JAMA Insights

Medical Use of Cannabis in 2019

Kevin P. Hill, MD, MHS

Nearly 10% of cannabis users in the United States report using it for medicinal purposes.[1] As of August 2019, 33 states and the District of Columbia have initiated policies allowing the use of cannabis or cannabinoids for the management of specific medical conditions. Yet, the federal government still classifies cannabis as illegal, complicating its medical use and research into its effectiveness as a treatment for the various conditions purported to benefit from cannabis pharmacotherapy. Because of this conflict and restrictions on cannabis research, evidence of the efficacy of cannabis to manage various diseases is often lacking. This article updates a review published in the June 23, 2015, issue of *JAMA*[2] and describes newer evidence regarding what is known and not known about the efficacy of cannabis and cannabinoids for managing various conditions.

Indications for Therapeutic Use Approved by the US Food and Drug Administration

Cannabis has numerous cannabinoids, the most notable being tetrahydrocannabinol, which accounts for its psychoactive effects. Individual cannabinoids have unique pharmacologic profiles enabling drug development to manage various conditions without having the cognitive effects typically associated with cannabis. Only a few cannabinoids have high-quality evidence to support their use and are approved for medicinal use by the US Food and Drug Administration (FDA). The cannabinoids dronabinol and nabilone were approved by the FDA for chemotherapy-induced nausea and vomiting in 1985, with dronabinol gaining an additional indication for appetite stimulation in conditions that cause weight loss, such as AIDS, in 1992. Recently, a third cannabinoid, cannabidiol (CBD), was approved by the FDA for the management of 2 forms of pediatric epilepsy, Dravet syndrome and Lennox-Gastaut syndrome, based on the strength of positive randomized clinical trials (RCTs).[3,4]

Other Medical Indications

Cannabinoids are often cited as being effective for managing chronic pain. The National Academies of Science, Engineering, and Medicine examined this issue and found that there was conclusive or substantial evidence that cannabis or cannabinoids effectively managed chronic pain,[5] based on their expert committee's assessment that the literature on this topic had many supportive findings from good-quality studies with no credible opposing findings. The panel relied on a single meta-analysis of 28 studies, few of which were from the United States, that assessed a variety of diseases and compounds. Although they concluded that cannabinoids effectively managed pain, the CIs associated with these findings were large, suggesting unreliability in the meta-analysis results.

A more recent meta-analysis of 91 publications found cannabinoids to reduce pain 30% more than placebo (odds ratio, 1.46 [95% CI, 1.16-1.84]), but had a number needed to treat for chronic pain of 24 (95% CI, 15-61) and a number needed to harm of 6 (95% CI, 5-8).[6] While a moderate level of evidence supports these recommendations, most studies of the efficacy of cannabinoids on pain are for neuropathic pain, with relatively few high-quality studies examining other types of pain. Taken together, at best, there is only inconclusive evidence that cannabinoids effectively manage chronic pain, and large numbers of patients must receive treatment with cannabinoids for a few to benefit, while not many need to receive treatment to result in harm.[6]

There is strong evidence to support relief of symptoms of muscle spasticity resulting from multiple sclerosis from cannabinoids as reported by patients, but the association is much weaker when outcomes are measured by physicians. There is insufficient evidence to support or refute claims that cannabinoids provide relief for spinal cord injury–related muscle spasms.[5]

Recent Clinical Trials

Two multicenter, international trials with substantial numbers of patients (n = 120 and n = 171) demonstrated the efficacy of CBD as an add-on drug to manage some seizure disorders. Over 14 weeks, 20 mg/kg of CBD significantly reduced the median frequency of convulsive seizures in children and young adults with Dravet syndrome as well as the estimated median difference in monthly drop seizures between CBD and placebo in patients with Lennox-Gastaut syndrome.[3,4] Although promising, these results were found in relatively uncommon disorders and the studies were limited by the use of subjective end points and incomplete blinding that is typical of cannabinoid studies because these drugs have readily identifiable side effects.[3,4]

