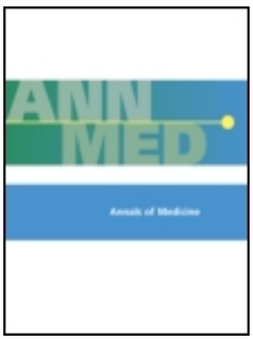

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REVIEW ARTICLE

Cannabinoids: Medical implications

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ABSTRACT

Herbal cannabis has been used for thousands of years for medical purposes. With elucidation of the chemical structures of tetrahydrocannabinol (THC) and cannabidiol (CBD) and with discovery of the human endocannabinoid system, the medical usefulness of cannabinoids has been more intensively explored. While more randomized clinical trials are needed for some medical conditions, other medical disorders, like chronic cancer and neuropathic pain and certain symptoms of multiple sclerosis, have substantial evidence supporting cannabinoid efficacy. While herbal cannabis has not met rigorous FDA standards for medical approval, specific well-characterized cannabinoids have met those standards. Where medical cannabis is legal, patients typically see a physician who "certifies" that a benefit may result. Physicians must consider important patient selection criteria such as failure of standard medical treatment for a debilitating medical disorder. Medical cannabis patients must be informed about potential adverse effects, such as acute impairment of memory, coordination and judgment, and possible chronic effects, such as cannabis use disorder, cognitive impairment, and chronic bronchitis. In addition, social dysfunction may result at work/school, and there is increased possibility of motor vehicle accidents. Novel ways to manipulate the endocannbinoid system are being explored to maximize benefits of cannabinoid therapy and lessen possible harmful effects.

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Cannabinoids; cannabinoid treatment; medical marijuana

➤ KEY MESSAGES

- The medical disorders with the current best evidence that supports a benefit for cannabinoid use are the following: multiple sclerosis patient-reported symptoms of spasticity (nabiximols, nabilone, dronabinol, and oral cannabis extract), multiple sclerosis central pain or painful spasms (nabiximols, nabilone, dronabinol, and oral cannabis extract), multiple sclerosis bladder frequency (nabiximols), and chronic cancer pain/neuropathic pain (nabiximols and smoked THC).
- Herbal cannabis has not met rigorous US FDA standards for medical approval, while specific well-characterized cannabinoids have met those standards, and more are being studied. However, herbal cannabis is legal for medical use in certain US states/countries, and patients must usually see a physician who "certifies" that a benefit may result. Participating physicians should be knowledgeable about cannabinoids, closely look at the risk/benefit ratio, and consider certain important criteria in selecting a patient, such as: age, severity, and nature of the medical disorder, prior or current serious psychiatric or substance use disorder, failure of standard medical therapy as well as failure of an approved cannabinoid, serious underlying cardiac/pulmonary disease, agreement to follow-up visits, and acceptance of the detailed explanation of potential adverse risks.
- The limitations of use of medical cannabis include the following potential adverse effects that are discussed with potential patients: *acute central nervous system* effects such as deficits in memory, judgment, attention, coordination, and perception (such as time and color), anxiety, dysphoria, and psychosis; *chronic central nervous system* effects such as cannabis use disorder, cognitive and memory deficits, and increased risk of psychosis; pulmonary effects such as *chronic bronchitis*; *social dysfunction,* such as work/school; *increased risk of accidents*, such as motor vehicle accidents; and preliminary data suggest possible risk for acute *cardiovascular* event, especially with underlying heart disease.
- The normal human endocannabinoid system is important in the understanding of such issues as normal physiology, cannabis use disorder, and the development of medications that may act as agonists or antagonists to CB1 and CB2. By understanding the endocannabinoid system, it may be possible to enhance the beneficial effects of cannabinoid-related medication, while reducing the harmful effects.

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Introduction

Medical history

In his book entitled *Marijuana: The First Twelve Thousand Years*, Dr. Ernest Abel reports that ancient Chinese emperors more than 4000 years ago were suggesting that marijuana be used for medical treatment purposes (1). In the US, marijuana was listed as a medication in the US Pharmacopeia from 1851 until 1942 (2). This has traditionally meant that a drug has met standards for safe use (3). In the 1800s, well before the existence of regulatory agencies such as the US Food and Drug Administration, the so-called "patent medications" were popular elixirs and cure-alls, frequently containing marijuana, along with opium and alcohol (4).

History of marijuana research

Despite a lengthy history of medical use, herbal marijuana became regarded more than 50 years ago as a severely dangerous drug with no significant medical usefulness by the United Nations Single Convention on Narcotic Drugs of 1961 (5). It was additionally labeled by the US Substance Abuse Act of 1970 as a Schedule I drug, like heroin, with the highest abuse potential. These laws not only restricted personal use, but also had the effect of significantly curtailing procurement of marijuana for research purposes in many countries. Despite these admonitions about marijuana's danger, and despite the lack of strong supportive evidence-based randomized clinical trials for certain medical conditions, many governments (including 23 US states and several countries) have now legalized the use of medical herbal marijuana. Thus, governmental agencies are paradoxically authorizing medical use of herbal marijuana, despite a dearth of comprehensive supportive research for some, but not all, of these disorders. This is a unique situation in the contemporary use of medication, and is referred to in a recent *JAMA* editorial as the proverbial cart pulling the horse (medical use before rigorous supporting research) (6). In 2015, the US government eliminated the US Public Health Service oversight for obtaining marijuana for research purposes (7).

