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Ethics and Science, Cannabinoids and Healthcare

The subject of cannabis use and regulation in the United States is evolving rapidly. The current regulatory environment surrounding cannabis is both contradictory and continually changing in response to broad-based popular pressure to end decades of marijuana prohibition. These pressures are bolstered by emerging scientific data that are refining and altering both the popular and scientific consensus regarding the potential risks and benefits of cannabis use. There is every reason to believe that the current high level of interest and use in the U.S. population will continue to increase as regulatory controls on marijuana ease in the future. Physicians should ensure that they are sufficiently informed to responsibly evaluate and discuss cannabis use in the context of patient care.

In modern medical practice, physicians commonly address cannabis use in detail as part of routine medical care. A medical history might include inquiries about marijuana use in drug abuse screenings, as part of a comprehensive social history or mental health visits. More extensive discussions typically have not played a large role in the daily practice of allopathic medicine. However, cannabis has gained much more mainstream attention in recent years. A number of states have passed laws permitting cannabis use, either for specific populations or for general recreational use by adults. With these shifts in legal status, and parallel shifts in the broader cultural presence of cannabis use, physicians should seek to increase their knowledge about cannabis and cannabinoids to counsel and manage patients appropriately.

Current Sociopolitical Context

The criminalization of marijuana and the associated rejection of its potential medicinal benefits by medical, legal, and mainstream culture is a relatively recent development that emerged over the course of the last century. This negative modern characterization of cannabis has been challenged by some scientists and other supporters of cannabis legalization in recent decades. The evolution of cannabis prohibition in the United States is complex. Some argue that it was driven as much by political and economic issues as by any concern for public health.[1-3] Strong anecdotal evidence of meaningful personal and medical benefits added to these sociopolitical concerns, motivating advocates who currently dispute the assertion that marijuana use is inherently dangerous or unhealthy.[4] The success of these advocates in changing public attitudes toward marijuana can be seen in the advancement of marijuana legalization efforts at the state level. California passed Proposition 215 in 1996, beginning a trend toward relaxing legal prohibitions against cannabis production and use. Over the course of several years, other states

EXECUTIVE SUMMARY

Perhaps no topic is more controversial than the use of marijuana in clinical practice. Within the United States, there are an estimated 55 million recent active users, defined as one to two uses within the previous year, and 35 million regular users, defined as one to two uses per month.

- Despite changes in many states' policies, federal policy has been slower to shift. The Centers for Disease Control and Prevention refers to marijuana as an illegal drug, and the Drug Enforcement Agency classifies marijuana as Schedule I along with heroin and lysergic acid diethylamide.
- Cannabis is one of humanity's oldest cultivated crops used as a source of fiber, food, oil, medicine, and intentional inebriation.
- The spectrum of effects includes euphoria, laughter, relaxation, increased appetite, deep thinking, difficulty in short-term memory, racing heart, agitation, anxiety, and nausea.
- The psychotropic effects likely are due to activation of CB1 receptors, whereas CB2 receptors in the periphery affect immune cells, thought to play a role in inflammation and immune response, such as in the treatment of multiple sclerosis.
- The wide range of clinical applications includes treatment of glaucoma, spasticity of multiple sclerosis, chronic cancer and noncancer pain, insomnia, anxiety, nausea, cachexia, seizures, fibromyalgia, and inflammatory bowel disease.
- The physician needs to exercise care in the approach to management in light of often conflicting state and federal law, as currently there are 22 states that do not legally authorize marijuana use.

have passed legislation allowing marijuana purchase, possession, and usage to some degree.

Despite these changes in state policy and a more normalized presence in mainstream culture, federal policies have been slower to shift. The Centers for Disease Control and Prevention (CDC) website currently refers to marijuana as an illegal drug and cites numerous resources promoting potentially negative or harmful effects.[5] The Drug Enforcement Agency (DEA) presently classifies marijuana as a Schedule I drug under the Controlled Substances Act. Schedule I drugs are considered primarily harmful and to lack legitimate beneficial application to outweigh the potential harm they may cause. Other Schedule I drugs include heroin and lysergic acid diethylamide. Other substances, like oxycodone and methamphetamine, are classified as Schedule II drugs. These agents have specifically approved medical indications, but are regulated stringently because of concerns about their potential to cause harm. Despite repeated attempts by advocates requesting reclassification of marijuana as a Schedule II drug, the DEA recently denied two petitions to reschedule cannabis.[6] In public statements regarding one such rejection in May 2017, DEA spokesmen referred to the Food and Drug Administration's (FDA) role in providing guidance to the DEA on drug policy and mentioned previous FDA guidance stating that cannabis does not have medical value.[7] However, this stance by the DEA may be outdated. The FDA currently acknowledges the interest in cannabinoids for potential medical benefits, but urges a cautious and reasoned approach to study and legislation rather than reacting to the tide of popular sentiment.[8]

The CDC also has loosened its stance on testing for cannabis use in opioid users. The most recent guidelines of Prescribing Opioids for Chronic Pain 2016 now recommend against the testing for substances such as cannabis for which there may be uncertainty about the effects that a positive test may have on patient management.[8] With this change, even the relatively conservative CDC may be beginning to acknowledge preliminary data showing cannabis' safety margin, efficacy for pain, and potential for de-escalating the use of opioids and other harmful drugs. Although this shift may presage further changes in federal policy toward cannabinoids in the years to come, the current dichotomy between legalization efforts at the state level and the more conservative approach of federal agencies toward easing the regulatory underpinnings of marijuana prohibition creates a difficult environment for physicians who answer to both state and federal authorities that regulate their practice of medicine.

