Medical marijuana and the developing role of the pharmacist

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In the United States, 11 states and several municipalities have legalized medical marijuana. These states include Alaska, California, Colorado, Hawaii, Maine, Montana, Nevada, Oregon, Rhode Island, Vermont, and Washington.[1] The state of Maryland has legislation that allows patients to claim a defense of medical necessity for medical marijuana use. Patients in these states can make an appointment with a licensed physician, receive a thorough diagnostic evaluation paid for by an insurance company, and depart with a recommendation for marijuana. Meanwhile, the patient may never encounter a pharmacist. Marijuana is illegal under federal law, and the Food and Drug Administration (FDA) has no role in the manufacture, composition, labeling, or purity of the final product. Patients may choose to purchase marijuana from a local "pot club" or grow their own, which raises further concern about the product's safety and potency.

Pharmacists must be aware of the increasing trend toward public acceptance of medical marijuana as a treatment option. California has an estimated 100,000 users of medi-

Purpose. The pharmacology, therapeutic uses, safety, drug–drug interactions, and drug–disease interactions of medical marijuana are reviewed, and the legal issues related to its use and the implications of medical marijuana for the pharmacist are presented.

Summary. Marijuana contains more than 460 active chemicals and over 60 unique cannabinoids. The legal landscape surrounding marijuana is surprisingly complex and unsettled. In the United States, 11 states and several municipalities have legalized medical marijuana. Another state provides legislation that allows patients to claim a defense of medical necessity. Nevertheless, patients using medical marijuana may never interact with a pharmacist. Marijuana is a Schedule I controlled substance and its use is illegal under federal law. Marijuana has a number of purported therapeutic uses with a broad range of supporting evidence. There are five general indications for medical marijuana: (1) severe nausea and vomit-ing associated with cancer chemotherapy or other causes, (2) weight loss associated with debilitating illnesses, including HIV infection and cancer, (3) spasticity secondary to neurologic diseases, such as multiple sclerosis, (4) pain syndromes, and (5) other uses, such as for glaucoma. Marijuana is associated with adverse psychiatric, cardiovascular, respiratory, and immunologic events. Moreover, marijuana may interact with a number of prescription drugs and concomitant disease states.

Conclusion. Several states have legalized the use of marijuana for chronic and debilitating medication conditions. Pharmacists need to understand the complex legal framework surrounding this issue so that they can protect themselves and better serve their patients.

Index terms: Cannabis; Drug interactions; Laws; Mechanism of action; Toxicity
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cal marijuana,[2] and San Francisco has twice as many medical cannabis dispensaries as McDonald's restaurants.[3] This article reviews the pharmacology, therapeutic uses, safety, drug–drug interactions, and drug–disease interactions of medi-cal marijuana. The current legal issues surrounding the use of medical marijuana are also addressed.

Background

Marijuana refers to the crude product (i.e., dried leaves and flow-

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ers) of the plant *Cannabis sativa.*[4-6] Marijuana contains more than 460 active chemicals and over 60 unique cannabinoids.[4,7,8] The major active ingredient in marijuana is δ-9-tetrahydrocannabinol (THC), which is primarily responsible for its therapeutic and psychoactive effects.[5,6] The quantity of THC in marijuana determines the potency and effect of the product.[8] Medical marijuana is typically smoked in hand-rolled cigarettes (i.e., joints) or a water pipe (i.e., bong), inhaled through a vaporizer, ingested in food, or applied topically as a balm.[2] Inhalation delivers a high percentage of active drug to the bloodstream.[8] Vaporizers are the optimal route of administration because they allow for rapid and complete absorption with minimal combustible byproducts, often con-

sidered the major health risk associated with smoking tobacco.