Discovery of the cannabinoids

Despite the difficulty in obtaining marijuana for research, Dr Raphael Mechoulam procured a supply of hashish from the Israeli national police in the early 1960s, and originated modern-day cannabinoid research (8). The chemical structure of the marijuana cannabinoid called *cannabidiol* (CBD) was first demonstrated in 1963 (9) by his research group, and then in 1964, the chemistry of marijuana's psychoactive cannabinoid *delta-9-tertrahydrocannabinol* (THC) was described (10). *Cannabinoid* is the term Dr Mechoulam's group coined to characterize this family of related compounds (11). The marijuana plant, also known by its botanical genus name of *cannabis,* produces more than 60 of these unique terpenophenolic cannabinoid compounds in sticky resinous stalks called trichomes, found mainly on the herb's flowers/leaves (12).

Purpose

General medical practitioners are often the first to have patients inquiring about cannabinoid use, or they discover their patients are already using it. The purpose of this systematic review is to answer the bottom-line question that most clinical medical practitioners want to know: what is the best evidence of cannabinoid usefulness in medical practice, and what are the associated risks? Current medical cannabinoids with demonstrated medical efficacy are matched with current recommended medical disorders by focusing on systematic reviews of randomized clinical trials. A basic and non-technical overview of the endocannabinoid system provides a medical practitioner with a general understanding of how cannabinoids may be useful. Guidance is provided to physicians in selection/certification of patients for cannabinoid use, and in the topics of discussion for adverse effects.

Literature review

A specific Pub-Med search of systematic reviews reported 147 results using "therapeutic use of cannabis," 160 results with "cannabinoids," and 20 results using "cannabinoid guidelines." Due to the rapid change in cannabinoid scientific knowledge, evidence from the most recent systematic reviews is the focus, including the 2015 *JAMA* meta-analysis (13) looking at 10 medical conditions, Cochrane Reviews in 2013–2014 looking at four medical disorders (14–17), and a 2014 neurologic systematic review evaluating three neurologic disorders (18,19). This systematic review represents a more comprehensive compilation of disorders that match to specific cannabinoids. Recommended physician guidelines for certification highlight suggestions from several countries (45,46).

Basic primer on the human endogenous cannabinoid system

Background

An understanding of the action of cannabinoid medications starts with an understanding of the normal

human endocannabinoid system itself. In the early 1990s, a previously unknown normal body system was discovered, consisting of cannabinoid natural neurotransmitters and endocannabinoid target receptors in multiple organs, such as the brain. The discovery was made that the psychoactive THC cannabinoid in the marijuana plant, discovered 25 years earlier, binds to a specific cannabinoid brain receptor. Knowing that a natural cannabinoid receptor existed, the natural cannabinoid ligands for these receptors were searched for and later discovered (11). This new normal body system was thusly named the endocannabinoid system.

Normal receptors

This first-discovered normal brain receptor with an affinity for the herb's psychoactive THC was appropriately named cannabinoid receptor type 1 (CB1) (20). CB1 receptors are located not only mainly in the central and peripheral nervous systems, but also in other body systems such as the cardiovascular, visual, and gastrointestinal systems. Later, cannabinoid receptor type 2 (CB2) was discovered in tissues of the immune system, such as lymphatic tissue, spleen, and macrophages (21,22). Compared to CB1 receptors, CB2 receptors have significantly lower affinity for THC.

Normal neurotransmitters

While several endogenous ligands for the endocannabinoid receptors are known, two major ligands have been identified: N-arachidonoyl-ethanolamine (known as anadamide or AEA) (23) and 2-arachidonyl-glycerol (known as 2-AG) (24,25). These normal endocannabinoid neurotransmitters are unusual in several ways: location in the post-synaptic neuron, not the pre-synaptic; retrograde travel with binding to target receptors in the pre-synaptic neuron; activated pre-synaptic cannabinoid receptors will inhibit release of normal neurotransmitters from pre-synaptic neurons.

Regulation of normal body systems

When normal cannabinoid neurotransmitters attach to normal cannabinoid target organ receptors, they appear to help to regulate numerous normal body functions such as cognition, coordination, memory, appetite, pain perception, heart rate, gastrointestinal motility, intraocular pressure, and immune function (26–30) (Table 1). Few cannabinoid receptors are present in the brainstem, which may explain why marijuana by itself is not associated with acute mortality.

Marijuana interaction

Since marijuana contains more than 60 cannabinoids, normal body systems may be activated and disrupted as the cannabinoids in marijuana compete with and mimic the normal neurotransmitters to bind to receptors (31) (Table 1). For example, clinical effects such as impaired judgment, alertness, cognition, and coordination can result, making vehicle operation unsafe. On the other hand, marijuana's effect to increase appetite may have medical use, as in weight loss associated with human immunodeficiency virus (HIV), and its ability to reduce pain perception has a wide potential for clinical application. Since more than 60 raw cannabinoids have such a broad effect on so many body systems, both harmful and helpful, research efforts focus on reducing the "shotgun" approach of herbal marijuana in favor of identifying well-characterized specific cannabinoids used for a specific purpose, in order to improve the risk/benefit ratio by maximizing good effects and lessening harmful effects.

Table 1. Examples of the association between endocannabinoid receptor location, probable physiologic function, and the potential effects of marijuana.

Normal Endocannabinoid Receptor Location	Endocannabinoid regulation of normal physiologic function	Potential effects of marijuana
Cerebral cortex, hippocampus, limbic system	Judgment, cognition, memory, alertness, mood and behavior, perception of time/color/sound	Impaired judgment, cognition, memory, alertness, changes in mood and behavior, altered or distorted perception of time/color/sound
Basal ganglia, cerebellum	Coordination, movement	Incoordination
Hypothalamus	Appetite	Increase in appetite
Medulla	Nausea and vomiting	Reduction in nausea/vomiting
Dorsal afferent spinal cord and peripheral nociceptors	Pain perception	Reduction in pain perception
Visual system	Intraocular pressure	Intraocular pressure reduction
Cardiovascular system	Heart rate, blood pressure	Acute increase in heart rate and supine or sitting blood pressure
Gastrointestinal system	Motility	Reduction in motility
Immune system	Immunity	Variable stimulation and/or suppression

Cannabinoids now approved for medical use by regulatory agencies like the US Food and Drug Administration

Variety of cannabinoid categories

The medical usefulness of the cannabis plant is regarded as arising from its cannabinoid compounds. The four most common cannabinoid categories that have potential use for medical treatment purposes are: *phytocannabinoids* (the raw marijuana plant), *synthetic cannabinoids* (dronabinol, nabilone), *purified cannabinoids* (nabiximols, CBD), and *endogenous cannabinoids* (32). While not being directly used in studies, *endogenous* cannabinoids (such as anandamide and 2-AG) are targeted for augmentation by the inhibition of their degradation enzymes (See future uses). All of these potential medical treatments are often broadly referred to as "cannabinoid treatment." Synthetic cannabinoids that are being used as illegal recreational drugs will not be discussed in this review.

Medications approved

Three cannabinoid drugs are currently approved, two by the US Food and Drug Administration (FDA), and one by other countries (Canada, Europe):

- *Dronabinol is synthesized THC* that is FDA-approved specifically for treatment of anorexia in human immunodeficiency virus (HIV) patients with weight loss, as well as cancer chemotherapy-associated nausea and vomiting which has failed standard therapies (33).
- *Nabilone is a synthetic THC analog* that is FDA-approved for cancer chemotherapy-associated nausea and vomiting which has failed standard therapy (34).
- *Nabiximols is about a 1:1 mixture of the purified marijuana plant constituents THC and cannabidiol (CBD)* delivered in spray formulation. It is approved in several countries (Canada, Europe) but not in the US, as adjunctive therapy for pain management and spasticity in certain types of patients (35).

Explanation for herbal marijuana disapproval by regulatory agencies

Regulatory requirements not attained

For drug approval, rigorous regulatory agencies like the US FDA require the demonstration of a consistent, pure, and well-defined chemical formulation of a drug along with its pharmacokinetics (36). The safety and effectiveness of the drug must be shown for the treatment of a specific medical disorder by the traditional gold standard of a randomized clinical trial that is double-blinded and placebo controlled. Regulatory agencies require warnings about all potential side effects.

The major reason behind denial for marijuana as a traditional prescriptive medication is that it is a natural, unprocessed plant containing more than 450 various chemical compounds (12), including more than 60 unique cannabinoids. In addition, these compounds may not be consistent from plant to plant, causing different effects (37). The plant material may have potential impurities such as pesticide residue or fungal contaminants (38,39). Traditional medication dosing cannot be well-regulated by the inhalation of marijuana smoke. Also, countries world-wide must consider their treaty obligations under the 1961 United Nations Single Convention on Narcotic Drugs.

The future

According to the well-respected US Institute of Medicine evaluation of marijuana as medication, the future of herbal cannabis lies in the isolation of its individual cannabinoid components and their synthetic derivatives, since the effects will be more predictable than the raw marijuana plant (40). Likewise, in a 2014 publication, the Canadian Centre on Substance Abuse suggests the future of medical marijuana is the development of "a new generation of cannabinoid medications" that focus on a narrow and specific treatment goal, as well as safety (41).

Cannabinoids showing evidence-based medical benefits

Landmark meta-analysis study

Suggested to be the first of its kind, a 2015 landmark meta-analysis looks at almost 40 years of world-wide randomized clinical trials for medical use of cannabis and cannabinoids from 1975–2014 (13) (Tables 2, 3). The meta-analysis analyzes the evidence presented in the best 79 clinical trials for 10 medical disorders and diseases as follows: (1) chronic pain, (2) chemotherapy-induced nausea and vomiting, (3) spasticity due to multiple sclerosis or paraplegia, (4) appetite stimulation in HIV/AIDS, (5) sleep disorder, (6) Tourette syndrome, (7) psychosis, (8) anxiety disorder, (9) intraocular pressure in glaucoma, and (10) depression. The quality of evidence and strength of recommendations is evaluated using the GRADE rating system (Grading of

Table 2. Types of cannabinoids evaluated with the supporting number of studies for specific medical disorders: results of 2015 meta-analysis (13).

Cannabinoid used	Number of studies for specific cannabinoids with some of the assessed medical disorders
Nabilone *capsules*	20 - Spasticity, pain, sleep disorder, and chemotherapy-induced nausea and vomiting
Nabiximols *oro-mucosal spray*	19 - Spasticity, pain and chemotherapy-induced nausea and vomiting
Dronabinol *capsules*	13 - Spasticity, pain, chemotherapy-induced nausea and vomiting, appetite stimulation in HIV/AIDS, and sleep disorders
Delta-9 tetrahydocannabinol (THC) (various types of formulations)	10 - *Capsules* – Pain, chemotherapy-induced nausea and vomiting, Tourette syndrome 5 - *Smoked* – Pain and spasticity 4 - *Oro-mucosal spray* – Pain and intraocular pressure in glaucoma
Cannabidiol (CBD) (various types of formulations)	3 - *Capsules* – Psychosis 1 - *Oro-mucosal spray* – Intraocular pressure in glaucoma
THC/CBD *capsules*	4 – Spasticity
Herbal Marijuana (various types of formulations)	1 - *Vaporized* – Pain 1 - *Smoked* – Appetite stimulation in HIV/AIDS
Levonantradol (Analog of dronabinol; not available for use; various types of formulations)	1 - *Capsules* – Chemotherapy-induced nausea and vomiting 3 - *Intra-muscular injection* – as above
Ajulemic Acid *capsules* (Not available for use)	1 – Pain
ECPOO2A *tablets* (Natural THC; not available for use)	1 – Spasticity

Table 3. Summary of results for medical use of cannabinoids in 10 medical disorders: 2015 meta-analysis results (13).

Medical disorder	Cannabinoid used	Number of studies/total participants	Results: comparison to placebo	Quality of evidence (GRADE rating)
Spasticity in multiple sclerosis	Nabiximols, Nabilone, Dronabinol, THC/CBD capsules	4/2280	Benefit	Moderate quality
Chronic cancer pain or chronic neuropathic pain	Smoked THC, Nabiximols	28/2454	Benefit	Moderate quality
Weight gain in HIV	Dronabinol	4/255	Benefit	Low quality
Chemotherapy-related nausea and vomiting	Dronabinol, Nabiximols	28/1772	Benefit	Low quality
Tourette syndrome	THC capsules	2/36	Benefit	Low quality
Sleep disorders	Nabilone, Nabiximols	2/54	Benefit	Low quality
Anxiety in public speaking	Cannabidiol	1/24	Benefit	Very low quality
Psychosis	Cannabidiol	2/71	No benefit	Low quality
Depression	Nabiximols	No direct study; five other studies documented depression as a treatment result	No benefit	Very low quality
Intraocular pressure in glaucoma	THC capsules, and Cannabidiol capsules and spray	1/6	Insufficient evidence	Not stated, but patient number was small (6)

The quality of evidence and strength of recommendations is evaluated by using the GRADE rating system (Grading of Recommendations, Assessment, Development, and Evaluation) of *high, moderate, low, very low,* or *insufficient evidence* (42).

Recommendations, Assessment, Development, and Evaluation) of *high, moderate, low, very low*, or *insufficient evidence* (42).

As shown in Table 2, a wide variety of cannabinoid medications were used in these clinical trials, but the majority of the studied cannabinoids are currently produced by pharmaceutical companies: nabilone capsules (20 studies), nabiximols oro-mucosal spray (19 studies), and dronabinol capsules (13 studies) (13) (Table 2). Additional cannabinoids evaluated in this meta-analysis include THC, CBD, and THC/CBD. Interestingly, this report included only two studies using herbal cannabis (smoked and vaporized).

The conclusions of this meta-analysis are summarized as follows (Table 3):

- *Moderate quality evidence supports a benefit* in using nabiximols (not approved in the US), nabilone, dronabinol, or THC/CBD tablets (not FDA approved) for spasticity in multiple sclerosis and for nabiximols or smoked THC (neither is FDA-approved) for chronic cancer pain or neuropathic pain.
- *Low quality evidence supports a benefit* for use of dronabinol or nabiximols in treatment of chemotherapy-induced nausea and vomiting, for dronabinol for weight gain in HIV/AIDS, for nabilone and nabiximols to treat sleep disorders, and for THC capsules to treat Tourette syndrome.
- *Low quality evidence shows no benefit* for use of cannabidiol in treating psychosis.
- *Very low quality evidence demonstrates no benefit* for using nabiximols in treating depression.
- *Insufficient evidence* is available to make a meaningful comment about treatment for glaucoma, since only one study of six participants was evaluated (13) (Table 3).

American Academy of Neurology/Cochrane Reviews

In 2014, a systematic review by the American Academy of Neurology looked at 65 years of publications (1948–2013) to assess the medical efficacy for use of cannabinoids in treatment of the following three neurologic conditions: multiple sclerosis, movement disorders, and epilepsy (Table 4) (18). Evidence-based recommendations have been made from the 33 best studies. The clinical study quality is rated according to the method of the American Academy of Neurology as follows: A (established with strong evidence as effective, ineffective, or harmful, supported by two Class I studies), B (established with moderate evidence as probably effective, ineffective or harmful, supported by one Class I study), C (established with weak evidence as possibly effective, ineffective, or harmful, supported by one Class II study), and U (insufficient, inadequate, or conflicting data to make a determination) (43).