Formal reclassification as a Schedule II drug at the federal level would resolve this difficulty by ceding a clear legal authority for physicians to determine whether cannabis use would be safe and effective for their patients. The legalization of cannabis at the various state levels does not necessarily reserve any legal authority for physicians to regulate and monitor cannabis and cannabinoid use. Some states have passed laws allowing for more broad adult use of cannabis that mirrors alcohol and tobacco regulation. By regulating cannabis and cannabinoid use as an exploited vice rather than medicinal therapy, state legislation may sidestep acknowledging, creating, or perpetuating a distinction between medicinal and recreational use of cannabinoids. In states that maintain a legislative distinction between "medicinal" and "recreational" cannabis use, laws that seek to bypass such distinctions not only may diminish the ability of physicians to monitor and advise patients regarding appropriate medicinal use of cannabinoids, but also may erode the rights of patients who use cannabis medicinally. The disparity between state and federal laws already is affecting the rights of state-registered medicinal cannabis users, who may be barred from lawful ownership of firearms, for example.[10]

The lack of clarity and consistency in the regulation of cannabinoids at the state and federal levels makes it especially imperative for physicians to educate themselves about the potential benefits and risks of cannabis use. In states in which medicinal use is permitted,

Figure 1. Leaves of Cannabis Species

Cannabis sativa

Cannabis indica

Cannabis ruderalis

Illustrations courtesy of Gabriel Sirius Black

physicians often must rely on sparse and inconsistent data regarding the safety and efficacy of cannabinoids for treating various health conditions. In states in which recreational use of cannabis is permitted, physicians may encounter patients who already have incorporated cannabinoids into their lifestyles. Whether they are doing so for specific medicinal purposes, patients may be using cannabis without any physician consultation regarding the potential beneficial or adverse effects of cannabinoids on their health.

To elicit and encourage constructive dialogue with patients about the potential health implications of cannabinoids and cannabis use, it is incumbent on physicians practicing in these environments to present an educated and informed perspective to patients who are considering or currently engaged in cannabis use. This article will review the pharmacology of cannabis and address the ethical determinants physicians must consider when counseling known or potential users. This knowledge will allow physicians to effectively engage their patients regarding how cannabinoids may affect their overall health.

Agricultural and Historical Background

Cannabis is one of humanity's oldest cultivated crops: a source of fiber, food, oil, medicine, and intentional inebriation since Neolithic times. Roman historian Pliny the Younger, in his pioneering encyclopedia on the natural world, mentions the use of cannabis as an intoxicant.[11] Although Western (European) culture emphasized hemp cultivation as a vital commodity for fibrous raw material used for manufacture of cloth and rope for many centuries, European naturalists began to rediscover and explore the medical potential of cannabis during the 19th century. In 1842, Dr. William O'Shaughnessy emphasized the efficacy of "Indian hemp," or psychoactive cannabis, as a painkiller, a muscle relaxant, and "an anticonvulsive remedy of the greatest value."[12,13]

Cannabis is an annual flowering plant that grows in tropical and temperate climates.[14] The taxonomy of cannabis is debated, but some have recommended three distinct species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*.[13] (*See Figure 1.*) A variety of *C. sativa*, commonly referred to as hemp, contains very low levels of psychoactive compound and is farmed for industrial uses such as manufacturing and biofuel.[15] *C. ruderalis* is a hardy species that originated in Russia. It is shorter than other species, can withstand harsher climates, and flowers with age as opposed to changes in light/dark ratios.[16] Despite having lower concentrations of psychoactive compounds, it may be crossbred with *C. sativa* or *C. indica* to promote the above-mentioned properties.[17]

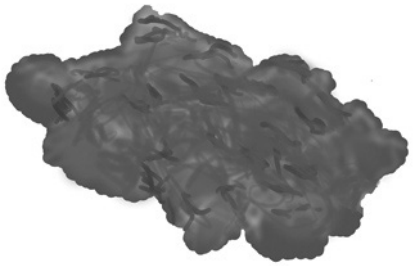
C. sativa and *C. indica* are the typical species cultivated for pharmacologic properties. The flowers or buds of unfertilized female plants may contain high concentrations of cannabinoids. (*See Figure 2.*) *C. sativa* and *C. indica* are different in size and shape as well as in their cannabinoid profile. *C. sativa* species typically have a higher ratio of psychoactive to non-psychoactive cannabinoids, but these ratios vary from plant to plant. Soil composition, temperature, carbon dioxide levels, and lighting, among other factors, can influence the cannabinoid profile of any plant.[18] The amount produced by each plant may vary greatly, as well. Cultivators can manipulate conditions to produce small plants that quickly yield small amounts up to a single ounce, or much larger plants yielding up to 25 ounces of usable cannabis.[19] The latter approach allows greater yields from the limited number of plants allowed to medical marijuana patients in some states.[20,21] Over time, and especially recently, humans have selected cannabis strains that contain higher concentrations of psychoactive cannabinoids.[22,23]

Producing these high concentrations of cannabinoids requires careful

Figure 2. Flowers of Cannabis Species

Flowering female cannabis plant

Cannabis flower or bud



Illustrations courtesy of Gabriel Sirius Black

and meticulous cultivation. In the wild, cannabis fertilization of female flowers by male plants results in the flower or bud-producing seeds rather than cannabinoids.[24] To achieve a high yield of buds rich in cannabinoids, growers not only must manipulate the conditions but also must isolate the female plants. Early generations of seeds produced during cultivation are more likely to have genetic weaknesses, such as being hermaphroditic. Harvesting a consistent and high-quality crop requires a great deal of time and care.[25]

Pharmacology of Cannabis

More than 100 cannabinoids have been isolated from the cannabis plant. These have been grouped into 11 distinct classes.[18,26] Although different in structure, all share a similar chemical precursor, geranyl pyrophosphate. The most well-understood classes are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). In the native form, cannabinoids usually are found as carboxylic acid derivatives (i.e., THC-A, CBD-A). Although both acid and neutral forms of cannabinoids may be bioactive, inducing psychoactive and inebriating effects requires decarboxylation into neutral, active forms, usually accomplished by smoking, vaping, baking, or otherwise processing the carboxylic acid forms of cannabinoids with heat (e.g., pyrolysis).[27]

The same biologic precursor of cannabinoids, geranyl pyrophosphate, is used by the cannabis plant to synthesize terpenoids. Terpenoids are aromatic essential oils, also found in many other plants, such as lemon (limonene), pine (alpha-pinene), lavender (linalool), and orange (nerolidol), that contribute to the characteristic aroma of cannabis.[11] Evidence suggests synergistic relationships between terpenoids and cannabinoids, as well as between the various cannabinoids themselves.[11] If this is true, preservation of the terpenoids through administration techniques that use lower and more carefully controlled temperatures for decarboxylation may result in a more complex cannabis experience.

