Clinical Crossroads

Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems
A Clinical Review

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IMPORTANCE As of March 2015, 23 states and the District of Columbia had medical marijuana laws in place. Physicians should know both the scientific rationale and the practical implications for medical marijuana laws.

OBJECTIVE To review the pharmacology, indications, and laws related to medical marijuana use.

EVIDENCE REVIEW The medical literature on medical marijuana was reviewed from 1948 to March 2015 via MEDLINE with an emphasis on 28 randomized clinical trials of cannabinoids as pharmacotherapy for indications other than those for which there are 2 US Food and Drug Administration–approved cannabinoids (dronabinol and nabilone), which include nausea and vomiting associated with chemotherapy and appetite stimulation in wasting illnesses.

FINDINGS Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications.

CONCLUSIONS AND RELEVANCE Medical marijuana is used to treat a host of indications, a few of which have evidence to support treatment with marijuana and many that do not. Physicians should educate patients about medical marijuana to ensure that it is used appropriately and that patients will benefit from its use.

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Dr Burns Mr Z is a 60-year-old man who fell at work 19 years ago and has had chronic low back pain and left leg radicular symptoms since that time. None of the numerous interventions performed in an effort to treat this pain were effective. These include an L2-3 laminectomy in 1996, multiple lumbar epidural steroid injections, selective nerve root blocks, lidocaine infusions, and a trial of a spinal cord stimulator. He has been to a pain psychologist and received physical therapy. Several medications have helped, such as gabapentin, sertraline, and nortriptyline.

His most recent magnetic resonance imaging scan showed posterior disk bulges at L2-3, L3-4, L4-5, and L5-S1, with the largest bulge at L2-3. Mild effacement of the thecal sac and narrowing of the left-sided neural foramina were seen. Mr Z was diagnosed as having failed back syndrome (chronic back pain following a laminectomy) and treated with long-term narcotics. He signed a narcotics contract with his primary care physician and has never violated the contract. Since signing his narcotics contract, Mr Z has decreased his narcotic requirements and is now taking oxycodone, 10 mg, along with ibuprofen, 600 mg, every 6 hours.

Because his overall goal remains pain relief, he has recently begun using marijuana. He received a recommendation from a cannabis clinic, a clinic whose primary function is to certify patients for the use of medical marijuana, but is now wondering if this is something his primary care physician could also agree with and therefore be responsible for the recommendation of in the future. He uses marijuana at home in the evening after returning from work. He has found marijuana to have a sedative effect, enabling him to get a good night's sleep and to have less pain the next day.

Mr Z's medical history is notable for hyperlipidemia, prediabetes, basal cell carcinoma, and anxiety. His other medications include bupropion, 150-mg sustained-release tablet twice daily; clonazepam, 0.5 mg twice daily as needed; and simvastatin, 20 mg once daily. Previously he was received disability benefits but currently

works as an arborist. He drinks alcohol socially and continues to smoke cigarettes, although he has been able to cut down from 1½ packs to a half pack daily since starting bupropion. He lives at home with his adult son.

Mr Z: His View

My first experience with what would later blossom into chronic pain was about 3 weeks postsurgically after I had the L2-3 and L4-5 levels of my back worked on. Since then, I went through everything from cortisone shots to lidocaine infusions. I actually had a test for the spinal cord stimulator and there was even talk about an intrathecal morphine pump. I totally exhausted every option that was there, and my final procedure was going to be a lysis of spinal adhesions.

When I first went through my medical requirements and was screened by the doctor, I told her that it really was not a matter of needing a lot of it, as I was going to use it at home after work. So there was no question of still being under its influence at any point in time where I would be going to work or driving. I felt that my medical history alone warranted at least my looking at it as an alternative medication. The [Massachusetts 2012 medical marijuana] ballot initiative made me more comfortable with my decision.

Search Methods and Results

Dr Hill Mr Z is a 60-year-old man with a long history of chronic low back pain refractory to multiple procedures and medications. In an effort to obtain better control of his chronic pain, he began using medical marijuana after receiving a certification from a local specialty medical marijuana clinic. He thought that medical marijuana improved his pain control and approached his primary care physician about continued use of medical marijuana.

The medical literature on medical marijuana was searched from 1948 to March 2015 using MEDLINE. The search terms used included *cannabis*, *cannabinoids*, and *tetrahydrocannabinol*. The limits used were "administration and dosage" "adverse effects" "therapeutic use," or "clinical trial." The MEDLINE search resulted in 562 articles. Articles that discussed cannabinoids as pharmacotherapy in a clinical trial were selected for an initial brief review. After additional citations were obtained from references, a total of 74 articles were reviewed. There are no meta-analyses on the topic of medical marijuana; there are 3 systematic reviews.[1-3] Similarly, there is only 1 set of guidelines that addresses the use of medical marijuana as a treatment.[4] As a result, the main emphasis was on randomized clinical trials.