In this systematic review, only the "oral cannabis extract" (a combination of the cannabinoids THC/CBD or CBD alone) is given an A-effective rating for treating multiple sclerosis patient-reported spasticity and for treating central pain or painful spasms. Other specific cannabinoids included in this systematic review are THC (dronabinol/nabilone), nabiximols, and smoked marijuana.

For use of cannabinoids in multiple sclerosis-related signs and symptoms, the conclusions of this systematic review are summarized as follows:

- *A – effective rating* for oral cannabis extract (CBD/THC or CBD) in treating patient-reported symptoms of spasticity and for treatment of central pain or painful spasms;
- *B – probably effective* for THC (dronabinol/nabilone) and nabiximols for treating patient-reported symptoms of spasticity, for THC and nabiximols in treating central pain or painful spasms, and for nabiximols for bladder frequency of urination;
- *B – probably ineffective* rating for oral cannabis extract and THC for treating bladder complaints and for THC and oral cannabis extract for treatment of tremors;
- *C – possibly ineffective* rating for nabiximols for treatment of tremors;

Table 4. Medical use of cannabinoids in three neurologic disorders (multiple sclerosis, epilepsy, and movement disorders): a systematic review of 65 years by the American Academy of Neurology (18,19).

Medical disorder	Cannabinoid recommendation and the quality of evidence (Rating by American Academy of Neurology)
Multiple sclerosis patient-reported symptoms of spasticity	Oral cannabis extract (THC/CBD or CBD) rated A = effective THC (dronabinol or nabilone) rated B = probably effective Nabiximols rated B = probably effective Smoked cannabis rated U
Multiple sclerosis central pain or painful spasms	Oral cannabis extract rated A = effective THC and nabiximols rated B = probably effective Smoked cannabis rated U
Multiple sclerosis bladder complaints	Oral cannabis extract and THC rated B = probably ineffective Nabiximols rated as B = probably effective for frequency of urination
Multiple sclerosis related tremors	Oral cannabis extract and THC rated B = probably ineffective Nabiximols rated C = possibly ineffective
Huntington disease	Nabilone and CBD capsules rated as U
Parkinson disease Levodopa-induced dyskinesia	Oral cannabis extract rated B = probably ineffective
Tourette syndrome	THC rated U
Cervical dystonia	Dronabinol rated U
Epilepsy	Cannabinoids rated as U

Evidence is rated according to the method of the American Academy of Neurology: A (established with strong evidence as effective, ineffective or harmful, supported by 2 Class I studies), B (established with moderate evidence as probably effective, ineffective or harmful, supported by 1 Class I study), C (established with weak evidence as possibly effective, ineffective or harmful, supported by 1 Class II study), and U (insufficient, inadequate or conflicting data to make a determination) (43).

Table 5. Medical cannabinoid evidence-based guidelines: Cochrane reviews (14–17).

Clinical medical disorder	Cannabinoid used	Result	Quality of evidence	Rating organization
Cannabis use disorder	THC	May be of Potential Value	Limited/Inconclusive	Cochrane Drugs and Alcohol Group, 2014 (14)
Schizophrenia	Cannabis, Cannabidiol	Insufficient evidence	Insufficient/inconclusive	Cochrane Schizophrenia Group, 2014 (17)
Epilepsy	Various Cannabinoids	Lack of evidence	Insufficient	Cochrane Epilepsy Group, 2014 (15)
AIDS-related Anorexia and Medical Use for HIV/AIDS	Various Cannabinoids	Lack of evidence	Insufficient	Cochrane HIV/AIDS Group, 2013 (16)

- *U – insufficient evidence* rating for smoked marijuana to treat patient-reported symptoms of spasticity and for treatment of central pain or painful spasm (18) (Table 4).

For the movement disorders of *Huntington disease, Tourette syndrome, cervical dystonia,* all cannabinoid evidence is rated as U-insufficient, and for *Parkinson levodopa-induced dyskinesia*, oral cannabis extract is rated as B-probably ineffective. For treatment of *epilepsy,* the studies are rated as U-insufficient evidence (18) (Table 4).

Cochrane Reviews in 2013–2014 (Table 5) conclude that evidence is *limited, inconclusive, or insufficient* to recommend cannabinoids for use in treatment of cannabis use disorder (14), seizures/epilepsy (15), HIV/AIDS (16), and schizophrenia (17).

The complementary and alternative medicine dilemma

Loosely defined as ''not presently considered a part of conventional medicine,'' complementary and alternative medicines show a dichotomy between the high usages by the US adults (about 40%) while a low physician/pharmacist confidence, education, and ability to guide patients in becoming involved with such treatments (44). Raw plant-based products such as marijuana often fall under the classification of *complementary and alternative medication*, partly due to the *imprecise* estimates of the potentially useful substances. That does not mean that complementary and alternative medicines are not helpful. However, traditional medical school pharmacology is focused on a prescriptive pill containing one precisely quantitated chemical element or possibly two, with well-studied efficacy and risks.