The effects of inhaled marijuana can be felt immediately.[8] THC, a cannabinoid, passes rapidly from the lungs into the bloodstream to a number of body organs. Two types of cannabinoid receptors have been identified: cannabinoid-1 (CB_1) and cannabinoid-2 (CB_2).[6,9] CB_1 receptors are present mainly in the central nervous system (CNS) and to a lesser extent in the peripheral tissue. CB_1 receptors have a heterogeneous distribution pattern in the brain, which accounts for the myriad of marijuana's effects on pleasure, memory, thought, concentration, sensory and time perception, and coordinated movement.[6,8] The effects of CB_1 are neuromodulatory in nature and affect a number of neurotransmit-

ters, including acetylcholine, norepinephrine, dopamine, serotonin, γ-aminobutyric acid, glutamate, and D-aspartate.[10] CB_2 receptors are present mainly on peripheral tissues and central immune cells.[6] Activation of these receptors leads to immunosuppressive, antiinflammatory, and antinociceptive effects.[10,11]

Cannabinoid receptors are G-protein-coupled receptors embedded in the cellular membrane (Figure 1).[12] A number of endogenous ligands, called endocannabinoids, are synthesized on demand to act on these receptors. Anandamide is the most widely studied of the endogenous cannabinoids.[12] Endocannabinoids bind to the extracellular portion of the receptor and trigger a highly complex signaling system whereby secondary messengers af-

Figure 1. Subtypes of cannabinoid receptors. Cannabinoid-1 (CB-1) receptors primarily modulate psychoactive effects. Cannabinoid-2 (CB-2) receptors primarily modulate immune responses. Illustration by Marie Dauenheimer, CMI. Adapted, with permission, from reference 6.
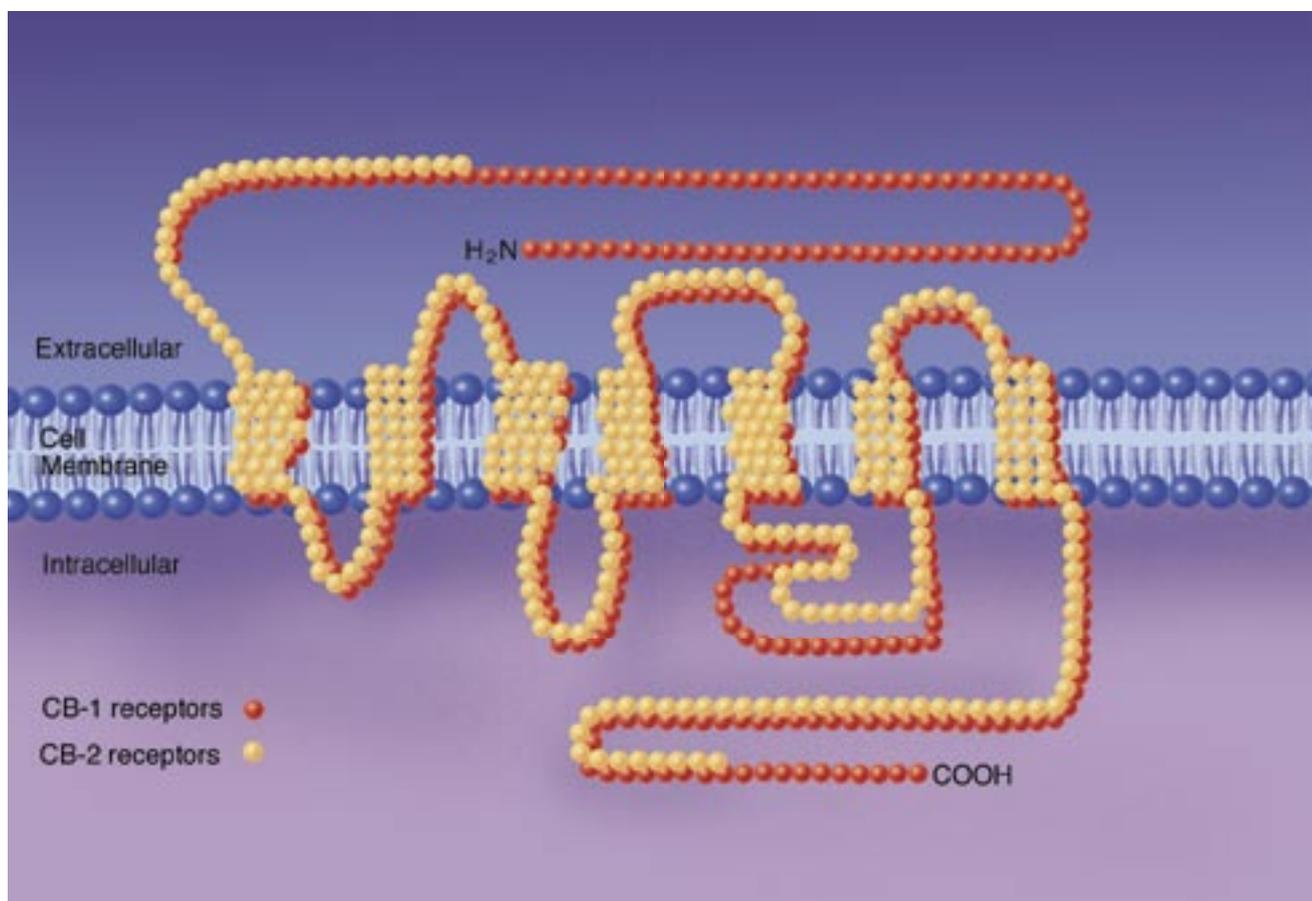
fect synaptic neurotransmission of excitatory and inhibitory circuits. THC is the primary cannabinoid in marijuana to act as a ligand for this system. The activation of cannabinoid receptors triggers a myriad of therapeutic and psychoactive effects in the body. Endocannabinoids are degraded through reuptake of a carrier transport molecule and enzymatically hydrolyzed to help maintain homeostasis and prevent overactivation (Figure 2).[12]