Numerous other medical conditions, including Parkinson disease, posttraumatic stress disorder, and Tourette syndrome, have a hypothetical rationale for the use of cannabis or cannabinoids as pharmacotherapy based on cannabinoid effects on spasticity, anxiety, and density of cannabinoid receptors in areas implicated in development of tics, such as the basal ganglia and cerebellum. The strength of the evidence supporting the use of cannabinoids for these diseases is weak because most studies of patients with these diseases have been small, often uncontrolled, or crossover studies. Few pharmaceutical companies are conducting cannabinoid trials. Thus, it is not likely that additional cannabinoids will be approved by the FDA in the near future. Public interest in cannabis and cannabinoids as pharmacotherapy continues to increase, as does the number of medical conditions for which patients are utilizing cannabis and CBD, despite insufficient evidence to support this trend.

Neurologic Adverse Effects Are Better Defined Than Physical Adverse Effects

Acute cannabis use is associated with impaired learning, memory, attention, and motor coordination, areas that can affect important activities of daily living, such as driving. Acute cannabis use can also affect judgment, potentially resulting in users making risky decisions that they would not otherwise make. While there is consensus that acute

cannabis use results in cognitive deficits, residual cognitive effects persisting after acute intoxication are still debated, especially for individuals who used cannabis regularly as adolescents.[7]

Chronic cannabis use is associated with an increased risk of psychiatric illness and addiction. There is a significant association—possibly a causal relationship—between cannabis use and the development of psychotic disorders, such as schizophrenia, particularly among heavy users.[8] Chronic cannabis use can lead to cannabis use disorder (CUD) and contributes to impairment in work, school, and relationships in up to 31% of adult users.[9] Regular cannabis use at levels associated with CUD (near-daily use of more than one-eighth ounce of cannabis per week) is associated with worsening functional status, including lower income, greater need for socioeconomic assistance, criminal behavior, unemployment, and decreased life satisfaction.[8] Cannabis use is associated with adverse perinatal outcomes as well; a 2019 study showed the crude rate of preterm birth was 12.0% among cannabis users and 6.1% among nonusers (risk difference, 5.88% [95% CI, 5.22%-6.54%]).[10]

Inadequate Evidence Supporting the Use of Cannabinoids for Many Medical Conditions

The quality of the evidence supporting the use of cannabinoids is suboptimal. First, studies assessing pain and spasticity are difficult to conduct, in part because of heterogeneity of the outcome measures used in these studies. Second, most RCTs that have evaluated cannabinoid clinical outcomes were small, with fewer than 100 participants in each, and small trials may overestimate treatment effects. Third, the timeframe for most studies is too short to assess the long-term effects of these medications. Fourth, tolerance, withdrawal, and potential for drug-drug interactions may affect the usefulness of cannabis, and these phenomena are not well understood for cannabinoids. The lack of high-quality evidence results in outsized claims of the efficacy of cannabinoids for numerous medical conditions. There is a need for well-designed, large, multisite RCTs of cannabis or cannabinoids to resolve claims of efficacy for conditions for which there are claims of efficacy not supported by high-quality evidence, such as pain and spasticity.

Conclusions

Insufficient evidence exists for the use of medical cannabis for most conditions for which its use is advocated. Despite the lack of evidence, various US state governments have recommended cannabis for the management of more than 50 medical conditions. Physicians may be appropriately reticent to recommend medical cannabis for their patients because of the limited scientific evidence supporting its use or because cannabis remains illegal in federal law. Cannabis is useful for some conditions, but patients who might benefit may not get appropriate treatment because of insufficient awareness regarding the evidence supporting its use or confusion from federal law deeming cannabis illegal.

ARTICLE INFORMATION

Author Affiliations: Division of Addiction Psychiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Department of Psychiatry, Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Kevin P. Hill, MD, MHS, Division of Addiction Psychiatry, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Rabb 2, Boston, MA 02215 (khill1@bidmc.harvard.edu).

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