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Medical *Cannabis*: A guide to the clinical and legal landscapes

If your patient expresses interest in medical marijuana, you'll find evidence on maximizing benefit while minimizing risk. But be cautious: Data are often contradictory.

PRACTICE RECOMMENDATIONS

› *Educate patients about the effects of the physiologically active therapeutic compounds in* Cannabis*; this is critical to prevent overconsumption of products with high levels of tetrahydrocannabinol.* (B)

› *Screen patients for serious mental health concerns before recommending or certifying medical* Cannabis*; this is essential because the rate of psychiatric hospitalization is increased in bipolar disorder and schizophrenia patients who use* Cannabis *heavily.* (B)

› *You can recommend medical* Cannabis *and certify patients for its use with the certainty that the risk of overdose or serious adverse effects is exceedingly low.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶

Barry S, a 45-year-old man with a new diagnosis of non-Hodgkin's lymphoma, recently started induction chemotherapy. He has struggled with nausea, profound gustatory changes, and poor appetite; various antiemetics have provided only minimal relief. He tells you that he is hesitant to try "yet another pill" but has heard and read that marijuana (genus *Cannabis*) is used to alleviate disruptive chemotherapy-induced adverse effects. He asks if this is a treatment you'd recommend for him.

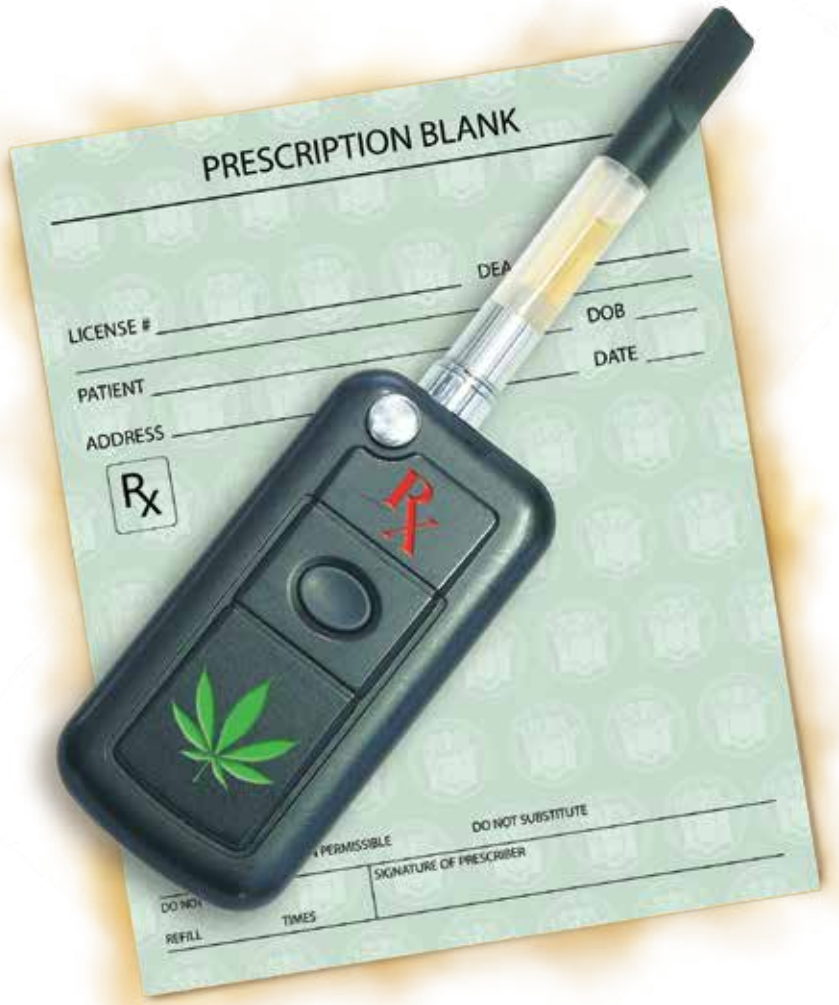
As Mr. S's physician, how do you respond?

Understandably, some family physicians are hesitant to recommend an unregulated, federally illegal substance characterized by conflicting or absent evidence of safety and effectiveness.[1] Nevertheless, throughout history and in the current court of public opinion, medical *Cannabis* has overwhelming support,[2] leading to legalization in most of the United States.

