



AN ONGOING CE PROGRAM  
of the University of Connecticut  
School of Pharmacy

## EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Identify the features of different state regulations that permit the use of marijuana for medical and non-medical purposes.
- Describe the characteristics, effects and potential risks associated with the use of marijuana and how this information may be used by pharmacists during counseling.
- Discuss the rationales for and against legalizing recreational marijuana and their historical context.
- Discuss the controversy between state and federal law as it applies to medical and non-medical use of marijuana and potential future directions of the regulation.

After participating in this activity, pharmacy technicians will be able to:

- Identify the features of different state regulations that permit the use of marijuana for medical and non-medical purposes.
- Describe the characteristics, effects and potential risks associated with the use of marijuana.
- Discuss the rationales for and against legalizing recreational marijuana and their historical context.
- Discuss the controversy between state and federal law as it applies to medical and non-medical use of marijuana and potential future directions of the regulation.



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

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## Law: Marijuana's Expanding Legality, Pot's Precarious Position

**ABSTRACT:** Despite being a Schedule I drug under the Federal Controlled Substances Act, marijuana regulations have loosened at the state level with 29 states approving it for medical use and nine states currently approving it for recreational use by adults. The regulations on recreational use differ among the states but generally permit sale and possession of small quantities by persons 21 years of age or older. They usually resemble regulations governing the sale of alcohol with restrictions against public use and operating a motor vehicle. Marijuana sales generate revenue for states and municipalities through taxation, typically at a higher rate than for most retail sales. It is expected that more states will enact similar regulations, and pharmacists need to anticipate an increase in marijuana availability and how use will affect practice, with increased risks of drug interactions and side effects. Although states have permitted some form of marijuana possession for more than two decades, these actions conflict with federal law; federal enforcement of marijuana sales has been lax, but may be heightened in the future, setting up a potential clash between the Federal government and the states.

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## INTRODUCTION

Few drugs generate the amount of controversy associated with the use of marijuana. Over the course of thousands of years, the drug has been viewed as a component of religious and cultural events, an important medicine, a major agricultural product, and a corrupting national menace.<sup>1</sup> In the U.S., it was grown as a source of fiber in the South and was listed in the U.S. Pharmacopeia (USP) between 1850 and 1941. In the 1930s marijuana began to be looked upon less favorably, depicted as "Public Enemy Number One" in the opening to the classic 1936 anti-drug film, *Reefer Madness*.<sup>2</sup>

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A year later, Congress passed the Marijuana Tax Act with little discussion and officially made the use of marijuana illegal.<sup>1,4</sup> Commentators believe anti-Mexican and anti-African-American racist undertones and economic concerns over the growing use of hemp helped fuel the change in attitude, which passed despite the AMA's opposition to the new law.<sup>3,4</sup> The act restricted the use of marijuana under federal law, although by 1937 virtually every state had already placed prohibitions on marijuana.<sup>4</sup>

When existing drug laws were consolidated in the 1970's, marijuana was placed in the most restrictive category (Schedule I) at the urging of an anti-drug administration in Washington in response to a perceived drug crisis.

The pendulum began to swing back in 1996 with the passage of the first state marijuana law by voter referendum, The Compassionate Use Act in California which permitted the purchase, growth, and possession of marijuana for medical use.<sup>5</sup> By 2018, 29 States (plus the District of Columbia) had enacted Medical Marijuana laws. In 2012 Colorado became the first state to legalize the use of marijuana for recreational purposes, growing to nine states plus the District of Columbia by 2018. These efforts promoting legalization occurred despite the continued presence of marijuana as a Schedule I drug under the Federal Controlled Substances Act (CSA).<sup>6</sup>

This continuing education activity reviews the rapidly-changing regulatory landscape of this important substance. Most pharmacists have an appreciation for the increased acceptance and use of medical marijuana and their role in providing guidance on its therapeutic use. However, the legalization of recreational marijuana is a more recent phenomenon and the pharmacist's role is murkier. Here, we provide a brief overview of marijuana as a medicine, but place greater emphasis on more recent trends towards loosening the restrictions on its recreational use by states and the ongoing conflict with federal laws.

## MARIJUANA

Marijuana refers to various preparations from different strains of the *Cannabis* plant. The medicinal use of *Cannabis* can be traced back at least 5000 years to the Chinese literature where it was recommended for treating malaria, constipation, rheumatic pains, gout, and "female disorders." It was considered an analgesic in Ancient Egyptian, Greek and Roman medical resources; its cultural use is believed to pre-date the medical applications.<sup>1</sup> Medical use in the U.S. and Europe became common in the 19<sup>th</sup> and 20<sup>th</sup> Century and included treatment of inflammation, cough, cramps, insomnia, arthritis, gout, epilepsy, and venereal disease. Many *cannabis*-containing products were marketed and sold in pharmacies in the U.S. in the 1900s, and manufacturers included Parke-Davis, Eli Lilly, and Squibb.<sup>1</sup>

Most of the active constituents in the *Cannabis* plant are a diverse group of lipophilic compounds collectively known as

*When existing drug laws were consolidated in the 1970's, marijuana was placed in the most restrictive category (Schedule I) at the urging of an anti-drug administration in Washington in response to a perceived drug crisis.*

### Pause and Ponder:

- Under what circumstances might a patient's use of marijuana be of concern to you?
- What are the differences between delta-9-THC and CBD?

cannabinoids.<sup>7</sup> More than 100 have been identified, most of which are unique to species of *Cannabis*. The two most abundant and well-known cannabinoids are

- delta-9-tetrahydrocannabinol (delta-9-THC), which, along with the closely related but less potent delta-8-THC, are believed to be the principal psychoactive compounds found in the plant, and
- the non-psychoactive cannabidiol (CBD).

THC and CBD are substances of great interest for their pharmacologic and therapeutic activity.

Cannabinoids act on cannabinoid receptors in the brain and other organs, although the cannabinoids likely act on other ligand receptors as well, which may mediate some of their pharmacological effects. At least two cannabinoid receptors have been identified: CB1 which is found predominately in the central nervous system (CNS), and CB2 which is located mostly in cells and organs mediating immune functions and other peripheral responses.<sup>7</sup>

Marijuana produces many well recognized effects including relaxation or sedation, contentment, a pleasurable "buzz," increased sociability, altered perception of time, and increased appetite, especially for sweet or fatty foods.<sup>8</sup> Marijuana also is reported to produce potential therapeutic effects including analgesia, appetite stimulation, and anti-emetic, anti-seizure, and anti-spasmodic effects. A full description of the therapeutic potential of marijuana is beyond the scope of this manuscript, but the interested reader is directed to a recent, detailed report by the National Academy of Medicine (<https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state>).<sup>8</sup>

Some reported adverse effects include decreased short-term memory, impaired motor skills and driving abilities; dry mouth; tachycardia, and other adverse cardiovascular events; reduced immunologic competence; bronchitis (when smoked); and depression, psychotic behavior, and altered cognitive function with high dose chronic use.<sup>8-9</sup>

## MARIJUANA AND THE CSA

In 1965, Harvard Professor and psychedelic guru, Timothy Leary, was arrested after a search of his car at the Texas-Mexico border uncovered some marijuana seeds. He was charged with violation of the Marijuana Tax Act. Leary filed a law suit alleging that his conviction under the Act violated his privilege against self-incrimination. The US Supreme Court agreed in a case decided in 1969, essentially making the Act virtually unenforceable.<sup>10</sup>

In 1970, Congress enacted the Controlled Substances Act (CSA),<sup>6</sup> the current law that regulates the manufacture, importation, sale, distribution, and possession of substances with potential for abuse. The CSA consolidated all existing drug abuse laws (said to number more than 200) and agencies responsible for their enforcement into one cohesive statute. The Drug Enforcement Agency (DEA) was established in 1973 to enforce the CSA.

As pharmacists are aware, the CSA places drugs into various categories from I to V, with Schedule I being the most restrictive. Schedule I is reserved for drugs with the highest degree of abuse potential and risk to the public health and having no recognized therapeutic use in the U.S. When the CSA was enacted, marijuana was placed temporarily into Schedule I, pending a report from a national commission (Schafer Commission), appointed by then-President Richard Nixon to provide a final recommendation.<sup>4</sup> The Schafer Commission concluded in 1972 that “(t)he existing social and legal policy is out of proportion to the individual and social harm engendered by the use of the drug,” and favored a public health approach rather than prohibition.<sup>4</sup> President Nixon, who had strong anti-drug opinions, rejected the committee’s findings<sup>11</sup> and marijuana remains in Schedule I to this day.

## MEDICAL MARIJUANA

Despite marijuana’s status as a Schedule I substance, 29 states have enacted laws permitting medical marijuana use within their borders.<sup>12</sup> It is anticipated that more states will authorize medical marijuana use in the near future. The laws in these states are non-uniform, differing in characteristics including medical conditions that qualify for marijuana, the amounts that can be purchased, whether patients can grow their own, the type of registration necessary, where it can be used, oversight of dispensaries and others.<sup>12,13</sup>

## CANNABIDIOL (CBD)

CBD, a non-psychoactive cannabinoid, occupies a special place in the regulatory landscape. Eighteen additional states authorize use of CBD, typically for treating forms of seizure disorders, often in younger patients.<sup>12</sup> Many of these states specify the dosage form/source that qualifies for the exemption. Usually, the approved form has very low concentrations of THC (typically less than 1% and often as little as 0.3%, but up to 5% in some states). It should be noted that CBD is also illegal under federal



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Law, despite dubious Internet claims to the contrary. The DEA considers it to be a Schedule I drug by definition as a “derivative” or “component” of marijuana.<sup>14</sup>

There have been several proposals in Congress to change the legal status of CBD, most recently a bill entitled “Charlotte’s Web Medical Access Act” introduced in 2017.<sup>15</sup> The bill has been referred to an appropriate house subcommittee and is still far from becoming law. If enacted in its current form, the bill would “amend the Controlled Substances Act to exclude cannabidiol and cannabidiol-rich plants from the definition of marijuana.” CBD’s eventual status if the law is eventually passed (e.g., Schedule II, Rx, OTC) remains unknown. Significantly, the FDA granted Fast Track designation in 2017 to a CBD oral solution in the treatment of Prader-Willi syndrome, a rare genetic disorder characterized by insatiable appetite in children often leading to the development of obesity and type 2 diabetes.<sup>16</sup>