To help resolve this dichotomy of use, the 2014 publication of the American Academy of Neurology's evidence-based guideline on Complementary and Alternative Medications for Treatment of Multiple Sclerosis serves as a good example of a helpful guide for medical practitioners (19).

Suggested practices for physicians considering medical herbal cannabis certification

Guidelines

In states/countries where medical marijuana is legal, the usual process mandates a physician sign a ''certification,'' but not a traditional prescription, certifying that a benefit may result. Some states expect physician participants to demonstrate cannabinoid knowledge, such as attendance at continuing education classes. For physician involvement in medical cannabinoid certification, Kahan (2014) discusses preliminary medical cannabis recommendations in Canada (45), and Hill (2015) discusses some helpful guiding principles (46). When deciding whether to certify a patient, a physician should consider the following important patient criteria:

- Has a ''debilitating medical disorder'' – a term used by almost all the US state-based medical cannabis guidelines – that is shown by strong randomized clinical trials to potentially benefit from medical marijuana/cannabinoids.
- Lives in a state/country that authorizes medical marijuana.
- Is not an adolescent/child (studies show that the adolescent brain may be more vulnerable to the chronic adverse effects of marijuana) (47).
- Has no prior or active serious psychiatric disorder or substance use disorder; does not have a strong family history of psychosis or cannabis use disorder.
- No underlying serious cardiovascular or pulmonary disorder.
- Failed multiple trials of standard medical therapy for their debilitating medical disorder.
- Failed in the use of an FDA-approved cannabinoid such as dronabinol or nabilone, and additionally, outside of the US, the approved nabiximols.
- Understands that the raw marijuana herb is a US Schedule I drug, and that purified CDB and oral cannabis extract such as THC/CBD are not FDA-approved, and agrees to accept the potential adverse risks, after a detailed explanation.
- Agrees to regular follow-up assessments.

Reasons for physician reluctance

As with all medication use, physicians should not certify use of medical marijuana unless they conclude that a patient may derive benefits compared to potential risks (the risk/benefit ratio), and the physician is comfortable using cannabinoids (46,48). Legitimate physician concerns with certifying medical marijuana as the raw cannabis herb or its constituent purified cannabinoids are the illegal US federal designation of cannabis, the potential route of administration (such as smoking), the potential need for a distributing dispensary to make decisions (such as a specific plant strain), concerns about potential potency, dosage, and how an individual patient may initially respond. Patient adverse risk concerns include cognitive, social, and coordination impairment (effecting school/work performance

and motor vehicle use), development of cannabis dependency/addiction (cannabis use disorder), and the unknown and possibly harmful effects of more than 450 other chemical compounds in herbal cannabis.

Topics for discussion with potential cannabinoid patients: evidence-based benefits versus possible adverse side effects

Approved cannabinoids

FDA-approved medications such as dronabinol will have a complete listing of possible side effects available from pharmaceutical companies (33–35). All of the approved medications contain the potentially addictive cannabinoid THC, and nabilone (cesamet) is listed as US Schedule II (high potential for abuse), while dronabinol (marinol) is Schedule III (potential abuse less than I and II) (49). However, a study with dronabinol reported a "low abuse potential," (50) a study with nabilone concluded that "abuse of nabilone is extremely rare," (51) and a randomized clinical trial showed nabiximols had some abuse potential at very high doses, but possibly less potential than dronabinol (52). It is suggested that the reported lower abuse potential of dronabinol and nabiximols, compared to smoked cannabis, may be related to the earlier and higher elevation of plasma THC concentration associated with smoking (52).

Unapproved cannabinoids

The difficulty arises in certification of a non-FDA approved cannabinoid such as raw cannabis or THC/CBD extracts. This is a situation in which significant time is allotted for patient discussions, questions, and answers regarding the following topics.

Addiction with marijuana

Patients considering medical cannabis therapy should be fully informed that medical marijuana has the potential for causing addiction with chronic use. According to epidemiological studies, about 9% of adult marijuana users will develop an addiction (53), but this percentage of addiction increases to about 17% when use starts as a teenager (54).

Addiction is a disease

In the past, addiction was often regarded as bad behavior, a failure in morality, and lack of self-discipline, but now is defined as a *disease* – a "chronic, often relapsing brain disease that causes compulsive drug seeking and use" (55). The chronic brain disease of addiction usually develops slowly, and involves alteration in normal chemical neurotransmitters, neurochemical circuits, and anatomic brain structures which transforms a simple choice whether to use a substance or not into a powerful and biologically driven compulsive desire to use it (56).

Cannabis addiction is most closely associated with the THC cannabinoid, and evidence shows the potency of THC in cannabis has been increasing over many years (57). THC acts on the dopaminergic system to increase dopamine production, like other drugs of abuse (58). Chronic THC-stimulated dopamine elevations cause a down-regulation of innate dopamine production as well as target dopamine receptors, and an up-regulation of CB1 receptors, such that additional THC intake is needed just to maintain the same effect, or the chronic use of the same THC dose produces less effect over time. This process is referred to as drug *tolerance* (55–58). The risk factors for addiction include academic problems in school, peer usage, and co-morbid psychiatric disorders (56), but genetic inheritance appears to account for at least 50% of risk (59–61).

