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Cannabinoids for epilepsy

A B S T R A C T

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 and safety of cannabinoids when used as monotherapy or add-on treatment for people with epilepsy.

Search methods
We searched the Cochrane Epilepsy Group Specialized Register (9 September 2013), Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2013, Issue 8), MEDLINE (Ovid) (9 September 2013), ISI Web of Knowledge (9 September 2013), CINAHL (EBSCOhost) (9 September 2013), and ClinicalTrials.gov (9 September 2013). In addition, we included studies we personally knew about that were not found by the searches, as well as searched the 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 the 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 trial reports that 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 studies. Details of randomisation were not included in any study report. There was no investigation of whether the control and treatment participant 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 generally for 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 to obtain better control. Marijuana, or cannabinoids, may be one such agent. This review assessed the efficacy of marijuana, or cannabinoids, as a treatment for epilepsy. No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. Further trials are needed.
fibre sprouting occurs in the human epileptic hippocampus even without hippocampal sclerosis (Sutula 1989). This fibre 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 gamma-aminobutyric acid secreting (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 N-methyl-D-aspartic acid (NMDA) receptors. NMDA receptors are glutamate receptors, 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 in reducing NMDA-induced seizures in mice (Feigenbaum 1989).

Why it is important to do this review
Marijuana is currently licensed in 22 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 people 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 was blinded (single- or double-blinded).
2. RCTs that were 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 include 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
Searches were run for the original review in July 2011. For the latest update we searched the following databases. There were no language restrictions.

- Cochrane Epilepsy Group Specialized Register (9 September 2013), using the search strategy outlined in Appendix 1.
- Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2013, Issue 8), using the search strategy outlined in Appendix 2.
- MEDLINE (Ovid) (searched 9 September 2013), using the search strategy outlined in Appendix 3.
- CINAHL (EBSCOhost) (searched 9 September 2013), using the search strategy outlined in Appendix 4.
- ISI Web of Knowledge (searched 9 September 2013), using the search strategy outlined in Appendix 5.
- ClinicalTrials.gov (searched 9 September 2013), using the search strategy outlined in Appendix 6.

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 cannabinoil or THC, and experts in the field, for information about any unpublished or ongoing studies. We handsearched selected journals.

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:

- type of intervention, including delivery system; dosage; frequency of use;
- outcomes, including number of dropouts; 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 randomization) included in the trials. We assessed statistical heterogeneity using the I² 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 was 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 involved 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 rejected three of those. We also found one ongoing clinical trial. In addition, we identified another 21 studies that we either knew about, found by a manual search, 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 21 studies either known or found, by the review authors outside the formal search, four were reviews, one was a paper about illicit drug use in general, and one was about marijuana potency, so it was not that surprising that we did not pick them up in the search. Another two were posters, four were book chapters, one was a paper awaiting publication in MEDLINE, two were from a journal not part of the journals indexed in PubMed; such gray literature is not found in formal searching. There were three surveys about marijuana use, but they did not talk about marijuana as a therapy. 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 12 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, that is 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 4.5 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 cannabidiol 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 was 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 was 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 22 excluded studies. Most were case reports and retrospective studies. Five 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 specified 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 was a 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 was a question about dropouts in Cunha 1980 because when the results were re-reported the number of patients changed 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 did not apply.

**Other potential sources of bias**
None of the studies had a table that compared baseline characteristics of the patients in the control group 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 for 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 in one study (Ames 1985) which reported mild drowsiness.

One of the 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 21 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 for 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 measured freedom from seizures 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.

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

References

References to studies included in this review

Ames 1985 {published data only}

Cunha 1980 {published data only}

Mechoulam 1978 {published data only}

Trembley 1990 {published data only (unpublished sought but not used)}

References to studies excluded from this review

Brust 1992 {published data only}

Carlini 1981 {published data only}

Consroe 1975 {published data only}

Consroe 1992 {published data only (unpublished sought but not used)}

Corral 2001 {published data only}

Davis 1949 {published data only}

Ellison 1990 {published data only}

Feeney 1976 {published data only}

Gieringer 2002 {published data only}
Cannabinoids for epilepsy (Review)

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Gordon 2001  [published data only]

Grinspoon 1997  [published data only]

Gross 2004  [published data only]

Grotenherman 2003  [published data only]

Keeler 1967  [published data only]

Lorenz 2003  [published data only]

Lorenz 2004  [published data only]

Lutz 2008  [published data only]

Mortati 2007  [published data only]

Ng 1990  [published data only]

Perez-Reyes 1974  [published data only]

Petro 1997  [published data only]

Pijlman 2005  [published data only]

Additional references

Annegers 1999

Buckmaster 1997

Buckmaster 2002

Dudek 1997

EMCDDA 2002

Feigenbaum 1989

Felder 1998

Franck 1995

Gowers 1881

Hauser 1993

Higgins 2011
Kwan 2010

Howlett 2004

Juul-Jensen 1983

Kirkham 2010

Kwan 2000

Kwan 2010

Lefebvre 2011

MacDonald 2000

Marsicano 2003

Matsuda 1990

Mechoulam 1970

Mechoulam 2007

Mohanraj 2006

Munro 1993

Murray 1994

Natsuka 2003

Olafsson 2005

Prevost 2000

Radwan 2009

Razdan 1983

RevMan 2011

Song 1993

Sutula 1989

Wilson 2001

Winokur 2004
Winokur RS, Kubal T, Liu D, Davis SF, Smith BN. Recurrent excitation in the dentate gyrus of a murine model...