Medical Marijuana: Scientific Rationale and Practical Implications

As of March 2015, 23 states and the District of Columbia have enacted medical marijuana laws to facilitate access to marijuana as a treatment for a variety of medical conditions (Table 1). This is concerning to some because marijuana is the most commonly used illicit drug in the United States: approximately 12% of people aged 12 years or older reported use in the past year, and use among teens has drifted upward in recent years while their perception of its risk has declined.[6,7] With decriminalization of medical marijuana and Washington, Colorado, Alaska, Oregon, and the District of Columbia legalizing the recreational use of marijuana, there has been an increase in marijuana use. As a result, physicians are increasingly faced with questions from patients about marijuana and its medical applications.[8]

Pharmacology of Marijuana

Marijuana comprises more than 60 pharmacologically active cannabinoids.[9] Both exogenous ligands, such as the cannabinoids from marijuana, and endogenous ligands or endocannabinoids, such as anandamide and 2-arachidonylglycerol, act on cannabinoid receptors located throughout the body but mostly in the brain and spinal cord.[10] Activation of 2 types of G protein–coupled receptors, CB1 and CB2, exerts multiple actions by directly inhibiting the release of multiple neurotransmitters including acetylcholine, dopamine, and glutamate while indirectly affecting γ-aminobutyric acid, *N*-methyl-D-aspartate, opioid, and serotonin receptors.[11] CB1 receptors are concentrated primarily in the basal ganglia, cerebellum, hippocampus, association cortices, spinal cord, and peripheral nerves and CB2 receptors are found mainly on cells in the immune system, which may in part explain cannabinoids' effects on pain and inflammation. The physiological responses that result from cannabinoid receptor activation are euphoria, psychosis, impaired memory and cognition, reduced locomotor function, increased appetite, and antiemetic, pain-relieving, antispasticity, and sleep-promoting effects.[3]

The primary cannabinoids contained in marijuana are Δ^9-tetrahydrocannabinol (THC) and cannabidiol. THC produces the euphoria that comes from using marijuana, but it also can produce psychosis. Cannabidiol is not psychoactive and is thought to have antianxiety and possibly antipsychotic effects as well.[12,13] Marijuana's therapeutic effects depend on the concentration of THC in a given formulation as well as the ratio of THC to cannabidiol because of cannabidiol's ability to mitigate the psychoactive effects of THC. As a result, the THC-cannabidiol ratio for many strains of marijuana has been engineered to achieve desired effects.

Medical Indications for Cannabinoids

There are currently 2 US Food and Drug Administration (FDA)–approved cannabinoids available in the United States: dronabinol and nabilone.[14,15] Both are available in pill form and are FDA approved for nausea and vomiting associated with cancer chemotherapy as well as for appetite stimulation in wasting illnesses such as human immunodeficiency virus infection or cancer. Medical marijuana, which may be identical in form to recreational marijuana, is dried material from the *Cannabis* plant consisting of THC, cannabidiol, and other cannabinoids. Medical marijuana is purchased from dispensaries in a variety of preparations (Table 2) or grown by patients for the treatment of myriad illnesses. It is not available from pharmacies because of its status as federally illegal.

Table 1. Medical Marijuana Laws by State[a]