The American Psychiatric Association's DSM-5 defines cannabis use disorder as a "problematic pattern of use" within a 12-month period by identification of at least two out of 11 clinical behavioral impairments, with 2–3 defined as *mild*, 4–5 is *moderate*, and 6 or more is *severe* (62). DSM-5 recognizes that "cannabis use disorder" is not necessarily a static life-long disorder, but can exacerbate and quiesce, and this dynamic is recognized by the diagnostic categories of "early remission" and "sustained remission" (62,63).

Comparison of "misused/abused" drugs

While the harmfulness of an addictive drug is difficult to measure, a British study published in *The Lancet* documents the comparison of 20 drugs of "misuse/abuse," using a nine category rating system. A drug's harmfulness was determined by an expert panel including psychiatrists, medical specialists, pharmacologists, and law enforcement (64). Based on a ranking order of 1–20, with 1 (heroin) being the most harmful, these experts ranked marijuana's "mean harm score" 11 out of 20 in overall comparative harmfulness, based on three categories of harm: physical, social, and tendency for dependence. Comparing the legal drugs to cannabis, alcohol was ranked number 5 in this study, while tobacco/nicotine was ranked number 9.

No use in children/adolescents

The maturing adolescent brain, which may not achieve complete anatomic development until the early 20's (65), appears to be more vulnerable to the long-term effects of marijuana use (47). Studies show that memory and other cognitive deficits, such as a reduction in IQ test scores, can be associated with prolonged use of cannabis, especially with use starting in adolescence (47). An increased prevalence of schizophrenia/psychosis appears associated with marijuana use as a teenager, particularly with a genetic pre-disposition (66).

Acute central nervous system effects

Patients should know that immediate reaction to first-time cannabis usage is variable, depending on such factors as the amount THC in the ingested cannabis and genetic pre-disposition. The typical acute psychological response to cannabis is euphoria and relaxation, and studies to determine why cannabis is used have found, not surprisingly, that the major reason for use is relaxation and controlling stress (67,68). Occasionally, however, the acute effect may be anxiety, dysphoria, and psychosis/hallucinations (69). Other potential acute reactions may include perceptual changes in colors, sounds, and time, cognitive changes such as impairment of judgment, reduction in memory, inattentiveness, and impairment of coordination.

Acute physiologic effects

Tachycardia, redness of the conjunctiva, stimulation of appetite, and dryness of the mouth are frequent acute physiologic effects of marijuana. Two or more of these physical findings/symptoms are part of the diagnostic criteria for acute cannabis intoxication (62).

Acute cardiovascular effects

Potentially acute adverse cardiovascular effects have been reported, such as tachycardia, increase in cardiac output, and elevation of blood pressure, usually occurring within 1 h of THC inhalation (70). This may result in increased myocardial oxygen demand, and studies have suggested a possible association with precipitation of angina and myocardial infarction (71–73). Thus, marijuana may have a cardiovascular risk, especially in individuals with known underlying cardiovascular disease.

Chronic central nervous system effects

Most affected by prolonged cannabis use, the brain may potentially have chronic adverse consequences such as cannabis use disorder, along with memory loss and other cognitive deficits, especially when use begins in adolescence (47,74,75). A recent systematic review found that chronic adult cannabis usage is a risk for the development of psychosis, and this risk increases with higher consumption of cannabis (76). Starting cannabis use in adolescence, compared to starting in adulthood, further increases the risk of psychosis development.

Chronic pulmonary effects

Evidence suggests that cannabis smoking is associated with respiratory immunological impairment and increased risk for respiratory infection (77). Similar to chronic cigarette smoke inhalation, studies suggest that chronic marijuana smoking is associated with airway inflammation and chronic bronchitis (78,79), but unlike the linear dose response decline in pulmonary function testing associated with tobacco smoking, a low level of marijuana smoking over many years did not show declines in pulmonary function testing (80). Cigarette smoke and cannabis smoke both contain carcinogenic chemicals, but a recent large international study did not show significant increased risk of lung cancer in chronic marijuana smokers (81).

Social problems

Studies show chronic marijuana use has an association with social dysfunction, especially when use begins at a young age. Problems include difficulty in school, higher unemployment, lower job income, and less satisfaction with life (82,83). Marijuana use may impact employment by potentially worsening job performance or by resulting in a positive urine drug screen, despite stopping marijuana weeks before the test. Interestingly, a recent systematic review of medical marijuana use and its risk to public safety and public health did not find strong evidence to support a detrimental risk (84).

Special warnings for patients

Acute cannabis usage is associated with increased risk of motor vehicle accidents, especially involving a death (85). While the blood level of THC to define intoxication has not been well established, the 2013 State of Colorado Legislature defined 5 ng of THC per milliliter

of blood or greater to signify an intoxication level (86), but blood levels often do not reflect the clinical picture due to tolerance as discussed earlier. Due to the pharmacokinetics of THC absorption, one recommendation is no driving for at least 3–4 h after smoking and at least 6 h after oral cannabinoid consumption (45). Acute toxicity of marijuana is usually greatest with smoking, since peak plasma concentration of THC will be higher, occurring in about 15 min, compared to oral ingestion, having a peak concentration at about 2–4 h (87). Failure to recognize the delayed effects of intoxication from oral ingestion can result in dangerous consequences later, such as motor vehicle accidents, falls, and other accidents.