Legal status

The legal landscape surrounding marijuana is surprisingly complex and unsettled. Federal and state legislation are conflicting, and court rulings have not addressed the source of the problem: the legitimacy of state medical marijuana laws. To fully understand the legal nuances of medical marijuana, one must first understand the basic way our government functions. The United States functions under a form of government called federalism, which means that federal, state, and local governments coexist. Each recognizes the limits and powers of the others while maintaining some degree of authority and autonomy.

The federal government can only legislate in constitutionally identified areas, such as intellectual property, bankruptcy, immigration, and taxes. Historically, states have had sole authority to legislate in the areas of health, safety, and welfare, the so-called "police powers" of a state. However, the federal government often impedes this authority through a "constitutional hook" known as the commerce clause. Article I, section 8, clause 3 of the Constitution specifically states that Congress has express authority to legislate in areas involving "commerce . . . among the several states." Since drugs move through interstate commerce, Congress has legal authority to legislate drug regulation. Accordingly, in 1938, Congress passed the Food, Drug, and Cosmetic

Act under authority of the commerce clause. This remains the basis of our current drug law.

In the United States, marijuana is considered a Schedule I controlled substance under the federal Controlled Substances Act (CSA) in Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970.[13] This means that marijuana has no accepted medical use, a high potential for abuse, and a lack of accepted safety. The CSA specifically prohibits and criminalizes all marijuana manufacture, possession, and distribution. There is no federally recognized use of medical marijuana.

Nevertheless, a number of states have legalized the use of marijuana for medical purposes. A version of California's Proposition 215 was the first state law to decriminalize medi-

cal marijuana for patient use in 1996. Since then, 10 additional states have approved similar legislation, with more states working on it. Another state, Maryland, provides for a defense of medical necessity.[1]

In areas of conflict between federal and state laws, the federal law prevails. When one law is stricter than another, the stricter law prevails. This is called preemption. On the surface, the CSA appears to preempt state medical marijuana laws and criminalize all marijuana use. However, a number of legal cases, including some heard by the U.S. Supreme Court, have skirted this issue, clouding the controversy and, in some sense, compounding the current problem. For example, the Supreme Court recently ruled in *Gonzales* v. *Raich* that the CSA is a