State	Approved Conditions	Legal Limit
Alaska, 1998	Cachexia, cancer, chronic pain, epilepsy and other disorders characterized by seizures, glaucoma, HIV/AIDS, MS and other disorders characterized by muscle spasticity, and nausea; other conditions are subject to approval by the Alaska Department of Health and Social Services	1 oz usable; 6 plants (3 mature, 3 immature)
Arizona, 2010	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Alzheimer disease, cachexia, severe and chronic pain, severe nausea, seizures (including epilepsy), severe or persistent muscle spasms	2.5 oz usable; 0-12 plants
California, 1996	AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms (including spasms associated with MS), seizures (including seizures associated with epilepsy), severe nausea, other chronic or persistent medical symptoms	8 oz usable; 6 mature or 12 immature plants
Colorado, 2000	Cancer, glaucoma, HIV/AIDS, cachexia, severe pain, severe nausea, seizures (including those characteristic of epilepsy), persistent muscle spasms (including those characteristic of MS); other conditions are subject to approval by the Colorado Board of Health	2 oz usable; 6 plants (3 mature, 3 immature)
Connecticut, 2012	Cancer, glaucoma, HIV/AIDS, Parkinson disease, MS, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, cachexia, Crohn disease, PTSD, or any medical condition, medical treatment, or disease approved by the Department of Consumer Protection	1-mo supply (exact amount to be determined)
Washington, DC, 2010	HIV/AIDS, cancer, glaucoma, conditions characterized by severe and persistent muscle spasms such as MS, patients undergoing chemotherapy or radiotherapy or using azidothymidine or protease inhibitors	2 oz dried; limits on other forms to be determined
Delaware, 2011	Cancer, HIV/AIDS, decompensated cirrhosis (hepatitis C), ALS, Alzheimer disease A chronic or debilitating disease or medical condition or its treatment that produces ≥1 of the following: cachexia; severe, debilitating pain that has not responded to previously prescribed medication or surgical measures for more than 3 mo or for which other treatment options produced serious adverse effects; intractable nausea; seizures; severe and persistent muscle spasms including but not limited to those characteristic of MS	6 oz usable
Hawaii, 2000	Cancer, glaucoma, HIV/AIDS, a chronic or debilitating disease or medical condition or its treatment that produces cachexia, severe pain, severe nausea, seizures including those characteristic of epilepsy, or severe and persistent muscle spasms including those characteristic of MS or Crohn disease; other conditions are subject to approval by the Hawaii Department of Health	3 oz usable; 7 plants (3 mature, 4 immature)
Illinois, 2013	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, agitation related to Alzheimer disease, cachexia/wasting syndrome, muscular dystrophy, severe fibromyalgia, spinal cord disease (including but not limited to arachnoiditis), Tarlov cysts, hydromyelia syringomyelia, rheumatoid arthritis, fibrous dysplasia, spinal cord injury, traumatic brain injury and postconcussion syndrome, MS, Arnold-Chiari malformation and syringomelia, spinocerebellar ataxia, Parkinson disease, Tourette syndrome, myoclonus, dystonia, reflex sympathetic dystrophy (complex regional pain syndromes type 1), causalgia, complex regional pain syndrome type 2, neurofibromatosis, chronic inflammatory demyelinating polyneuropathy, Sjogren syndrome, lupus, interstitial cystitis, myasthenia gravis, hydrocephalus, nail patella syndrome or residual limb pain, or treatment of these conditions	2.5 ounces usable cannabis during 14-d period
Maine, 1999	Epilepsy and other disorders characterized by seizures, glaucoma, MS and other disorders characterized by muscle spasticity, and nausea or vomiting as a result of AIDS or cancer chemotherapy	2.5 oz usable; 6 plants
Maryland, 2014	Cachexia, anorexia, or wasting syndrome, severe or chronic pain, severe nausea, seizures, severe or persistent muscle spasms, or other conditions approved by the commission	30-d supply, amount to be determined
Massachusetts, 2012	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Parkinson disease, MS, and other conditions as determined in writing by a qualifying patient's physician	60-d supply (10 oz) for personal medical use
Michigan, 2008	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, agitation of Alzheimer disease, nail patella syndrome, cachexia or wasting syndrome, severe and chronic pain, severe nausea, seizures, epilepsy, muscle spasms, MS, PTSD	2.5 oz usable; 12 plants
Minnesota, 2014	Cancer (if the underlying condition or treatment produces severe or chronic pain, nausea, severe vomiting, or cachexia or severe wasting), glaucoma, HIV/AIDS, Tourette syndrome, ALS, seizures/epilepsy, severe and persistent muscle spasms/MS, Crohn disease, terminal illness with a life expectancy of <1 y	30-d supply of nonsmokable marijuana
Montana, 2004	Cancer, glaucoma, HIV/AIDS, or the treatment of these conditions; cachexia or wasting syndrome, severe or chronic pain, severe nausea, seizures including those caused by epilepsy, severe or persistent muscle spasms including those caused by MS or Crohn disease, or any other medical condition or treatment for a medical condition adopted by the department by rule	1 oz usable; 4 plants (mature); 12 seedlings
Nevada, 2000	AIDS, cancer, glaucoma, and any medical condition or treatment for a medical condition that produces cachexia, persistent muscle spasms or seizures, severe nausea or pain, PTSD; other conditions are subject to approval by the health division of the state department of human resources	1 oz usable; 7 plants (3 mature, 4 immature)
New Hampshire, 2013	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, muscular dystrophy, Crohn disease, agitation of Alzheimer disease, MS, chronic pancreatitis, spinal cord injury or disease, traumatic brain injury, or ≥1 injuries that significantly interferes with daily activities as documented by the patient's clinician; a severely debilitating or terminal medical condition or its treatment that has produced ≥1 of the following: elevated intraocular pressure, cachexia, chemotherapy induced anorexia, wasting syndrome, severe pain not responding to previously prescribed medication or surgical measures or for which other treatment options produced serious adverse effects, constant or severe nausea, moderate to severe vomiting, seizures, or severe, persistent muscle spasms	Two oz of usable cannabis during a 10-d period
New Jersey, 2010	Seizure disorder including epilepsy, intractable skeletal muscular spasticity, glaucoma, severe or chronic pain, severe nausea or vomiting, cachexia or wasting syndrome resulting from HIV/AIDS or cancer, ALS, MS, terminal cancer, muscular dystrophy, IBD including Crohn disease, terminal illness (physician-determined prognosis of <12 mo of life), or any other medical condition or its treatment approved by the Department of Health and Senior Services	2 oz usable
New Mexico, 2007	Severe chronic pain; painful peripheral neuropathy, intractable nausea/vomiting, severe anorexia/cachexia, hepatitis C, Crohn disease, PTSD, ALS, cancer, glaucoma, MS, damage to the nervous tissue of the spinal cord with intractable spasticity, epilepsy, HIV/AIDS, hospice care, cervical dystonia, inflammatory autoimmune-mediated arthritis, Parkinson disease, Huntington disease	6 oz usable; 16 plants (4 mature, 12 immature)

(continued)

Table 1. Medical Marijuana Laws by State[a] (continued)

