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More is known about the psychiatric risks than the benefits.

The movement to legalize marijuana for medical use in the United States has renewed discussion about how this drug affects the brain, and whether it might be useful in treating psychiatric disorders.

Unfortunately, most of the research on marijuana is based on people who smoked the drug for recreational rather than medical purposes. A review by researchers in Canada (where medical marijuana is legal) identified only 31 studies (23 randomized controlled trials and eight observational studies) specifically focused on medical benefits of the drug.

A separate review by the American Medical Association (AMA) also concluded that the research base remains sparse. This was one reason that the AMA urged the federal government to reconsider its classification of marijuana as a Schedule 1 controlled substance (prohibiting both medical and recreational use), so that researchers could more easily conduct clinical trials.

Consensus exists that marijuana may be helpful in treating certain carefully defined medical conditions. In its comprehensive 1999 review, for example, the Institute of Medicine (IOM) concluded that marijuana may be modestly effective for pain relief (particularly nerve pain), appetite stimulation for people with AIDS wasting syndrome, and control of chemotherapy-related nausea and vomiting.

Given the availability of FDA-approved medications for these conditions, however, the IOM advised that marijuana be considered as a treatment only when patients don't get enough relief from currently available drugs. Additional research since then has confirmed the IOM's core findings and recommendations.

Although anecdotal reports abound, few randomized controlled studies support the use of medical marijuana for psychiatric conditions. The meager evidence for benefits must be weighed against the much better documented risks, particularly for young people who use marijuana.

Key points

- Medical marijuana may be an option for treating certain conditions, such as nerve pain or chemotherapy-related nausea.
- There is not enough evidence to recommend medical marijuana as a treatment for any psychiatric disorder.
- The psychiatric risks are well documented, and include addiction, anxiety, and psychosis.

Challenges in drug delivery

Marijuana is derived from the hemp plant, *Cannabis*. Although marijuana contains more than 400 chemicals, researchers best understand the actions of two: THC (delta-9-tetrahydrocannabinol) and cannabidiol.

THC is the chemical in marijuana primarily responsible for its effects on the central nervous system. It stimulates cannabinoid receptors in the brain, triggering other chemical reactions that underlie marijuana's psychological and physical effects — both good and bad.

Less is known about cannabidiol, although the research suggests that it interacts with THC to produce sedation. It may independently have anti-inflammatory, neuroprotective, or antipsychotic effects, although the research is too preliminary to be applied clinically.

Drug delivery remains a major challenge for medical marijuana. The FDA has approved two pills containing synthetic THC. Dronabinol (Marinol) combines synthetic THC with sesame oil. Most of the active ingredient is metabolized during digestion, however, so that only 10% to 20% of the original dose reaches the bloodstream. Nabilone (Cesamet) uses a slightly different preparation of synthetic THC that is absorbed more completely into the bloodstream. Among the concerns about both of these drugs, however, are that they do not work rapidly, and the amount of medication that reaches the bloodstream varies from person to person.

Another medication under investigation in the United States (and already approved for sale in Canada) combines THC and cannabidiol. In Canada, it is marketed as Sativex. This drug is sometimes referred to as "liquid cannabis" because it is sprayed under the tongue or elsewhere in the mouth, using a small handheld device. However, it takes time to notice any effects, as the drug has to be absorbed through tissues lining the mouth before it can reach the bloodstream.

Inhalation is the fastest way to deliver THC to the bloodstream, which is why patients may prefer smoking an herbal preparation. But while this method of drug delivery works fast, smoking marijuana exposes the lungs to multiple chemicals and poses many of the same respiratory health risks as smoking cigarettes. Limited research suggests that vaporizers may reduce the amount of harmful chemicals delivered to the lungs during inhalation.

More psychiatric risk than benefit

Part of the reason marijuana works to relieve pain and quell nausea is that, in some people, it reduces anxiety, improves mood, and acts as a sedative. But so far the few studies evaluating the use of marijuana as a treatment for psychiatric disorders are inconclusive, partly because this drug may have contradictory effects in the brain depending on the dose of the drug and inborn genetic vulnerability.

Much more is known about the psychiatric risks of marijuana (whether used for recreational or medical purposes) than its benefits.

Addiction. Observational studies suggest that one in nine people who smokes marijuana regularly becomes dependent on it. Research both in animals and in people provides evidence that marijuana is an addictive substance, especially when used for prolonged periods.

Addiction specialists note with concern that THC concentration has been increasing in the herbal form of marijuana. In the United States, THC concentrations in marijuana sold on the street used to range from 1% to 4% of the total product; by 2003, average THC concentration had risen to

7%. Similar trends are reported in Europe. This increased potency might also accelerate development of dependence.

