsy with a baseline of diffuse spike and wave during sleep. During sleep, he had an infusion of cannabidiol, and the frequency of spike and wave increased. No statistics were done. This was a case report, and so was excluded.
Consroe 1975	A patient with seizures resistant to phenobarbital and diphenylhydantoin became seizure-free when he smoked marijuana. His seizures returned when he ran out of medications, suggesting it was the combination of medications and marijuana that controlled his seizures. This is a case report, and so was excluded.
Feeney 1976	This letter described that a physician sent out 330 surveys about prescribed and illegal drug use of patients from the Convulsive Disorder Unit of the Bernalillo County Medical Center. Of the 98 responses, 72 were considered epileptics. Of these, 13 reported using marijuana, and one felt it made his seizures better and another felt is made his seizures worse. This is a cross-sectional study, and so was excluded.
Carlini 1981	This article reported the effects of cannabidiol in healthy volunteers, people with insomnia, and people with epilepsy; however the sample with epilepsy was already reported by Cunha 1980 (which is in this review). No additional information was included in this paper than the original study. This study included information published in another article, Cunha 1980, and so was excluded.
Ng 1990	This study examined illicit drug use among 308 patients with first seizure versus 294 controls admitted for an acute surgical condition as an emergency. While there were more men in the group of cases, there was significantly less marijuana use than the controls, and significantly more heroin use than controls. The authors suggest that this means that heroin is pro-convulsant and marijuana is anticonvulsant. This is a case-control study, and so was excluded.

Study	Reason for exclusion
Ellison 1990	A 29-year-old with bipolar disorder and alcohol abuse, who had an electrical shock. He was smoking marijuana. When he stopped, he began to have confusional episodes with an aura of burnt batteries. He had focal spike and wave on EEG (electroencephalogram). He was started on an AED (antiepileptic drug) and resumed marijuana use. When he stopped marijuana again, his spells returned. He restarted the marijuana, and his spells stopped This was a case report, and so was excluded.
Brust 1992	This is a follow-up of the Ng 1990 study using the same patients. They found that, for men, the odds ratio (OR) of unprovoked seizures was: OR 0.36 (0.18 to 0.74) and provoked seizures: OR 0.18 (0.04 to 0.84), if the patient had used marijuana within the last three months. A similar effect was not seen among women. The authors suggest that their data proves marijuana is protective of both provoked and unprovoked seizures, for men. This is still a case-control study, and so was excluded.
Consroe 1992	This book chapter includes additional information that was not included in Trembly 1990, which we have included when describing the abstract. It does not contain any additional studies. We tried to contact the authors of this chapter for more information and did not get a response.
Gordon 2001	The authors of this study informally spoke with more than 215 patients in their practice with active epilepsy, who either used marijuana intermittently or regularly. They found that 194 patients (90%) did not identify a relationship between marijuana use and seizure frequency. Sixteen (7%) believed their seizures were less frequent, and 5 (2%) believed their seizures were less frequent. This is a descriptive study, and so was excluded.
Lorenz 2003	This abstract from the International Association for Cannabis as Medicine 2003 conference described eight children aged three to 14 who were treated with THC (Δ^9-tetrahydrocannabinol). Four of these children had epilepsy. Of these four, the effect of THC could not be assessed in one, one had no effect on his seizures, and for two the frequency of their seizures decreased (without explicitly saying what decreased meant). This is an observational study, and so was excluded.
Lorenz 2004	This is the published form of the abstract Lorenz 2003. There remains no quantification about what decrease was for the two patients. It remains an observational study, and so remains excluded.
Gross 2004	Of 138 patients who agreed to participate in a survey, 28 were active users of marijuana. Of those 28, 19 felt that their seizure severity was improved, and 15 felt that their seizure frequency was improved. None felt that either become worse. In addition, three felt that medication side effects were improved and one felt that medication side effects were worsened. This is a cross-sectional study, and so was excluded.
Mortati 2007	A 45-year-old with cerebral palsy and epilepsy had marked improvement of his seizures with marijuana use. While taking marijuana his seizure frequency went from multiple per day to rarely. This was a case report, and so was excluded.
Lutz 2008	This review talks about how the endocannabinoid system may be implicated in showing how febrile seizures in children may lead to long term changes. This paper is expert opinion, and so was excluded.

