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Clinical perspectives on medical marijuana (cannabis) for neurologic disorders

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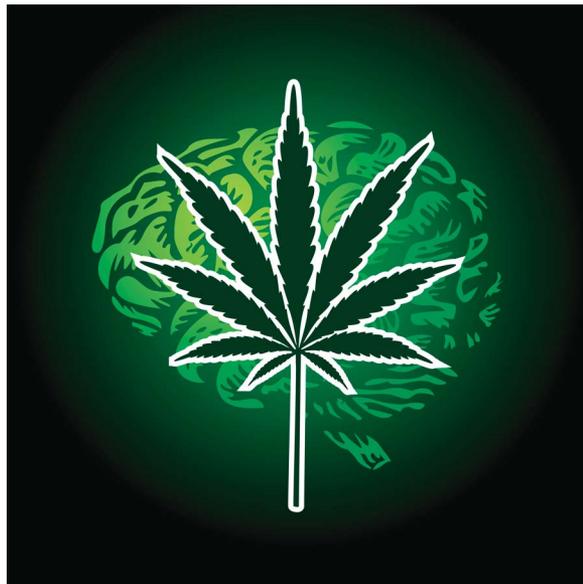
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Summary

The American Academy of Neurology published an evidence-based systematic review of randomized controlled trials using marijuana (*Cannabis sativa*) or cannabinoids in neurologic disorders. Several cannabinoids showed effectiveness or probable effectiveness for spasticity, central pain, and painful spasms in multiple sclerosis. The review justifies insurance coverage for dronabinol and nabilone for these indications. Many insurance companies already cover these medications for other indications. It is unlikely that the review will alter coverage for herbal marijuana. Currently, no payers cover the costs of herbal medical marijuana because it is illegal under federal law and in most states. Cannabinoid preparations currently available by prescription may have a role in other neurologic conditions, but quality scientific evidence is lacking at this time.



This article from the Payment Policy Subcommittee of the American Academy of Neurology (AAN) is a companion to the systematic review on medical marijuana in neurologic diseases published in 2014 by the AAN.¹ Conclusions and findings discussed in this companion are consistent with the findings in the systematic review. The systematic review included clinical studies not only of herbal marijuana (mainly

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Table 1 Cannabinoid formulations^a

Generic (trade name)	Constituents	US FDA approval	Legal under federal/state laws
Marijuana	THC, CBD, multiple other components	No	No/yes (in some states) ^b
Dronabinol (Marinol)	THC in tablet form	Yes	Yes/yes
Nabilone (Cesamet)	Synthetic cannabinoid in tablet form	Yes	Yes/yes
Nabiximols (Sativex)	Oromucosal spray mixture of THC and CBD	No ^c	No/no

Abbreviations: CBD = cannabidiol; FDA = US Food and Drug Administration; THC = delta-9-tetrahydrocannabinol.

^aAdapted from Koppel et al. 2014.¹

^bSee table 3 for states where marijuana for medical use is legal.

^cSativex has been approved in the United Kingdom, Spain, Canada, and New Zealand. In the United States, it is available only in FDA-approved clinical trials.

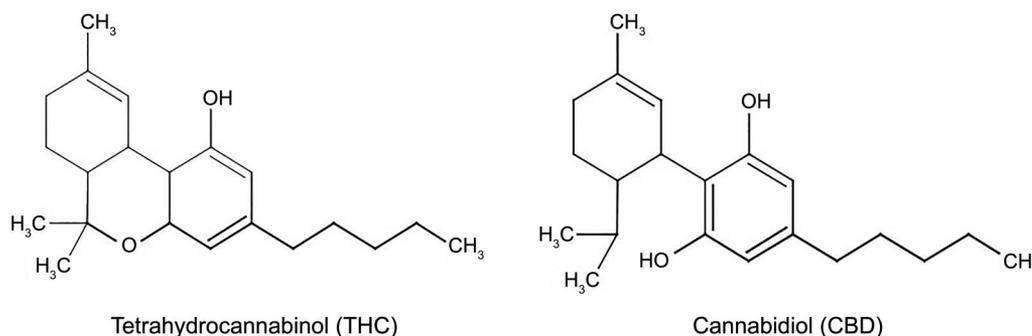
Cannabis sativa) but also of other cannabinoids (table 1) such as dronabinol (Marinol [schedule III: modest potential for abuse, low or moderate potential for dependence, has an accepted medical use]) and nabilone (Cesamet [schedule II: high potential for abuse, severe dependence is possible, has an accepted medical use]) in neurologic disorders.¹ Dronabinol and nabilone are commercially produced cannabinoids that are US Food and Drug Administration (FDA)-approved for management of chemotherapy-induced nausea and vomiting and for AIDS-related anorexia and wasting.