## CHARACTERISTICS OF STATE RECREATIONAL MARIJUANA LAWS

Paralleling the move to prohibit marijuana in the 1930’s, individual states have led the way to ease restrictions on marijuana. As of January 31, 2018, nine states [Alaska, California, Colorado, Maine, Massachusetts, Oregon, Nevada, Vermont, Washington] plus the District of Columbia have passed laws permitting the personal use, and possession of marijuana by adults. Most permit sales (see [Figure 1](#)), although not all these laws have been fully implemented, and others are still being modified. Many other states have decriminalized marijuana possession (typically imposing civil fines instead of incarceration for possession of small quantities). As is the case with medical marijuana, each state’s regulations have different characteristics. While medical marijuana laws can often markedly differ from state to state,

the recreational regulations tend to be more uniform. In general, states have patterned recreational marijuana use after retail sale and use of alcohol. For example, the purchaser must ordinarily be at least 21 years of age; the amount that can be possessed in public is generally around one ounce, although higher amounts are permitted in some states (in contrast some states permit possession of as much as 8-24 oz of medical marijuana); retailers must be licensed by the state; driving under the influence of marijuana is prohibited, as is use in or near schools and other public locations; local municipalities can prohibit use and sale of marijuana; and most states permit purchases by non-residents. More details on selected states are presented below.

## Colorado

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In 2012, Colorado became the first state to establish a recreational marijuana program. The state had previously enacted a medical marijuana program in 2000. Colorado legalized possession of up to an ounce of marijuana by an individual 21 years of age or older in 2012, and in 2014 marijuana became available for retail purchase in licensed stores.

Since Colorado was the first state to permit retail marijuana sales, many of their provisions may serve as a model for understanding the characteristics of legislation and how it came to fruition.

The act was instituted “in the interest of efficient use of law enforcement resources, enhancing revenue for public purposes, and individual freedom.”<sup>17</sup> The ballot initiative faced formidable opposition but prevailed in the 2012 election with 55% of voters approving. An analysis of the political climate surrounding the campaign stated that the successful effort “was a perfect storm of impotent opposition coupled with organized, motivated, and well-funded support.”<sup>18</sup> Proponents emphasized the theme of comparing marijuana to alcohol, and developed political support. They also used more refined messaging to appeal to targeted populations, for example, telling “soccer moms” that taxes from marijuana sales would supplement depleted education budgets and appealing to Tea Party and libertarian conservatives by referring to prohibition as an example of preventable government waste and misguided governmental intrusion.<sup>18</sup> The amendment’s supporters raised almost four times as much money as opponents did.<sup>18</sup>

The Act made the use of marijuana legal in Colorado for persons aged 21 or older and enabled taxation and regulation “in a manner similar to alcohol.”<sup>17</sup> An individual may possess, use, purchase, transport, or display up to one ounce of marijuana or no more than six marijuana plants and may possess “marijuana accessories.”<sup>17</sup> (Marijuana preparations are not

### Pause and Ponder:

In the continuum of states that allow or do not allow medical or recreational marijuana, where is the state in which you practice?

standardized, and many factors will contribute to the variation in the amount smoked, but a published study<sup>19</sup> estimates that on average a joint contains approximately 0.35 grams of plant material.) The term “marijuana accessories” refers to equipment or materials used in cultivation or storage, or that are used to introduce marijuana into the body. Transferring one ounce or less to another individual 21 years of age or older without remuneration is also permitted. A non-resident of Colorado may purchase up to ¼ ounce. Purchases must be made from a licensed facility.<sup>17</sup>

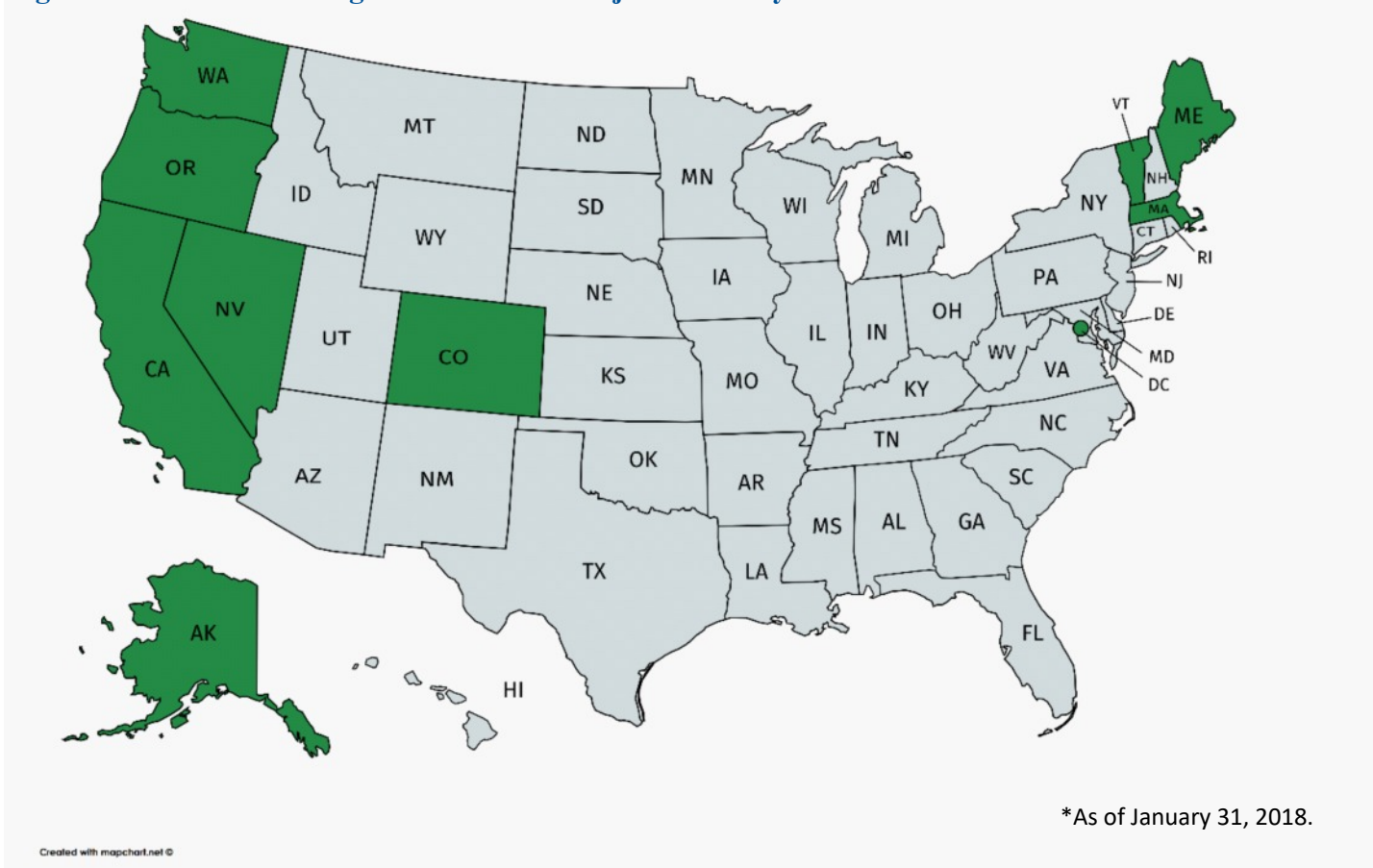
The law also has a provision to protect privacy such that a consumer is not required to provide a retailer with personal information other than a government-issued identification to provide proof of age. The retailer is not required to obtain or record personal information about the consumer “other than information typically acquired in a financial transaction conducted at a retail liquor store” and there is no requirement to track or record purchases.<sup>20</sup> While recreational users are limited to possessing no more than one ounce of marijuana (by contrast, a registered medical marijuana patient may possess up to 2 ounces), there are no restrictions on the number of purchases that a customer can make within any time frame (including daily).<sup>20</sup>

Under state law, stores cannot open before 8 AM and cannot remain open later than midnight. Local municipalities can set more restrictive hours for retail stores. For example, recreational marijuana shops in Denver must close by 7 PM.<sup>20</sup> Municipalities can further restrict retail establishments and can even ban them altogether. However, municipalities that ban sales will not benefit from state sharing of tax revenues and those permitting retail outlets can add an additional local tax.<sup>18</sup>

The Colorado law also imposes other restrictions. Generally, marijuana cannot be smoked in public. A person cannot take his or her purchase out of state, even if the travel is to another state that permits marijuana possession.<sup>20</sup> Marijuana possession is banned at Denver International Airport even if one is just carrying it through the airport (e.g., dropping off or picking someone up).<sup>21</sup> The airport does not search bags nor used drug-sniffing dogs, but if a person is found in possession of marijuana, he or she would be subject to a \$999 administrative fine.<sup>21</sup> Moreover, under TSA policy, if marijuana is found in someone’s belongings, they can be asked to dispose of the material and can face arrest.<sup>21</sup> Similarly, marijuana cannot be mailed.<sup>20</sup> Individuals attempting to send marijuana through the mail can face federal charges.

An applicant for a dispensary must be at least 21, pass a background check, and not have been convicted of a felony within the past five years nor convicted of a felony involving a controlled substance within the past ten years.<sup>20</sup>

Figure 1: States Permitting Recreational Marijuana Use By Adults. \*



### California

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In California, Proposition 64 (The Adult Use of Marijuana Act [AUMA]<sup>22</sup>) became effective on January 1, 2018 to great fanfare. One of the stated goals of the new Act is to, “Take non-medical marijuana production and sales out of the hands of the illegal market and bring them under a regulatory structure that prevents access by minors and protects public safety, public health, and the environment.”<sup>22</sup>

As in Colorado, adults 21 years of age or older may possess up to 28.5 grams of marijuana (and six plants per residence; no growing limits for medical marijuana) or eight grams of concentrated *Cannabis* (separated resin/hashish), and may purchase it from a licensed commercial facility.<sup>22</sup> A person may also grow up to six plants within a private home so long as the area is locked and not visible from the street. California prohibits smoking in all public places and where tobacco smoking is prohibited (except that businesses can apply for a special license to host *Cannabis* events, such as festivals<sup>23</sup>); smoking or ingesting while operating a motor vehicle; and possession of an open container (discussed below) in a vehicle by a driver or passenger. Possession on the grounds of schools, day care centers, or youth centers while children are present is also prohibited. The

use of vaporizers or e-cigarettes that dispense marijuana is also prohibited where smoking tobacco is banned. Shops must close by 10 PM and need 24-hour video surveillance. Municipalities may also adopt local ordinances.<sup>23</sup>

The new regulations made some changes in marijuana regulations.<sup>24</sup> Under the former medical marijuana regulations, an individual could hold no more than two types of licenses (cultivator, manufacturer, retailer, and distributor). These restrictions effectively prevented direct farm-to-consumer sales and farms were limited to one-half acre indoors or one acre outdoors. Under the new regulations, an individual may hold any combination of licenses and a special license was created with no limit set on farm size. A prior conviction for a controlled substance offense may not in itself be the sole grounds for rejecting a license, but the state can revoke a license for controlled substance offenses committed after licensing.