Figure 2. Endocannabinoid agonism–degradation pathway. Endocannabinoids are formed within neurons and other cell types via multiple biosynthetic pathways (1). Rather than being stored as active molecules, they are produced on demand from membranous fatty acid precursors via the activity of phosphodiesterase (PD) enzymes such as phospholipase D (anandamide) and phospholipase C (2-AG). This process occurs after cellular stimulation by signals (2) such as neuronal depolarization (Ca^{2+} influx) to cause the extracellular release of active endocannabinoids (3). After release, the endocannabinoid can either bind cannabinoid receptors (agonism pathway) or be degraded. After receptor binding (4), the receptor signals the second messenger system that signals the cannabimimetic activities (5). There is also a degradation pathway expressed on either receptor-bearing or other cells. The endocannabinoids are degraded through reuptake by a diffusion-facilitated transport molecule (6) and then hydrolytically cleaved by enzymes (7) such as fatty-acid-amide hydrolase. Reprinted, with permission, from reference 12.
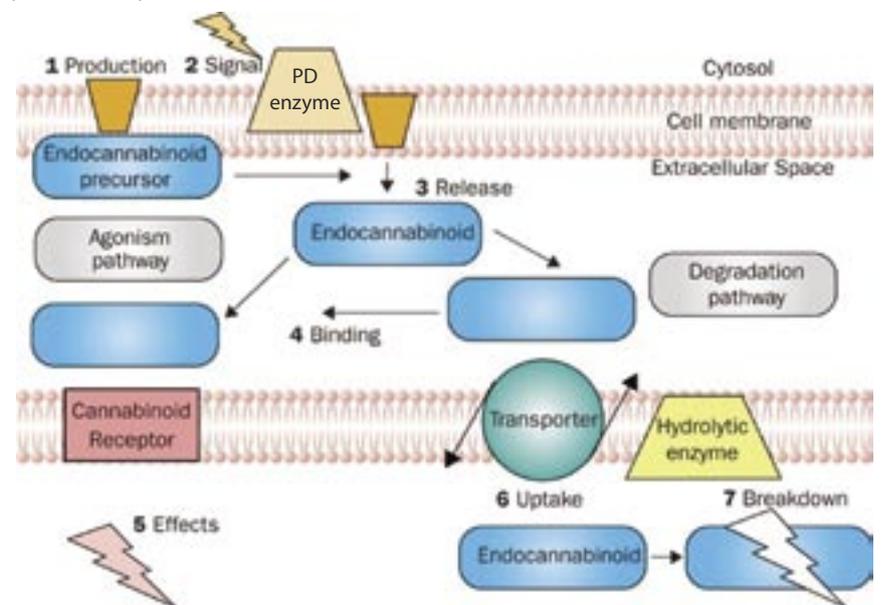
constitutional exercise of Congress's commerce clause authority and that even locally cultivated marijuana possession is unlawful.[14] However, the court did not address the validity of California's medical marijuana law or ban the existing law.

Most drug convictions in this country are state crimes, as only 1% of convictions involving marijuana are federal offenses.[2] Therefore, in states permitting the medical use of marijuana, criminal conviction is highly unlikely. Furthermore, since state boards of licensing regulate health care professionals, disciplinary action involving marijuana is also unlikely. Nevertheless, federal agents, including the Drug Enforcement Administration (DEA), have the authority to enforce the CSA. In addition, since DEA issues registration numbers to pharmacies and physicians, violations of the CSA could result in termination or suspension of these privileges. Pharmacists and pharmacies must strictly comply with all aspects of the CSA, as any violation constitutes a federal offense subject to criminal prosecution and loss of DEA-issued privileges.

Therapeutic uses

A vast number of therapeutic uses for marijuana have been identified in the literature. A comprehensive review of the clinical efficacy of medical marijuana is beyond the scope of this article. Instead, this article identifies the most common uses of medical marijuana.

State laws permitting medical marijuana typically define appropriate indications as serious, chronic, or debilitating medical conditions, such as (1) severe nausea and vomiting associated with cancer chemotherapy or other causes, (2) weight loss associated with debilitating illnesses, including HIV infection and cancer, (3) spasticity secondary to neurologic diseases, such as multiple sclerosis, (4) pain syndromes, and (5) glaucoma. Marijuana has been

used alone and in combination with other antiemetics to treat the nausea and vomiting associated with chemotherapy.[4,6,15] It has also been used to increase appetite and counteract weight loss in patients with debilitating illnesses, such as AIDS and advanced cancer.[4,6,15]