Marijuana, the plant, and its chemical components

Marijuana is a plant of the species *Cannabis sativa* or *Cannabis indica* and contains many chemical compounds in varying concentrations depending on growing conditions and plant variety. The chief psychoactive chemical constituent of the plant is delta-9-tetrahydrocannabinol (THC) (figure). The second most prevalent chemical is cannabidiol (CBD), which has minimal or no psychoactive effects (figure). Other cannabinoid constituents without psychoactive properties include cannabigerol and cannabinol. THC can be measured in the blood, whereas one of the nonpsychoactive metabolites, carboxy THC is detected only in urine.² Hemp, the natural fiber made from the stem of the plant, is used to make clothing and paper but contains only traces of THC.

Cannabinoids and the CNS

To produce their effects, cannabis and cannabinoids appear to activate specific endocannabinoid receptors, mainly in the CNS. Endocannabinoids are endogenous molecules that react and bind to cannabinoid receptors. There are 2 main cannabinoid receptors: CB1 and CB2. Both types of receptors are G-protein-coupled receptors. G-protein-coupled receptors are transmembrane protein receptors involved in many diseases that represent a target for many pharmacologic medications.³ CB1 is found mainly in the CNS, with the highest receptor concentration in the hippocampus, but it is also widely found in the cerebellum, basal ganglia, prefrontal cortex, and limbic system. CB1 binds the endogenous fatty acid-derived cannabinoids anandamide and 2-arachydonylglycerol, both produced mostly in the postsynaptic membrane, to effect adenylate cyclase inhibition.^{4,5} CB2, which is located mainly on immune cells, regulates cytokine release.⁶ The endocannabinoid system may have a regulatory role in modulating excessive excitation or inhibition through effects on other neurotransmitters.⁷

Figure Molecular structure

Molecular structure of delta-9-tetrahydrocannabinol (THC) (left), which has psychoactive properties, compared to molecular structure of cannabidiol (CBD) (right), which has little or no psychoactive effect.

Current state of efficacy of cannabinoids in neurologic disorders

Table 2 summarizes the scientific evidentiary findings on the use of cannabinoids.¹ The evidence indicates the effectiveness of cannabinoids (nabiximols, oral cannabis extract, and THC) in treating the central pain and painful spasms caused by multiple sclerosis. Cannabinoids are ineffective in dyskinesias in Parkinson disease. Evidence specifically supporting inhaled marijuana is lacking, so efficacy is inferred by extrapolation from the effects of marijuana-constituent chemicals. Much remains unknown.

It is interesting that the data are insufficient regarding effectiveness for seizure disorders, largely due to the lack of well-designed studies. However, most states where marijuana has been legalized list seizures as an indication. Recently, the FDA granted orphan drug designation to an oral liquid formulation of plant-derived CBD (Epidiolex) for a clinical trial investigating its effectiveness in Dravet syndrome, Lennox-Gastaut syndrome, and neonatal hypoxic-ischemic encephalopathy. A recent presentation found that Epidiolex in doses up to 25 mg/kg reduced seizure frequencies in multiple drug-resistant epilepsy syndromes and seizure types in an open-label trial.⁸

Consideration of the problems with generating evidence on cannabis

Studying cannabinoids for medicinal use creates interesting challenges. Medical marijuana is available in many forms, each having different methods of administration. Oral extract formulations are standardized and produced by pharmaceutical companies in the United States and other countries. The studies with the best evidence in the recent AAN systematic review were done using these formulations.¹ Many states and countries allow medicinal usage of marijuana, which is often smoked but can also be ingested or vaporized. These preparations are not standardized and vary widely in the dosage delivery of THC and CBD, which makes comparison of studies especially difficult.

Overall, there is a lack of evidence regarding the efficacy and safety of cannabinoid use in many neurologic illnesses. Most published studies on the use of cannabis in neurologic illness are surveys, case reports, small case series, or non-placebo-controlled studies. These studies predominantly rely on subjective patient-reported improvement and do not include objective measures. Many of the neurologic symptoms cannabis is proposed to treat are best measured by subjective rating scales, and improvements in patients' perceptions of symptoms should be an important outcome of these studies.

The effects of cannabis are difficult to mask in placebo-controlled studies, and there is a strong placebo effect. This problem may be reduced by using cannabis preparations lower in THC or those that have fewer psychoactive side effects (e.g., CBD).