Less conclusive is the notion that marijuana is a "gateway drug" that leads people to experiment with "hard" drugs such as cocaine. The research is conflicting.

Anxiety. Although many recreational users say that smoking marijuana calms them down, for others it has the opposite effect. In fact, the most commonly reported side effects of smoking marijuana are intense anxiety and panic attacks. Studies report that about 20% to 30% of recreational users experience such problems after smoking marijuana. The people most vulnerable are those who have never used marijuana before.

Dose of THC also matters. At low doses, THC can be sedating. At higher doses, however, this substance can induce intense episodes of anxiety.

It is not yet known whether marijuana increases the risk of developing a persistent anxiety disorder. Observational studies have produced conflicting findings. Studies of recreational users suggest that many suffer from anxiety, and it's difficult to know what underlies this association. Possibilities include selection bias (e.g., that anxious people are more likely to use marijuana), a rebound phenomenon (e.g., that marijuana smokers feel worse when withdrawing from the substance), and other reasons (e.g., genetic vulnerability).

Mood disorders. Little controlled research has been done about how marijuana use affects patients with bipolar disorder. Many patients with bipolar disorder use marijuana, and the drug appears to induce manic episodes and increases rapid cycling between manic and depressive moods. But it is not yet clear whether people who use marijuana are at increased risk of developing bipolar disorder.

The small amount of research available on depression is also muddled. In line with what studies report about anxiety, many marijuana users describe an improvement in mood. Animal studies have suggested that components of marijuana may have antidepressant effects. Yet several observational studies have suggested that daily marijuana use may, in some users, actually increase symptoms of depression or promote the development of this disorder.

For example, an Australian study that followed the outcomes of 1,601 students found that those who used marijuana at least once a week at ages 14 or 15 were twice as likely to develop depression seven years later as those who never smoked the substance — even after adjusting for other factors. Young women who smoked marijuana daily were five times as likely to develop depression seven years later as their non-smoking peers. Although such studies do not prove cause and effect, the dose-outcomes relationship is particularly worrisome.

Psychosis. Marijuana exacerbates psychotic symptoms and worsens outcomes in patients already diagnosed with schizophrenia or other psychotic disorders. Several large observational studies also strongly suggest that using marijuana — particularly in the early teenage years — can increase risk of developing psychosis.

An often-cited study of more than 50,000 young Swedish soldiers, for example, found that those who had smoked marijuana at least once were more than twice as likely to develop schizophrenia as those who had not smoked marijuana. The heaviest users (who said they had used the drug more than 50 times) were six times as likely to develop schizophrenia as the nonsmokers.

Until recently, the consensus view was that this reflected selection bias: Individuals who were already vulnerable to developing psychosis or in the early stages (the prodrome) might be more likely to smoke marijuana to quell voices and disturbing thoughts. But further analyses of the Swedish study, and other observational studies, have found that marijuana use increases the risk of psychosis, even after adjusting for possible confounding factors.

Although cause and effect are hard to prove, evidence is accumulating that early or heavy marijuana use might not only trigger psychosis in people who are already vulnerable, but might also cause psychosis in some people who might not otherwise have developed it.

Certainly genetic profile mediates the effect of marijuana. People born with a variation of the gene COMT are more vulnerable to developing psychosis, for example. Because there is as yet no reliable way for clinicians to identify vulnerable young people in advance, however, it is safest to restrict use of medical marijuana to adults.

Other effects

A review of side effects caused by medical marijuana found that most were mild. When compared with controls, people who used medical marijuana were more likely to develop pneumonia and other respiratory problems, and experience vomiting, and diarrhea.

There's no question that recreational use of marijuana produces short-term problems with thinking, working memory, and executive function (the ability to focus and integrate different types of information). Although little research exists on medical marijuana, anecdotal reports indicate that some patients take the drug at night to avoid these types of problems.

The real debate is about whether long-term use of marijuana (either for medical or recreational purposes) produces persistent cognitive problems. Although early studies of recreational users reported such difficulties, the studies had key design problems. Typically they compared long-term marijuana smokers with people who had never used the drug, for example, without controlling for baseline characteristics (such as education or cognitive functioning) that might determine who continues to smoke the drug and who might be most at risk for thinking and memory problems later on.

Studies suggest that although overall cognitive ability remains intact, long-term use of marijuana may cause subtle but lasting impairments in executive function. There is no consensus, however, about whether this affects real-world functioning.

Additional research, focused on the benefits and consequences of medical marijuana use for specific disorders, may help to clarify some issues. In the meantime, there is not enough evidence to recommend marijuana as a medical treatment for any psychiatric disorder.

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For more references, please see www.health.harvard.edu/mentalextra.