REVIEW ARTICLE

Marijuana: A Time-Honored but Untested Treatment for Epilepsy

Richard S. McLachlan

ABSTRACT: The biology of the endocannabinoid system in the brain provides a possible basis for a beneficial pharmacological effect of marijuana on seizures. However, evidence for efficacy of cannabis treatment of epilepsy is anecdotal because no acceptable randomized controlled trials have been done. Proper dosage and means of administration remain unknown. Cannabis is safer than other controlled substances, including tobacco or alcohol, and appears to be relatively safe compared with most pharmaceuticals used to treat epilepsy. This is a review of this topic from a Canadian perspective.

RÉSUMÉ: La marijuana : un vieux traitement de l'épilepsie qui n'a jamais été mis à l'épreuve. La biologie du système endocannabinoïde dans le cerveau constitue une base possible pour expliquer un effet pharmacologique bénéfique de la marijuana sur les crises convulsives. Cependant, les données concernant l'efficacité du cannabis pour traiter l'épilepsie sont anecdotiques parce qu'aucun essai clinique contrôlé randomisé qui soit valable n'a jamais été effectué. On ne connaît pas quel serait un dosage et un mode d'administration adéquats. Le cannabis est plus sûr que les autres substances contrôlées incluant le tabac ou l'alcool et semble relativement sûr comparé à la plupart des produits pharmaceutiques utilisés pour traiter l'épilepsie. Nous avons effectué une revue du sujet dans une perspective canadienne.

Keywords: Cannabinoids, epilepsy, seizures

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Marijuana (cannabis) is an illegal drug in Canada. The Government of Canada does not endorse the use of marijuana, but beginning in 2001, Health Canada, responding to decisions rendered by Canadian courts, has granted access to marijuana for certain medical conditions. This includes "seizures from epilepsy" as approved under what are now called the Marijuana for Medical Purposes Regulations.[1] Recent media publicity about dramatic reductions in seizures in children with a rare form of severe epilepsy who were treated with cannabis oil[2] have fueled an increased demand for marijuana from those whose seizures continue despite standard medical management.

However, there is little enthusiasm from physicians for prescribing medical marijuana. The Canadian Medical Association has "several causes for concern" and the College of Physicians and Surgeons of Ontario has stated that physicians filling out a medical declaration for medical marijuana "are advised to proceed with caution." A recent assessment of physician attitudes in Colorado, where medical marijuana is legal, found only 19% who would recommend it.[3] Almost two thirds indicated they thought marijuana poses serious physical and mental risks.

Cannabis has been used for centuries as treatment for epilepsy, but the evidence for its efficacy remains anecdotal. Although more is known about the adverse effects of this form of treatment, their frequency and severity remain controversial. This review presents the scientific basis for the potential effect of cannabis on seizures and addresses the clinical evidence regarding efficacy and safety of marijuana in the treatment of epilepsy.

What Is Marijuana and Why Does it Have Such a Bad Reputation?

Called hemp or by its scientific name cannabis until the 20th century and named marihuana in Mexican Spanish, marijuana is the dried leaves, stems, and flowers of a 1 to 5 meter weed originating from central Asia. There are many varieties, the most common of which are Cannabis sativa and indica. It is usually inhaled as smoke but can also be used as a vapor, taken by mouth as a spray, ingested in tea or as butter in baked goods, or in capsule form and used as an oil. Hashish is a purified particularly potent resin or oil derived from parts of the marijuana plant.

Anthropological evidence reveals cannabis use by many societies over thousands of years. In addition to recreational and religious use for its psychoactive properties, the hemp plant has many industrial applications. Cannabis has also been widely used to treat many medical conditions including seizures. North American attitudes at the beginning of the 20th century demanded the prohibition of many drugs including opium, cocaine, alcohol, and marijuana—but interestingly not tobacco. Because marijuana was not widely used at the time, the reason for its inclusion as an addictive "narcotic" is debated. Some suggest overtones of racial discrimination as the main recreational users were Mexicans and southern blacks.[4] Others point to pressure from prominent business interests such as the Dupont Company and WR Hearst who wanted to eliminate competition from the increasing commercial use of hemp. Organized efforts to influence public opinion included characterization of marijuana as "the weed of madness" in the 1922 Canadian book The Black Candle[5] and allegations by the Federal Bureau of Narcotics that the drug caused insanity and criminal behavior as promoted by such Hollywood B movies as *Reefer Madness*.