Table 2 Conclusions of systematic review of medical marijuana in neurology

Neurologic disorder	Conclusion
Spasticity	OCE is effective; THC and nabiximols are probably effective for patient-rated spasticity scores
	OCE is probably ineffective for short-term reduction of objective spasticity scores
	OCE and THC are possibly effective in reducing both patient-rated and objective spasticity measures at 1 y
	Smoked marijuana is of uncertain efficacy for spasticity
Central/neuropathic pain and painful spasms of MS	OCE is effective in reducing central pain
	THC and nabiximols are both probably effective in MS-related pain or painful spasms
	Smoked marijuana is of uncertain efficacy for MS pain
Bladder dysfunction	Nabiximols is probably effective in reducing the number of bladder voids per day at 10 wk but is of unknown efficacy in reducing bladder complaints overall
	THC and OCE are both probably ineffective in bladder complaints
Tremor in MS	THC and OCE are probably ineffective in MS-related tremor
Huntington disease	Nabilone and CBD are of uncertain efficacy in HD as the studies were underpowered
Dopamine-related dyskinesia in PD	Cannabinoids probably ineffective in PD dyskinesia
Tourette syndrome; cervical dystonia	THC efficacy for Tourette syndrome and dronabinol efficacy in cervical dystonia are both unknown
Epilepsy	There is insufficient quality evidence regarding the efficacy of cannabinoids in reducing seizure frequency for patients with epilepsy

Abbreviations: CBD = cannabidiol; HD = Huntington disease; MS = multiple sclerosis; OCE = oral cannabis extract; PD = Parkinson disease; THC = delta-9-tetrahydrocannabinol.

Patient recruitment is a problem for studies on cannabis. Cannabis may cause dose-related impairment of driving, although scientific study on who is impaired and at what level is insufficient and state laws vary widely on the issue. Limits on driving may deter patient enrollment.

The political backdrop of medical marijuana

Marijuana is the most widely used illicit drug in the United States, accounting for approximately 75% of all illegal drug use.⁹ Due to the widespread recreational use of marijuana, many have raised concerns about legalizing the possession and use of marijuana, even for medical purposes.

Despite the fact that 2 of the cannabinoids were approved by the FDA in 1985 in the form of dronabinol and nabilone, the medicinal use of the marijuana plant (herbal marijuana) itself is illegal under federal law and in most states. Marijuana is classified by the FDA as a schedule I drug, a designation that it has held since President Richard Nixon signed the Controlled Substances Act in 1970 as a prelude to the government's "war on drugs" declared in 1971. Per the act, a schedule I drug is defined as a drug with "high potential for abuse" and "no currently accepted medical use." However, findings of the systematic review as well as the FDA-approved indications for dronabinol appear to suggest an accepted medical use.^{1,10} The schedule I designation also impedes the rigorous scientific study of potential medical uses of marijuana within the United States.^{11,12}

Citing the need to better investigate the possible clinical use of marijuana, the American Medical Association, the Institute of Medicine, the American College of Physicians,¹³ and others¹⁴ have called for the reclassification of marijuana as a schedule II drug¹¹ and have called for more research.¹⁵ In a recent position paper on the use of medical marijuana for neurologic disorders, the AAN joined the chorus of medical and scientific bodies requesting

There are legitimate concerns about the use of plant marijuana because the relative dosages of THC, CBD, and other components vary with plant species and preparations.

reclassification of marijuana based on current evidence to permit institutional review board–approved research.¹⁶ In states where marijuana has been legalized (table 3), laws permitting medicinal marijuana vary widely in their medical indications (i.e., the symptoms or diseases for which it may be offered), which in many instances are only loosely linked to scientific evidence.

The problems with herbal marijuana

There are legitimate concerns about the use of plant marijuana because the relative dosages of THC, CBD, and other components vary with plant species and preparations. Potential inconsistencies in the plant-derived formulations can make it difficult to know what dosage will have what effect in clinical care. Furthermore, concerns about quality, possible contamination, and lack of close regulation of methods of preparation are ongoing.

For years, many health educators have expressed concern that marijuana is a “gateway drug,” meaning that the use of marijuana in some manner causes later use of other illicit drugs.^{17,18} Although limited statistical and circumstantial evidence supports this hypothesis, it is not established. Much of the supporting data for the hypothesis was derived from young people experimenting with recreational drugs. Possible confounding factors include selection of people more apt to experiment with drugs, more likely to have access to other illicit drugs, and more likely to have social networks associated with greater acceptance of using other illicit drugs.¹⁹ Moreover, even if the gateway theory applies to young recreational drug users, there is no evidence that it is generalizable to most people under the care of a physician that are using cannabis for medical purposes.

