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Clinical & 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. While 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 both 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 paper reviews clinical, research and policy issues related to herbal cannabis in order 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 U.S despite continuing controversies over its efficacy and safety. This paper explores important considerations in the use of plant Cannabis to better prepare clinicians to care for patients who use it and to identify needed directions for research.

1. Introduction

History

The herb cannabis, also called marijuana, has been used medicinally for millennia.[59, 75] 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, 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,"[88] a designation which 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 both clinical and recreational use as State laws governing cannabis are rapidly changing. States differ significantly in their policies regarding availability and use of herbal (plant) cannabis, with twenty-three states, the District of Columbia and Guam at the time of this writing making cannabis available for therapeutic use, four for recreational use (and medical use), and fifteen 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-FDA approved extracts for clinical purposes with both 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 to opioid analgesics and may clinically replace opioids in some contexts and there-by 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 due to 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 both 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.[5]

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 in the field of 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. And it 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. While the paper 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.

2. Science of Cannabis and Cannabinoids

Herbal nature of cannabis

Cannabis, has three 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).[61] Delta-9-tetrahydrocannabinol (THC) is the most studied and a major active molecule of Cannabis. The concentration of THC determines many of Cannabis's effects. Medical use of THC is related mostly to its reported ability to reduce pain, spasticity, and nausea and to increase appetite in patients with anorexia or with wasting syndrome in AIDS.[94] In addition THC has well-characterized psychotropic effects including euphoria, relaxation, heightened sensory perception, laughter, and altered perception of time.[94] Cannabidiol (CBD), another important cannabinoid has been shown to modulate inflammation, pain, spasticity, epilepsy, and nausea and, in contrast to THC, does not appear to produce euphoria.[94] Cannabinol (CBN), cannabichromene (CBC), and tetrahydrocannabivarin [1](THCV), other cannabinoids found in cannabis, are also under study. Terpenes are other constituents found in *Cannabis sativa* (and other types of plants) that bind and activate cannabinoid receptors.[29] The biological actions and interactions of these constituents are not yet well characterized.

The number of known constituents of cannabis has increased from 489 to 537 in four years (2005-2009),[61] in a similar fashion to the number of known cannabinoids, which has increased from 70 to 109.[61] Of particular relevance is the increase in cannabis THC concentration over time. While in the 1980's the average cannabis THC concentration was 3%, currently (2009 data) it is 13%.[26] It is worth noting that the highest concentration of THC found in 2009 was 37% for cannabis, 66% for hashish, and 81% for hash oil.[26] These higher concentrations of THC result in a greater effect per amount of material consumed. A similar trend in the average concentration of CBD in cannabis has been observed: 0.3-0.1% in the 70's to 0.2-0.4% between the 80's and 2008.[26]

The endocannabinoid system

Humans, like all mammals, produce endogenous cannabinoids (endocannabinoids), which are similar to cannabinoids found in herbal cannabis (phytocannabinoids).

1

Anandamide and 2- arachidonoylglycerol are the better-known endocannabinoids. These molecules bind to and activate specific receptors: cannabinoid receptors type 1 (CB1) and type 2 (CB2). Two major enzymes can metabolize endocannabinoids- fatty acid amide hydrolase (FAAH) that predominantly degradates anandamide, and monoacylglycerol lipase (MGL) that predominately degradates 2-arachidonoylglycerol. Thus, endocannabinoid agonists, cannabinoid receptors, and endocannabinoid degradative enzymes constitute the endocannabinoid system.[33] The activity of endocannabinoids are involved in multiple physiological functions: temperature control, pain modulation, appetite induction, nausea modulation, cellular migration, control of inflammation, etc. Due to extensive expression of CB1 receptors in several areas of the brain, the activation of this system by THC (which is a CB1 and CB2 receptor agonist) results in its psychotropic effects. CB2 receptors are mostly expressed outside the brain, mainly in leukocytes and peripheral cells; their activation results in modulation of inflammation[76]and their role in central neural processes through expression on astrocytes and microglia is receiving increased attention.[106]

Current and promising cannabinoid drugs

Pharmacological modulation via synthetic cannabinoids is directed towards activation or inactivation of cannabinoid receptors (agonists or antagonists respectively). Also, there are compounds that inactivate the actions of degradative enzymes (FAAH or MAGL) that results in an increase of the bioavailability of endocannabinoids and a subsequent activation of cannabinoid receptors. Currently there are two FDA-approved pharmacological entities that activate cannabinoid receptors: dronabinol (synthetic THC) approved and marketed in 1985 and nabilone (a synthetic molecule similar to THC) approved in 1985 but not marketed in the U.S. until 2005. Approved for treatment of nausea induced by chemotherapy and of wasting syndrome caused by AIDS, both, nabilone[87] and dronabinol[20] have shown efficacy to treat pain in humans. In Canada and other countries in Europe a combination of THC and CBD ~1:1 proportion, nabiximols (Trade name: Sativex™) is approved for chronic neuropathic pain or spasticity induced by multiple sclerosis[70] and a U.S. study recently showed dose dependent reductions in

diabetic neuropathic pain.[96]This compound has shown mixed results in treating cancer pain[26, 73] and it is currently in a phase III clinical trial in the U.S. for this condition. Another potentially useful pharmaceutical cannabinoid is a CBD-based investigational new drug (non-FDA approved, Epidiolex™) for the treatment of certain epilepsies in children.