The law also imposes state taxes: a 15% excise tax on the retail sale price of marijuana, and state cultivation taxes on marijuana of \$9.25 per ounce of flowers and \$2.75 per ounce of leaves. Municipalities can also add additional taxes. Medical patients with voluntary ID cards are partially exempted from the sales tax but not the excise tax.<sup>24</sup>

The act requires every package of marijuana and marijuana products to carry a specific label<sup>22</sup>:

"GOVERNMENT WARNING: THIS PACKAGE CONTAINS MARIJUANA, A SCHEDULE I CONTROLLED SUBSTANCE. KEEP OUT OF REACH OF CHILDREN AND ANIMALS. MARIJUANA MAY ONLY BE POSSESSED OR CONSUMED BY PERSONS 21 YEARS OF AGE OR OLDER UNLESS THE PERSON IS A QUALIFIED PATIENT. MARIJUANA USE WHILE PREGNANT OR BREASTFEEDING MAY BE HARMFUL. CONSUMPTION OF MARIJUANA IMPAIRS YOUR ABILITY TO DRIVE AND OPERATE MACHINERY. PLEASE USE EXTREME CAUTION."

It would be prudent of pharmacists to reinforce these warnings in appropriate circumstances.

The Act also includes some restrictions on advertising, prohibiting "misleading claims" and banning the marketing of marijuana to minors. Also banned are billboards along interstate highways, and the use of cartoon characters, language, or music known to appeal to children.<sup>22</sup>

### Alaska



Alaska has more restrictions on operators, prohibiting the issuance of a retail license to an individual who has been convicted of a felony, a misdemeanor involving a controlled substance (within five years), or underage sales of alcohol.<sup>25</sup> Retail owners must be state residents.

### Massachusetts



Massachusetts voters passed a recreational marijuana law in 2016 and the state legislature revised it in 2017.<sup>26</sup> Retail shops are expected to open in July 2018. Massachusetts permits possession of 10 ounces of marijuana and up to 12 plants in a private residence, and one ounce outside the primary residence. However, residents of a leased property

require their landlord's permission to possess any marijuana. Smoking is not allowed in public areas. However, regulations are expected to permit businesses, such as *Cannabis* cafes, where individuals can gather socially and consume marijuana. At the time that this manuscript was being prepared, it was not decided whether smoking would be allowed or if consumption would be restricted to edibles and similar products.<sup>27</sup> Mixed use establishments, such as restaurants or massage parlors are also under consideration.<sup>27</sup> Home delivery is also possible; drivers would be required to obtain positive identification proof that the purchaser is 21 or older and recipients must sign for the delivery, which would only occur during the seller's normal business hours.<sup>26</sup>

Individuals 18 to 21 years old possessing less than two ounces are subject to civil penalties. Employees of retail shops are subject to a background check, but a prior drug possession conviction will not disqualify employment or ownership. Products will be sold in child-resistant, opaque containers and will be labelled with the amount of THC. Edible products will have a single serving limit of 10 mg of THC and cannot resemble any current non-marijuana food product.<sup>26</sup>

Voters approved a 12% tax on marijuana, but the legislature raised it to 20% (a 6.25% sales tax, a 10.75% excise tax, and a 3% "local option" that cities and towns will be able to levy), which is still one of the lowest rates in the U.S.

Massachusetts does not tax medical marijuana.<sup>26</sup>

### Maine



Maine's voters narrowly passed a referendum to legalize marijuana in 2016 and the state's legislature approved the measure in 2017. Regardless, Governor LePage, a long-time opponent of marijuana, vetoed the bill citing concerns about loopholes in the proposed law.<sup>27</sup> The referendum allowed possession of up to 2.5 ounces or growing

up to six plants, but did not establish a system to regulate retail sales and production.<sup>27</sup> Efforts to come up with a compromise to establish a regulatory framework for the sale, production and taxation of marijuana were continuing as this manuscript was being prepared.<sup>28</sup> The disputes included regulatory agency authority and the size and scope of anticipated tax revenue.

### Vermont



Vermont's legislature approved a bill permitting recreational use of marijuana in January of 2018, becoming the first state to approve this practice via legislative action rather than a referendum.<sup>30</sup> The Vermont law will permit possession of one ounce of marijuana or two mature plants but does not authorize retail sales nor authorize a sales tax at this time. The

law becomes effective July 1.

Vermont and other states allowing possession, but not retail sales, are concerned about a "gift loophole." Since giving marijuana to another is legal, entrepreneurs are offering free items but charging a handling or delivery fee or requiring a purchase of an additional item.<sup>30</sup>



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## ECONOMIC IMPACT

One incentive for state legalization of recreational marijuana is the revenue that will be generated. For example, one of the stated goals of California's AUMA is to "Generate hundreds of millions of dollars in new state revenue annually for restoring and repairing the environment, youth treatment and prevention, community investment, and law enforcement."<sup>24</sup>