As with many traditionally accepted therapies (whether they are or are not supported by substantial evidence), physicians are expected to provide individualized guidance regarding minimizing risk and maximizing benefit of the therapeutic use of *Cannabis*. The rapidly growing scientific and commercial fields of medical *Cannabis* guarantee that information on this topic will constantly be changing—and will often be contradictory. In this article, we review the most common concerns about medical *Cannabis* and provide up-to-date evidence on its use.

The pharmacology of cannabis

Cannabis sativa was among the earliest plants cultivated by man, with the first evidence of its use in China, approximately



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Common forms of plant-based *Cannabis* include leaf that is smoked or vaporized, oral tincture, pill, and oil concentrate that can be vaporized.

4000 BC, to make twine and rope from its fibers.[3] Records of medicinal *Cannabis* date back to the world's oldest pharmacopoeia, a written summary of what was known about herbal medicine through the late 16th century.[4]

The 2 principal species of *Cannabis* are *sativa* and *indica*. There is no good medical evidence to separate the impacts of either strain; however, a staggering amount of lay information exists about the reported differing effects of each strain.[5]

Chemical constituents. Phytocannabinoids derived from *C sativa* are the plant's best-known proteins, constituting a complex lipid-signaling network involved in numerous physiological processes. There are more than 100 known phytocannabinoids, the most well-recognized being Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Additional sources of cannabinoids include endogenous cannabinoids, or endocannabinoids, and synthetic cannabinoids.

The endocannabinoid system, comprising cannabinoid receptors, endocannabinoids, and their specific enzymes, is a potential therapeutic target for a variety of pathologic processes.[6,7] The 2 most well-studied targets for cannabinoids in the human body are the cannabinoid receptors CB_1 and CB_2, found throughout the body: CB_1, predominantly in the central and peripheral nervous system, and CB_2 in a more limited distribution in the immune and hematopoietic systems. Other pathways activated or antagonized by THC and CBD exist, but are less well-mapped than CB_1 and CB_2.

Botanical or synthetic? It is important to distinguish between synthetic and plant-based cannabinoids, for you and your patients' benefit. Pharmaceutical (synthetic) THC is just that: THC alone. Whole-plant *Cannabis*, on the other hand, has hundreds of additional chemicals—most notably, phytocannabinoids and terpenoids. Data on the mechanisms of action and interactions of these additional chemicals are limited.

Although clinical trials have been undertaken with synthetic cannabinoids, there is increasing understanding and interest in the medical community of whole-plant

A tolerable therapeutic starting point is a THC:CBD ratio of 1:1.

Cannabis as a distinct entity. For example, nabiximols is a novel development in plant-based *Cannabis* products. Available as an oromucosal spray, a dose provides THC and CBD at 2.7 mg/100 mcL. Nabiximols is not approved by the US Food and Drug Administration (FDA) but is widely used in Canada and Europe.

A third class of *Cannabis* comprises non-regulated synthetic cannabinoids that have no medically recognized benefit. They are solely a drug of abuse; common names include "K2" and "Spice." These cannabinoids are outside of the scope of our discussion, but patients and providers should be aware of these cannabinoids because they are street-available. Unsuspecting patients might not know the difference between abusive and therapeutic formulations.[8]

Delivery and strength. Common forms of plant-based *Cannabis* include leaf that is smoked or vaporized, oral tincture, pill, and oil concentrate that can be vaporized. All forms come in a range of THC:CBD ratios—from as high as 90% THC content to 0% THC and all CBD-based content. Patients who are naïve to *Cannabis* might be concerned about formulations with a high THC concentration because of the psychoactive effects of this substance. Given the minimal CNS activity of CBD, a tolerable therapeutic starting point often is a THC:CBD ratio of 1:1, which contains a lower percentage of THC.[4]

Physiologic effects. THC is a partial agonist of CB_1 and CB_2 receptors; CBD functions as an antagonist at both receptors. The primary effects of THC result from activation of CB_1 receptors, which exist in various areas of the cerebrum and cerebellum, as well as in the spinal cord.[7] THC exerts its psychotropic effects at CB_1 sites in the central nervous system; CBD can antagonize these THC effects at CB_1 receptors. CBD also has anti-inflammatory and other effects that are mediated through peripherally distributed CB_2 receptors.[9]

THC has tremendously complex capacity for activation and inhibition within various neuronal circuits, resulting in effects on mood, appetite, and movement.[1,7] Adverse effects associated with *Cannabis* are wide-ranging: Most commonly, nausea, drowsiness, fatigue, dry mouth, and dizziness are reported alongside cognitive effects. Rarely, tachycardia, hypotension, hyperemesis, and depression can be seen.

Clinical implications and indications

Clinical indications for legal medical *Cannabis* vary by state; typically, indications include human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS), cachexia, cancer, glaucoma, epilepsy and other seizure disorders, severe and chronic pain, spasticity from neurodegenerative disorders, and irritable bowel syndrome and Crohn's disease, as well as a wide range of less-universal diagnoses. A patient may have a so-called qualifying diagnosis (ie, having the potential to allow the patient to be certified to purchase and use *Cannabis*) in one state but not have the same standing in a neighboring state, posing a complex legal issue. Given the significant complexities of performing medical research with plant-based *Cannabis* in the United States, little research has been done. The result? Policymakers are grappling with questions that only scientific research can answer:

- For which conditions does *Cannabis* provide medicinal benefit equal to or superior to alternatives?
- What are the appropriate dosages (or CBD:THC ratios), formulations (plant-derived or synthetic), and routes of administration (smoked, ingested, or topical) for various conditions?

Bird's-eye view of clinical research. A meta-analysis of isolated synthetic and plant-based cannabinoids for medical use was published in 2015.[10] The analysis included more than 6000 patients in 79 trials, most of which assessed whether dronabinol or nabilone (both synthetic isolates) were effective compared to placebo or alternative non-*Cannabis*-based therapy. The studies examined chemotherapy-induced nausea and vomiting, appetite stimulation in HIV and AIDS, chronic pain, spasticity, depression and anxiety, sleep disorders, and psychosis.

Twenty-eight studies assessed chemotherapy-induced nausea and vomiting. All of these studies indicated a greater benefit from cannabinoids than from alternative antiemetic regimens and placebo; however, that finding did not reach statistical significance across all studies.

There was moderate evidence to suggest the use of *Cannabis* for neuropathic and nonneuropathic cancer-related pain. However, there is an increased short-term risk of adverse events with synthetic isolates dronabinol (when used for pain) and nabilone (when used for nausea and vomiting).

The primary conclusion of the meta-analysis is that further study is required because little evidence exists on the effects and the adverse events of plant-based *Cannabis*.

HIV infection. Data on *Cannabis* for the treatment of refractory neuropathy and appetite stimulation in HIV infection is mixed.[10,11] Smoked *Cannabis* for medically refractory neuropathy was examined in several trials:

- In a randomized crossover trial, researchers found statistically significant subjective improvement in neuropathic pain, with minimal intolerable adverse effects, in the 28 HIV-infected participants who completed the trial.[11]
- In another study, *Cannabis* ingested in various forms resulted in appetite stimulation in late-stage HIV infection but did not produce statistically significant weight gain.[10]

Pediatric epilepsy. Research on pediatric patients who have epilepsy characterized by refractory seizures has shown that the impact of *Cannabis* on their disease is promising. Specifically, CBD has shown tremendous potential impact: Patients experienced a statistically significant reduction in the number of seizures.[9] In 2018, the FDA approved the first plant-based derivative of *Cannabis*: an oral cannabidiol (marketed as Epidiolex [Greenwich Biosciences, Inc.]) for the treatment of intractable seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, rare and severe forms of epilepsy. Epidiolex is the first FDA-approved drug that contains a purified drug substance derived from marijuana.

CASE ▶

Mr. S's diagnosis of cancer is broadly included in the list of *Cannabis*-qualifying illnesses in all 34 states that certify patients for medical *Cannabis*. He qualifies both because (1) he is a cancer patient and (2) he has not found relief from chemotherapy-induced nausea and vomiting with several targeted therapies, including 5-hydroxytryptamine-receptor antagonists, steroids, and antipsychotics. Evidence supports CB_1 and CB_2 as potential targets for antiemetic treatment.

Given Mr. S's consequent anorexia, his frustration with taking an increasing number of medications, and possible adverse effects of additional therapy, *Cannabis* is a reasonable course of action to treat nausea and vomiting. He would be able to use oral tincture or vaporization of oil to further limit his pill burden—likely, with a THC:CBD ratio of 1:1 or similar.

Based on recent observational data from New York *Cannabis* dispensaries, cancer patients pursing *Cannabis* to treat chemotherapy-induced symptoms report that (1) either products with a high concentration of THC or products that contain THC and CBD in a 1:1 ratio are most effective and (2) products in 1:1 ratio of THC and CBD are most tolerable.

A legal system at odds over the status of medical *Cannabis*

The core legal issue underlying medical *Cannabis* is a contradiction between federal and state laws.

At the federal level. The federal government regulates the lawful production, possession, and distribution of controlled substances through the Controlled Substances Act (CSA).[12] The CSA is the basis for categorizing certain plants, drugs, and chemicals into 5 schedules, based on the substance's medical use, potential for abuse, and safety or dependence liability.[13] Under the CSA, marijuana (along with substances such as heroin and methamphetamine) is categorized as Schedule I[14]; ie, the substance

- has high potential for abuse,
- has no accepted therapeutic medical use in the United States, and
- lacks acceptable safety for use under medical supervision.

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Research suggests that the use of *Cannabis* for pediatric patients with refractory seizures is promising.

Physicians are protected from prosecution or revocation of their prescriptive authority based on their First Amendment right to discuss medical marijuana with patients.

Despite waxing and waning efforts to protect states from federal prosecution, *any use of a Schedule-1 substance violates federal law*.[15]

In June 2018, a bipartisan group of federal lawmakers introduced a bill designed to amend the CSA and guarantee the rights of states and territories to self-determine marijuana regulation. The bill established a so-called STATES (Strengthening the Tenth Amendment Through Entrusting States) Act that "amends the Controlled Substances Act (21 U.S.C. § 801 et seq.) so that—as states and tribes comply with a few basic protections—its provisions no longer apply to any person acting in compliance with state or tribal laws relating to the manufacture, production, possession, distribution, dispensation, administration, or delivery of marijuana."[15]

The bill was referred to the Senate and House Judiciary Committees but, ultimately, the STATES Act was blocked from debate in 2018.

On April 4, 2019, the Act was reintroduced in the House (H.R. 2093) and Senate (S. 1028) of the 116th Congress. Although there is bipartisan support for this bill, the timeline for moving it forward is unclear.[16,17]

At the state level. Thirty-four states have comprehensive public medical marijuana and *Cannabis* programs. The National Conference of State Legislatures[18] (www.ncsl.org) designates a program "comprehensive" if it

- includes protection from criminal penalties for using marijuana for a medical purpose,
- allows access to marijuana through home cultivation, dispensaries, or other system,
- permits a variety of strains, including those more potent than what is labeled "low-THC," and
- allows smoking or vaporization of marijuana products, plant-based material, or extract.

An additional 14 states allow for "low-THC, high-CBD" products for medical reasons, in limited situations, or as a legal defense. Regulation in these states varies widely, however: Some states allow industrialized hemp products only; others do not provide for any in-state production.[18]

Last, many states have some form of so-called "affirmative-defense" statutes that allow people charged with marijuana possession to mention use of marijuana for medical purposes as a possible defense.

Physician shield. Despite inconsistent and evolving state and federal laws, physicians are protected, based on the *Conant v Walters* decision, from prosecution or revocation of their prescriptive authority for the professional "recommendation" of the use of medical marijuana.[19] In 2002, the US Ninth Circuit Court of Appeals upheld the permanent injunction, based on a physician's First Amendment right to discuss medical marijuana with patients.

CASE ▶

Mr. S is amenable to trial of *Cannabis* to relieve nausea and anorexia. He asks you if he is allowed to use *Cannabis* at work, were he to return to an office-based desk job—even part-time—during treatment for cancer.

How would you answer Mr. S? Patients are legally protected from workplace penalties and dismissal for using and consuming *Cannabis* in states with a medical *Cannabis* law (including the state in which Mr. S resides). However, all employers have some variability in corporate policy, especially if a person works in a federally supported or regulated occupation. It's always helpful to advise patients who will be using medical *Cannabis* to be proactive and speak with a human resources or employee health department staff member before beginning a course of medical *Cannabis*. Additionally, *Cannabis* with any amount of THC has the ability to alter focus, concentration, and perceptions of time. Thus, if a patient using medical *Cannabis* with THC asks about driving to work, he should be given the same advice one would offer about driving after consuming alcohol or ingesting opioids.