Long-term effects of cannabis

The question of whether there are long-term (>6 months) adverse psychological or cognitive effects of cannabis in persons without preexisting mental illness is controversial. Limited evidence suggests that long-term use of cannabis might be associated with a small reduction in hippocampal volume in users compared with nonusers; however, clinical effects associated with this observation are not evident.²⁰ There is some suggestion that chronic heavy use of marijuana may be associated with a decline in conceptual planning and decision-making ability,²¹ and long-term memory may be adversely affected in a dose-dependent manner in chronic marijuana users.²² Although heavy smoking of marijuana probably has adverse respiratory effects, a 20-year longitudinal study of marijuana smokers using the equivalent of a joint every day for up to 7 years did not demonstrate a decline in lung function (forced expiratory volume in 1 second and forced vital capacity), as was seen in cigarette smokers; rather, values remained normal or paradoxically improved.²³

Weighing the risks and benefits: counseling patients about cannabis use

The use of medical marijuana has received a great deal of public attention in recent years. Marijuana has a long history as an illicit drug, with outspoken proponents and opponents both attempting to influence public opinion and policy. The complex background may color

Table 3 States that have legalized medical marijuana^a

State	Year medical marijuana first approved	Medical cannabis laws only	Cannabis decriminalization and medical cannabis laws	Limited recreational use of marijuana ^b
Alaska	1998		✓	✓ (2015)
Arizona	2010	✓		
California	1996		✓	
Colorado	2000			✓ (2012)
Connecticut	2012		✓	
Delaware	2011	✓		
Hawaii	2000			
Illinois	2013	✓		
Maine	1999		✓	
Maryland	2014	✓		
Massachusetts	2012		✓	
Michigan	2008	✓		
Minnesota	2014		✓	
Montana	2004	✓		
Nevada	2000		✓	
New Hampshire	2013	✓		
New Jersey	2010	✓		
New Mexico	2007	✓		
New York	2014		✓	
Oregon	1998		✓	✓ (2015)
Rhode Island	2006		✓	
Vermont	2004		✓	
Washington	1998			✓ (2012)

^aAdapted from 23 Legal Medical Marijuana States and DC: Laws, Fees, and Possession Limits, Medical Marijuana Pros and Cons, ProCon.org (Available at: <http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881>. Accessed March 3, 2015).

^bTypically legal recreational use of marijuana is subject to restrictions on age and amount.

perceptions of medical marijuana use in the eyes of some neurology patients, necessitating an explanation of the effectiveness, side effects, risks, and benefits.

The systematic review is helpful to neurologists in evaluating what quality scientific studies have shown on the use of cannabinoids for a range of neurologic disorders. Medical marijuana does not appear to have curative effects on any neurologic condition, but it may ameliorate unwanted symptoms and ease suffering. Undoubtedly, THC and smoked marijuana may have cognitive side effects that must be weighed against their benefits, particularly in patients already affected cognitively by a primary neurologic disease.²⁴

Legal issues and third-party payer coverage of cannabis

Without FDA approval, commercial insurers will not approve herbal medical marijuana; consequently, no insurance carrier in the United States covers the cost of medical marijuana. In states that have approved the use of medical marijuana, dispensaries have been set up to provide medical marijuana to patients who have been evaluated and provided with usage cards through the state. At present, the full cost of medical marijuana, as well as applicable state taxes and fees, is paid by patients.

Medical marijuana does not appear to have curative effects on any neurologic condition, but it may ameliorate unwanted symptoms and ease suffering.

Insurance companies do cover approved cannabinoid products. These include dronabinol and nabilone. Nabiximols (Sativex) (table 1) is currently in phase 3 clinical trials for advanced cancer pain and has “Fast Track” designation by the FDA, so it may receive approval in the foreseeable future if trials find it to be safe and effective.²⁵ Dronabinol and nabilone may require prior authorization and may be subject to a tiered formulary approach that first requires trials of alternative medications before a cannabinoid is authorized.

The AAN systematic review found quality scientific evidence that dronabinol and oral cannabis extract reduce patient-reported symptoms of spasticity and ameliorate central pain or painful spasms in patients with multiple sclerosis.¹ It is possible that such findings could lead to reimbursement coverage of oral cannabis extract, but this formulation must first be approved by the FDA.

Under federal law, licensed physicians cannot legally prescribe herbal marijuana but can prescribe nabilone or dronabinol. For physicians who wish to support a trial of herbal marijuana in most states that have legalized medical marijuana, the documentation of a medical condition that justifies the use of marijuana under that state’s law is sufficient. Patients may then proceed to acquire the herbal marijuana under the particulars of the laws of their state. The US District Court for the Northern District of California held that a physician may recommend medical marijuana without sanction (*Conant v McCaffrey*).²⁶ This ruling notwithstanding, certain institutions, including the Department of Veterans Affairs, may have policies banning physicians from discussing medical marijuana with their patients.

Future considerations

Presently, evidence supports the therapeutic benefits of medical marijuana for certain neurologic disorders (table 2). Additional research may demonstrate more tailored uses of cannabinoids and clarify their role in medical therapeutics. Federal legislation to reclassify marijuana as a schedule II drug would likely improve the pace and quality of scientific study of medical marijuana.

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AUTHOR CONTRIBUTIONS

Drs. Fife, Moawad, Moschonas, and Hammond all contributed to drafting/revising the manuscript, information and data acquisition, and critical revision of the manuscript for intellectual content. Katie Shepard assisted in manuscript review.

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