Several sources suggest the economic impact from marijuana sales could be substantial. New Frontier Data (NFD), a company that analyzes the burgeoning marijuana industry, reports that legal sales of marijuana have become a \$6.6 billion industry with, currently, 70% of the total coming from medical marijuana sales and 30% from recreational.<sup>31</sup> They project growth to \$24.1 billion in sales by 2025, with half of sales derived from recreational marijuana. Two factors fuel the projected expansion: new markets as more states permit *Cannabis* use and increased demand as users transition from illicit sources to the legal market. Based upon their model, NFD estimates the legal *Cannabis* industry could generate 280,000 new jobs by 2020.<sup>31</sup> Similarly, the Tax Foundation, a non-profit tax policy organization, estimated in a 2016 report that a "mature" marijuana industry could generate \$22 to \$28 billion in federal, state, and local tax revenues, with an estimated \$7 billion federal revenue share, including payroll taxes.<sup>32</sup>

Colorado has raised more than \$367 million from taxes on sales of medical and adult use marijuana since implementation of the recreational program in 2014.<sup>31</sup> This far exceeds the state's initial projections of \$70 million per year. Significantly, the *Cannabis* tax revenues exceeded revenues generated by taxes on alcohol or cigarettes.<sup>33</sup> The state has distributed \$256 million to a range of programs, nearly half going into the state's school construction fund and \$7.2 million into substance abuse prevention programs.<sup>31</sup>

## WHERE DOES THE PHARMACIST FIT?

In the case of medical marijuana, this question is more straightforward. Pharmacists should be willing to counsel patients on appropriate use, side effects, interactions, and other therapeutic issues when the drug is used for medical purposes. However, of the 29 states with medical marijuana programs, only five have regulations requiring pharmacist involvement.<sup>34</sup> Connecticut, New York, and Minnesota permit only a pharmacist in either the distribution of medicinal *Cannabis* or supervision of activities within the dispensary. Pennsylvania leaves the responsibility of dispensing to either an onsite physician or pharmacist. Arkansas has the least pharmacist involvement; each dispensary must have an appointed pharmacist consultant. In the other states, the pharmacist's role is more erratic.

When the drug is used recreationally, the issue becomes murkier. If equivalence with alcohol use becomes the prevailing standard for legalized marijuana use, pharmacists will likely play an even less prominent role. Should pharmacists inquire about (non-medical) marijuana use during counseling sessions since marijuana use can affect therapy (see [Table 1](#))? Pharmacists should be cognizant of factors such as pharmacodynamic and pharmacokinetic interactions, unexplainable side effects, lack of adherence to conventional medicine/self-treatment, interference with activities requiring motor control and attention, abuse, and other considerations.<sup>35-37</sup>

A general rule of thumb for pharmacists would be to monitor for common CYP 2C9, 2C19, and 3A4 inhibitors (e.g., paroxetine, fluoxetine, calcium channel blockers, macrolides, antifungals, HIV antiretrovirals), as these may increase THC's pharmacologic effect and duration in patients using recreational marijuana.<sup>35</sup> Pharmacists should also inform patients that concomitant use may potentiate adverse effects. For instance, in patients taking other CNS depressants or self-medicating and taking daily anti-hypertensives, risk of cardiovascular adverse effects like hypotension and syncope would greatly increase. Additionally, marijuana smoke is a CYP 1A2 inducer and therefore would decrease the pharmacologic effect of 1A2 substrates potentially leading to treatment failures. (See [Table 1](#))

Pharmacists should be able to communicate other issues as well. A significant concern is adolescent marijuana use.<sup>38,39</sup> Cerebral reorganization and other morphological changes occur during puberty<sup>38</sup> and many of the adverse psychological health effects (addiction/dependence, psychosis, cognitive impairment) are amplified when marijuana use begins in adolescence.<sup>39</sup> Evidence also indicates that *Cannabis* use in adolescence and early adulthood is associated with poor social outcomes, including unemployment, lower income, and lower levels of life and relationship satisfaction.<sup>39</sup> These concerns may be somewhat mitigated by the requirement in all states to date that users be at least 21 years old, but experience with ethanol show that youths often circumvent these barriers easily.