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In Canada, "Indian hemp" was declared an illegal drug in the Narcotic Drug Act of 1923. The United States effectively banned marijuana use with the Marijuana Tax Act of 1937, despite opposition from the American Medical Association before it later joined the Federal Bureau of Narcotics in condemning the drug.[6]

What Is the Mechanism of Action of Cannabis and Why Might it Have Any Effect on Seizures?

The biologically active components of marijuana are called cannabinoids, of which there are more than 80 compounds. Delta-9-tetrahydrocannabinol (THC) is thought to be the main psychoactive ingredient, but how it and other cannabinoids such as cannabidiol (CBD) contribute to the potential medicinal effects of the drug remains unclear. Antiepileptic, anxiolytic, antipsychotic, analgesic, antispastic, antiemetic, neuroprotective, anti-inflammatory, and many other possible benefits have been described.[7] There is evidence that CBD may be the main contributor to any antiepileptic effect of marijuana.

Over the past 25 years, considerable basic research has documented the existence of an intrinsic endocannabinoid system on which cannabis acts.[8-10] This consists primarily of two distinct cannabinoid cell membrane receptors (CB1 and CB2) and two endogenous ligands called anandamide and 2-AG that activate these receptors. CB2 receptors are mostly distributed outside of the nervous system on cells associated with the immune system, providing a basis for putative anti-inflammatory and immunosuppressive actions of cannabis. CB1 receptors reside mainly on presynaptic nerve terminals and are widely distributed in the central nervous system. Endocannabinoid ligands released by the postsynaptic neuron act on these presynaptic CB1 receptors to provide regulatory feedback for control of neurotransmitter release and other cell functions. The system acts primarily to decrease GABA-mediated transmission at inhibitory synapses but also regulates release of excitatory neurotransmitters such as glutamate.[11] There is increasing evidence that, in epilepsy, CB1 receptor expression is upregulated at inhibitory synapses and downregulated at excitatory synapses with associated alterations in endogenous cannabinoid levels.[12] The impact of such changes on seizures and the potential effect of altering the cannabinoid system with exogenous cannabinoids (i.e. cannabis) are not yet known. Further, any antiseizure effect of cannabis could be exerted either directly by activation of cannabinoid receptors by CBD or indirectly through anxiolytic stress-relieving properties of the drug (mainly THC).

How Safe Is Cannabis?

If one begins with the premise that no drug is totally safe, the question to be asked is where does cannabis stand with respect to other drugs, both recreational and medicinal? Regulatory agencies indicate that cannabis is such a harmful drug it should remain illegal, but the medical evidence for this position is not convincing. From the viewpoint of official drug policy makers, marijuana causes dependence, respiratory and mental illness, poor motor performance, impaired cognitive and immune system functioning, distorted perceptions, difficulty in thinking and problem solving, and problems with learning and memory.[13] They imply an association between chronic marijuana use and increased rates of anxiety, depression, suicidal thoughts, schizophrenia, and cancer.

Marijuana clearly can cause adverse effects.[14] However, these are mild to moderate with limited use. A commercial mouth spray