State	Approved Conditions	Legal Limit
New York, 2014	Cancer, HIV/AIDS, ALS, Parkinson disease, MS, spinal cord damage causing spasticity, epilepsy, IBD, neuropathies, Huntington disease The Department of Health commissioner has the discretion to add or delete conditions and must decide whether to add Alzheimer disease, muscular dystrophy, dystonia, PTSD, and rheumatoid arthritis within 18 mo of the law becoming effective	30-d supply nonsmokable marijuana
Oregon, 1998	Cancer, glaucoma, HIV/AIDS, or treatment of these conditions; a medical condition or treatment for a medical condition that produces cachexia, severe pain, severe nausea, seizures including those caused by epilepsy, or persistent muscle spasms including those caused by MS; other conditions are subject to approval by the Health Division of the Oregon Department of Human Resources	24 oz usable; 24 plants (6 mature, 18 immature)
Rhode Island, 2006	Cancer, glaucoma, HIV/AIDS, hepatitis C, or treatment of these conditions; a chronic or debilitating disease or medical condition or its treatment that produces cachexia or wasting syndrome, severe debilitating chronic pain, severe nausea, seizures including but not limited to those characteristic of epilepsy, or severe and persistent muscle spasms including but not limited to those characteristic of MS or Crohn disease, agitation of Alzheimer disease, or any other medical condition or its treatment approved by the state department of health	2.5 oz usable; 12 plants
Vermont, 2004	Cancer, HIV/AIDS, MS, or the treatment of these conditions if the disease or the treatment results in severe, persistent, and intractable symptoms; a disease, medical condition, or its treatment that is chronic, debilitating, and produces ≥1 severe, persistent, intractable symptoms of cachexia or wasting syndrome, severe pain or nausea, or seizures	2 oz usable; 9 plants (2 mature, 7 immature)
Washington, 1998	Cachexia, cancer, HIV/AIDS, epilepsy, glaucoma, intractable pain (defined as pain unrelieved by standard treatment or medications), chronic renal failure, MS Crohn disease, hepatitis C with debilitating nausea or intractable pain, or diseases including anorexia that result in nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, or spasticity when those conditions are unrelieved by standard treatments or medications	24 oz usable; 15 plants

Abbreviations: ALS, amyotrophic lateral sclerosis; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; MS, multiple sclerosis; PTSD, posttraumatic stress disorder.

[a] For up to date medical marijuana regulations, see http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.[5]

Aside from the 2 FDA-approved indications for cannabinoids, the scientific evidence supporting the medical use of marijuana and cannabinoids varies widely by disease entity from high-quality evidence to poor-quality evidence. High-quality evidence is defined herein as multiple randomized clinical trials with positive results (**Table 3**). Despite the variability in evidence supporting various uses for medical marijuana, state policies suggest the use of medical marijuana for many medical problems beyond nausea, vomiting, and anorexia. For some of the medical conditions approved for use in some states (eg, glaucoma), there are only preliminary data supporting the use of medical marijuana as pharmacotherapy.

Data from more than 40 clinical trials of marijuana and cannabinoids have been published; beyond the 2 indications for which dronabinol and nabilone are already approved by the FDA, the strongest evidence exists for the use of marijuana and cannabinoids as pharmacotherapies for chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis. As of March 2015, there were 6 trials (n=325 patients) examining chronic pain, 6 trials (n=396 patients) that investigated neuropathic pain, and 12 trials (n=1600 patients) that focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications. The American Academy of Neurology (AAN) recently published evidence-based guidelines that recommended an oral cannabis extract containing both THC and cannabidiol (not available in the United States as an FDA-approved medication) as having the highest level of empirical support as a treatment for spasticity and pain associated with multiple sclerosis.[4] The AAN also published a systematic review of medical marijuana as a treatment for neurological disorders, suggesting nabiximols, a spray containing both THC and cannabidiol, as probably effective in treating spasticity, central pain, and urinary dysfunction associated with multiple sclerosis, and dronabinol as probably effective as a treatment for spasticity and central pain associated with multiple sclerosis.[6] Thus, while medical marijuana is not a first-line treatment for Mr Z's chronic pain, it is reasonable to consider medical marijuana as a treatment after other treatments have failed. In general, the evidence supporting the use of marijuana and cannabinoids for other conditions aside from the FDA indications and chronic pain, neuropathic pain, and spasticity resulting from multiple sclerosis is either equivocal or weak.

Marijuana contains numerous cannabinoids. It is not known how individual cannabinoids affect the various diseases currently treated by marijuana. Two of the cannabinoids, dronabinol and nabilone, are available in the United States and can be prescribed. When treating patients for conditions that would otherwise be treated by marijuana itself, it is reasonable to initiate therapy with dronabinol or nabilone. If these are not successful, treatment can be escalated to marijuana itself because it contains numerous pharmacologically active cannabinoids.

Some conditions might respond to cannabinoids not yet available in the United States such as cannabidiol. Under these circumstances, it is reasonable to treat with marijuana itself. A variety of cannabinoids are in development, so new cannabinoids, likely with new FDA indications, should reach the market in the future.

Risks and Benefits of Cannabinoids

Medical marijuana and cannabinoids have health risks and benefits. Mr Z and the physician recommending medical marijuana for him should discuss these risks and benefits thoroughly prior to starting treatment with medical marijuana because many adverse effects may result from either short-term (single-use or sporadic) or long-term use.[4,5] The acute effects of marijuana include impaired short-

Table 2. Common Cannabis Preparations

Preparations	Description
Marijuana[a]	Dried plant product consisting of leaves, stems, and flowers; typically smoked or vaporized
Hashish	Concentrated resin cake that can be ingested or smoked
Tincture[a]	Cannabinoid liquid extracted from plant; consumed sublingually
Hashish oil	Oil obtained from cannabis plant by solvent extraction; usually smoked or inhaled; butane hash oil (sometimes referred to as "dabs"), for example
Infusion[a]	Plant material mixed with nonvolatile solvents such as butter or cooking oil and ingested

[a] These preparations are available from state-approved medical marijuana dispensaries.