Cannabinoids are produced in secretory glands called trichomes, which are highly concentrated along the flowering surface of the female plant. When mature, these trichomes and their contents contribute to the unique crystalline color, smell, and sticky texture of cannabis. From a functional standpoint, cannabinoids are classified as secondary metabolites. Although primary metabolites are directly responsible for the plants' developmental processes, such as cellular respiration and photosynthesis,[28] secondary metabolites are likely a result of adaptive mechanisms against predators and infection.[29,30] Indeed, cannabinoids have been found to be toxic to some larvae.[30]

Pharmacodynamics

The effects of cannabis depend on a number of factors, including dose, cannabinoid profile, and individual response. As with other pharmacologic agents, the effects of cannabis are subject to inter-individual variations. For example, hormone levels and pharmacogenetic variations of drug-metabolizing enzymes and receptors may play a role in altering individual responses.[31,32] The spectrum of cannabis effects have been well-characterized, and include euphoria; laughter; relaxation; increased appetite; deep thinking; changes in consciousness, vision, respiration, and perception of time; difficulty with short-term memory; racing heart; agitation; anxiety; and nausea. Prolonged or "hangover" effects, as well as withdrawal symptoms in heavy users, have been reported.[33,34] Effects are produced through binding of cannabinoids to endogenous cannabinoid and non-cannabinoid receptors located in the central nervous system (CNS) and throughout the body. (*See Table 1.*)

The psychotropic effects of cannabis primarily are a result of cannabinoids interacting with the cannabinoid 1 receptor (CB1). This is one of two endogenous receptors identified that make up the endocannabinoid system. Both CB1 and cannabinoid receptor 2 (CB2) are G-protein-coupled receptors that initiate a cascade of downstream secondary messengers when activated.[48] An endogenous ligand for these receptors, 2-arachindonylglyceral (2-AG), has been identified. At physiologic levels, it is hypothesized that 2-AG functions to attenuate or "calm" neurotransmission during times of accelerated excitation. An abbreviated description of the mechanism is as follows: During periods of neuroexcitation, 2-AG is released and binds to cannabinoid receptors on presynaptic nerve terminals in the CNS. Through secondary messenger cascade, calcium influx is inhibited and neurotransmitter release is decreased.[49,50]

Table 1. Cannabinoid and Non-cannabinoid Receptors[18,35-47]

Receptors/Pathways	Physiologic Effect	THC Effect	CBD Effect
CB1 (expressed in central nervous system)	Neurotransmission, psychotropic effects, analgesia,[18] vascular tone	Partial agonist	Allosteric modulator (influences activity of other ligands without activating receptor)[18]
CB2 (expressed in periphery and immune cells)	Immune regulation, inflammation	Partial agonist	Antagonist,[38] inverse agonist[38]
GPR55	Inflammation, analgesia, osteoclast formation and function[18]	Conflicting findings: agonist and inhibitor[18]	Antagonist[39]
Transient receptor potential cation channel subfamily V member 1 (TRPV1); Vanilloid Receptor 1 (VR1); "capsaicin receptor"	Inflammation and nociception[40]	N/a	Agonist[41,42]
5-HT_{1A}	Antiemetic, antinausea,[18] increased cerebral blood flow (neuroprotection for ischemia),[43] anxiolysis[44]	?	Partial agonist[45]
5-HT_{3A}	Pain and emesis[18]	?	Antagonist[18]
PPARγ	Multiple: vasorelaxation of aorta and superior mesenteric arteries (similar to rosiglitazone); inhibition of vasorelaxation in resistance mesenteric arteries; antitumor proliferation; adipogenesis; gastro-inflammatory disorders[18]	Agonist	N/a
Glycine (GlyR)	Anti-inflammatory, neuropathic pain, dopamine release from ventral tegmental area[18]	Potentiation[18]	Agonist?
Adenosine signaling	Immunosuppression,[46] anti-inflammatory, antiarrythmic[18]	N/a	Inhibition of adenosine uptake[47]

THC: delta-9-tetrahydrocannabinol; CBD: cannabidiol.

Thus, the psychotropic effect of cannabis is likely due to the pronounced activation of CB1 receptors by cannabinoids and subsequent alterations in neurotransmission. Importantly, it should be noted that other receptors also may play a role in the psychotropic effects of cannabis.[51] CB1 receptors also are located on vascular smooth muscle cells, where they may play a role in regulating vascular tone. Another endogenous ligand, anandamide, also has been discovered that acts as a partial agonist for the CB1 receptors. Authors speculate its physiologic role may be in other systems, outside the endocannabinoid system.[49,50]

In contrast to CB1 receptors, CB2 receptors occupy the periphery, more specifically the immune cells (e.g., macrophages, eosinophils, natural killer cells, dendritic cells). Here, the endocannabinoid system is thought to play a role in inflammation and immune response.[50] For this reason, cannabis is of particular interest for the treatment of immune system disorders such as multiple sclerosis.[52]

The specific effect on receptors varies between cannabinoids. THC is a partial agonist for CB1 and CB2, whereas its metabolite, 11-OH-THC, is equipotent[53,54] and potentially a more potent agonist for both receptors.[55-57] Both contribute to the psychoactive properties of cannabis. On the other hand, CBD is an antagonist for these receptors and, as such, it lacks psychoactive or high-inducing effects.[58] Researchers have been particularly interested in studying THC and CBD in combination and at different ratios because of the reported synergies between these two cannabinoids.[36] (*See Table 2.*)

Pharmacokinetics

The cannabinoid concentration that ultimately reaches systemic exposure depends on a number of factors, including product purity, dose, preparation, and

route of administration.[66] The changes to the molecular structure of cannabinoids through the drying process and the various modes of pyrolysis also pose a unique challenge when it comes to evaluating dosage and effects.