Table 1: Addiction potential of cannabis

1.	Nicotine	32%
2.	Heroin	22%
3.	Cocaine	17%
4.	Alcohol	15%
5.	Marijuana	9%

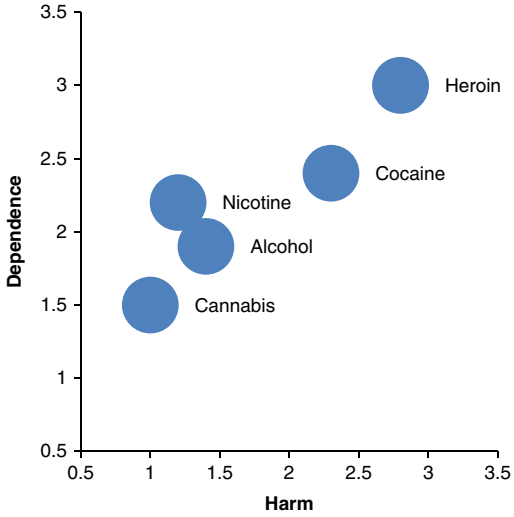

Figure 1: *Relative harmfulness of recreational drugs (adapted from reference 25)*

preparation of cannabis (nabiximols) used for several years for the treatment of spasticity and pain has been found to cause not infrequent effects such as dizziness, tiredness, or trouble concentrating,[15,16] which are similar to many drugs' side effects used in epilepsy treatment. A recent review of the pulmonary effects of marijuana smoking found "far lower risks for pulmonary complications" of even heavy marijuana use compared with smoking tobacco.[17] Although intoxication with cannabinoids (mainly THC) can cause acute cognitive, affective, and psychiatric symptoms, the evidence that chronic use results in permanent impairment remains controversial.[18] Several studies found an increased risk of psychosis in marijuana users[19] but systematic reviews of the data question a causal link.[20] There have been no deaths directly attributable to the drug and the lethal dose to kill 50% of mice is six times higher than that for caffeine. In contrast, the street drug known as Spice, K2, or Black Mamba is a combination of very potent synthetic cannabinoids mixed with crushed plants that can cause serious acute toxicity in the form of psychosis, seizures, and even stroke.[21]

As with any drug, excessive use may cause harmful effects, but even these appear to be less severe than with other commonly used recreational drugs. A comprehensive national survey in the United States revealed that marijuana has low addictive potential (Table 1).[22] Another British paper ranked the tendency of cannabis to cause physical harm or dependence as less than that from tobacco or alcohol (Figure 1).[23] There is no good evidence that cannabis use leads to harder drugs or causes criminal behavior, although those who engage in such behaviors may be more likely

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to smoke marijuana. Although cannabis clearly has potential adverse effects, the overall medical evidence suggests that it is less toxic than tobacco or alcohol as well as most pharmaceutical drugs currently used for the treatment of epilepsy.

What Is the Evidence for Efficacy of Cannabis in the Treatment of Epilepsy?

Cannabis has been used to treat many neurological disorders including multiple sclerosis and chronic pain.[24,25] Up until the 20th century, before the introduction of modern antiseizure drugs, marijuana was one the few treatments thought to be effective for controlling seizures.[26] Several studies in animal models of epilepsy, most done in the 1970s, have documented the anticonvulsant effect of THC and cannabidiol,[27-29] but other reports have found they can also augment seizures.[30-32] Other cannabinoids have not been well studied.

Other than anecdotal reports, there is little clinical evidence for or against the efficacy of cannabis to control seizures. The Cochrane database lists four small trials of cannabidiol 200-300 mg daily done between 1978 and 1990, including a total of 48 patients from which no reliable conclusions about efficacy can be drawn.[33] No safety concerns were identified in these trials. Surveys of outpatients treated at two epilepsy centers found 21 to 33% were using marijuana and more than 50% thought there was a beneficial effect on seizures.[34,35] Unpublished data from 215 consecutive intractable epilepsy patients admitted to our Epilepsy Monitoring Unit revealed 38% had used marijuana in the past year, with more than three quarters of these perceiving a benefit to seizure control. A recent case based series from Saskatchewan found that medically prescribed marijuana (mean dose 2 g/day) was being used primarily by young males with drug-resistant epilepsy and psychiatric comorbidity, all of whom found the drug benefitted both seizures and mood.[36]

Recent highly publicized reports of seizure reduction in young children with treatment-resistant epilepsy, mainly the rare genetic syndrome of Dravet with the use of cannabidiol enriched cannabis oil,[37] have caught the attention of many other patients with intractable epilepsy. One third of the 250,000 people with epilepsy in Canada have continuing seizures despite optimal medical management. It is mainly this group that is looking to try medical marijuana as an alternative treatment.