3. Clinical Actions of Herbal Cannabis: Efficacy and Risks

Methods of use

Cannabis can be self-administered by smoking, vaporization, eating, orally applied tinctures, and topical application as salves. Evidence suggests that vaporization (heating until volatile active cannabinoids are vaporized) reduces combustion products in the inhalant and may therefore be a safer method than smoking, though some toxins or carcinogens may be present in vapor.[35] Smoked or vaporized cannabis, is more rapid in onset than other routes of administration with onset of effects within minutes allowing for rapid titration of effects for pain or other symptom management, as well as psychotropic effects. Devices are under study that would provide metered doses of vaporized cannabis.[24]

Edibles are increasingly utilized, but are slower in onset and have the added risk that dosages in cookies, brownies, fudge, butter, lozenges, tincture, soda, candy, syrup or other formulations may vary dramatically and have unpredictable side-effects.[93]Orally ingested herbal cannabis undergoes an unpredictable first pass effect and metabolism and is difficult to titrate as effects of a given dose might take 90 minutes or longer to manifest.[32] In addition, edibles are sometimes mistaken for non-cannabis containing treats with potentially serious unwanted effects, particularly in children.[97]

Cannabinoids are highly lipophilic and if topically applied in a salve or as an herbal cannabis poultice under an occlusive dressing, may be absorbed and potentially have

either a local or systemic effect. However, no studies have evaluated the efficacy of this route of administration. Smoking remains the most common route of administration.

Therapeutic effects [2]

Expanding evidence indicates that herbal cannabis has analgesic effects in both neuropathic and non-neuropathic pain.[53, 54] The most robust evidence exists for neuropathic pain and there are at least five high quality randomized controlled clinical trials establishing analgesic efficacy of smoked cannabis.[2, 6, 25, 96, 101, 108] Reductions in mean visual analogue scores in these studies are modest and similar to mean VAS reductions for opioids, antidepressants or anticonvulsants. The number needed to treat for a 52% reduction in pain (compared to 24% in placebo group) was approximately 2 in one study[2] and for a 30% reduction, 3.5 in another.[25] Similar data exists for pain associated with fibromyalgia[84] and rheumatoid arthritis[14, 55] and for vaporized cannabis.[96, 109] One study demonstrated significant sustained reduction in chronic pain at 12 months with continued use of cannabis containing 12.5% THC an average of 2.5 grams per day [99]; other long-term studies are not available.

There is some uncertainty regarding the relative analgesic actions of different component(s) of herbal cannabis. The two cannabinoids typically in highest concentration in herbal cannabis are THC and CBD and there is evidence that they are both potentially useful as analgesics. This is clinically relevant in that THC has reward (euphorigenic) effects while CBD does not. One well-conducted study showed no difference in analgesia between smoked cannabis and dronabinol, an FDA approved THC based medication marketed in the U.S.[20]

In addition to pain, there is some evidence and ongoing study of potential therapeutic efficacy of cannabis for common symptoms and conditions associated with pain, including: spasticity associated with MS or stroke,[11, 44] anxiety and PTSD,[68] nausea &

vomiting,[56] cachexia,[27] inflammatory bowel diseases,[62] migraine,[58] and sleep disturbance.[80, 100] Patients with pain may elect cannabis use for these symptoms as well.

Side Effects and Risks

It is important to note that most of the known risks of cannabis use have been identified through the study of recreational cannabis use; care should be exercised in assuming that the risk profile is the same among medical users. Risks could be lower because of a different pattern and purpose of use, and could be higher because of potential drug interactions or co-occurring conditions. The adverse effects of prescription cannabinoids in clinical trials have been reviewed[98] and are mostly mild-moderate in severity with dizziness, drowsiness and dry mouth being most common. A recent study found a higher rate of adverse events among persons using cannabis for pain for one year at an average dose of 2.5 grams herbal cannabis with 12.5% THC than that of controls, but not higher for serious adverse events. [99]

Psychobehavioral: Cannabis can produce cognitive, psychomotor and perceptual alterations, as well as euphoria, which generally last in the range of 3-8 hours depending on dose and method of use.[36] Cannabis use can worsen the course of psychotic illness, may precipitate psychosis in vulnerable individuals, and early or heavy use may be associated with increased risk of schizophrenia in adulthood.[107]

Cannabis has a lifetime risk for users to develop dependence of 9% compared to 67.5% for nicotine and 22.7% for alcohol;[51] it may be as high as 17% in those initiating cannabis use in early adolescence[7] and gradually declines with age of onset of use.[46] Adult onset of initiation, low to moderate use, and use for therapeutic rather than recreational purposes, might alter risk of addiction. Cannabis use is positively associated with anxiety disorders but causality and direction of the relationship is not clear.[42] Regular, heavy users of cannabis may demonstrate persistent intellectual, cognitive, and motivational changes.[21]

Developmental: Prenatal exposure to cannabis through maternal use has been associated with neurodevelopmental differences in neonates and subsequent developmental changes in children.[38] Cannabis may affect brain development in children and adolescents who use it resulting in possible delayed psycho-developmental maturation, and reductions in intellectual function and motivation.[52] Given current levels of evidence, cannabis should not be utilized by pregnant or lactating women and an especially careful risk/benefit analysis should be done in persons under the age of 18 years.

Cardiopulmonary: Cannabis can cause orthostatic hypotension in frail or elderly cannabis naïve patients potentially increasing risk of falls.[92] It induces mild tachycardia at onset of effect and its use has been temporally associated with stroke, myocardial infarction, and arteritis;[86] however, evidence is mostly case report and epidemiologic; further research is needed to explore these associations. Adverse pulmonary effects of chronic heavy use of cannabis including chronic bronchitis and large airway inflammation may occur and exacerbation of existing COPD and asthma have been reported. However, evidence regarding a causative role in emphysema or de novo COPD for cannabis use alone in the absence of tobacco use is equivocal.[40, 48] The pulmonary effects of cannabis smoking might be mitigated by using an alternative delivery system to smoking

Oncogenic: Risk of cancer in association with cannabis smoking has been a concern because of the potential carcinogens in products of combustion. However, a clear relationship between lung cancer and cannabis smoking has not been established when tobacco use is controlled for.[40, 112] There is evidence that cannabinoids may have antineoplastic activity through anti-metastatic and anti-angiogenic mechanisms.[22, 74] and this is an area of intense study.

Other: Cannabis use may cause a syndrome of nausea, hyperemesis, and abdominal pain that, curiously, can be ameliorated by taking a hot shower or discontinuing use.[83] Driving intoxicated by cannabis, including cannabis use alone in the absence of other intoxicants, appears to increase the risk of being in a motor vehicle accidents over non-impaired driving.[9, 34, 49]

4. Public Health Issues

Public health concerns regarding potential consequences of increased availability cannabis for clinical treatment have been raised and many of these are under study. Full discussion of public health issues is beyond the scope of this white paper; however, as clinicians develop their practices with respect to care of patients who use cannabis it is important that they be aware of emerging evidence regarding cannabis-related public health issues and consider how their practice with respect to cannabis may impact the public health, as well as providing education to patients regarding potential consequences of diversion and misuse of medical cannabis.

Among public health concerns which have some supportive evidence:

- Framing cannabis as a medicinal substance could reduce perceptions of drug-related risk, particularly among youth.[81, 95]
- Increased legal access to cannabis (and its diversion) could increase impaired driving and associated motor vehicle accidents.[78]
- Increased availability of cannabis for medical use could result in rising rates of cannabis diversion, illicit use, misuse and dependence.[16]
- Increased cannabis use could increase the prevalence of cannabis-associated adverse health consequences discussed in the risk section above, including developmental, mental health, addiction, and physical effects, with cumulative impact on societal well-being and productivity. (theoretical without population level evidence reported to date)

One potentially positive public health benefit has been reported; a recent study that suggested that states with medical cannabis access had reduced rates of opioid overdose deaths.[10] Further study of this reported association is needed.

Evidence related to the impact of medical cannabis on the public health is evolving and is expected to be clearer over time if appropriate monitoring programs are in place. Most States rely on large existing data bases to track relevant cannabis related public health issues such as risk perception, cannabis associated MVAs, addiction treatment demand, prevalence of use, misuse and dependence and others; to our knowledge, no U.S. state is currently collecting patient level data on the personal health effects on authorized users (e.g. cardiovascular, pulmonary or mental health changes) so the population health impacts of legal access to medical cannabis based on cumulative health experiences of individuals are not known. In May 2015, however, the Canadian province of Quebec launched a Cannabis registry that will collect information on health effects and side effects of cannabis in registered medical users.[90, 102]

5. Regulatory, legal and professional considerations

Regulatory oversight of herbal cannabis content and purity

The U.S. Food and Drug Administration (FDA) is charged with assuring that available pharmaceutical products have been well studied in terms of effects and side effects, that they have precise and uniform content, and are free of toxins and contaminants. The FDA has approved two cannabis derived medications for use in the U.S. with a third in phase three trials; however, neither the FDA nor other federal regulatory agencies in the United States oversee or regulate the production, processing, distribution, marketing or sales of herbal cannabis.

Although many growers and processors aim to control the relative content of different cannabinoids in various strains of herbal cannabis and cannabis-derived edibles and other products and work to assure freedom from toxins or contaminants such as fungi or pesticides,[60] at this time there is no designated Federal authority to hold growers, processors, distributors, marketers or sales persons accountable for the content and purity of herbal cannabis or for assertions regarding the effects and side effects of different strains and product. Similarly, extracts of cannabis, some with reported concentrations or relative ratios of different cannabinoids, are currently sold without regulatory oversight. Therefore the therapeutic effects and side effects of herbal cannabis and its extracts in the U.S. cannot at this time be reliably predicted nor the purity of herbal cannabis assured.

Tighter quality controls and oversight appear to be in evolution in some jurisdictions where cannabis use has become legal. For example, Oregon's recently passed cannabis legalization act designates the Oregon liquor commission to work with the Department of Agriculture and the Department of Health to "create a regulated and licensed marketplace."[39] In addition, laboratories that test for cannabinoid content and contaminants, such as pesticides and fungus, appear to be proliferating,[79] albeit as of yet without regulatory oversight.

Variability of clinician and patient responsibilities under state laws

State laws vary significantly with respect to herbal cannabis[57] and it is important that clinicians know the statutes that govern herbal cannabis in clinical care in the States in which they practice. In 2013, then U.S. Attorney General, Eric Holder, stated that his office would not prosecute the use of cannabis in accordance with the laws of a State in which a person uses cannabis (with several important caveats related to use by minors, use or growing on public lands, and involvement in criminality or violence.[19] However, this policy could change with transition of Attorneys General or Federal administrations and it is important for clinicians to remain aware of federal policy trends.

The proscribed role of clinicians in a patient's initiation and use of cannabis for symptom management differs in different states. In some states, the clinician certifies a condition or symptoms that then qualify a patient to register to use cannabis; in other states physicians must recommend a trial of cannabis. States differ in the physician role with respect to determination of potential risks or contraindications for patients and regarding responsibilities for risk-benefit counseling, follow-up, and re-certification of patients with respect to cannabis use. Because cannabis is not an FDA approved pharmaceutical, no State requires a physician to write a prescription for cannabis.

States also differ in the amount of cannabis that can be possessed for medical purposes, whether the herb can be grown by individuals or bought at a dispensary or both, and whether other products such as edibles are available. Possession by designated care-givers is addressed differently in different State regulations. Rules governing dispensary roles, staffing and responsibilities also vary between states. Currently no third party payers in the U.S. provide coverage to pay for herbal cannabis.

Professional obligations

The AMA code of ethics states that physicians are obligated to "present the medical facts accurately to the patients…and to make recommendations for management in accordance with good medical practice. The physician has an ethical obligation to help the patient make choices from among the therapeutic alternatives consistent with good medical practice."[4] Counseling regarding herbal cannabis presents unusual challenges in meeting these obligations since scientific evidence regarding herbal cannabis effects and side effects in different therapeutic contexts is relatively limited and because of variability and uncertainty regarding cannabis products to which a patient may have access.

Nonetheless, it is appropriate for physicians to educate themselves regarding what is known about the potential benefits and risks of herbal cannabis, to consider the individual patient's symptoms, conditions, and personalized risks, and to share a reasoned perspective with the patient. Similarly, it is appropriate for the supervising physician to follow patients who elect to use cannabis to assess clinical effects on pain or other target symptoms, presence of side-effects or adverse consequences, and impact on function and quality of life and to advise the patient based on these observed outcomes.

6. Research Issues Related to Herbal Cannabis

The need for research

In January 1997, the White House Office of National Drug Control asked the Institute of Medicine (IOM) to conduct a review of scientific evidence to assess health risks/benefits of cannabis; this was performed and published in 1999.[103] The 1999 IOM report recommended that research focus on physiologic effects of synthetic and plant-derived cannabinoids, development of new delivery systems, psychological effects of cannabis and health risks of smoked cannabis. At the time of the IOM report, a review of the world literature on the efficacy and safety of cannabinoids for pain and spasticity revealed only nine randomized studies of acceptable quality had been conducted, all of which were single dose studies comparing synthetic THC (or cannabinoid analogs or congeners) to codeine or placebo. As a group, the trials appeared to be superior to placebo and at least as effective as codeine 60 mg.

In November 1996, California and Arizona were the first states to pass referenda designed to permit the use of cannabis as medicine (Arizona's referendum was invalidated but was later passed and legally implemented). The lack of high quality evidence on uses of medicinal cannabis has led to criticism over legalization. Shortly after the IOM report, the State of California passed SB 847 (State of California Medical

Cannabis Research Act of 1999) which allocated funding for rigorous scientific studies to assess the safety and efficacy of cannabis for treating medical purposes. From SB 847, the University of California Center for Medicinal Cannabis Research (CMCR) was established to focus on disease and conditions as specified by the National Academy of Sciences, IOM, and the Workshop on the Medical Utility of Cannabis.[12, 41, 103] These studies were conducted under the auspices of the Department of Health and Human Services, the National Institute on Drug Abuse, and the Food and Drug Administration. The CMCR funding resulted in several placebo-controlled studies showing efficacy in neuropathic and cancer pain.[2, 25, 96, 108, 109] There have also been positive studies out of Canada.[6, 101]

Regulations and oversight of cannabis research

Cannabis is subject to control under Schedule I of the Controlled Substances Act (CSA)(21 U.S.C. 801 et. Seq.). This scheduling results in obstacles to research including highly restrictive regulations and regulatory oversight. The production and distribution of cannabis for clinical research is carefully restricted under a number of Federal laws and international commitments. Medicinal cannabis research falls under the auspices of multiple agencies including the Drug Enforcement Agency,[30] Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), National Institute of Drug Abuse (NIDA) and certain state agencies (i.e. Research Advisory Panel of California).

Persons who wish to conduct research using cannabis must obtain a special registration under the CSA from the DEA (21 U.S.C. 823[f]). To receive a Schedule I license, a researcher must first be determined by HHS to be qualified and competent and the proposed research must be determined by HHS to have merit. A requirement that studies using cannabis must be submitted to an interagency review panel convened by the Office of Public Health and Science (PHS) of the DHHS was removed in June 2015, one step towards simplifying the approval process. After HHS approval, studies must

then be submitted to the FDA under an Investigational New Drug (IND) application. Once approved by the FDA and assigned an IND number, the study must be submitted for further review by NIDA and by the Federal office of the DEA. Simultaneously, approval must be obtained from the local DEA office; generally involving inspection of the location and practices for storage and dispensing. Storage and security requirements for cannabis provided for research typically exceed those of most other investigational drugs. Additional state-level review and approval may be necessary as well (e.g. California requires all research with Schedule I or II controlled substances be reviewed and approved by the Research Advisory Panel of California, a branch of the Office of the Attorney General, in the California State Department of Justice).

Sources of investigational cannabis

Herbal cannabis used in research in the U.S. is provided through the NIDA Drug Supply Program. Since 1968, the University of Mississippi has been the sole supplier of cannabis for research in the U.S. through its contract with NIDA. It is unclear what strains NIDA cultivates, but the agency has made cannabis available with different concentrations of THC, the primary active ingredient. Studies conducted in the CMCR used concentrations of THC that came in high (7%), medium (4%), and low (1%). The level of other cannabinoids in cannabis used were typically very low (e.g. CBD <1%) and sometimes below the threshold of detection when assayed. NIDA has stated that they are able to provide cannabis of greater or lesser potency as necessary. Review of the website of the University of Mississippi National Center for Natural Products Research[85] shows they are actively pursuing CBD oil for use in research, suggesting they are capable of providing cannabis from non-THC focused strains. In May 2015, NIDA announced that they now have several new strains of marijuana available for research, many with high concentrations of CBD.[64] Furthermore, in the same month, NIH released PA-15-188: Developing the Therapeutic Potential of the Endocannabinoid Systems for Pain Treatment (R01).

Because of the regulatory, source and funding challenges of cannabis research in the U.S., the majority of high quality cannabis research is being done outside the U.S. including in countries such as Canada, Israel, Brazil and the Netherlands.[66]

Funding for cannabis research

NIDA tracks funding for research on the therapeutic effects of cannabis and the NIDA website indicates that as of June, 2014 NIDA funding had been provided for 28 studies on therapeutic effects of cannabis or cannabinoids and that an additional 16 independently funded studies had received research grade cannabis through NIDA since 1999.[63] Limited one-time funding was provided by the State of California to support cannabis research, however, this funding has been exhausted. In at least two instances, researchers who previously conducted studies with CMCR funding have been successful in conducting cannabis research with Federal grants.[91, 110]

The State of Colorado recently established a program to support research with cannabis, and has announced the first round of projects recommended for funding.[8]

A search of clinicaltrials.gov showed several cannabis research studies in countries outside of the U.S., including Canada, Israel and the Netherlands.[89] However, it does not indicate the laws and regulations regarding cannabis research in those countries.

7. Recommendations

A. Clinical Management

Basis of recommendations

While cannabis is increasingly available for clinical use under many State laws, there is a paucity of evidence to guide clinical management of patients who use herbal cannabis. The recommendations that follow draw from limited available evidence on the clinical effects and side-effects of herbal cannabis, from the clinical experience of the authors

with patients who use cannabis, and from extrapolation of experience with patients using other controlled substances on a clinical basis. As evidence and experience evolves best practices in management of patients who use clinical cannabis will undoubtedly evolve as well.

Cannabinoid medication versus herbal cannabis

At discussed earlier, the only FDA-approved cannabinoids available in the U.S. at the time of this writing are dronabinol (synthetic THC) and nabilone (a molecule similar to THC), with nabiximols, a 1/1 mix of THC and CBD, currently in phase III clinical trials. Although initially approved for appetite stimulation in AIDS patients and treatment of chemotherapy-induced nausea and vomiting,[15] dronabinol has been widely used off label for pain, despite limited empirical support.[53] Common side effects of dronabinol include drowsiness, unsteady gait, dizziness, inability to focus thoughts, confusion, mood changes, delusions, and hallucinations,[104] which limit its therapeutic tolerability. A recent study of dronabinol for the treatment of chronic pain, indicated that the medication produces the same psychoactive effects as smoked cannabis[37] also limiting utility in the chronic pain population. Nabilone has been observed to present similar challenging side effects.

The relatively low number of prescriptions issued for currently approved cannabinoid medications and widespread clinical anecdote suggest that the utility of THC-based medication in clinical practice may be limited due to side-effects, bioavailability issues, and slow onset, although cost, inconsistent insurance coverage and lack of physician awareness may play roles as well.

Accruing evidence suggests that CBD and other active constituents may contribute significantly to analgesic effects of plant cannabis[77]and others active constituents in plant cannabis may contribute as well. However, the relative concentrations and interactions of different constituents in diverse strains of plant cannabis are not generally known to the user making both its efficacy and side effect profile

unpredictable. CBD extracts are currently available in dispensaries in many States. However, few comparative studies of herbal cannabis with FDA approved medications or with specific cannabinoid extracts for pain are available to guide decision-making regarding choice of cannabinoid medications versus herbal cannabis versus CBD extracts in different pain contexts. Therefore physicians must use clinical judgment and consider contextual therapeutic and regulatory issues when providing guidance to patients who are weighing use of FDA-approved THC medications or herbal cannabis or CBD or other cannabinoid extracts.

Benefit-risk counseling and risk screening

As with use of any therapeutic intervention it is important to consider the potential risks and benefits of treatment for the patient and to establish clear goals for use. Given the subjective nature of pain and other commonly targeted symptoms of cannabis treatment, such as treatment of nausea or improvement in appetite, establishing functional goals in addition to goals of symptom reduction may provide more objective measures of response. Individualized counseling on potential side effects and risks, as discussed in Section 3, is appropriate. Patients should be counseled not to drive or engage in potentially dangerous activities while experiencing perceptual or sensory disturbances related to cannabis.

Misuse risks and assessment

Because cannabis can produce euphorigenic effects leading to a risk of misuse and associated harm, it is prudent to engage risk screening and clinical management strategies for medical cannabis similar to the use of universal precautions in opioid therapy of pain.[31]

Medical cannabis use for some patients may blend with non-medical use, with the authors of one study concluding that medical use often occurs within the context of chronic recreational use.[65] A study of persons using prescribed opioids for pain found that those with UDTs positive for cannabinoids, were more likely to screen positive for

other illicit substances as well, suggesting that in the context of pain treatment, use of marijuana may not be solely for it analgesic properties. [72] Conversely, however, a study of medical cannabis users did not find concurrent use of prescription pain medications to be correlated with greater use of illicit drugs. [71] Further, the addition of vaporized marijuana has been demonstrated to improve analgesia in patients using opioids and could therefore have an opioid sparing effect.[1] Clearly the interplay between therapeutic and non-therapeutic use of cannabis, opioids and other substances is complex and may be difficult to parse in some patients. A recent study[43] indicated that 94% of applicants for authorization listed "severe pain" as their reason for applying to use cannabis; the subjective nature of pain makes verifying treatment indications difficult. This underscores the need for clinicians to counsel patients who elect to use cannabis for pain management on the potential benefits and risks of cannabis (discussed in section 3) with reference to their specific health issues supporting an informed decision and to monitor closely to identify and intervene in harmful patterns of use.

Risk factors for misuse of State authorized cannabis in the context of clinical care have not to our knowledge been studied; however, because both marijuana and opioids confer risk of misuse through the production of reward or euphoria, it is reasonable to consider that risk factors associated with misuse of opioids in pain treatment may predict some risk for misuse of clinical cannabis. Diverse risk factors for opioid misuse have been identified including: personal history of substance misuse or substance use disorder, family history of SUD, mental health disorder, history of significant trauma, history of incarceration and younger age. [82] Whether use of screening instruments developed to predict risk of opioid misuse such as the ORT or SOAPP or similar tools (REF) have value in identifying risk of cannabis misuse and in shaping care remains to be determined. In the interim, special care in management of patients with histories of substance use or mental health disorders would seem prudent. In management of prescription opioids, risk assessment and stratification have emerged as an important

tool for determining the structure of care and intensity and frequency of monitoring and these may prove to have value as well.

Counseling on routes of administration

Understanding of the relative merits and risks of different routes of cannabis administration is evolving and it is important for clinicians to counsel patients regarding routes of administration of medical cannabis based on available evidence. Despite numerous recent reviews pointing to adverse pulmonary effects of smoking cannabis,[28, 44, 94] this remains the most common route of administration.[47] Some evidence suggests vaporization averts many of these risks although the authors of a recent review[44] noted that "smoking and possibly even use of vaporized preparations expose users to carbon monoxide and other respiratory toxins." Patients who elect to use herbal cannabis should be made aware of alternative delivery options including vaporization, edibles, extracts, and others as they emerge. (See section 3 for fuller discussion.)

Counseling on cannabis strains and cannabinoid content

More research is needed to fully understand the ideal cannabinoid and other active cannabis constituent content and ratios for effective analgesia in different types of pain and other symptom management. However, discussion of the potential effects of different cannabis strains or products given their different THC:CBD ratios and/or other cannabinoid content, in light of evolving understanding of cannabinoid pharmacology, may be considered a responsibility of providers who authorize/certify the drug. As discussed earlier, high-THC cannabis is associated with physical and mental health risks and currently available evidence suggests that for many types of pain, a relatively high level of CBD may be preferred. As extracted CBD is becoming more readily available in some states, some physicians are authorizing or certifying patients for use with the understanding that they will use CBD and not seek whole-plant cannabis. As knowledge, experience and availability of various cannabis-related products are rapidly changing, clinicians who seek to guide patients effectively must remain aware of evolving information and resources.

Preventing diversion

Counseling against diversion of medical cannabis should be routine when authorizing use. Patients should be informed of cannabis's potential risks to others, particularly if misused by vulnerable populations such as adolescents. Protecting against diversion – beyond counseling – however, is extremely difficult. As cannabis has become ubiquitous in American society, convincing patients of its potential dangers and successfully discouraging them from sharing with friends or selling on the street may be impossible. As challenging as it is to protect against diversion of opioids -with a specified number of units on a monthly basis- strategies such as pill counts and urine drug screening can have at least some effect. This is not the case currently with herbal cannabis since dose requirement and plant content are often not predictable and private growing is permitted in many states. Although there is no supportive empirical evidence, it is likely that a patient whom a provider believes is at risk for utilizing authorized cannabis for recreational purposes may be more likely to divert as well.

Monitoring of patients

Monitoring of patients who use cannabis for pain or other symptom control is important, yet can be challenging. As with all therapeutic treatments, follow-up should assess progress towards the goals of treatment, identify side effects, and help revise treatment as indicated. In addition, as with other drugs that have potential for misuse, it is important to consider use of universal precautions such as cannabis agreements[111] and urine drug screens (UDTs) and to assess the treatment's impact, not only on the target symptom, but on function and quality of life.

The use of UDTs provides objective information on the individual's use of cannabis and cannabinoids as well as on the use of other substances, including illicit substance. Specific UDT monitoring strategies will vary depending on what the provider's expectations are regarding the products the patient will use. The cannabinoid medication dronabinol (Marinol@) will be detected as THC in most urine drug screen immunoassays, however, the THC analogue nabilone (Cesamet@) will not be detected

on immunoassay; each can be identified in confirmatory gas chromatography/mass spectroscopy (GCMS) testing.

Should the provider's intent be for the patient to utilize CBD extract (available only in some states) rather than cannabis products containing THC, a simple immunoassay UDT can identify THC, the presence of which would suggest use of whole plant or an alternative cannabis product, an aberrant behavior in that context. If the provider's intention is that the patient use whole-pant cannabis, THC is expected to be present in a UDT screen. UDT screening is also valuable to identify other potential drugs of misuse, including prescription drugs or illicit substances, which the prescriber may be unaware the patient is using and that may put the patient at risk.

Just as sound opioid prescribing aims to improve not only pain but function and quality of life, so response to medical cannabinoids should consider function as well as symptom management. Heavy cannabis use may be associated with significant psychobehavioral changes[94] including possibly an a motivational syndrome;[45] therefore, when a patient utilizing medical cannabis does not experience improved function in association with pain relief, or actually becomes less functional, treatment should be revised with consideration of cessation if appropriate. Given the easy access to cannabis, there is no guarantee that cessation of use will occur. Providers recommending medical cannabis to a patient who is a non-user should be aware of the risk of the patient developing chronic cannabis use or addiction, analogous to development of opioid misuse or addiction in some patients with legitimate chronic pain. Referral for treatment of cannabis use disorder is appropriate should this occur.

Practice considerations

Practice contexts

In order to provide continuity of clinical care, authorization of medical cannabis ideally should be done in the course of a clinician's usual medical practice with his or her own

patients. However, some eligible clinicians will likely decline to become involved in authorization of cannabis so some physicians willing to authorize patients will likely accrue patients beyond their usual panel. In such cases clinicians must take care to do due diligence with respect to assessment, management and communication with relevant other co-care providers.

Medical cannabis-only practices could be dangerous and potentially illegal. Reports of cash-only practices without a patient examination prior to obtaining a medical cannabis certificate have been documented. A 2012 study in Arizona found that only 24 physicians accounted for almost 75% of all certifications for medical cannabis use,[113] with the state's Health Services Director stating "that he suspects such doctors are more likely to cut corners or be in it for the money".[13] Seventeen of the 24 authorizations came from naturopaths, with only 7 provided by MDs or DOs.[113] This approach to medical cannabis authorization can be analogous to opioid pill mills and not consistent with the spirit of any state's medical cannabis laws.

On the other hand, just as some opioid clinics that model best practices in prescribing provide a needed support to other clinicians who are not set up to do due diligence in prescribing,[105]it is possible that some higher volume cannabis specialty clinics could evolve in a manner that actually supports best practices in the community.

Declining patient cannabis requests

Some providers may elect to not authorize cannabis for any patients based on a decision to practice within Federal law or on concerns about the unpredictable nature and perceived risks of herbal cannabis or for other reasons. A provider who does authorize or certify some patients for cannabis (Physician Perceptions Regarding Herbal Marijuana Clinical Effects , 2014), may not support the use of medical cannabis for a particular patient, in which case the patient has the option to seek an alternative provider to authorize its use. However, referral to another clinician who will authorize medical

cannabis for the patient for whom the referring physician believes cannabis is unwise may not always be prudent. A useful analogy would be having a patient request opioids for analgesia when the provider does not believe that this is a wise course of action; referring to a colleague who is more indiscriminate in his/her opioid prescribing may not be in the best interest of the patient.

Discharging patients for unauthorized use

From a legal perspective, discharging a patient from one's practice when a clinician disagrees with a patient's choice to utilize cannabis for pain or other symptom management is not problematic, if done correctly. Having a frank discussion with the patient, making a referral to another qualified pain management physician, and providing a month's worth of any prescription medications the patient is prescribed by the clinician should cover one's legal bases.[69]

From an ethical perspective, one must consider what serves the best interests of the patient. On the one hand, discharge might violate the principle of respect for patient autonomy. On the other, how much autonomy should a patient have when it comes to electing a course that the physician believes could cause harm? Continuing to follow the patient to provide other needed care, while declining to authorize cannabis, (analogous to declining to prescribe opioids when they appear contraindicated) and working to help the patient understand the clinicians medical concerns regarding their use of cannabis, is often an appropriate course.

Clinician engagement in dispensaries

Physician ownership of or engagement in cannabis dispensaries, while legal in some states, raises ethical concerns that deserve consideration. Ownership of a dispensary can constitute a conflict of interest if physician owners are more likely to authorize because they will benefit from revenues from sales. This could also result in over-authorization of a potentially dangerous substance. Empirical support for such a

phenomenon can be found in the medical literature. For example, in a recent General Accountability Office audit, growth in self-referred imaging was found to outpace the growth rate of non-physician-owned counterparts by a 3.5:1 margin for computed tomography and a 7:1 margin for magnetic resonance imaging.[3]

However, thoughtful physician engagement at the dispensary level could serve to improve dispensing practice if, for example, evidence-based risk-benefit counseling, data collection or other quality practices are cultivated. Prior to considering engaging with a dispensary, a physician should ascertain the legality of doing so by reviewing his/her state's medical cannabis laws and consider the potential ethical implications.

Table 1. Clinical practice recommendations/considerations for care of patients using cannabis as therapy. *For all authorizing/certifying clinicians & for other care-providers (primary care, psychiatrists and others) who are aware of a patient's use of cannabis.*
Be aware of Federal laws and prevailing interpretation & enforcement
Be aware of and work within State laws governing use of medical cannabis
Establish and/or learn the patient's goals for therapeutic use of cannabis
Screen for risk of misuse, addiction & diversion
Counsel patients on individualized clinical risks and potential benefits of cannabis based on their symptoms, conditions and co-morbidities
Advise on cannabis strains, cannabinoid medications or extracts as possible recognizing limitations due to lack of herbal/substance uniformity and regulatory oversight
Advise on routes of administration based on current evidence
Be guided in all advising by available scientific evidence, not relying on messaging of commercial interests
Consider written informed consent and agreement to assure mutual understanding
Monitor as for opioids and other controlled substances: o Regular intervals o Assess control of targeted symptoms, functional status, pattern of use of cannabis of other substances and medications o Obtain periodic urine drug screens for objective information on substance use
Continue or discontinue based on observed outcomes: o Continue authorization if goals of treatment being met without harm o Discontinue if not helpful in moving towards goals or if major intolerance or unsafe medication or substance use
Intervene through counseling or referral if harmful use or declining function apparent

Renew or recommend authorization/certification, or not, based on observed outcomes:
- Continuation if goals of treatment being met without harm
- Discontinuation if not helpful in moving towards goals or if unsafe medication or substance use

B. Future Research

Reducing barriers to cannabis research

The current scheduling of cannabis results in obstacles to clinical research. Although the CMCR has successfully funded and completed multiple high quality clinical research trials, lessons learned from the CMCR highlight the challenges faced in doing research in the U.S. with a scheduled I agent. Multiple agency oversight leads to significant delays and higher costs. Rescheduling cannabis to a schedule II class would be expected to greatly reduce these barriers.