Cannabis can be delivered by nearly all routes of administration, including inhaled, oral, topical, rectal, and vaginal.[67-71] The inhaled and oral routes of administration are the most common, but other routes, such as topical, are gaining popularity.[72] Topical administration of CBD is used for local pain, via the peripheral CB1 pathway as well as the TRPV1 pathways on which capsaicin works, albeit without the adverse side effects of capsaicin. Topical formulations generally are not psychoactive.[73,74] The flower of the marijuana plant can be smoked or vaporized for inhalation. Oil extracts of the plant also can be smoked, vaporized, or ingested. Inhaled cannabis has an almost immediate onset of action and can produce psychoactive effects within minutes. Peak effects are achieved at about 15 minutes, and the duration of action is about four hours. (*See Table 3.*)

Vaporization (vaping) is a process of heating either the flower or concentrated extracts ("wax," "shatter," "butter," "oil," etc.) to much lower temperatures than smoking where cannabinoids become volatile and can be inhaled. This is becoming an increasingly common form of cannabis delivery.[72] Vaping may release less contaminants compared to smoking,[75] may be easier to titrate, may have higher purity (if concentrates are used), and also may preserve the plant's cannabinoids and terpenoids.[68] This said, it also may be easier to overdose with a vaporizing pen[76] and may increase the risk of unintended pediatric exposure.[77]

The systemic availability of oral cannabis is poor, achieving only about one-third of the systemic exposure as smoking.[78] Compared to the inhaled route, the onset of effects of oral therapy is delayed, occurring between 60 to 90 minutes, with peak effects at two to three hours and duration lasting up to six hours. (*See Table 3.*) Edible cannabis can be made with almost any food. Formulations that are sprayed or dissolve in the mouth via the oral mucosa also are available, and these may provide improved bioavailability and enhanced effects as a result of avoiding first-pass metabolism.[71]

Table 2. Human Evidence of THC and CBD Interplay

Findings	Dosage Form
When CBD and THC extracts were coadministered as sublingual drops, the rate of appearance of THC in serum was increased marginally, possibly suggesting a stimulation of THC absorption.	Sublingual[59]
The appearance of 11-OH–THC was reduced when CBD was coadministered with THC extracts.	Sublingual[59]
THC time to maximum concentration occurred later following the 1:1 mixture compared to high-THC, possibly as a result of CBD delaying THC absorption.	Sublingual[36]
CBD decreased psychotic symptoms, post-THC paranoia, and memory impairments compared to THC alone.	Oral CBD, IV THC[60]
CBD at doses 15 to 60 mg attenuated effects of 30 mg THC including tachycardia, disturbed time tasks, and strong psychological reactions.	Oral[61]
CBD changed THC symptoms in such a way that the subjects receiving the mixtures showed less anxiety and panic but reported more pleasurable effects.	Oral[61]
CBD delayed THC onset and prolonged effects.	Oral[62]
High of THC was significantly attenuated when CBD was present: 11 out of 15 subjects felt the effects of THC alone as greater than the combination.	Smoked[63]
CBD attenuated THC effects including tachycardia, impairment on stance stability on a wobble board, and ability to track on a pursuit meter.	Smoked[54]
CBD antagonized THC-induced anxiety, but extended other effects.	Oral[64]
High CBD cannabis was associated with significantly lower degrees of positive psychotic symptoms, but not negative symptoms or depression.	Smoked[65]

THC: delta-9-tetrahydrocannabinol; CBD: cannabidiol.

Drug Interactions

The potential for drug-to-drug interactions should be considered in patients using cannabis. Pharmacodynamic interactions to consider include additive effects with medications that cause CNS depression, cognitive dysfunction, and adverse cardiovascular events. In terms of pharmacokinetic interactions, cannabinoids undergo drug metabolism and transport and, thus, have potential for interaction. THC is a substrate for the CYP450 2C9[79-81] and 3A4[80,81] enzyme pathways, while CBD is metabolized by CYP2C19 and CYP3A4. CBD also inhibits CYP3A4 and CYP2D6. THC and CBD also may affect the P-glycoprotein transporter, but data are conflicting.[82] In chronic smokers, induction of CYP1A2 may occur.[83-86] There have been reports of tacrolimus toxicity and loss of risperidone efficacy secondary to CYP3A4 inhibition and P-glycoprotein induction, respectively.[82,87] Furthermore, clinical studies have shown higher THC area under the curve (AUC) and increased sedation in CYP2C9 poor metabolizers (*3/*3) compared to CYP2C9 normal metabolizers.[88] However, cannabis has

Table 3. Cannabis Onset and Duration of Effects by Route of Administration[78]

	Inhaled	Oral
Methods	11 subjects smoked cannabis cigarettes during 5 to 7 minutes, until the maximum desired "high;" between 11.6 to 15.6 mg THC smoked	11 subjects ate 20 mg THC in chocolate cookie
Time to maximum concentration (Tmax)	Within 3 minutes	60 to 90 minutes (two subjects occurred between 240 and 300 minutes)
Subject reported "high"	Begins within minutes, maximum effect achieved in 15 minutes, after which there is a moderate to rapid decline in effects over the next 4 hours	Maximum effect within 2 to 3 hours, remaining elevated until 4 hours post-dose, followed by a gradual decline of effects over the next 2 hours
Total duration of effects	4 hours	6 hours
Peak duration of effects	Minutes	2 hours
Systemic availability	N/a	About one-third of what is achieved with smoking
Other notes		Oral administration may result in increased conversion of THC to more potent psychoactive 11-OH-THC via more extensive hepatic metabolism

THC: delta-9-tetrahydrocannabinol.

also been studied with a number of other drugs and failed to show meaningful interactions: docetaxel[89] (significantly metabolized by CYP3A490), irinotecan[89] (significantly metabolized by CES290), nelfinavir[91] (significantly metabolized by CYP2C19 and CYP3A490), indinavir[91] (significantly metabolized by CYP3A490), and antiretroviral therapy.[92]