Discussion about the cannabinoid known as cannabidiol

The well-known non-addictive and non-psychoactive properties of cannabidiol (CBD) make this cannabinoid a topic of much interest for treatment purposes, even though not FDA-approved. With its low affinity for the CB1 and CB2 receptors, CBD shows possible therapeutic use by its action in multiple other pathways, producing helpful effects such as anti-inflammation, anti-oxidation, and neuro-protection (11) Suggesting that CBD may ameliorate THC's propensity for psychosis, a 2015 systematic review, looking at plant-derived CBD in humans as a treatment for psychosis, concluded that CBD has potential as an antipsychotic agent, but large randomized clinical trials are needed to support regular clinical use (88). A systematic review of evidence suggests CBD has potential in the treatment of addiction to tobacco and opioids, pending additional studies (89). Recently, a parent survey of 117 children with intractable seizures supported the use of CBD, by reporting an 85% perceived reduction in seizures with use of plant-derived, enriched CBD (90).

Future potential cannabinoids/drugs that target the endocannabinoid system

Pharmacologic therapeutic strategies for manipulation of the endocannabinoid system focus primarily on the cannabinoid/drugs that either directly or indirectly acts as agonists or antagonists to the endocannabinoid receptors (91).

The CB1 receptor antagonist/blocker *rimonabant* which decreases appetite (92) was approved by the European Union to treat obesity, but was then discontinued about 2009 due to side effects (93). The similar, but not identical, cannabinoid blockers known as *surinabant and taranabant* are now being tested for the treatment of nicotine addiction (94).

Ajulemic acid is a synthetic cannabinoid analog of a metabolite of THC, and is non-psychoactive, anti-inflammatory, and described as an agonist to immune system CB2 endocannabinoid receptors. This cannabinoid is now being tested for treatment of systemic sclerosis (scleroderma) (95,96).

A plant extract mixture of the cannabinoids *tetrahydrocannabivarin and CBD* is being tested for treatment of diabetes and the metabolic syndrome (94). A recent systematic review suggests tetrahydrocannabivarin may have potential properties useful in the treatment of type 2 diabetes mellitus (97). An epidemiologic study supports potential use in diabetes and the metabolic syndrome by concluding that marijuana use is associated with smaller waist circumference, lower fasting insulin levels, and lower insulin resistance (98).

The major endocannabinoid ligands AEA and 2-AG are produced on demand and are quickly degraded. The major enzymes responsible for degradation of these endogenous receptor agonists are *free fatty acid amide hydrolase* (for AEA) and *monoacylglycerol lipase* (for 2-AG) (94). Finding a drug that inhibits the enzyme responsible for degradation of AEA or 2-AG will result in enhanced levels of these endogenous receptor agonists, and thus a potential therapeutic benefit. At this time, a *free fatty acid amide hydrolase inhibitor* is being tested for treatment of pain (94). This inhibitor appears not to be associated with addictive potential.

Conclusion

By looking at multiple randomized clinical trials of the best quality, some evidence-based recommendations can be made regarding medical cannabinoid therapy for certain medical disorders. At this time, the FDA-approved cannabinoids are not considered first-line, but should be considered when multiple standard medical therapies have failed for a debilitating medical disorder. If the FDA-approved cannabinoids (or nabiximols in other countries) are ineffective, a patient can be physician-certified for possible benefit with raw cannabis or purified cannabinoids in the US states/countries that have legalized medical cannabis. A clinical trial of the purified cannabinoids or the natural cannabis herb can be considered, only after closely reviewing the risk/benefit ratio, the selection criteria for any given patient, and having a detailed discussion of possible adverse effects.

At this time, the medical disorders with best supporting evidence for cannabinoid use are as follows (Table 6): multiple sclerosis patient-reported symptoms

Table 6. Medical disorders with current best evidence supporting cannabinoid use.

Medical disorder	Cannabinoid
Multiple sclerosis patient-reported symptoms of spasticity	Nabiximols, THC (dronabinol/nabilone), Oral cannabis extract (THC/CBD or CBD)
Multiple sclerosis central pain or painful spasms	Nabiximols, THC (dronabinol/nabilone), Oral cannabis extract (THC/CBD or CBD)
Multiple sclerosis bladder frequency	Nabiximols
Chronic cancer pain/neuropathic pain	Nabiximols, smoked THC

of spasticity (nabiximols, synthetic THC such as dronabinol and nabilone, and oral cannabis extract), multiple sclerosis central pain or painful spasms (nabiximols, synthetic THC such as dronabinol and nabilone, oral cannabis extract), multiple sclerosis bladder frequency (nabiximols), and chronic cancer pain/neuropathic pain (nabiximols, smoked THC).

As governments relax the regulatory restraints on marijuana use in the general public, more information about the risks and benefits of cannabinoids is needed.

New discoveries of ways to manipulate the endocannabinoid system may prove increasingly beneficial to the practice of medicine.

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