term memory, motor coordination, and judgment. This is especially relevant for driving; short-term use of marijuana doubles the risk of involvement in a motor vehicle crash.[46] Paranoid ideation and psychotic symptoms, albeit rare, may occur in response to high doses of THC. Long-term regular (daily or nearly every day) marijuana use is especially problematic for young people, whose brains continue to develop into their mid-20s.[47] A recent study showed structural brain changes in the nucleus accumbens and the amygdala in occasional marijuana users compared with controls, underscoring the need for additional research into the effects of nonregular marijuana use on the developing brain.[48] Impaired brain development as measured by functional connectivity may contribute to the association between early, regular marijuana use and decline in IQ.[45,49]

Marijuana is potentially addictive, causing significant problems for work, school, and relationships in about 9% of adult and 17% of adolescent users.[50,51] Regular marijuana use is associated with an increased risk of anxiety, depression, and psychotic illness, and marijuana use can worsen the courses of these disorders as well.[52-57] Mr Z has an anxiety disorder for which he takes multiple medications; this anxiety must be monitored closely if medical marijuana pharmacotherapy is used. Functional outcomes are also affected, with regular marijuana use leading to poor school performance, lower income, increased likelihood of requiring socioeconomic assistance, unemployment, criminal behavior, and decreased satisfaction with life.[58-60] The cessation of regular marijuana use is associated with a withdrawal syndrome marked by anxiety, irritability, craving, dysphoria, and insomnia.[61]

Regular marijuana use results in physical problems as well. It is associated with increased incidence of symptoms of chronic bronchitis and increased rates of respiratory tract infections and pneumonia. Preliminary research points to an association between marijuana use and myocardial infarction, stroke, and peripheral vascular disease.[62]

Evaluation of a Patient for Medical Marijuana Certification

Patient requests for medical marijuana are now common in clinical practice. Determining which patients may be appropriate for a medical marijuana certificate (eAppendix in the Supplement) is complicated (Box). Patients administered marijuana should have a condition known to be responsive to marijuana or cannabinoids based on high-quality evidence such as randomized clinical trials. Before receiving marijuana, patients should have undergone adequate trials of other evidence-based treatments. Medical conditions such as major depressive disorder, anxiety disorders, and viral upper respiratory tract infections that may be exacerbated by marijuana should not be present. Patients present to their primary care physicians seeking medical marijuana certification or they may be already using marijuana. Mr Z's case was the latter—he raised the issue with his primary care physician after initiating medical marijuana pharmacotherapy outside of his usual medical care with the assistance of a medical marijuana clinic.

Medical marijuana evaluations should be comprehensive assessments that include risk-benefit discussions. Certifications should only be written by physicians who have thoroughly assessed a patient, know him or her well, and have a full understanding of the patient's debilitating condition requiring treatment. If the certification does not come from the patient's primary care physician or the specialist treating the debilitating condition, it is essential for the certifying physician to communicate with the patient's other health care clinicians in the same manner as any other specialists would be expected to.

The clinical evaluation should start with the patient expressing how they think medical marijuana will be helpful to treat their medical condition. The physician should take a careful history with special focus on previous treatments for the debilitating condition and possible contraindications for medical marijuana such as anxiety disorders, mood disorders, psychotic disorders, and substance use disorders. A thorough risk-benefit discussion should follow, covering both the adverse health effects of marijuana along with the scientific evidence from studies investigating marijuana or cannabinoids as pharmacotherapy for the debilitating condition being treated. It may be useful to provide a context for medical consensus by informing the patient that there currently is little support from major medical organizations for the use of medical marijuana.[63]

If the physician decides to write the certification for medical marijuana, a discussion of marijuana's federal legal status and that state's regulations must follow. According to the US government, marijuana is an illegal drug that is classified as Schedule I under the Controlled Substances Act, meaning that it has no currently accepted medical use and a high potential for abuse.[64] Marijuana's status as a Schedule I substance that is illegal according to the federal government is the reason that physicians cannot prescribe medical marijuana and can only certify its use. Although the US Department of Justice has stated that it plans to leave the issue of medical marijuana to the states and not enforce the federal statute, the federal stance on marijuana still is a cause for concern for some physicians who are considering recommending medical marijuana as a treatment or aligning with medical marijuana dispensaries or treatment centers.

The medical marijuana certification must state the medical condition that the physician believes would be treated effectively with medical marijuana and, in some states, the recommended amount of marijuana needed to treat the condition. For example, a physician in Massachusetts must state the medical condition for

Table 3. Randomized Clinical Trials Beyond Current FDA Indications for Cannabinoids[a]

