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Focus Article

Cannabis in Pain Treatment: Clinical and Research Considerations

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Abstract: **Cannabinoids show promise as therapeutic agents, particularly as analgesics, but their development and clinical use has been complicated by recognition of their botanical source, cannabis, as a substance of misuse. Although research into endogenous cannabinoid systems and potential cannabinoid pharmaceuticals is slowly increasing, there has been intense societal interest in making herbal (plant) cannabis available for medicinal use; 23 U.S. States and all Canadian provinces currently permit use in some clinical contexts. Whether or not individual professionals support the clinical use of herbal cannabis, all clinicians will encounter patients who elect to use it and therefore need to be prepared to advise them on cannabis-related clinical issues despite limited evidence to guide care. Expanded research on cannabis is needed to better determine the individual and public health effects of increasing use of herbal cannabis and to advance understanding of the pharmaceutical potential of cannabinoids as medications. This article reviews clinical, research, and policy issues related to herbal cannabis to support clinicians in thoughtfully advising and caring for patients who use cannabis, and it examines obstacles and opportunities to expand research on the health effects of herbal cannabis and cannabinoids.**

Perspective: ***Herbal cannabis is increasingly available for clinical use in the United States despite continuing controversies over its efficacy and safety. This article explores important considerations in the use of plant Cannabis to better prepare clinicians to care for patients who use it, and identifies needed directions for research.***

Key words: *Cannabis, marijuana.*

In this article important considerations in the use of cannabis are presented to better prepare clinicians to care for patients who use it and needed directions for research are identified.

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Introduction

History

The herb cannabis, also called marijuana, has been used medicinally for millennia.[59,74] It was formally introduced into the U.S. Pharmacopeia in 1850 and diverse cannabis products and extracts were marketed through the early 1900s. As whole plant medicines and herbs were gradually replaced in western allopathic medicine by highly regulated pharmaceuticals with identified active constituents at known doses, and as public concern increased related to street use of cannabis, cannabis prescribing became less common in medical practice. It continued to have a valued role until the Cannabis Tax Act of 1937, which was opposed by the American Medical Association, and resulted in the removal of cannabis from the National Formulary

and the U.S. Pharmacopeia in 1941.[23] In 1970, with implementation of the U.S. Controlled Substances Act, cannabis was placed in Schedule I, which is reserved for drugs with "high potential for abuse," "no currently accepted medical use," and "lack of acceptable safety for use under medical supervision,"[89] a designation that is now controversial.

Current Availability

Although possession and use of cannabis remains illegal under U.S. federal law, cannabis is increasingly available in the United States for clinical and recreational use because state laws governing cannabis are rapidly changing. States differ significantly in their policies regarding availability and use of herbal (plant) cannabis, with 23states, the District of Columbia, and Guam at the time of this writing making cannabis available for therapeutic use, 4 for recreational use (and medical use), and 15 others decriminalizing possession of small amounts of cannabis.[57]

Diversity of Opinions

There is a broad range of opinion among pain clinicians and researchers regarding the use of herbal cannabis and its non-U.S. Food and Drug Administration (FDA)-approved extracts for clinical purposes with advocates and opponents within the field.

Common arguments supporting the clinical use of herbal cannabis include:

- Cannabis contains numerous cannabinoids and other active constituents that combine to make whole plant cannabis and its extracts more clinically effective than currently available cannabinoid medications.
- Cannabis has very low or no potential for overdose and relatively low rates of addiction and harmful use compared with opioid analgesics and may clinically replace opioids in some contexts and thereby reduce opioid-related harm.
- Cannabis is an ancient medication with millennia of experience supporting its use as a safe and effective treatment.
- Cannabis is relatively inexpensive to grow and produce.

Common arguments opposing the clinical use of herbal cannabis include:

- The chemically active content of herbal cannabis is complex, variable, and often unknown, making dosing and predictability of effects uncertain; it would not meet FDA criteria for approval as a medication.
- Cannabis is widely used recreationally with associated harm to individual and public health; making cannabis available as a medication will increase general availability and associated harm.
- Few patients cannot be managed well clinically without cannabis; the push for medical cannabis is part of a well structured and funded strategy to legalize cannabis for general use.
- Smoking cannabis may be harmful because of products of combustion and other delivery systems are not well studied.

Despite continuing debate on these and other cannabis-related issues, many pain clinicians and researchers agree that cannabinoids are clinically promising chemical compounds and that there is a critical need for robust research on herbal cannabis to identify targets for medication development and to assess outcomes of clinical availability to better inform understanding and policies related to its use, positions also supported by the leadership of organized medicine.[4]

Need for Clinical and Research Guidance

Regardless of whether a pain care provider believes that cannabis should—or should not—be available for use, all clinicians must be prepared to address the reality that some patients will elect to use cannabis for pain or other symptom management or for recreational purposes and should be able to counsel patients on herbal cannabis use in clinical contexts. Researchers must consider how best to expand cannabis research to fill gaps in knowledge regarding the clinical and public health effects of expanded use.

This paper is a consensus document with input from clinical experts and researchers on pain who hold diverse opinions related to the appropriate roles of cannabis in medicine and in society. It is intended to assist clinicians in thoughtfully advising and caring for patients who elect to use herbal cannabis for clinical purposes in the absence of robust evidence to guide clinical care. It also identifies obstacles and opportunities for research to fill gaps in our understanding of the personal and public health effects of broadened access to herbal cannabis for pain treatment. Although this article focuses on the use of herbal cannabis in pain treatment, many considerations will be relevant to broader clinical and research considerations related to herbal cannabis.

Science of Cannabis and Cannabinoids

Herbal Nature of Cannabis

Cannabis has 3 major species, *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. *Cannabis sativa* is the most commonly used species, from which other more concentrated resin derivatives (hashish and hash oil) are typically obtained. Cannabis (including sativa, indica, and their hybrids) has been cultivated and manipulated in such a way that there are currently a large variety of phenotypes available with different concentrations of major active ingredients.

Cannabis Content and Changes Over Time

Cannabis has 537 constituents, 107 of which are unique to cannabis (cannabinoids).[60] Delta-9-tetrahydrocannabinol (THC) is the most studied and a major active molecule of cannabis. The concentration of THC determines many of the effects of cannabis.