**Table 1: Counseling Points for Pharmacists**

Drug Interactions	<ul style="list-style-type: none"> <li>• THC metabolized by CYP3A4 and CYP2C9 <ul style="list-style-type: none"> <li>o 3A4, 2C9 inhibitors = ↑ THC levels</li> <li>o 3A4, 2C9 inducers = ↓ THC levels</li> </ul> </li> <li>• CBD metabolized by CYP3A4, CYP2C9, 2C19 and CYP1A1; UDP-glucuronosyltransferases. <ul style="list-style-type: none"> <li>o 3A4, 2C9, 2C19 inhibitors = ↑ CBD levels</li> <li>o 3A4, 2C9, 2C19 inducers = ↓ CBD levels</li> </ul> </li> <li>• Marijuana smoke (specific cannabinoids unsettled) is a CYP1A2 inducer <ul style="list-style-type: none"> <li>o ↓ 1A2 substrate levels (i.e. clozapine, olanzapine, naproxen, chlorpromazine, haloperidol, duloxetine, cyclobenzaprine)</li> </ul> </li> <li>• CBD is a CYP3A4 and CYP2D6 inhibitor <ul style="list-style-type: none"> <li>o ↑ 3A4 substrate levels (i.e. macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil, antihistamines, atorvastatin, simvastatin, HIV antiretrovirals)</li> <li>o ↑ 2D6 substrate levels (i.e. selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, beta blockers, codeine, oxycodone)</li> </ul> </li> </ul>
Adverse Effects	<ul style="list-style-type: none"> <li>• Central Nervous System related: <ul style="list-style-type: none"> <li>o Lethargy, sedation, cognitive impairment, slowed reaction time, psychological dysfunction (impaired coordination, memory formation, recollection, focus), visual disturbances, dizziness, headache, anxiety</li> </ul> </li> <li>• Cardiovascular related: <ul style="list-style-type: none"> <li>o Tachycardia, orthostatic hypotension, hypertension, palpitations, paroxysmal atrial fibrillation, peripheral vasodilation</li> </ul> </li> <li>• Respiratory related: <ul style="list-style-type: none"> <li>o Coughing, wheezing, sputum production</li> </ul> </li> </ul>
Precautions	<ul style="list-style-type: none"> <li>• Use with caution in HIV/AIDS, diabetes, lupus, cancer, and transplant patients due to potential immunosuppressive properties</li> <li>• Use with caution in psychiatric disorders, including but not limited to, schizophrenia, bipolar disorder, depression, panic, and anxiety disorders due to psychoactive effects</li> <li>• Patients with a history of cardiovascular disease or at an increased risk of stroke or myocardial infarction are at an increased risk of cardiovascular effects associated with marijuana</li> <li>• Marijuana smoke may be carcinogenic and has similar effects on the lung as tobacco smoke, suggesting an association with respiratory diseases like COPD and asthma, and an increased risk for developing lung cancer</li> </ul>
Other Patient Counseling	<ul style="list-style-type: none"> <li>• Not recommended and should be avoided during pregnancy as it may impair intrauterine growth and cause structural and neurobehavioral defects<sup>b</sup></li> <li>• Do not drive or operate machinery when using marijuana<sup>b</sup></li> <li>• Withdrawal symptoms may or may not occur upon discontinuation<sup>b</sup> <ul style="list-style-type: none"> <li>o Symptoms reported within 48 hours of discontinuation include irritability, anxiety, restlessness, sleep disturbances</li> </ul> </li> <li>• Side effects are dose dependent and likely to resolve after discontinuation<sup>b</sup></li> </ul>
Adapted from references 35-37	

Marijuana is the most commonly used illicit drug in the U.S.<sup>41</sup> and policy makers often cite concerns that marijuana may be a gateway drug.<sup>40</sup> Regular or heavy use in adolescence may be associated with an increased risk of abuse or dependence of other drugs, although it is not clear if this is a causal relationship or a reflection of individual behavioral and social factors.<sup>38</sup>

Another concern with the expansion of marijuana accessibility is the observation that THC concentrations in marijuana in seized samples have been increasing,<sup>9,38</sup> so users are being exposed to higher doses than in the past. A recent review not

ed that there is the potential for a dose-dependent increased risk of psychiatric hospitalization.<sup>38</sup> Moreover, in states like Colorado there are no dosing recommendations, even for medical marijuana, and some edible forms are sold in doses that could pose risks to children.<sup>42</sup>

*Marijuana is the most commonly used illicit drug in the U.S.*



## Pause and Ponder:

What might your patients want to know about marijuana potency in your area?

## CONFLICT WITH FEDERAL LAW

While efforts to legalize marijuana for medical and recreation use are gaining momentum, it is important to appreciate that these state actions conflict with federal law. Marijuana is a Schedule I drug under the CSA.

*Gonzales v Raich*,<sup>43</sup> a case decided by the U.S. Supreme Court in 2005, dealt with a situation in which Federal DEA agents raided homes of seriously ill patients who were using marijuana on a physician's recommendation under California's medical marijuana law. The agents seized their marijuana plants. The patients sued the U.S. arguing that this was an unlawful exercise of the government's authority, essentially that the CSA did not apply to their circumstances. The Court decided that the application of the CSA in this situation was a proper use of that power and that no matter how valid a state's law may be under state law, when it comes into conflict with federal law, the federal law prevails.

So, why hasn't the DEA cracked down on the states? Fundamentally, it comes down to the decision by the Justice Department about how vigorously to enforce the CSA. In 2009, the U.S. Deputy Attorney General sent a memo to each of the U.S. attorneys announcing a policy that would deprioritize marijuana prosecutions of persons complying with existing state laws for the medical use of marijuana.<sup>44</sup>

The memo went on to say that "(a)s a general matter, pursuit of these priorities should not focus federal resources in your States on individuals whose actions are in clear and unambiguous compliance with existing state laws providing for the medical use of marijuana. For example, prosecution of individuals with cancer or other serious illnesses who use marijuana as part of a recommended treatment regimen consistent with applicable state law, or those caregivers ... who provide such individuals with marijuana, is unlikely to be an efficient use of limited federal resources."<sup>44</sup>

When Colorado took the next step to legalize recreational marijuana, the state sought further guidance from the Justice Department.<sup>18</sup> This resulted in a letter and accompanying memorandum (known as the Cole memo<sup>45</sup>) to Governor Hickenlooper clarifying the Justice Department's position. The memo indicated that the Department would continue to enforce the CSA but would not challenge the state's ability to regulate the retail marijuana industry under state law, based on the expectation that state and local governments would implement strong, effective regulatory and enforcement systems to address public safety, public health and other public interest.<sup>18,45</sup>



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The Cole Memo listed the Federal government's eight enforcement priorities:

- Preventing distribution of marijuana to minors;
- Preventing revenue from the sale of marijuana from going to criminal enterprises, gangs, and cartels;
- Preventing the diversion of marijuana from states where it is legal under state law in some form to other states;
- Preventing state-authorized marijuana activity from being used as a cover or pretext for the trafficking of other illegal drugs or other illegal activity;
- Preventing violence and the use of firearms in the cultivation and distribution of marijuana;
- Preventing drugged driving and the exacerbation of other adverse public health consequences associated with marijuana use;
- Preventing the growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands; and
- Preventing marijuana possession or use on federal property.