References to other published versions of this review

Gloss 2012  
* Indicates the major publication for the study
### Characteristics of included studies  
*ordered by year of study*

**Mechoulam 1978**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Controlled trial of 9 individuals with uncontrolled temporal lobe epilepsy who had failed treatment with multiple medications were randomized into two groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>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</td>
</tr>
<tr>
<td>Interventions</td>
<td>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</td>
</tr>
<tr>
<td>Outcomes</td>
<td>At three months, two of the Group I patients were seizure-free for the entire three months, one showed partial improvement, and one did not show any improvement. No definition of improvement was given. No toxic effects were observed. None of the placebo patients showed improvement</td>
</tr>
<tr>
<td>Notes</td>
<td>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</td>
</tr>
</tbody>
</table>

### Risk of bias

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

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.

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.

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.

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.

<table>
<thead>
<tr>
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<td>No information given</td>
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<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>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. This increase may have unblinded the patients so treated. Also, this changing suggests that the investigators were not blinded</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>No time for outcome given in trial</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All patients were evaluated weekly</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>There was no comparison between Group I and Group II to determine if their baseline characteristics were similar</td>
</tr>
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</table>
### 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.

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</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
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<td>One of the experimenters was not blinded. Charts submitted to the unblinded experimenter to analyse the data</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>No information given</td>
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<tr>
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<tr>
<td>Other bias</td>
<td>High risk</td>
<td>There was no comparison between Group I and Group II to determine if their baseline characteristics were similar</td>
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</table>
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.

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<td>Unclear risk</td>
<td>Information not specified</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Single-blind for first part of study. The second part was double-blind</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Information not specified</td>
</tr>
</tbody>
</table>

Cannabinoids for epilepsy (Review)
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Selective reporting (reporting bias) | Unclear risk | Information not specified
---|---|---
Other bias | High risk | Unclear why the information from original abstract is different from 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]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis 1949</td>
<td>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.</td>
</tr>
<tr>
<td>Keeler 1967</td>
<td>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.</td>
</tr>
<tr>
<td>Perez-Reyes 1974</td>
<td>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.</td>
</tr>
<tr>
<td>Consroe 1975</td>
<td>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.</td>
</tr>
<tr>
<td>Feeney 1976</td>
<td>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 it made his seizures worse. This is a cross-sectional study, and so was excluded.</td>
</tr>
<tr>
<td>Carlini 1981</td>
<td>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 in the original study. This study included information published in another article, Cunha 1980, and so was excluded.</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
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<td>-------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ellison 1990</td>
<td>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 (anti-epileptic 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.</td>
</tr>
<tr>
<td>Ng 1990</td>
<td>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.</td>
</tr>
<tr>
<td>Consroe 1992</td>
<td>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.</td>
</tr>
<tr>
<td>Brust 1992</td>
<td>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 0.36 (95% CI 0.18 to 0.74) and provoked seizures OR 0.18 (95% CI 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.</td>
</tr>
<tr>
<td>Grinspoon 1997</td>
<td>The authors allow three people to talk about their personal experiences with marijuana. Two of the patients were able to be seizure-free with marijuana. The third was able to markedly decrease his seizure frequency. This was a case series, so was excluded.</td>
</tr>
<tr>
<td>Petro 1997</td>
<td>This is a retrospective case review of 11 patients with epilepsy. The only information that is provided is that the patients were males, aged 19-43 years, and that five of seven had complex partial seizures with secondary generalization. This is a case series, so was excluded.</td>
</tr>
<tr>
<td>Corral 2001</td>
<td>77 patients in a medical marijuana program were surveyed; 3 gave epilepsy as their primary diagnosis, 1 gave epilepsy as a secondary diagnosis for the use of medical marijuana. This was a descriptive study, so was excluded.</td>
</tr>
<tr>
<td>Gordon 2001</td>
<td>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 was a descriptive study, so was excluded.</td>
</tr>
<tr>
<td>Gieringer 2002</td>
<td>2480 medical marijuana patients in California were interviewed. The primary ICD-9 diagnosis for medical marijuana use among this cohort was epilepsy for 25 patients. This was a descriptive study, so was excluded.</td>
</tr>
</tbody>
</table>
A questionnaire was sent to patients in Germany and Austria. 165 patients responded and were included. 3 patients with epilepsy responded. One patient said his physician refused to prescribe THC (the other two did not respond to this question).

This was an observational study, so was excluded.

This abstract from the International Association for Cannabis as Medicine 2003 conference described eight children aged three to 14 who were treated with THC (Δ9-tetrahydrocannabinol). Four of these children had epilepsy. Of these four, the effect of THC could not be assessed in one, for one it had no effect on his seizures, and for two the frequency of their seizures decreased (without explicitly saying what decreased meant).