Common concerns

Ignorance of legal status. Theoretically, the *Conant v Walters* decision protects physicians from investigation for recommending medical *Cannabis* even in states where it is illegal.

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Delayed onset of edible products and variation of THC concentration increase risk of overconsumption.

However, you should adhere closely to procedures set out by your state. The National Council of State Legislatures provides up-to-date information on each state's procedures and programs,[18] and the American Society of Addiction Medicine (www.asam.org) has established standards of professionalism for physicians who discuss medical *Cannabis* with patients (**TABLE**).[20]

Exposure to smoke. *Cannabis* smoke carries many of the same carcinogens found in tobacco smoke; furthermore, use of *Cannabis* and tobacco are highly correlated, confounding many population-based studies. The manner of inhalation of *Cannabis* can result in significantly higher levels of tar and carbon dioxide than with tobacco smoking. Because the effects of *Cannabis* last longer, however, people who smoke *Cannabis* may smoke it less often than tobacco smokers smoke tobacco.[21]

Large cross-sectional and longitudinal studies have not found a link between *Cannabis* smoking and long-term pulmonary consequences, such as chronic obstructive pulmonary disease and lung cancer.[22,23] The technology of *Cannabis* delivery systems has progressed far more rapidly than the clinical evidence for or against such technology.

"Vaping" is an informal term for inhalation of aerosolized *Cannabis* components and water vapor. Vaporizers do not heat *Cannabis* to the point of combustion; therefore, they provide less exposure to smoke-related toxicants while providing similar time of onset.

Neuropsychiatric adverse effects. Data regarding the relationship between *Cannabis* use and psychiatric disorders are incompletely understood, in conflict, and related to cannabinoid type. Consider Pennsylvania's addition of anxiety disorder as a "serious medical condition" covered under the Pennsylvania Medical Marijuana Act.[24] Although patients often report the use of medical *Cannabis* to treat anxiety,[25] panic attacks are often associated with *Cannabis* use.[26]

While there is a clear association between *Cannabis* use and psychotic disorder, a causal link has yet to be unequivocally established. However, the rate of psychiatric hospitalization is increased in bipolar disorder and schizophrenia patients who use *Cannabis* heavily.[27]

We recommend, therefore, that physicians screen patients for serious mental health concerns before recommending or certifying them to use medical *Cannabis.*

Overconsumption of edibles. *Cannabis* edibles (ie, food products infused with *Cannabis* extract) are distinct from inhaled *Cannabis* in regard to onset, duration, and potential for adverse effects. *Cannabis* edibles might be more popular than inhaled products among older medical *Cannabis* users.[28]

Edible *Cannabis* has a reported onset of 1 to 3 hours (compared to 5-10 minutes with inhaled *Cannabis*) and a duration of effect of 6 to 8 hours (compared with 2-4 hours for inhaled products).[29] These qualities might render *Cannabis* edibles preferable to inhaled formulations for controlling chronic symptoms and conditions. However, delayed onset of edible products and wide variation in the concentration of THC also increase the risk of overconsumption, which

TABLE

Discussing medical use of *Cannabis*? Consider these standards of professionalism[20]

The American Society of Addiction Medicine offers the following advice:
• Adhere to established professional tenets of proper patient care
- History-taking and good faith examination of the patient
- Development of a treatment plan with clinical objectives
- Provision of informed consent
- Consultation, as necessary, with other clinical colleagues
- Proper record-keeping that supports the clinical decision
• Have a *bona fide* relationship with the patient
• Ensure that the issuance of "recommendations" is not a disproportionately large aspect of the practice
• Have adequate training in identifying addiction and unhealthy substance use

can lead to overdose and self-limited *Cannabis*-induced psychosis. We recommend providing patient education about the effects of the physiologically active therapeutic compounds tetrahydrocannabinol and cannabidiol, to prevent overconsumption of high-THC products.[30]

CASE ▶

Mr. S returns to your office after a trial of *Cannabis* as vaporized oil and reports some relief of nausea and a mild increase in appetite, but no weight gain. He is concerned about overconsumption or overdose, and asks you what the risks of these problems are.

How should you counsel Mr. S? Explain that ingestion of *Cannabis* has a prolonged onset of action; vaporization has a more rapid onset of action; therefore, he could more easily self-regulate ingestion with the vehicle he has chosen. In states where edible *Cannabis* products are legal, education is necessary so that patients know how much of the edible to consume and how long they will wait to feel the full impact of the effects of THC.[30]

Cannabis use disorder in the context of medical marijuana

Cannabis use disorder (CUD) incorporates general diagnostic features of a substance use disorder, including behavioral, cognitive, and physiologic symptoms such as cravings, tolerance, and withdrawal, in the setting of persistent use despite significant substance-related problems.[31] Features of *Cannabis* withdrawal syndrome include irritability, anger or aggression, anxiety, depressed mood, restlessness, sleep difficulty, and decreased appetite or weight loss.[31] *Cannabis* use disorder can develop in people who use medical *Cannabis*; however, physiologic symptoms of tolerance and withdrawal can also develop in the setting of appropriate medical use and do not, in isolation, represent CUD.

A recent study considered nationwide cross-sectional survey data from the US National Survey of Drug Use and Health to examine the relationship between medical marijuana laws and CUD.[32] Study findings did not show an increase in the prevalence of CUD or marijuana use among adults in states with a legalized medical marijuana program. Importantly, when researchers looked at marijuana use among adolescents and young adults, they found no increase in measured outcomes (eg, active [ie, past-month] marijuana use, heavy [> 300 d/yr] use, and a diagnosis of CUD) after medical marijuana laws were passed.[32]

A paucity of pediatric data

The adolescent brain might be more vulnerable to the adverse long-term effects of *Cannabis*; there is potential significant harm associated with *Cannabis* in children and adolescence. However, accurate data concerning risk and benefit are limited.

The most recent policy statement of the American Academy of Pediatrics (AAP) reflects this paucity of data.[33] The AAP opposes the use of medical *Cannabis* outside regulation by the FDA, although the organization allows for consideration of compassionate use of medical *Cannabis* for children who have life-threatening or severely disabling conditions. The AAP does support (1) additional research into pharmaceutical cannabinoids and (2) changing *Cannabis* from Schedule I to Schedule II to facilitate this process. Since the publication of the policy statement, *Pediatrics*, the official journal of the AAP, has published a review of medical cannabinoids and found (1) strong evidence for benefit in chemotherapy-induced nausea and vomiting and (2) accumulating evidence of benefit in epilepsy.[34]

Recognized risk: Not supporting medical *Cannabis*

As with all medical decisions, the risks and benefits of certifying patients for medical *Cannabis* must be balanced against the risks and benefits of not doing so. The risks that accompany failure to certify a patient for medical marijuana fall into 3 categories:

Blocking access to a substance that has potential therapeutic benefit. More data regarding the potential benefits and risks of medical *Cannabis* will, undoubtedly, dispel some of the uncertainty regarding the decision to certify a patient for medical *Cannabis*.

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***Cannabis* smoke carries many of the same carcinogens found in tobacco smoke.**

When you recommend medical *Cannabis* and certify patients for its use, you do so with the certainty that the *Cannabis* safety index (ie, risk of overdose or serious adverse effects) is exceedingly low.[35]

Limiting patients to other medications that, potentially, carry a risk of more or greater harmful effects. An example is the decision to prescribe an opioid for chronic pain instead of certifying a patient for medical *Cannabis*. For certain other conditions, including chemotherapy-induced nausea and vomiting, FDA-approved pharmaceuticals might have more reported serious adverse events and interactions than medical *Cannabis*.[36]

Resigning patients to obtain *Cannabis* from an illegal source. This speaks to harm reduction and social justice, because obtaining *Cannabis* from an illegal source carries health and legal risks:

- Increased health risks result from lacing or cutting botanical or synthetic *Cannabis* products with potentially toxic substances. Cocaine, the rodenticide brodifacoum, methamphetamine, and phencyclidine are all known, or have been reported, to be added to botanical and synthetic *Cannabis*.[37]
- Legal repercussions of *Cannabis* possession are disproportionately racially based, with a significantly higher arrest rate among people of color, even in states where medical *Cannabis* has been legalized.[38] JFP

At press time, the CDC issued a statement on respiratory illnesses reported after use of e-cigarette products. To learn more, go to www.cdc.gov/media/releases/2019/s0830-statement-e-cigarette.html.

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