Clinical Implications

In addition to its use for euphoria, relaxation, and changes in perception, cannabis has a wide range of clinical applications.[33] It has seen use for the treatment of glaucoma, spasticity in multiple sclerosis, chronic cancer and noncancer pain, insomnia, anxiety, post-traumatic stress disorder, nausea, cachexia, seizures, fibromyalgia, and inflammatory bowel disease, to name a handful.[93] Many reviews have been conducted on the use of whole cannabis and isolated cannabinoids for the treatment of various diseases. (*See Table 4.*)

To date, only isolated cannabinoids have received FDA approval for use. Dronabinol, an oral form of synthetic THC, is approved as an appetite stimulant in AIDS-related anorexia and for nausea/vomiting in chemotherapy patients.[108] Nabilone, an oral synthetic analog of THC, is approved for nausea/vomiting in chemotherapy patients.[109] A third agent, Epidiolex® (CBD oral solution) has received orphan designation from the FDA for the treatment of Dravet syndrome, Lennox-Gastaut syndrome, tuberous sclerosis complex, and infantile spasms.[110] Results from a recently completed Phase III study showed that Epidiolex® 20 mg/kg added to background anticonvulsant therapy resulted in a significant reduction in monthly seizure frequency compared to placebo in treatment-resistant children.[111]

From a logistical standpoint, it makes sense to study cannabinoids in isolation; it is much easier to manage purity, control dose, predict interactions, and determine effect. In a recent meta-analysis of more than 79 randomized, controlled trials for various ailments, inhaled whole cannabis was used in only two studies, while all the other studies investigated isolated cannabinoids.[100] There are also deeply rooted political biases against the study and use of whole cannabis.[36,112]

Numerous authors have suggested that an ideal approach to studying cannabis is to study the effects of the entire flower, with particular opposition against isolating THC or developing THC analogues. In 2013, Borglet et al provided examples of six studies that showed statistically significant improvements in pain in whole smoked cannabis users.[66,68,113-117] All were able to do this with enrollment numbers of 56 or less. Data from these studies demonstrate a very large effect of cannabis on treating pain. Statistical power depends on both effect size and sample size. If the effect size of the intervention is large, it is possible to detect a similar effect in smaller sample numbers. However, a smaller effect size requires larger sample sizes, and huge sample sizes may detect small, and possibly trivial, differences.[118] Indeed, while only reported in one of the above-mentioned studies, Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial,[113] the Cohen's d (a calculation used to determine effect size) was determined to be 0.6. Effect sizes commonly are recognized as: 0.2, small effect; 0.5, medium effect; and 0.8, large effect.[119] Whether whole cannabis is superior to isolated cannabis would require head-to-head trials, but the effect demonstrated in these studies makes a strong case to continue investigating the whole cannabis

Table 4. Compilation of Review Articles for Various Clinical Conditions

Condition	Review Article
Anxiety	Turna J, Patterson B, Van Ameringen M. Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? *Depress Anxiety* 2017;34:1006-1017.[94]
Cancer	Davis MP. Cannabinoids for symptom management and cancer therapy: The evidence. *J Natl Compr Canc Netw* 2016;14:915-922.[95] Todaro B. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. *J Natl Compr Canc Netw* 2012;10:487-492.[96]
Dermatology	Mounessa JS, Siegel JA, Dunnick CA, Dellavalle RP. The role of cannabinoids in dermatology. *J Am Acad Dermatol* 2017;77:188-190.[97]
Epilepsy	Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. *N Engl J Med* 2015;373:1048-1058.[98] Rosenberg EC, Tsien RW, Whalley BJ, Devinsky O. Cannabinoids and epilepsy. *Neurotherapeutics* 2015;12:747-768.[99]
General Review	Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 2015;313:2456-2473.[100]
Glaucoma	Panahi Y, Manayi A, Nikan M, Vazirian M. The arguments for and against cannabinoids application in glaucomatous retinopathy. *Biomed Pharmacother* 2017;86:620-627.[101]
Inflammatory bowel	Hasenoehrl C, Storr M, Schicho R. Cannabinoids for treating inflammatory bowel diseases: Where are we and where do we go? *Expert Rev Gastroenterol Hepatol* 2017;11:329-337.[102]
Insomnia	Babson KA, Sottile J, Morabito D. Cannabis, cannabinoids, and sleep: A review of the literature. *Curr Psychiatry Rep* 2017;19:23.[103]
Multiple Sclerosis	Koppel BS, Brust JCM, Fife T, et al. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014;82:1556-1563.[104]
Pain and Headache	Kim PS, Fishman MA. Cannabis for pain and headaches: Primer. *Curr Pain Headache Rep* 2017;21:19.[105]
PTSD	Mizrachi Zer-Aviv T, Segev A, Akirav I. Cannabinoids and post-traumatic stress disorder: Clinical and preclinical evidence for treatment and prevention. *Behav Pharmacol* 2016;27:561-569.[106] Steenkamp MM, Blessing EM, Galatzer-Levy IR, et al. Marijuana and other cannabinoids as a treatment for posttraumatic stress disorder: A literature review. *Depress Anxiety* 2017;34:207-216.[107]

plant or at the very least THC/CBD combinations.

It is important to note that cannabis horticulture has invested more time and effort than the scientific and medical community to exploring the effects of cannabinoids in varying concentrations and combinations on cannabis and cannabinoid users. This is especially significant in light of the possible regulatory and synergistic effects of various cannabinoids in coadministration, including THC, CBD, and terpenoids that occur naturally within the cannabis plant. Sufficient preliminary data about the nature of these interactions is not available to begin isolating how these cannabinoids work together. Before isolating or synthesizing cannabinoids in combination to generate consistent data for rigorous study, medical science should consider leveraging the advantage that cannabis horticulture can offer. Studying the effects of cannabinoids in naturally occurring combinations may offer a better approach.