This was an observational study, and so was excluded.

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.

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 was a cross-sectional study, and so was excluded.

This paper talked about the increase in potency in marijuana. It does not specifically mention epilepsy.

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.

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 (Δ9-tetrahydrocannabinol)
DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

#1 MeSH DESCRIPTOR Cannabis Explode All WITH AE AH CH CL CY DE EM EN GE GD IM ME MI PS PH PO RE TO UL VI
#2 MeSH DESCRIPTOR Cannabinoids Explode All WITH AD AE AG AN AI BI BL CF CS CH CL CT DU EC GE HI IM IP ME PK PD PO RE SE ST SD TU TO UR
#3 cannabis or cannabinoids or marijuana or tetrahydrocannabinol or cannabinol or dronabinol
#4 (#1 OR #2 OR #3) AND >2011:YR

Appendix 2. CENTRAL search strategy

The following search strategy was used for the latest update.
#1 (epilep* or seizure* or convuls*):ti,ab,kw (Word variations have been searched)
#2 MeSH descriptor: [Epilepsy] explode all trees
#3 MeSH descriptor: [Seizures] explode all trees
#4 (#1 or #2 or #3)
#5 MeSH descriptor: [Cannabis] explode all trees
#6 MeSH descriptor: [Cannabinoids] explode all trees
#7 cannabis or cannabinoid* or marijuana or tetrahydrocannabinol or cannabinol or dronabinol
#8 #5 or #6 or #7
#9 #4 and #8 from 2011, in Trials

The following was the original 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 3. MEDLINE (Ovid) search strategy

The following search strategy was used for the latest update.
This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in Lefebvre 2011.

1. exp Cannabis/
2. exp Cannabinoids/
3. (cannabis or cannabinoids or marijuana or tetrahydrocannabinol or cannabinol or dronabinol).tw.
4. 1 or 2 or 3
5. exp Epilepsy/
6. exp Seizures/
7. (epilep$ or seizure$ or convuls$).tw.
8. 5 or 6 or 7
9. (randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly).ab.
10. clinical trials as topic.sh.
11. trial.ti.
12. 9 or 10 or 11
13. exp animals/ not humans.sh.
14. 12 not 13
15. 4 and 8 and 14
16. limit 15 to ed=20120515-20130909

The following was the original search strategy.

#1 "Cannabis"[Mesh]
#2 cannabis[Text word]
#3 "Cannabinoids"[Mesh]
#4 cannabinoids[Text Word]
#5 marijuana[Text Word]
#6 tetrahydrocannabinol[Text Word]
#7 cannabino[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 4. CINAHL search strategy

The following search strategy was used for the latest update.

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<th>S6</th>
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<th>TX ( randomi* OR random* assign* or random* allocat* or placebo* or clinical trial*) OR TI ( single blind or double blind or treble blind or triple blind ) OR AB ( single blind or double blind or treble blind or triple blind ) OR MJ placebo</th>
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<table>
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<th>TX marijuana or TX tetrahydrocannabinol</th>
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<table>
<thead>
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<th>(S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8)</th>
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<table>
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Appendix 5. ISI Web of Knowledge search strategy

The following search strategy was used for the latest update.

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<td></td>
<td>DocType=All document types; Language=All languages;</td>
</tr>
<tr>
<td>#3</td>
<td>Topic=(cannabis or cannabinoid* or marijuana or tetrahydrocannabinol or cannabinol or dronabinol)</td>
</tr>
<tr>
<td></td>
<td>DocType=All document types; Language=All languages;</td>
</tr>
<tr>
<td>#2</td>
<td>Topic=((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind*) NEAR/2 (trial OR method OR procedure OR study))</td>
</tr>
<tr>
<td></td>
<td>DocType=All document types; Language=All languages;</td>
</tr>
<tr>
<td>#1</td>
<td>Topic=((epilep* OR “infantile spasm” OR seizure OR convuls* OR (syndrome NEAR/2 (aicardi OR angelman OR doose OR dravet OR “landau kleffner” OR “lennox gastaut” OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR “sturge weber” OR “unverricht lundborg” OR west)) OR “ring chromosome 20” OR “R20” OR “myoclonic encephalopathy” OR “pyridoxine dependency”) NOT “eclampsia”)</td>
</tr>
<tr>
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<td>DocType=All document types; Language=All languages;</td>
</tr>
</tbody>
</table>

The following was the original search strategy.
### Appendix 6. ClinicalTrials.gov search terms

The following search strategy was used for the latest update.

(Epilepsy OR Seizures) AND (marijuana OR cannabis OR cannabinoids OR tetrahydrocannabinol OR cannabinol OR dronabinol)

The following was the original search strategy.

- 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
WHAT'S NEW

Last assessed as up-to-date: 9 September 2013.

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<th>Event</th>
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<td>New search has been performed</td>
<td>Searches updated 9 September 2013.</td>
</tr>
<tr>
<td>9 September 2013</td>
<td>New citation required but conclusions have not changed</td>
<td>No new trials identified. Conclusions remain unchanged.</td>
</tr>
</tbody>
</table>

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 cannbinol 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