Editorials

Effectiveness, Adverse Effects, and Safety of Medical Marijuana

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Increasingly, physicians across the country are being asked about medical marijuana. Although marijuana has been around for centuries, there is no consensus on its safety and effectiveness. In 1970, the U.S. Food and Drug Administration (FDA) classified marijuana as a schedule I substance with no accepted medical use and a lack of accepted safety.[1] Twenty-three states and the District of Columbia have legalized marijuana for medicinal purposes despite federal law that prohibits the prescribing, purchase, or sale of marijuana.[2] Although the current U.S. administration does not recommend strict enforcement of this law, the U.S. Supreme Court ruled that following a state-approved medical cannabis program is a violation of federal law.

Marijuana contains more than 60 cannabinoids, some of which have psychoactive effects. The clinical effectiveness and adverse effects depend on the ratio of tetrahydrocannabinol (THC) to nonpsychoactive cannabidiol components. Cannabinoid receptors are located in the brain, spinal cord, and lymph tissue.[3] Cannabinoids from marijuana can be inhaled, consumed in food, or used as oral cannabinoid extract.[4]

There are two FDA-approved cannabinoids currently available in the United States for refractory chemotherapy-induced nausea and vomiting: dronabinol (Marinol) and nabilone (Cesamet). Nabilone is also indicated for AIDS-associated wasting and spasticity due to spinal cord injury. A cannabis extract, nabiximols (Sativex), is in phase 3 clinical trials for use in multiple sclerosis and neuropathic and cancer-related pain, and is already available in Europe and Canada.[5]

The evidence for medicinal use of cannabinoids is summarized in *Table 1*.[3,6-11] Cannabinoids are not effective for acute pain.[3] However, a recent meta-analysis in patients with mixed chronic pain from rheumatic arthritis, fibromyalgia, and cancer found a significant reduction in pain and improved sleep and quality of life, regardless of administration route.[3] Adverse effect rates were high, demonstrating a narrow therapeutic window. Oral cannabinoid extract is effective for the treatment of spasticity, central pain, and painful spasms.[3,6] Nabiximols and THC are probably effective as ▶

Table 1. Clinical Effectiveness of Cannabinoids

Effective
Central chronic pain/painful spasms refractory to opioids[3]
Chemotherapy-induced nausea and vomiting*[6,7]
Chronic pain associated with cancer[7]
Chronic pain associated with rheumatoid arthritis[8]
Chronic spasticity[3,8]
Neuropathic pain[6]
Probably effective
Insomnia associated with fibromyalgia[8]
Urinary frequency associated with multiple sclerosis†[3]
Insufficient evidence
Huntington disease[3]
Inflammatory bowel disease[10]
Morbidity and mortality from AIDS and human immunodeficiency virus infection[9]
Seizure disorders[11]
Tourette syndrome[3]
Probably not effective
Acute pain[8]
Glaucoma[6]
Parkinson disease[3]
Tremor[3]

**—Based on low-quality evidence.*

†—Nabiximols (Sativex) is probably effective for bladder dysfunction; other oral cannabis extracts and tetrahydrocannabinol are probably ineffective.

Information from references 3, and 6 through 11.

well.[3,6] Although marijuana has been proven effective for the treatment of chronic pain in most placebo-controlled studies, five randomized, controlled, head-to-head studies did not show that it is superior to diphenhydramine (Benadryl), codeine, or amitriptyline for pain relief.[8]

Despite a case report showing benefit for Dravet syndrome[12] and testimonials on television programs, there is little evidence supporting the use of marijuana for the treatment of epilepsy. A Cochrane review and guideline from the American Academy of Neurology found no well-designed trials demonstrating significant benefit for patients with seizure disorder.[3,11] A Cochrane review also found little evidence that cannabinoids are safe or effective in persons with human immunodeficiency virus infection or AIDS.[9] Conditions without reliable evidence of effectiveness are listed in *Table 1*.[3,6-11]

Adverse effects of marijuana are summarized in *Table 2*.[4,5,7,9,13,14] Addiction is common, with 9% of all experimental users becoming addicted, including 17% of those who use during adolescence.[4] Compared with adults, adolescents may have larger declines in IQ scores with persistent use, resulting in a decreased likelihood of completing high school or attending college.[4,14] The use of marijuana during pregnancy is associated with negative effects on the child later in life, including decreased academic ability, cognitive function, and attention.[14] Although marijuana smoke does not contain nicotine, it does contain harmful toxins and may injure large airways, causing symptoms similar to those that occur with chronic bronchitis.[7,13] For these reasons, smoking is not recommended as a route of administration.

Physicians cannot prescribe medical marijuana; they can only certify its use. Patients requesting certification should have a condition for which medical marijuana has proved beneficial in high-quality research. Patients must have tried and not responded to first- and second-line therapies, including an FDA-approved cannabinoid. They should undergo a comprehensive assessment, including a discussion of the risks and benefits of medical marijuana, and should be advised that it is not endorsed by most major medical organizations and that insurance will not cover it. Patients cannot have a substance use, psychotic, or unstable mood disorder, and they must live in a state in which the use of medical marijuana is legal. Follow-up visits should occur at least every three months. If the patient is taking opioids concurrently, the narcotics contract should stipulate safeguards for marijuana use, including the purchase location and requirements for random urine drug screening.[15]

Table 2. Adverse Effects of Marijuana

Addiction[4]
Altered brain development[4,5]
Chronic bronchitis[4,7,13]
Depression and anxiety[4]
Diminished lifetime achievement[4]
Motor vehicle crashes*[4,7,14]
Psychoses and exacerbation of schizophrenia[4]
Use of illicit drugs[4]

**—Risk of a motor vehicle crash doubles among drivers with recent marijuana use.[9]*

Information from references 4, 5, 7, 9, 13, and 14.

Current medical marijuana laws address access but not testing for quality and consistency. Only FDA-approved medications are tested for dosage equivalency. Studies have shown nonregulated products to be subpotent, superpotent, or contaminated.[16]

Oral cannabinoids should not be sold in forms appealing to children. In 2014, at least 14 children were hospitalized—including seven in a Colorado intensive care unit—after accidentally ingesting cannabinoids. These incidents may have resulted from improper packaging or high THC content (more than 100 mg) in edible products. An adult who ingests 100 mg of THC may experience delirium, whereas a child consuming this amount can develop respiratory arrest.[17] Packaging laws are needed to protect against accidental ingestion.

An estimated 86% of Americans say physicians should be able to recommend medical marijuana,[18] but without federal guidance, lawmakers have not addressed issues of ▶

safety and medical indications. Many states have vague indications for use, and most do not address quality, purity, packaging, or labeling. There are still many unanswered questions regarding optimal dosing and delivery routes. Research to help answer these questions will likely not occur until cannabis is reclassified by the FDA as a schedule II substance. Finally, it is important that growers and producers of cannabis develop standards similar to the FDA's regarding purity, consistency, and quality of their product.

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