Source	Drug (Maximum Dose), Route	Control	Sample Size, Experimental Condition/Control	Primary Outcome	Results
Chronic pain					
Skrabek et al,[16] 2008	Nabilone (2 mg) orally	Placebo	n=20 Nabilone; n=20 placebo (fibromyalgia)	VAS	Significant decrease in VAS (−2.04; $P < .02$)
Narang et al,[17] 2008	Dronabinol (20 mg) orally	Placebo	n = 29 Placebo; n = 30 dronabinol, 10 mg; n = 29 dronabinol, 20 mg	Total pain relief at 8 h	Significant increase in Total pain relief, dronabinol conditions (20 mg vs placebo at $P < .01$; 10 mg vs placebo at $P < .05$)
Frank et al,[18] 2008	Dihydrocodeine (240 mg), nabilone (2 mg) orally	Crossover	n=48 Dihydrocodeine followed by nabilone; n=48 nabilone followed by dihydrocodeine (chronic neuropathic pain)	VAS	Dihydrocodeine provided better pain relief than nabilone (6.0; 95% CI, 1.4-10.5; $P=.01$)
Pinsger et al,[19] 2006	Nabilone (1 mg) add-on orally	Placebo	n=30 Crossover	VAS	Significant decrease in VAS ($P < .006$)
Wissel et al,[20] 2006	Nabilone (1 mg) orally	Placebo	n=13 Crossover	11-Point box test (pain rating)	Significant decrease in pain rating ($P < .05$)
Blake et al,[21] 2006	Nabiximols: THC (15 mg)/ cannabidiol (13.5 mg) oromucosal spray	Placebo	n=31 Nabiximols; n=27 placebo	Pain on movement	Significant decrease in pain (−0.95; 95% CI, −1.85 to −0.02, $P=.04$)
Neuropathic pain					
Ellis et al,[22] 2009	Cannabis (1%-8% THC) smoked	Placebo	n=34 Crossover	Change in pain intensity	Significant decrease in pain ($P=.02$)
Abrams et al,[23] 2007	Cannabis (3.56% THC) smoked	Placebo	n=27 Cannabis; n=28 placebo	VAS, percent achieving >30% pain reduction	Significant decrease in pain ($P=.03$); 52% cannabis group vs 24% placebo reported >30% pain reduction ($P=.04$)
Wilsey et al,[24] 2008	Cannabis (7%, THC) smoked	Placebo	n=38 Crossover	VAS	Significant decrease in pain (−0.0035; 95% CI, −0.0063 to −0.0007 ($P=.02$)
Nurmikko et al,[25] 2007	Nabiximols: THC (30 mg)/ cannabidiol (27.5 mg) oromucosal spray	Placebo	n=63 Nabiximols; n=62 placebo	Change in pain intensity (NRS)	Significant decrease in pain ($P=.004$; 95% CI, −1.59 to −0.32)
Berman et al,[26] 2004	Nabiximols: THC (129.6 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=48 Crossover	Mean pain severity	Significant decrease in pain (THC/cannabidiol, −0.58, 95% CI, −0.98 to −0.18, $P=.005$; THC, −0.64, 95% CI, −1.05 to −0.24, $P=.002$)
Multiple sclerosis					
Zajicek et al,[27] 2003, and Freeman et al,[28] 2006	OCE: THC (25 mg), cannabidiol (12.5 mg); THC (25 mg) orally	Placebo	n=211 OCE; n=206 THC; n=213 placebo	Change in spasticity (Ashworth scale)[27]; incontinence episodes[28]	No effect ($P=.40$) on spasticity; decrease in episodes for both OCE and THC ($P=.005$ OCE; $P=.04$ THC)
Zajicek et al,[29] 2012	OCE (THC, 25 mg) orally	Placebo	n=144 OCE; n=135 placebo	Change in muscle stiffness	Significant decrease in muscle stiffness (odds ratio, 2.26; 95% CI, 1.24-4.13; $P=.004$)
Aragona et al,[30] 2009	Nabiximols: THC (27 mg)/ cannabidiol (25 mg) oromucosal spray	Placebo	n=17 Crossover	Psychopathology, cognition (Paced Auditory Serial Addition Test, Symptom Checklist 90-Revised)	No effect (Symptom Checklist 90-Revised, $P=.36-.91$; Paced Auditory Serial Addition Test, $P=.39$)
Collin et al,[31] 2007	Nabiximols: THC (129 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=124 nabiximols; n=65 placebo	Change in spasticity (NRS)	Significant decrease in spasticity (−0.52; 95% CI, −1.029 to −0.004, $P=.048$)
Kavia et al,[32] 2010	Nabiximols: THC (129 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=67 Nabiximols; n=68 placebo (overactive bladder)	Incontinence episodes	No difference ($P=.57$)
Vaney et al,[33] 2004	OCE: THC (30 mg) orally	Placebo	n=57 Crossover	Change in spasticity (self-report, frequency of symptoms)	No difference (frequency, $P=.01$; 95% CI, 1.76-4.63)
Ungerleider et al,[34] 1987	THC (7.5 mg) orally	Placebo	n=13 Crossover	Change in spasticity (self-report)	Significant decrease in spasticity ($P < .03$)
Svendsen et al,[35] 2004	Dronabinol (10 mg) orally	Placebo	n=24 Crossover (central pain)	Median spontaneous pain intensity (NRS) in last week of treatment	Significant decrease in median spontaneous pain intensity ($P=.02$)
Rog et al,[36] 2005	Nabiximols: THC (129.6 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=34 Nabiximols; n=32 placebo (central pain)	Pain, sleep disturbance (NRS)	Significant decrease in pain ($P=.005$), significant decrease in sleep disturbance ($P=.003$)
Fox et al,[37] 2004	OCE: THC (10 mg) orally	Placebo	n=14 Crossover (upper limb tremors)	Change in tremor index	No significant improvements ($P=.55$)

(continued)

Table 3. Randomized Clinical Trials Beyond Current FDA Indications for Cannabinoids[a] (continued)