What Is the Current Situation for Prescribing Medical Marijuana in Canada?

Any physician and some nurse practitioners in Canada can legally "prescribe" medical marijuana for certain medical conditions designated by Health Canada.[1] Regulations are vague regarding specific indications or contraindications, so practitioners must be cautious about patients engaging in drug-seeking behavior. There is no prescription in the usual sense, merely a confirmation that the person applying for medical marijuana has one of the conditions for which it is approved. However, the application form also requires the physician to designate the daily amount in grams to be used and for how long. A sample of the brief medical form can be downloaded from Health Canada or directly from the company the patient has chosen to supply his or her marijuana. There are now more than a dozen authorized suppliers who list various concentrations of THC and CBD from which to choose. Based on limited evidence, as described here, strains high in CBD and low in THC would seem most appropriate for treatment of seizures. An ongoing challenge in the courts seeks to allow patients to continue growing their own marijuana once they have been approved for medical use. The reason is the high cost of commercial marijuana at around $10 per gram compared with about $1-2 per gram for the homegrown product.

The dosing of cannabinoids for medical conditions is not well studied. The effective dose for an individual patient can vary depending on route of administration, potency of the preparation, the concurrent use of other medications, and various other factors. Patients should be advised that the drug is legally approved only as the crushed plant components. Those wanting to use the drug by ingesting it orally will have to know how to transform the supplied product to a suitable form because these cannot be legally purchased under Health Canada regulations. However, this is under challenge in the courts since a recent Supreme Court of British Columbia ruling has recommended that parliament enact amendments allowing consumption of medical marijuana to include "orally, topically or by inhalation."[38] Bioavailability of cannabinoids taken orally is only 10% compared with 25% through smoking marijuana; thus, the effective oral dose may be up to 2.5 times that obtained by smoking. The duration of drug effect is also prolonged with oral use.

Patients using cannabis for other medical conditions such as pain or spasticity can self-titrate the dose (i.e. amount smoked or ingested) to obtain the desired immediate effect.[39] This is more difficult with respect to control of seizures unless the user is relying on the recognizable relaxing properties of marijuana to indirectly reduce seizures. Based on an estimated 0.5 to 1 g of cannabis in a single marijuana joint, a general range of 0.5 to 3 g per day for medical use is reasonable according to Health Canada. The actual dose of THC or CBD will depend on the particular commercial product used. Because cannabinoids are metabolized in the liver, there may be induction of the cytochrome P450 enzyme system, creating the potential for drug interaction with antiepileptic or other drugs that are metabolized using the same system. Health Canada has a comprehensive online review that offers guidance about the pharmacology of cannabis.[40]

What Remains to Be Done?

Cannabis is a relatively safe drug, but is it effective for decreasing seizures? Because the drug has until recently been highly regulated, appropriate therapeutic trials for epilepsy have not been done by clinical researchers and because it cannot be patented, major pharmaceutical companies have had no interest in developing it. Anecdotal reports by epilepsy patients of the benefits of marijuana, no matter how dramatic, are not sufficient to determine: (1) Does cannabis improve seizure frequency and severity? (2) If so, what is the proper dose and route of administration? (3) What combination of cannabinoids is most effective? (4) Is it effective for all types of epilepsy? (5) Does tolerance develop to the drug? (6) Do cannabinoids affect other drugs used by the patient? (7) How much of any impact on seizures is a secondary effect of mood stabilization and decreasing stress levels? (8) Can cannabis cause worsening of seizures in some patients?

Proper clinical trials are most likely to be carried out by university-based epileptologists who have access to disease-based research funding, but these may be difficult to undertake

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considering the current political climate.[41] Such trials are now under way in the United States and Britain to determine the efficacy of oral nonpsychoactive cannabidiol (Epidiolex) in children with Dravet syndrome.[42]

Disclosures

The author has nothing to disclose.

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