Marijuana may also alleviate symptoms associated with certain neurologic disorders. For instance, marijuana has been used to treat muscle spasticity in patients with multiple sclerosis (MS) and spinal cord injuries.[4,6,15-17] In patients with MS, marijuana is primarily used to treat lower urinary tract symptoms, including urge incontinence.[16] Patients with amyotrophic lateral sclerosis reportedly use marijuana for analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction.[18]

Marijuana is also used in the treatment of various movement disorders including dystonia, Parkinson's disease, Huntington's disease, and tics associated with Tourette's syndrome.[19] Marijuana is also used to prevent seizures in patients with epilepsy and is believed to have neuroprotective properties.[4,6,15,20,21]

Due to its analgesic and antiinflammatory properties, marijuana is used in the treatment of a variety of pain disorders.[4-7,17] It has been used for the prophylactic and symptomatic treatment of migraine headache and phantom limb pain and may reduce the opiate requirements in patients with gastrointestinal pain.[7,20,22-24] Marijuana may also have a role in the treatment of acute pain associated with sickle cell disease.[25]

Marijuana is used for a number of miscellaneous indications. Evidence suggests that marijuana can reduce intraocular pressure in patients with glaucoma,[4,6,15,17,26] relieve symptoms of asthma and other pulmonary disorders,[4,6,15,17,27-29] and serve as a mood stabilizer.[30] Furthermore, marijuana is used to reduce anxiety and improve sleep,[24] and has reportedly

been used in the treatment of intractable hiccups.[31]

An overall evaluation of the efficacy of marijuana is difficult to ascertain. Because it is a tightly regulated product, quality-controlled clinical trials of medical marijuana are limited. The available studies are generally characterized by a lack of quality-control groups, small numbers of patients, short duration, and imprecise outcome measures. Nevertheless, there is sufficient anecdotal evidence to suggest that marijuana may have utility in a number of patient populations.[32] Accordingly, the general consensus in the medical community appears to be cautious certitude. Reports issued by the Institute of Medicine,[6] the House of Lords,[17] and a National Institutes of Health workshop[15] identified a possible role for medical marijuana but stressed the need for further research in the field.

Safety

Marijuana use is associated with a number of adverse effects that impair the cardiovascular, respiratory, and nervous systems. Its use may cause a multitude of visual disturbances and lead to psychological dysfunction and addiction. Marijuana is considered the most commonly reported drug of abuse in the United States and carries with it a number of important sociopolitical implications.[8]

Cardiac effects reported with marijuana include tachycardia, hypertension, syncope, palpitations, orthostatic hypotension, stroke, and paroxysmal atrial fibrillation.[33-35] Preliminary evidence suggests that marijuana can trigger acute myocardial infarction.[34] Marijuana has also been reported to cause transient ischemic attacks in patients with a low risk of developing cardiac abnormalities.[36]

Marijuana smoke contains 50–70% more carcinogenic ingredients than cigarette smoke that can lead to lung cancer.[8,37] Evidence also suggests that marijuana may increase the risk

of head and neck cancer.[38,39] Chronic marijuana use is associated with increased symptoms of chronic bronchitis (e.g., coughing, production of sputum, wheezing).[37]

CNS effects reported with marijuana include dry mouth, flu-like symptoms, nausea, drowsiness, numbness, dizziness, nightmares, and difficulty sleeping.[9,40,41] Marijuana has been linked to seizures and is believed to have both proconvulsant and anticonvulsant effects.[7,42-44] Marijuana has also been reported to cause visual disturbances, blurred vision, dry eyes, reddening of the conjunctiva, mydriasis, and photophobia.[40,41,45]

Heavy marijuana use can result in psychological dysfunction, affecting a person's ability to form memories, recall events, and focus.[8] Acute toxic psychosis induced by marijuana may be characterized by hallucinations, delusions, depersonalization (a loss of the sense of personal identity or self-recognition), fear of dying, paranoia, anxiety, changes in mood (e.g., depression), and altered mental astuteness.[8,46] Marijuana has been reported to cause dose-related impairments in cognitive and behavioral functions and may impair the ability to drive a motor vehicle or operate heavy machinery.[47-49] One study demonstrated that driving under the influence of marijuana increases a person's likelihood of being involved in a fatal crash, though this risk is generally thought to be lower than with alcohol.[47]

