



Slim Evidence for Cannabinoids for Epilepsy

Cannabinoids for Epilepsy.

Gloss D, Vickrey B. *Cochrane Database of Systematic Reviews*. 2012; Issue 6. Art. No.: CD009270. doi: 10.1002/14651858.CD009270.pub.2.

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.

Commentary

Most practitioners who treat epilepsy will encounter patients using marijuana (*Cannabis sativa*) as alternative therapy. Anecdotal evidence of its efficacy against seizures is common—in one study of an epilepsy center, 21% admitted using marijuana in the prior year, with the majority of these individuals feeling that it benefited seizure control (1). However, other patients may report marijuana as a possible seizure precipitant (2). This issue is particularly relevant to today's clinical practice because 18 U.S. states and the District of Columbia have medical marijuana laws or policies, as do Canada, the Netherlands, and Israel. What is the actual evidence that marijuana or its component substances can prevent seizures?

Marijuana contains more than 500 chemical compounds (cannabinoids), including tetrahydrocannabinol (THC), felt

primarily responsible for its psychoactive effects (3). THC and other cannabinoids have been demonstrated to have some antiseizure effects in animal models (4, 5), with one mechanism felt to be NMDA-receptor blockade (6). However, low-dose THC infusion has been shown to induce seizures in one strain of rabbits (7). Indirect evidence for the benefit of marijuana itself for human seizures comes from a study demonstrating that marijuana use was less common in patients admitted to an urban hospital for new onset seizures, than it was in a control group of patients admitted for other reasons (8).

This Cochrane review searched for direct evidence that cannabinoids can prevent human seizures in studies using the only acceptable standard, the randomized controlled trial. By dint of great effort, they identified four studies, with a total of 48 patients randomized to placebo or to 200–300 mg of cannabidiol per day. This particular cannabinoid has few psychotropic effects and is not a controlled substance. Overall, these studies demonstrate the short-term tolerability of this treatment, with the only noted adverse effect being drowsiness in one study. Except for one study that



reported two of four treated patients becoming seizure free for 3 months, the studies either reported no benefit, or the effect was not clearly stated. Methods of randomization or determining outcome were inadequate or not clearly detailed.

Marijuana itself has major shortcomings as an epilepsy treatment. Its psychotropic action can only be regarded as an adverse effect. It is a biological product containing multiple compounds with unclear, possible, anti- or pro-convulsant effects, delivered in varying amounts from dose to dose. Long-term safety has not been adequately investigated. In the United States, it is illegal under federal law. Evidence for efficacy in treating seizures does not meet the necessary standard to recommend it to patients.

However, new treatments for epilepsy are sorely needed. Cannabidiol or other individual cannabinoids with minimal adverse effects could be extracted and given in precise doses in rigorously designed, blinded, randomized clinical trials to test efficacy and safety. This is a reasonable route for development of new antiepileptic drugs.

by John W. Miller, MD, PhD

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