Cannabis for Chronic Pain: Not Ready for Prime Time

See also Carr et al., p. 17; and also the *AJPH* Pain Management section, pp. 30–72.

Cannabis has been used since antiquity for recreational and medical purposes. Current US medical usage is most commonly for pain, although it is also used for anorexia, nausea, glaucoma, and seizures. In 1996, California's Compassionate Use Act was the first state law legalizing its use, primarily as another option for analgesia and antiemesis for patients with AIDS. State laws authorize cannabis use for varied indications; all include pain. At a time when the unexpected negative consequences of the liberalization of opioid prescribing are a crisis, it is useful to examine whether cannabis offers a better benefit-to-risk ratio than opioids or other available analgesics.

Pain arises from a myriad of etiologies, some with a clear pathogenesis (e.g., postsurgical or cancer-related pain syndromes)[1] and others vaguer (e.g., chronic back pain). Generally, pain is conceptualized as "nociceptive," signaling impending or actual tissue injury, or "neuropathic," meaning that the nervous system is itself the source of pain. These two categories are not exclusive and may coexist with inflammatory pain.

As is often the case for controversial treatments with limited evidence bases characterizing their effectiveness, zealotry permeates discussions of their merits, limits, and downsides. Cannabis has developed a cult following, with certain cultures (e.g., Rastafarians) integrating it into religious practices. Similar enthusiasm is evident among those claiming that because cannabis is "natural" it is perfectly safe. Schatman has suggested that uncritical enthusiasm of "medical marijuana neuromysticism" among both users and empirical investigators[2] has slowed rigorous evaluation of its risks and benefits, contributing to cannabis's failure to become a legitimate medicine.

The use of cannabis (particularly its principal psychoactive constituent, Δ^9-tetrahydrocannabinol or THC) is associated with health risks including lung disease (when smoked), cardiovascular disease, acute pancreatitis, and cannabinoid hyperemesis syndrome.[3] Cannabis users are also at increased risk for occupational injuries, and cannabis-associated "drugged driving"—sometimes fatal—is increasing. Cannabis use during pregnancy has been associated with increased neonatal morbidity or death.[4] Finally, the myth that marijuana is nonaddictive has been dispelled by studies of forced abrupt cessation of use indicating potential rebound hyperalgesia and craving. As the health risks associated with cannabis come under increasing scrutiny, pharmacovigilance during its use in growing numbers of people may uncover other problems.

Besides organ-specific toxicity, cognitive risks have been associated with cannabis use.[5] Diminution of gray matter in the brain in chronic cannabis users has long been recognized. Empirically established deficits following months to years of use involve—but are not limited to—executive functioning, information retrieval, learning, abstraction, motor skills, and verbal abilities, with use of higher-THC cannabis resulting in more profound deficits. Such deficits appear greatest when cannabis is used by younger persons, as the brain is thought to develop into the mid-20s. Psychopathological consequences of cannabis use include acute psychosis, schizophrenia, worsened social functioning in schizophrenia, bipolar disorder, depression, and anxiety (particularly with increasingly common high-sativa content strains).

Objective data on the efficacy of cannabis for pain management are not particularly encouraging.[6] Cannabis can be helpful in relieving neuropathic pain, with the magnitude of analgesia generally contingent on the amount of THC. Unfortunately, higher-THC cannabis, similar to opioids, also produces more cognitive side effects, often rendering patients impaired at work and in activities of daily living. Moreover, much of the earlier clinical trial literature on cannabis for neuropathic pain has been rendered obsolete by advances in phenotypic profiling that distinguishes etiological subgroups—including genetic subgroups—that respond differently to the same therapeutic agent. Evidence of efficacy for conditions including fibromyalgia, headaches, and rheumatoid illnesses is less compelling than that for neuropathic pain, limiting the ability to conduct systematic reviews of efficacy for these other indications or when such reviews are performed, concluding that cannabis use for these disorders is not supported. Even cannabis's efficacy for cancer pain has been questioned, with a recent review[7] noting that it may have potential use but that existing human studies are of poor quality, limited size, and outdated. In defense of cannabis as an analgesic agent are studies suggesting that it may achieve synergistic analgesia when coadministered with opioids, and some investigations[8,9] point toward an opioid-sparing effect.

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Unfortunately, it remains extremely difficult to conduct clinically relevant medical cannabis research in the United States because of the drug's Schedule I status, and the requirement that all cannabis used be obtained from a single farm at the University of Mississippi. Although the US Drug Enforcement Administration (DEA) is considering other potential growers, the school continues to have a monopoly, and it is permitted to grow only 1000 pounds of cannabis for research purposes each year. Even more problematic is that until very recently, the University of Mississippi was permitted to cultivate cannabis with a maximum THC content of 7%, yet 67% of medical cannabis consumers choose to use oils and other concentrates with THC contents as high as 90%. Cannabis for investigation with a higher THC content (13.4%) was obtainable only recently from the National Institute on Drug Abuse (NIDA). Thus, research on the analgesic efficacy of what the DEA considers "strong marijuana" has been flawed.

Adding to these reservations concerning cannabis as an analgesic is that THC is not the most medically relevant constituent of cannabis. Cannabidiol (CBD) is a noneuphoriant cannabinoid with a good safety profile (NIDA Director Nora Volkow, MD, has asserted that CBD appears to be a "safe" drug) and has activity both as an analgesic and anti-inflammatory. Importantly, CBD modulates the euphoria produced by THC and provides mild anxiolysis. Although it is thought that cannabis contained equal amounts of THC and CBD in preagricultural times, when the plant grew wild, users' and hence growers' desire to maximize THC content for its euphoric effects has resulted in CBD being all but bred out of the vast majority of cultivated cannabis. Efforts to find cannabis that contains low concentrations of THC and high levels of CBD in dispensaries are often futile. Few if any health care providers who authorize medical cannabis educate their patients specifically to seek the most "medicinal" forms of the drug. Even if this aspect of sourcing a uniform, well-characterized supply of cannabis for research or clinical purposes were overcome, another fundamental challenge for such studies is that (unlike for morphine or other opioids) blood levels of these agents do not consistently correlate with their in vivo effects.

In summary, the unsettling safety profile of cannabis, the lack of strong empirical support for its efficacy, the general absence of CBD in what is used "medically," and the methodological challenges in conducting research suggest that, at present, cannabis should not necessarily be considered an optimal choice as a drug for pain management.[10] AJPH

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