THC (Δ^9-tetrahydrocannabinol)

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Epilepsy explode all trees

#2 MeSH descriptor Seizures explode all trees

#3 epilep* or seizure* or convulsion*

#4 (#1 OR #2 OR #3)

#5 MeSH descriptor Cannabis explode all trees

#6 (marijuana)

#7 (cannabis)

#8 MeSH descriptor Cannabinoids explode all trees

#9 (cannabinoid*)

#10 (tetrahydrocannabinol)

#11 (cannabinol)

#12 (dronabinol)

#13 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

#14 (#4 AND #13)

Appendix 2. MEDLINE (PubMed) search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in Lefebvre 2011.

#1 "Cannabis"[Mesh]
#2 cannabis[Text word]
#3 "Cannabinoids"[Mesh]
#4 cannabinoids[Text Word]
#5 marijuana[Text Word]
#6 tetrahydrocannabinol[Text Word]
#7 cannabinol[Text Word]
#8 dronabinol[Text Word]
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 "Epilepsy"[Mesh]
#11 epilep*[Text Word]
#12 "Seizures"[Mesh]
#13 seizure*[Text Word]
#14 convuls*[Text Word]
#15 #10 or #11 or #12 or #13 or #14
#16 #9 and #15
#17 randomized controlled trial[pt]
#18 controlled clinical trial[pt]
#19 randomized[tiab]
#20 placebo[tiab]
#21 clinical trials as topic[Mesh:NoExp]
#22 randomly[tiab]
#23 trial[ti]
#24 #17 or #18 or #19 or #20 or #21 or #22 or #23
#25 animals[Mesh] not humans[Mesh]
#26 #24 not #25
#27 #26 and #16

Appendix 3. CINAHL search strategy

S19	S9 and S13 and S18
S18	S14 or S15 or S16 or S17
S17	TX cannabinol or TX dronabinol
S16	TX marijuana or TX tetrahydrocannabinol
S15	TX cannabis or TX cannabinoid*
S14	(MH "Cannabis")
S13	S10 or S11 or S12
S12	(MH "Seizures+")
S11	(MH "Epilepsy+")
S10	epilep* or seizure* or convulsi*
S9	(S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8)
S8	MJ placebo
S7	KW random* assign* or KW random* allocat* or KW placebo*
S6	TI random* assign* or TI random* allocat* or TI placebo*
S5	AB random* assign* or AB random* allocat* or AB placebo*
S4	TI clinical trial* or AB clinical trial* or KW clinical trial*
S3	AB single blind or AB double blind or AB treble blind or AB triple blind
S2	TI single blind or TI double blind or TI treble blind or TI triple blind
S1	TI randomi* or AB randomi* or KW randomi*

Appendix 4. ISI Web of Knowledge search strategy

#7	#6 AND #5 *DocType=All document types; Language=All languages;*
#6	Title=(random*) OR Title=(placebo*) OR Title=(double blind) OR Title=(trial) OR Title=(study) *DocType=All document types; Language=All languages;*
#5	#4 AND #1 *DocType=All document types; Language=All languages;*

(Continued)

#4	#3 OR #2 *DocType=All document types; Language=All languages;*
#3	Topic=(tetrahydrocannabinol) OR Topic=(cannabinol) OR Topic=(dronabinol) *DocType=All document types; Language=All languages;*
#2	Topic=(cannabis) OR Topic=(cannabinoid*) OR Topic=(marijuana) *DocType=All document types; Language=All languages;*
#1	Topic=(epilep*) OR Topic=(seizure*) *DocType=All document types; Language=All languages;*

Appendix 5. ClinicalTrials.gov search terms

Epilepsy AND marijuana

Epilepsy AND cannabis

Epilepsy AND cannabinoids

Epilepsy AND tetrahydrocannabinol

Epilepsy AND cannabinol

Epilepsy AND dronabinol

Seizures AND marijuana

Seizures AND cannabis

Seizures AND cannabinoids

Seizures AND tetrahydrocannabinol

Seizures AND cannabinol

Seizures AND dronabinol

CONTRIBUTIONS OF AUTHORS

Dr. Gloss created and wrote the review. It was edited and agreed to by Dr. Vickrey.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There was a single error in the protocol, where cannabinol was replaced with cannabinoid.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Cannabidiol [*therapeutic use]; Epilepsy [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans