

Medical marijuana

Between a plant and a hard place



David S. Gloss, MD
Edward H. Maa, MD

Medical marijuana (MMJ) is a multifaceted and complicated issue involving far too much information to convey in a single review article. In this article, we touch on points that we hope will help the practitioner make more informed decisions about the use of MMJ in the field of neurology. In particular, we discuss the systematic review published in *Neurology*[®] and describe the 2 agents that have been approved for general use by the US Food and Drug Administration (FDA). In addition, we address quality assurance, prescribing, and legal concerns and provide information about the use of Epidiolex, a liquid formulation of highly purified cannabidiol (CBD) extract, as a treatment for various orphan pediatric epilepsy syndromes.

The systematic review of MMJ published in *Neurology* provides practitioners (in states that allow marijuana to be prescribed by physicians) with evidence on manufactured agents as well as whole plant agents and offers preliminary guidance for practicing evidence-based medicine.¹ The systematic review examined off-label indications for the medications reviewed as well as evidence for medications not approved by the FDA.

The key recommendations of the systematic review are that MMJ is effective for a variety of symptoms of multiple sclerosis (MS), that oral cannabinoids are probably ineffective for treating Parkinson-related levodopa-induced dyskinesias, and that nabilone may be modestly effective in treating the chorea of Huntington disease (HD).² There was not enough evidence regarding MMJ for non-chorea-related symptoms of HD, Tourette syndrome, cervical dystonia, and epilepsy. There was a 1% risk of serious psychiatric side effects, causing symptoms ranging from depression to hallucinations and suicidality. MMJ use in a susceptible patient with family history of schizophrenia may unmask previously subclinical symptoms.³

In the United States, 2 agents are approved by the FDA and can be prescribed, under the right circumstances, by any properly licensed physician in any state. The first agent is dronabinol, a synthetic version of tetrahydrocannabinol (THC), the main compound in cannabis. Dronabinol is indicated by the FDA for anorexia-associated weight loss in adult patients with AIDS and for nausea and vomiting associated with cancer chemotherapy in patients who have not responded adequately to conventional antiemetic treatments. The second agent is nabilone, a synthetic cannabinoid that mimics the effects of THC. Nabilone is indicated for nausea and vomiting associated with chemotherapy in patients who have not responded adequately to conventional antiemetic treatments.

According to the FDA rules, “off-label” use of dronabinol and nabilone is allowed under certain conditions: “If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s

Department of Neurology (DSG), Geisinger Health System, Danville, PA; Department of Neurology (EHM), University of Colorado, Denver; and Denver Veterans Affairs Medical Center (EHM), Denver, CO.

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Correspondence to: davy.gloss@gmail.com

use and effects.”⁴ One of the main purposes of the MMJ systematic review was to find out which off-label conditions have evidence. Whole plant marijuana is a third agent. While legal in some states, its legality remains somewhat murky. Special legal issues related to use of plant forms will be discussed later.

If we look at the systematic review from the perspective of these 3 agents, we may conclude that dronabinol is probably effective for reducing patient-reported scores of MS-related spasticity and/or central pain, excluding neuropathic pain (the systematic review specifically excluded neuropathic pain). Dronabinol is probably ineffective for reducing MS-related bladder complaints or tremor.¹ Nabilone may be modestly effective in treating chorea of HD.²

The systematic review had data that included standardized oil extracts, which do not have a clear equivalent in the US system, each of which has a specified ratio of THC:CBD, with some having CBD only. This is further complicated by the fact that currently no consistent mechanism of testing, labeling, or quality assurance exists within the states that allow for marijuana use. For instance, a brownie sold at a local dispensary claiming “100 mg of marijuana” does not translate to quantity of THC, CBD, or any of the other 80+ cannabinoid compounds, which all can vary according to the strain-specific trait, harvest time, and technique of harvesting. In addition, the method of ingestion changes the chemical composition and efficacy of the different agents contained in MMJ, further confusing the issue. In particular, different cannabinoids have different vaporization points, so vaporized cannabis may have quite different ratios of cannabinoids from smoked cannabis.⁵ One way to compare smoked to ingested cannabis is to use a conversion factor (0.20–0.33 of the dose smoked is the same amount as the dose ingested).⁶

While the systematic review did examine many conditions, it did not explicitly review symptoms related to headache, dementia, peripheral neuropathy, or other conditions. It also did not look at the anti-inflammatory effects of cannabis on the underlying disease process in conditions such as Alzheimer disease or MS. Of the conditions it explored, nearly half the included studies were rated as having such a high risk of bias that they were no more trustworthy than expert opinion. Many studies on MMJ do not have comparison groups or have outcomes rated by the practitioner. The high risk of bias of studies in this area adds uncertainty for the practitioner facing patients who are self-medicating with marijuana that they may consider “medical.” When adding MMJ to a patient’s previous drug combination, there is a cumulative risk of interactions and worsened side effects.

This leaves the neurology practitioner in a difficult situation. From the viewpoint of evidence-based medicine, except for a few narrow uses in MS and HD, the systematic review does not provide specific guidance.

At the same time, it is imperative to ask whether patients are using MMJ. In Colorado where MMJ has been available for more than a decade and recreational marijuana has been available since January 2014, a surprising number of patients are using marijuana, typically without the knowledge of the treating physician. In an anonymous survey on the use of complementary medicine modalities in the Refractory Epilepsy Clinic at Denver Health, marijuana was being used by one-third of consecutively polled patients with epilepsy.⁷ This finding points to a critical need for openness and frank discussion. The frequency of dosing, amount of MMJ being used, and perceived effect may all be helpful in understanding whether the marijuana is serving as a “medicine” or is merely recreational. The constituent cannabinoids, as well as other hydrocarbon compounds, may affect the metabolism of the patient’s concomitant medications. The data on human interactions are very limited. It is possible CYP1A2 is induced by smoking marijuana.⁸ There are some animal data suggesting inhibition of CYP2C and CYP3A and induction of CYP 2B1/6.⁹ Other non-antiepileptic drug (AED) interactions should be carefully investigated and education provided as needed.

Especially in conditions such as medication-resistant epilepsy, patients are very interested in alternative therapies.⁷ MMJ seems most reasonable as a possible therapy following failed epilepsy surgery or if surgery is not an option. In the case of childhood catastrophic epilepsy

syndromes, MMJ may be considered after failure of 2 or more traditional AEDs and ketogenic diet but perhaps prior to surgical intervention or following failed surgical intervention.

The legal morass surrounding MMJ results from the conflict between state and federal law. To be clear, marijuana use is illegal at the federal level because the FDA classifies marijuana as a schedule I drug. This means that marijuana has no medicinal value in the eyes of the US government. Yet more than 20 states allow MMJ, and 2 have approved the use of recreational marijuana. The legal ramifications of recommending MMJ are beyond the scope of this article, but common sense should prevail: if endorsing the use of marijuana in patients, the letter of the law should be followed. Avoiding involvement in the sale or growth of MMJ is strongly advised.

Federal law still supersedes state control, and a different political environment may bring different attitudes about the enforcement of the federal laws surrounding marijuana use. Currently physicians in states that allow MMJ can recommend MMJ without fear of losing their Drug Enforcement Administration license.¹⁰ There are a series of memos from the Department of Justice outlining when they will prosecute someone no matter the state's laws about MMJ^{11–13} (see appendix e-1 at Neurology.org/cp).

Given the ambiguous legal situation, most insurance companies do not cover any form of whole plant marijuana; however, a court case may change this policy.¹⁴ The New Mexico appeals court required a worker's employer to reimburse him for the cost of MMJ. The employer's lawyers had argued that the employer was prohibited from covering marijuana on the grounds that it is schedule I drug, but the court did not find the argument compelling.

Results of a parental survey published since the systematic review¹ reported a cohort of children with catastrophic epilepsies who were significantly helped with CBD-enriched cannabis.¹⁵ Because the data were from a survey there was high risk of bias, but the data were convincing enough for the FDA to offer an orphan drug designation.

There are multiple trials in progress investigating the effect of cannabinoids in wide-ranging neurologic conditions: spinal cord injury, motor neuron disease, dementia, MS, and Dravet syndrome/Lennox-Gastaut syndrome. According to clinicaltrials.gov, most of these trials are either completed or not yet accepting participants. Two trials on epilepsy are accepting patients (NCT02397863 and NCT02229032). It is hoped that as these studies are completed and we learn more about the effects of cannabinoids in a variety of neurologic disorders, clearer guidelines will emerge. Such guidelines will become increasingly important as more states legalize MMJ or marijuana in general.

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Supplemental Data

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