In addition, current scheduling of cannabis limits availability, quality and funding of future research. The schedule I status has restricted availability to one government source with limited resources for high quality cultivation and purity and limited options for diverse strains (see Research Issues Related to Herbal Cannabis). Furthermore, funding is limited for research on schedule I drugs as therapeutics since they are by definition deemed as having no medicinal value.

However, a change in cannabis scheduling from schedule I to schedule II for the purpose of increasing research could also have clinical implications. A schedule II classification would reflect a shift in Federal policy towards wider clinical availability and would theoretically permit prescribing of marijuana by all DEA registrants under DEA regulations. However, the fact that no herbal cannabis product is currently FDA approved would remain an obstacle to actual prescribing.

Arguments relevant to clinical care that support a change from schedule I to II include:

1. Emerging evidence on the medicinal value of marijuana
2. A higher safety profile of cannabis over many schedule I, II and III drugs in that it has no known lethal dose and no reports of death from cannabis alone.
3. Less addiction potential than drugs such as opioids already in schedule II and III

Arguments against rescheduling (https://learnaboutsam.org/the-issues/rescheduling-marijuana/) include:

1. Would lessen perception of cannabis risks among youth
2. Would be a symbolic victory for those seeking legalization
3. Would not make cannabis or cannabis products more available as proponents anticipate

These controversies within science and politics hopefully can be reconciled as evidence continues to emerge on efficacy, safety and the individual and public health consequences of greater marijuana access in States where it is more available.[17, 18]

The value of larger scale clinical trials

Although there have been significant gains in cannabis clinical research, they have been limited to small proof-of-concept studies. Although these small studies are important and have significantly contributed to our understanding of safety and efficacy issues with herbal cannabis, they do not always translate to real world medicine. This underscores the need for large-scale phase III trials; however, until the barriers described above are lifted, we may never see this level of research. In addition to the aforementioned barriers, the cost of phase III studies may prove prohibited without a sponsor.

The Dutch Ministry has been successful in cultivating medicinal grade cannabis and supplying it to patients through a pharmacist.[67]Federal oversight of medical cannabis production is evolving in Canada as well.[50]These programs allow physicians to authorize medicinal cannabis and know that their patients are receiving the cannabis from a reliable source with high quality control. If the federal government were to open the

door for the pharmaceutical industry to provide a path from cultivation to pharmacists to patients, it would then be more feasible to perform high quality, large-scale research that could expedite development of approved cannabinoid products and/or lead to rescheduling.

Pain-related research targets

Most research with herbal cannabis has focused on neuropathic pain with promising results. There is one study in rheumatoid arthritis that suggested positive effects, however, research should be expanded into diverse clinical syndromes such as musculoskeletal pain and fibromyalgia. Studies on the effective dosing and plasma concentrations of diverse cannabinoids and metabolites as they correlate with pain relief are needed. Correlations on plasma levels of THC and neurocognitive performance (especially driving) are needed; the legal intoxication level of THC is not currently established.

Although research should continue with specific cannabinoids and extracts such as THC and CBD, it cannot preclude high quality research on herbal cannabis as the leaf contains nearly 500 known compounds, of which 80 are classified as cannabinoids. In addition to the cannabinoids, the non-cannabinoids such as the terpenes also have analgesic and anti-inflammatory effects. Larger scale research on plant cannabis has promise to identify new pharmacologic targets for medication development.

Finally, research on cultivation of cannabis is needed. If patients can legally use cannabis as a therapeutic modality, sources of high quality medicinal grade cannabis with strict quality control and known constituents will be required. Avenues will need to be opened to allow the cannabis to be dispensed through pharmacists who acquires medicinal grades of cannabis from sources with adequate quality control. Until that happens, the line between medicinal cannabis and recreational cannabis will continue

to be blurred. Development, regulation of and access to validated and licensed testing laboratories would enable strict quality control measures to be implemented.

Table 2. Research Recommendations/Considerations
Increase Federal funding for pain-related cannabis research
Increase research aimed at both herbal cannabis and cannabinoids
Broaden pain conditions being studied to include actions of cannabis in non-neuropathic pain
Support larger scale e.g. phase III clinical trials
Ease regulatory restrictions that impede approvals of cannabis and cannabinoid research (including consideration of rescheduling from CS schedule I)
Improve access to high quality plant cannabis for research studies including access to diverse strains and derivatives with varying cannabinoid contents and ratios
Encourage states to collect both individual & population level data on patients receiving medical cannabis to advance understanding of individual and public health impacts of cannabis

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Highlights

- 23 U.S. states permit cannabis for clinical use but it remains illegal under Federal law.
- Cannabis strains have variable content of over 100 different cannabinoids.
- U.S. regulatory hurdles result in most cannabis research being done elsewhere.
- Cannabidiol may be anti-inflammatory, anxiolytic & anti-seizure with no euphoria.
- Cannabis addiction develops in about 9% of non-medical users.

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