For primary care providers, one area in which cannabis has shown significant efficacy is for the management of chronic pain and opioid use. Pain management is becoming an especially complicated process, with mounting regulatory pressure to limit and reduce opioid prescribing because of the opioid use disorder (OUD) epidemic. With a 400% increase in overdose deaths since 2000 and an estimated 91 overdose deaths every day in the United States, OUD has more than 2.4 million sufferers.[120]

Two recent surveys help characterize cannabis use and experience for pain/opioid use. The first survey queried members of New England medical cannabis dispensaries (n = 1,513). Of the 215 participants who used opioids regularly, 76.7% were able to reduce their opioid use to "some degree" and 40.9% were able to reduce opioid pain medication by "a lot" with the help of cannabis. Participants also reported decreases in medications used for anxiety (n = 308; 71.8% "some degree"/38.6% "a lot"), migraine, sleep, alcohol, and antidepressants.[121] The second survey was conducted in California among medical cannabis patients belonging to a digital cannabis health and wellness platform, HelloMD (n = 2,897). In this online survey, pain was the most common

condition reported for using cannabis at 16% (63% when all pain-related conditions were considered). Thirty percent (841) of the participants reported using opioids for control of pain. Of those, 61% also used cannabis. In patients who used both opioids and cannabis, 97% "strongly agreed/agreed" that they were able to decrease the amount of opioids they consumed when also taking cannabis; 81% "strongly agreed/agreed" that taking cannabis alone was more effective at treating their condition than taking cannabis with opioids. Seventy-one percent "strongly agreed/agreed" that cannabis produces the same amount of pain relief as their opioid-based medications. Anxiety was the second most common condition for which participants in this survey reported cannabis use at 13%.[9]

These emerging findings likely are contributing to the changes in long-standing resistance by agencies like the CDC and Veterans Affairs (VA), which are beginning to change their policies with regard to cannabis use. The CDC no longer recommends the inclusion of cannabinoids in urine drug screening results in patients receiving opioids for chronic pain management.[122] Furthermore, the VA now encourages patients to discuss their cannabis use with their VA providers without fear of losing access to VA medical care.[123]

Another area of interest to primary care providers for which cannabis may have some promise is in the treatment of anxiety. Anxiety disorders, an umbrella term including panic, social and general anxiety disorders, agoraphobia, and other specific phobias, have a lifetime prevalence of 29%.[94,124] Up to 60% of patients who receive treatment continue to have residual and impairing symptoms.[125] Although data supporting the use of cannabis for management of pain and opioid use are impressive, data for anxiety are less robust. However, anecdotal claims of anxiolytic effects can be found. In another recent survey conducted among users of HelloMD, anxiety was the most prevalent reason cited by participants for cannabis use.[126] There have been no published prospective studies with smoked or vaporized cannabis targeting anxiety as an endpoint, but THC and CBD in isolated form both have been found to have anxiolytic properties in healthy populations.[94]

Safety

Limitations in cannabis literature make it difficult to understand and evaluate the real-world harms and problems caused by cannabis use and identify the risks of adverse effects. These limitations include significant heterogeneity in study designs and reporting systems, failure to categorize cannabis users according to the nature and frequency of use, underreporting of effect sizes, and inadequate control of confounders.[127] These disparities must be addressed to make evidence-based decisions about cannabis safety in various patient populations.

Short-term adverse effects of cannabis have been characterized, but data on long-term effects are less well-understood. Short-term adverse effects include dizziness, increases in heart rate and systolic blood pressure,[128] paranoia, panic attacks, somnolence, abdominal pain, nausea, vomiting, and hyperemesis.[33,93] Acute adverse effects tend to have a dose-dependent onset and can be minimized by using careful titration.[129]

Attention should be given to the risks some adverse effects present to particular patient groups.

Respiratory Risks

There are several factors to consider with regard to the respiratory risk of smoked and vaporized cannabis. First, there is potential for contamination of products with pathogens and/or pesticides. Both whole-plant cannabis and concentrates have the potential to be contaminated with bacteria, molds, and spores. The majority of pathogens are destroyed during pyrolysis or vaporization, but spores may remain and lead to infection, especially in susceptible patients.[27] Pesticide residues can be volatilized by pyrolysis, resulting in toxicities. Many pesticides also are carcinogenic. Cannabis can increase the risk of infection through direct physical damage of respiratory cilia when smoked as well as through immunosuppressive properties.[46] Clinicians also should be concerned about respiratory exacerbations, particularly in asthmatics and patients with chronic obstructive pulmonary disease. Acute irritation of inhaled substances in these patients may exacerbate respiratory conditions. This route of administration should be avoided in such patients if possible.

Lung cancer risk is another concern. The data are difficult to discern, as many of the studies investigating lung cancer included individuals who are also tobacco smokers. Furthermore, the quantity and frequency of cannabis smoking varies greatly in these studies. Nonetheless, smoking cannabis does produce carcinogenic byproducts that could be harmful.[130-133] The use of vaporizing pens may be a preferred mode of inhalation because of the decarboxylation of desired cannabinoids at lower temperatures, resulting in less physical damage to the airway and also potentially producing less carcinogens.

Cardiovascular Risks

Cannabis may affect vascular tone, increase heart rate, and alter heart rate variability.[66] Researchers have hypothesized that it may decrease myocardial oxygen delivery, increase myocardial oxygen demand, and decrease the time to develop angina during exercise.[134] Similar to rosiglitazone, cannabis may increase the risk of heart failure by acting through PPARγ pathway. However, teasing out the mechanisms is difficult, as many of the studies involving cardiovascular risk have included patients who are tobacco and poly-substance abusers.[128] Cardiovascular effects may be worsened if the patient is receiving other medications that increase heart rate (e.g., anticholinergics, alpha-agonists, theophylline, TCAs, naltrexone, amphetamine, etc.).[66] Vasoconstrictive effects may increase the risk of cerebrovascular accidents.[128]

Psychiatric Risks

Reports have suggested that cannabis use may precipitate and exacerbate schizophrenia and other symptoms of psychosis.[26] However, such studies do

not adequately resolve the question about whether it is correlated, confounding, or causative.[112] These exacerbations may be due to high concentrations of THC, and CBD may inhibit or attenuate some of these effects.[36]

The association between cannabis use and short-term panic attack and anxiety seems to be a transient effect, with no corresponding association to chronic anxiety disorders.[112] Impairment to executive functioning (attention, concentration, decision-making, risk-taking, inhibition and impulsivity, working memory, verbal fluency) appears to vary between occasional and chronic users; there may be some neuroadaptation with frequency of use.[135]

Hyperemesis Syndrome Risks

Hyperemesis syndrome is a rare but severe adverse event that may occur with chronic cannabis use.[45] It is characterized by severe nausea. Vomiting and dehydration may occur. The mainstay of therapy is supportive therapy with aggressive hydration. Frequent hot showers provide temporary relief of symptoms. It appears to be most prevalent in young adults with a long history of cannabis use. In most cases, individuals had used daily for 15 years, but in four cases individuals developed hyperemesis with a history of less than three years of chronic use.[45]

Pediatric Exposure Risks

Pediatric exposure to cannabis with resulting toxicity is uncommon,[136] but occurrences seem to be increasing[137] because of increases in cannabinoid potency and more teens using who become parents.[137] Legalization may make cannabis more appealing and easier for minors to ingest, especially if it is readily available in edible formulations such as candies, beverages, etc.

It is important to acknowledge these risks with users and discuss preventive strategies where appropriate. Although the identification of successful preventive strategies is currently an area of research interest,[138] discussion of cannabis use with at-risk populations certainly should be approached with care and caution. Patients with psychiatric, respiratory, or cardiovascular conditions, long-term chronic cannabis smokers, users combining cannabis with tobacco, and patients with small children should be counseled regarding the risks of cannabis use. Higher-risk patients who elect to use cannabis should be advised about administration alternatives and which methods of administration present a higher or lower risk for their particular situation. As with any treatment modality that introduces potential risk, close monitoring and follow-up is strongly recommended.

Contemporary Trends

Physicians should inform themselves about contemporary use trends in their communities to facilitate more effective discussion with patients. The epidemiology of cannabis use is challenging because of underreporting and geographical variation. Frequency and quantity of use also vary widely. Nevertheless, a significant proportion of the U.S. population (about 10%) are identified as regular cannabis users.

Within the United States, there are an estimated 55 million recent active users, defined as one to two uses within the previous year.[139] Furthermore, it's estimated that 35 million citizens are considered regular users, defined as using once or twice every month.[139] In the United States, it is thought that most individuals begin use during adolescence and young adulthood at a incidence rate of 6%.[112] Approximately 30% of children aged 15 to 16 years have tried cannabis. Incidence rates are predicted to increase as states continue to adopt laws that allow legal marijuana sales, possession, and use.[112] Common observation shows the movement of cannabis from a subcultural context into the general cultural mainstream.[140] This movement is especially marked in states in which direct retail sales of cannabis to adult consumers have been legalized, and it may well increase with the advent of direct-to-consumer advertising by cannabis retailers. The prevalence of medical cannabis use is not fully known, but it is estimated that one in eight cannabis users do so at the direction of their physicians.[112]

In states in which legalization has occurred, legislation typically dictates a strict chain of custody and meticulous tracking of the cannabis plant, from seed to harvested products.[141] Growers of cannabis specialize in obtaining seeds and/or clones and growing them to maturity via artificial growing conditions. Many different methods may be used to produce various strains and cannabinoid profiles from the cannabis plants. These efforts often require use of tremendous amounts of electricity to power the special lighting required to grow high-yielding cannabis. Some growers are adopting more sustainable, environmentally conscious methods of growing by incorporating lower wattage fluorescent lighting in an effort to reduce their carbon footprint.[142] Some growers also are focused on producing cannabis with organic methods, forgoing the use of traditional fertilizers and pesticides.[143]

Depending on the state, quality control testing requirements may vary.[144] The purpose of this testing is to screen for pathogens, pesticides, and heavy metals and to determine cannabinoid concentration (as well as terpenoid concentration in some states).[27] Physicians should be aware of a concern that state-mandated testing requirements may not go far enough to ensure quality product free of pathogens and other toxins.[145]

It also should be noted that in states in which recreational use has been legalized, suppliers are combining cannabis with other products for the relief of symptoms. Combinations include valerian root or melatonin for insomnia; caffeine, ginseng, or green tea for energy and concentration; St. John's wort for depression; and kava kava for anxiety. This pattern of product development shows signs that cannabis use may share some of the culture associated with nutritional supplements and over-the-counter medicaments.

Ethical Considerations

The rapid changes in the legislative and cultural environment with regard to cannabis and cannabinoids, as well as the lack of consensus on the efficacy, hazards, and concerns surrounding

cannabis use, create an environment of uncertainty and mistrust for many current and potential cannabis users. Physicians must develop a strong understanding and application of ethical principles when approaching discussions about cannabis and cannabinoid use with their patients. Biomedical ethics typically recognizes four fundamental principles that must be weighed against each other in the consideration of medical issues from an ethical standpoint. These principles are beneficence, respect for autonomy, non-maleficence, and justice.[146] A brief discussion of these principles in the context of cannabinoid use should provide ample reason for physicians to recognize the necessity for educating themselves and expanding their knowledge of cannabinoid use by their patients.

Beneficence — The ethical mandate for physicians to help their patients.

Although evidence on the potential efficacy of cannabinoids for treating specific conditions remains mixed, it is increasingly unethical to continue supporting the traditionally accepted position that there are no legitimate medical applications for cannabis. Studies are continuing to emerge showing compelling benefits in many common disease states, including pain, anxiety, seizure disorders, and multiple sclerosis.

Respect for Autonomy — The ethical right of every patient to direct his or her own health choices.

Failure to discuss a reasoned risk-benefit perspective of a potentially viable pharmacologic agent puts predetermined biases of physicians and agencies external to the physician-patient relationship (law enforcement, etc.) at odds with patient autonomy.

Non-maleficence — The ethical mandate for physicians to avoid harm to their patients, or to maximize benefit relative to harm where some degree of harm is unavoidable.