Source	Drug (Maximum Dose), Route	Control	Sample Size, Experimental Condition/Control	Primary Outcome	Results
Wade et al,[38] 2004	Nabiximols: THC (129.6 mg)/cannabidiol (120 mg) oromucosal spray	Placebo	n=80 Nabiximols; n=80 placebo	VAS, most troublesome symptom	No significant improvements (P=.12); significant decrease in spasticity (−22.79; 95% CI, −35.52 to −10.07; P=.001)
Killestein et al,[39] 2002	Dronabinol (5 mg); OCE; THC (5 mg) orally	Placebo	n=16 Crossover (spasticity)	Change in spasticity (Ashworth scale)	No significant improvements
Parkinson disease					
Carroll et al,[40] 2004	OCE: THC (10 mg) orally	Placebo	n=19 Crossover (levodopa-induced dyskinesia)	Change in Unified Parkinson Disease Rating Scale dyskinesia score	No significant improvements (P=.09)
Crohn disease					
Naftali et al,[41] 2013	Cannabis: THC (115 mg) smoked	Placebo	n=11 Cannabis; n=10 placebo	Induction of remission (Crohn's Disease Activity Index score <150 after 8 wk)	No significant difference (P=.43)
Amyotrophic lateral sclerosis					
Weber et al,[42] 2010	Sesame oil: THC (10 mg) orally	Placebo	n=27 Crossover (cramps)	VAS, cramp intensity	No significant difference (0.24; 95% CI, −0.32 to 0.81; P=.38)
Neurogenic symptoms					
Wade et al,[43] 2003	Nabiximols: THC (120 mg)/cannabidiol (120 mg); THC (120 mg); cannabidiol (120 mg) oromucosal spray	Placebo	n=24 Crossover (n=18 multiple sclerosis; n=4 spinal cord injury; n=1 brachial plexus damage; n=1 limb amputation due to neurofibromatosis)	VAS	Significant decrease in pain with cannabidiol, THC; significant decrease in spasm with THC, cannabidiol, THC; significant decrease in spasticity with THC (P < .05)

Abbreviations: NRS, numerical rating scale; OCE, oral cannabis extract; THC, δ-9-tetrahydrocannabinol; VAS, visual analog scale.

[a] Randomized clinical trials are graded as level 2 evidence (level 1 includes systematic reviews of randomized clinical trials) according to the Oxford Centre for Evidence-Based Medicine 2011 levels of evidence.[44]

Box. Practical Considerations for Medical Marijuana

An appropriate medical marijuana candidate should have

1. A debilitating medical condition that data from randomized clinical trials suggest would respond to medical marijuana pharmacotherapy, such as nausea and vomiting associated with cancer chemotherapy, anorexia from wasting illnesses like AIDS, chronic pain, neuropathic pain, or spasticity associated with multiple sclerosis
2. Multiple failed trials of first- and second-line pharmacotherapies for these conditions
3. A failed trial of an US Food and Drug Administration–approved cannabinoid (dronabinol or nabilone)
4. No active substance use disorder or psychotic disorder or no unstable mood disorder or anxiety disorder
5. Residence in a state with medical marijuana laws and meets requirements of these laws

which medical marijuana is the treatment and a recommended amount per 60-day period. The amount should be estimated from the route of administration and the anticipated number of treatments per day. Patients receive advice on which marijuana species or strain to purchase and dosing and administration from the dispensary, which differs from the manner in which prescriptions of FDA-approved medications are specified. Once the patient begins medical marijuana pharmacotherapy, close follow-up with the physician is imperative, as it would be with any medications having significant adverse effects and abuse potential. The patient should be seen in follow-up within a month's time with additional telephone contact as necessary. Patients may be followed up monthly for 3 months, with further follow-up determined by the patient's clinical situation.

Patients requesting medical marijuana may already be taking opioids for chronic pain. In these instances, narcotics contracts may be in effect as an additional safeguard to mitigate the potential for abuse. Physicians recommending medical marijuana to these patients can use the narcotics contract to their advantage because in addition to the patient specifying where her or she will fill narcotics prescriptions, the patient can be asked to specify where he or she will obtain marijuana. The contract may also stipulate that random urine drug screening results positive for substances other than the prescribed opioids and recommended medical marijuana may be grounds for discharge.

Recommendations for Mr Z

Mr Z has had extensive treatment for his chronic pain over an extended period. He was referred to a variety of health care practitioners from multiple disciplines for his chronic pain. His clinicians used multiple modalities including multiple medications resulting in limited pain control before Mr Z considered medical marijuana as a treatment for his chronic pain. Overall, it appears that his treatment course was reasonable and likely a result of thoughtful collaboration between Mr Z and his primary care physician.

Mr Z appears to meet all but 1 of the criteria listed in the Box: he has a debilitating condition that data suggest may respond to marijuana, he has had multiple failed treatment trials of first- and second-line medications, his anxiety disorder appears to be clinically stable, and he resides in Massachusetts, a state with an active medical marijuana law. Only a previous trial of an FDA-approved synthetic cannabinoid was not done.