Colorado's regulations were written to be consistent with these priorities.<sup>18</sup> Whether the current Justice Department chooses to follow the same hands-off path is open to question.



## Sidebar: Other Legal Considerations

**Americans with Disabilities (ADA):** Marijuana use is not protected under the ADA and employers may still require drug tests and can make employment decisions based upon the results.

**Financial:** Marijuana transactions are largely a cash business. Banks are subject to Federal regulations and there are restrictions on credit card use and banks can be prosecuted for providing accounts to marijuana related businesses. The IRS also has restrictions on deductible business expenses for marijuana sellers.

**Personal Possession:** Possession is limited to a private residence or establishment. In most states, possession in a leased property is subject to the terms of the lease and the landlord's permission. In many states, possession limits, especially for plants, are based upon a per residence basis and not per person/occupant basis. Some regulators have also argued that smoking a joint on the front porch of one's home visible from the street may constitute prohibited open and public use.

**"Open Container":** Many jurisdictions do not allow driving with an "open container" of marijuana, analogous to alcohol restrictions. For example, the California statutes (see: [https://leginfo.ca.gov/faces/billNavClient.xhtml?bill\\_id=201720180SB94](https://leginfo.ca.gov/faces/billNavClient.xhtml?bill_id=201720180SB94)) state that it is "an infraction punishable by a fine not exceeding \$100 for a person to possess a receptacle containing *Cannabis* or *Cannabis* product that has been opened, or a seal broken, or to possess loose *Cannabis* flower not in a container, while driving a motor vehicle ... unless the receptacle is in the trunk of the vehicle or the person is a qualified patient carrying a current identification card or a physician's recommendation and the *Cannabis* or *Cannabis* product is contained in a container or receptacle that is either sealed, resealed, or closed."

## SUMMARY AND CONCLUSION

Legislation at the state level has rapidly expanded access to medical marijuana and more recently to adult marijuana use. As this manuscript was being finalized, Vermont became the ninth state to permit possession of small amounts of marijuana by adults and six other states (NJ, MI, DE, RI, CT, OH) are poised to join the list, possibly as early as 2018.<sup>46</sup> The future of these efforts is, however, uncertain. Polls show public support for legalizing marijuana; a national survey by NDF<sup>31</sup> conducted in 2017, found that 55% of respondents favored regulation and taxation similar to alcohol or tobacco while 9% favored keeping it illegal.

However, changes at Federal level may dampen the momentum for further loosening marijuana regulation. As noted above, under the Obama administration, the Justice Department took a hands-off approach on pursuit of enforcement of

marijuana use. Current Attorney General Sessions, on the other hand, has consistently taken a stand opposing legalization of marijuana and has criticized the Obama administration for its lax attitude towards marijuana prohibition.<sup>31</sup> On January 4, 2018, AG Sessions issued a memorandum to the U.S. Attorneys reminding them that the CSA and other statutes "reflect Congress's determination that marijuana is a dangerous drug and that marijuana activity is a serious crime" and that "previous nationwide guidance specific to marijuana enforcement is unnecessary and is rescinded, effective immediately."<sup>47</sup>

Similarly, numerous lawsuits and other efforts by individuals and organizations to reschedule marijuana since 1972 have been unsuccessful.<sup>13,48</sup> Most recently, the DEA responded to a petition by the then-Governors of Washington and Rhode Island (states with medical marijuana programs). The governors argued that Federal law makes it impossible for state governments to ensure a safe supply of marijuana for serious medical conditions without putting its employees at risk of prosecution. They stated further that the classification of *Cannabis* in the United States as a Schedule I substance is fundamentally wrong.<sup>49</sup> The DEA responded in 2016 with a lengthy analysis of the "Eight Factor Test" that the FDA/DEA use to determine issues of scheduling. It concluded that marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the U.S., and a lack of accepted safety for use even under medical treatment and rejected the petition.<sup>49</sup>

Also uncertain is whether legalizing adult recreational marijuana will impact medical marijuana programs. Some developments have been observed but it is premature to conclude they are long-term trends. First, in Colorado, medical marijuana sales have declined since the implementation of the recreational program.<sup>50</sup> Second, in California and Oregon, some dispensaries that provided medical marijuana have switched to recreational dispensaries, thereby reducing availability for medical marijuana patients, especially those under 21.<sup>51</sup> Interestingly, alcohol sales, especially beer, have also declined in states with medical marijuana programs.<sup>52</sup> In the long-term it may prove to be impractical and burdensome for states to have two parallel regulatory strategies for marijuana and, if so, they are likely to opt for recreational programs due to the higher revenue stream as California did.

Marijuana continues to generate an important conversation among policy makers and the public who need to be well informed to facilitate their decisions. Pharmacists become an especially valuable resource in these settings since they can provide unbiased information in a non-stigmatizing manner, while also monitoring for drug-drug and drug-disease interactions. Pharmacists are also in a prime position to be leaders in the policy debate over the proper regulation of marijuana, whatever their opinions may be, and should be active and willing participants.

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