Finally, marijuana is considered a gateway drug leading to exposure and possible addiction to more harmful drugs.[50] In 1999, more than 200,000 Americans entered substance-abuse treatment due to marijuana use.[50] It has been estimated that 10% of marijuana users are at risk of dependence.[51] Withdrawal symptoms associated with marijuana include restlessness, anxiety, irritability, insomnia, muscle tremor, sweating, and changes in heart rate.[45] No medi-

cations are approved for the amelioration of withdrawal symptoms associated with marijuana abuse or dependence.[8]

Drug–drug interactions

Documentation of drug–drug interactions with marijuana is limited. However, the available information and data extrapolated from the information available for cannabinoids with FDA-approved indications provide some guidance for the practitioner. Marijuana appears to interact with a variety of drugs, including opioids,[9] barbiturates,[9,40] CNS depressants,[9,40] protease inhibitors,[40] selective serotonin-reuptake inhibitors,[9,40] sildenafil,[40] theophylline,[9,40] tricyclic antidepressants,[9,40] anticholinergics,[9] sympathomimetics,[9] α-agonists,[40] naltrexone,[9] disulfiram,[9,45] lithium,[51] neuroleptic antipsychotics, and anesthetic agents.[52]

Opioids used in combination with marijuana can lead to cross-tolerance and mutual potentiation of effects.[9] Marijuana taken with alcohol, benzodiazepines, and muscle relaxants can result in excessive CNS depression.[9,40] There is also evidence to suggest that marijuana can decrease the effectiveness of protease inhibitors and theophylline by increasing their clearance.[40] Additional interactions include those with fluoxetine and sildenafil that may lead to manic episodes and myocardial infarction, respectively.[53,54] There have been several reports of tachycardia and delirium in patients receiving tricyclic antidepressants and marijuana concurrently.[55-58] In addition, the concurrent concomitant use of anticholinergic agents and α-agonists with marijuana can lead to tachycardia and exacerbate hypertension.[40]

Naltrexone can increase the subjective effects (e.g., euphoria) of marijuana, and the concomitant use of disulfiram and marijuana can lead to hypomanic episodes.[9,45] According to one case report, marijuana can increase serum lithium concen-

trations.[51] Marijuana may also interact with neuroleptic antipsychotics by decreasing their effectiveness and increasing the risk of extrapyramidal effects.[59,60] Marijuana may complicate surgical anesthesia through a myriad of effects.[52] Lastly, marijuana may interact with systemic corticosteroids due to the increased risk of immunosuppression.[61]

Drug–disease interactions

Based on its pharmacology, marijuana may adversely affect patients with certain diseases, including immunosuppression, psychiatric disturbances, cardiac disease, respiratory disease, vertigo, cancer, pregnancy, and obesity.

Since marijuana is reported to have immunosuppressive properties, it may pose health risks to patients with diabetes, HIV, lupus, rheumatoid arthritis, cancer, or an organ transplant.[61,62] Marijuana use has been reported as a risk factor for invasive pulmonary aspergillosis.[61] Nevertheless, marijuana use may lead to increased food intake in patients with HIV who have low muscle mass and is often used safely in a subset of this population.[63]

Marijuana may exacerbate psychiatric disorders in patients with schizophrenia, psychosis, bipolar disorder, depression, eating disorders, or panic and anxiety disorders and in patients predisposed to such disorders.[64] Marijuana abusers are four times more likely to develop depression than people who do not use marijuana.[65] Furthermore, hallucinations, delusions, and violent behavior have been reported in schizophrenic patients using marijuana.[46]

Patients with cardiovascular disease or at risk of stroke or myocardial infarction may have an increased risk of cardiovascular effects from marijuana.[8,40,45] As long-term marijuana use has been associated with respiratory diseases, it may worsen chronic obstructive pulmonary disease, asthma, and tuberculosis.[37]