The course of treatment may have been altered if Mr Z had a discussion with his primary care physician prior to obtaining a medical marijuana certification. Mr Z and his primary care physician may have opted for a trial of one of the FDA-approved cannabinoids dronabinol or nabilone, despite Mr Z's medical history of anxiety. This anxiety, which appears to be clinically stable now, should have been monitored closely and medications adjusted accordingly. A trial of dronabinol still makes sense at this time because it would allow for the use of an FDA-approved (and thus likely safer in terms of composition and quality control) medication under the close supervision of Mr Z's primary care physician. He went to a specialty medical marijuana clinic, however, and 4 to 6 weeks elapsed without follow-up prior to Mr Z notifying his primary care physician that he was taking a medication with potentially significant adverse effects. This lack of follow-up is one of the major concerns about specialty medical marijuana clinics that often certify large numbers of new patients for medical marijuana each day. Regardless of where patients receives certification, they must be followed up closely by the certifying physician because of the potential for significant adverse effects, and the certifying physician should communicate with all other health care professionals delivering care that may be affected by a patient's use of medical marijuana.

Initiation of medical marijuana pharmacotherapy by patients before consulting their physician is becoming more common as additional states enact medical marijuana laws. These patients, along with others contemplating medical marijuana pharmacotherapy for their own medical problems, will likely continue to comprise a growing proportion of physicians' patients. Although the medical marijuana landscape will change as novel cannabinoids are approved for additional medical indications, the question of the role of medical marijuana as a pharmacotherapy in medicine persists. Physicians must educate patients about proper use of medical marijuana to ensure that only appropriate patients use it and limit the numbers of patients inappropriately using this treatment.

Questions and Discussion

QUESTION One of my patients said that he found one strain that worked better than others for chronic pain. Do different strains of marijuana that are available at the dispensaries have different effects?

DR HILL Different strains may have different effects because of their THC and cannabidiol content and differing ratios of THC to cannabidiol in the strain.[65] Just as different people may respond differently to the same drug, some may report better results from a particular strain than other people might. Medical marijuana dispensaries may make claims about certain strains being useful for particular illnesses, but those claims are theoretical or anecdotal in nature and may be made with marketing in mind.

QUESTION As it stands right now in Massachusetts, can any physician write a medical marijuana certification? What if a physician wants to write a certification for a patient to use medical marijuana for a medical condition that is not specified by the laws?

DR HILL Yes, in Massachusetts, any physician can write a medical marijuana certification for any medical indication they choose, provided the physician has completed the requisite training.[66] This training usually consists of a few hours of continuing medical education activities related to the risks and benefits of marijuana.

QUESTION In Massachusetts, the state allows the certifying physician to stipulate how much medical marijuana a patient may possess in a 60-day period, and the recommended 60-day supply of marijuana is 10 oz. Is that an unnecessarily high amount? How does one determine the correct dose of marijuana to use?

DR HILL The 60-day supply of 10 oz is a recommended amount, but this may be exceeded if a physician provides a rationale for it in writing. According to the World Health Organization, a standard marijuana cigarette contains as little as 0.5 g of marijuana, so a 60-day supply of 10 oz is up to 560 marijuana cigarettes or almost 10 per day.[67] Thus, based on the estimate of 0.5 g per marijuana cigarette, a patient requiring the marijuana equivalent of 1 to 2 marijuana cigarettes per day would need 0.5 to 1 oz of marijuana per month. Although no one wants to keep a medication away from someone who might benefit from it, this 60-day supply estimate appears to be another example in which marijuana policy is ahead of the science. Circumstances in which people need 10 oz per 60 days to make tinctures or other forms of marijuana-based medicines should be rare. There are little data available for optimal dosing of marijuana for particular medical conditions.[68] Dosing differs based on the route of administration, which determines the pharmacology of the various cannabinoids in marijuana as well as the processes of absorption and metabolism.[69] Dosing is determined for an individual patient using a titration process. The marijuana dose is increased until the desired clinical effect—pain relief in Mr Z's case—is achieved. The necessary dose is highly dependent on the THC concentration of the marijuana being used. If using a vaporizer to heat the plant material into a vapor for inhalation, a patient should start with a single inhalation of marijuana vapor and monitor for effect. If 20 minutes pass with no effect, the patient may take 2 inhalations consecutively, then monitor for another 20 minutes. Inhalations are spaced out because numerous consecutive inhalations may result in missing the window of optimal treatment effect. This titration process must be repeated if a different strain of marijuana is used.

QUESTION What is the state of insurance coverage on some of these FDA-approved cannabinoid medications and medical marijuana?

DR HILL No insurance companies cover medical marijuana, and there has not been any movement toward increased coverage by insurance companies. The cannabinoids dronabinol and nabilone are expensive medications that are covered by insurance companies for their FDA indications as well as for other indications on a case-by-case basis.

Conclusions

Medical marijuana use is now common in clinical practice, and it is critical for physicians to understand both the scientific rationale and the practical implications of medical marijuana laws. Medical marijuana and cannabinoids have significant health risks as well as many potential medical benefits. While medical marijuana has been at times a controversial and contentious issue, physicians have a responsibility to provide evidence-based guidance on this important issue.

- With more states enacting medical marijuana laws, it is imperative for physicians to understand both the scientific rationale and the practical implications of medical marijuana laws.
- Aside from nausea and appetite stimulation, indications for which there are 2 FDA-approved cannabinoids (dronabinol and nabilone), chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis are the indications for medical marijuana supported by high-quality evidence.
- Medical marijuana and cannabinoids have significant potential health risks, such as addiction and worsening of psychiatric illnesses such as some anxiety disorders, mood disorders, psychotic disorders, and substance use disorders, as well as many potential medical benefits.
- Evaluations to determine the appropriateness of medical marijuana for a patient should be comprehensive assessments that revolve around risk-benefit discussions.

ARTICLE INFORMATION

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