Since marijuana use has been shown to cause dizziness, it may complicate the diagnosis and treatment of vertigo.[40,66] Marijuana may also cause significant and undesirable weight gain in patients with diabetes and obese patients.[4,6,15] Marijuana may impair intrauterine growth in pregnancy and cause structural and neurobehavioral defects in the fetus.[67] Moreover, prenatal exposure to marijuana may increase the risk of childhood leukemia.[68]

Discussion

Pharmacists are medication experts and serve to ensure safe and appropriate medication use. Medical marijuana poses a unique challenge and a novel opportunity for pharmacists. Patients using medical marijuana should be advised to follow all appropriate laws and procedures with painstaking detail. Patients should be urged to consult regularly with a physician and maintain a bona fide patient–physician relationship. Violations may be costly, and medical necessity is not an accepted defense for violations of the CSA.[69] Although marijuana may be legal in a particular jurisdiction, large amounts may be prima facie evidence of intent to distribute and criminalized accordingly. Patients should comply with possession limits in the state where they reside[1] and should not use or display marijuana publicly, though law enforcement officers may use discretion in ticketing.[70]

Patients using marijuana should be screened for potential drug–drug interactions and counseled about the risks associated with marijuana use. Patients with a history of immunosuppression, psychiatric illness, cardiovascular disease, respiratory illness, or substance abuse should avoid marijuana use. Patients who use marijuana should drive with extreme caution and be counseled to avoid heavy machinery, as marijuana can impair reaction time and motor control.[47] Also, patients who

use marijuana should avoid alcohol, as the effects of both drugs may be potentiated. Marijuana may cause significant and undesirable weight gain and pose further health risks in susceptible patients. Smoking marijuana poses many of the same respiratory risks as regular cigarettes, and alternative routes of administration may be preferred, such as the use of a vaporizer. Pregnant and lactating women should be advised against using medical marijuana, as the risks appear to outweigh any potential benefits.[67]

Pharmacists should conduct thorough medical and social histories, including asking about the possible use of medical marijuana, especially if a patient is receiving drug therapy for a serious, chronic, or debilitating medical condition or resides in a state where medical marijuana is permissible. If a patient appears to have a drug-induced disease, the pharmacist should evaluate the role of marijuana as a causative agent. At a minimum, pharmacists must make the appropriate inquiries and investigations. Pharmacists should also carefully maintain patient records. Any evidence of marijuana use should be held in strict confidence, and all records should comply with the requirements of the Health Insurance Portability and Accountability Act of 1996. Until the legal landscape is settled, pharmacists should not routinely advocate marijuana use or assist patients in obtaining the drug.

Although pharmacists have a first amendment right to communicate the legal status of medical marijuana with patients and present the available evidence in support of treatment, they should do so carefully and thoughtfully.[1] Marijuana remains illegal under the CSA, and state-licensing boards can impose disciplinary action on pharmacists acting outside their scope of practice. Furthermore, recommending marijuana may subject the pharmacist to

civil litigation, such as negligence or malpractice arising from subsequent harm.

In general, pharmacists should develop a systematic approach, such as the following, to deal with the issue of medical marijuana:

1. Keep abreast of local, state, and federal laws regarding medical marijuana.
2. When practicing in areas with medical marijuana laws, know all relevant procedures and protocols.
3. Develop a working knowledge of the risks and benefits of medical marijuana.
4. Conduct thorough medical and social histories and inquire about illicit drug use, including medical marijuana.
5. Consider patients treated for serious and chronic debilitating conditions as possible users of medical marijuana.
6. Screen patients who use medical marijuana or are inclined to use it for drug–drug and drug–disease interactions and counsel them accordingly.
7. Advise patients with psychological disease or a tendency toward addiction against marijuana use.
8. Ensure that patients using marijuana for medical purposes are under appropriate and continuous medical supervision and have met all statutory requirements.
9. Develop the necessary literature retrieval and evaluation skills to address drug information questions involving medical marijuana.
10. Never recommend a source of or provide specific instructions on how to obtain marijuana.

Conclusion

Several states have legalized the use of marijuana for chronic and debilitating medical conditions. Pharmacists need to understand the complex legal framework surrounding this issue so that they can protect themselves and better serve their patients.

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