Other treatment modalities may cause harm and potentially could be avoided with use of cannabinoids. Opioids and benzodiazepines are prescribed commonly but are known to have substantial risks and adverse effects. Bias against cannabis users may affect the physician-patient relationship negatively and cause harm through undermining trust in the physician and his/her recommendations.[121] Failure to discuss cannabis openly might lead to legal and social harms and undesirable accidental or intentional pediatric exposure.

Justice — The ethical consideration of distribution of health resources in light of relative scarcity, fairness, and equality.

Stigmatization of cannabis users may cause harm to self-esteem and mental health and may affect the care users receive from medical providers and the healthcare system as a whole. Furthermore, restricting legal access to cannabinoids creates an artificial scarcity. Patients who seek treatment within prescribed legal boundaries are forced to make use of modalities with far more significant associated risks and whose benefits relative to cannabinoids could be questionable in light of emerging data.

In an ethical discussion of cannabis, it's important to highlight areas of bias that cannabis research has received over the years. In the 1990s, the World Health Organization (WHO) commissioned several experts (Robin Room, Wayne Hall, and Harold Kalant) to conduct an epidemiologic review comparing the adverse effects of cannabis to other drugs of abuse, namely alcohol, tobacco, and opioids. In their research, the authors keenly pointed out the challenges of comparing the adverse effects of cannabis to other substances because the population of users was much smaller. Nonetheless, they stated that the magnitude of these risks was more modest for cannabis than for alcohol (e.g., car crash risk) and tobacco (e.g., respiratory disease and cancers). They speculated that if cannabis received legalization, it was still unlikely to cause as much harm as alcohol because unlike alcohol, cannabis does not cause liver and other gastrointestinal disease and in overdose does not appear to be as neurotoxic as alcohol, nor does it result in as many motor vehicle collisions. Similarly, compared to tobacco use, since there are far fewer cannabis users who consume daily, cannabis use is less likely to affect respiratory disease as severely.[147] Not surprisingly, the commissioned work was met with resistance, and while the work eventually was published in full, albeit not by the WHO, it was later learned that chairs of the committee and members of the U.S. National Institute on Drug Abuse (NIDA) expressed concerns that the information could be used to advocate for cannabis legalization.[147]

Another example of how bias potentially has affected policy regarding cannabis and cannabinoids can be seen stemming from the pivotal work of Karniol and Carlini in the 1970s. The researchers began isolating the various cannabinoids to determine their independent effects. In one of their pivotal papers, the authors stated that CBD appears to enhance the pleasurable effects of THC. This was viewed negatively by regulatory agencies, and even was cited as evidence that CBD served no medicinal purpose. The fact that this work was based on observations of patients using whole cannabis extracts, rather than isolated cannabinoids, also may have led to the dismissal of whole plant extracts in favor of the pursuit of isolated cannabinoids in research targeting cannabis-derived therapeutic agents. This is unfortunate because of the evidence that suggests that cannabinoids (including terpenoids) may have synergistic effects affecting efficacy and tolerance for patients seeking therapeutic outcomes from cannabis and cannabinoid use.

Some authors have proposed that cannabis should be considered only when treatment with standard therapies has failed or when adjunct therapy is appropriate.[66] This approach may fail to recognize the plethora of data demonstrating significant benefit in specific patient populations. Allowing cannabis use as a therapeutic approach earlier in the course of disease, and not necessarily as a last-line therapy, may be a more ethical approach for some patients, especially where the risks might be considered low. For example, one probably would not consider cannabis as a

second- or third-line therapeutic agent for pain in a patient with known significant cardiovascular disease or schizophrenia. However, an otherwise healthy pain sufferer who desires to taper off of opioids might represent a suitable candidate for cannabis as a second- or third-line agent in the management of his or her pain.

Conclusion

Physicians should use care to approach cannabis management in accordance with federal and state laws as well as state medical board policies. These interests often conflict and also may be at odds with current trends in cannabis use in the general population as well as patterns of use within specific groups. Currently, there are 22 states in the United States that do not legally authorize marijuana use, either in narrowly prescribed circumstances (such as the various "medical marijuana" laws) or far more broadly (i.e., California, Washington, Oregon, or Colorado legislation allowing legal sale and possession of various forms of cannabis for any adult older than 21 years of age). Even within these two broad categories, these laws vary greatly from state to state. Important information to be considered may include limits to the amount of usable ounces or the number of plants an individual cannabis user may legally possess.[66] Possession of cannabis or cannabis products could result in misdemeanor or felony charges, depending on the state and the quantities involved. Furthermore, many businesses will continue to test employees for controlled substances, including marijuana. Although not yet as common as legislation allowing marijuana use, antidiscrimination laws for marijuana users are beginning to be put in place in some states (i.e., Washington, Arizona, Delaware, Illinois, Minnesota, New Hampshire).

Antidiscrimination laws may help to address the biases inherent to state laws regulating cannabis use as an exploited vice. Extensive evidence exists that exploited vices like alcohol and tobacco cause harm, and there is little evidence or recognition of any significant medical or social benefit. The equivalence implied by such legislation fails to reflect data that show far less evidence of significant harm from cannabis use and the increasing number of studies that suggest significant benefits from cannabis use in appropriate patient populations. Physicians, in their role as patient advocates within their communities, should speak out in favor of evidence-based and appropriate legislative and regulatory policies regarding cannabis use.

To facilitate better communication with regard to medicinal or recreational cannabis use, it is necessary for physicians to be knowledgeable and capable of informing patients on matters related to cannabis. Physician focus should be on established safety and efficacy data from credible trials, risk vs. benefit concepts, relevant pharmacologic data, and contemporary use trends. Physicians should elicit cannabis use in standard medical histories and consider the pharmacologic implications of cannabis alongside other medications as part of overall medication management. To accomplish this, cannabis use should be addressed in a manner that avoids bias, presumption, or implicit judgment.

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References

1. Timeline of marijuana policy in the U.S. and Netherlands. PBS NewsHour. Available at: http://www.pbs.org/newshour/updates/timeline-marijuana-policy-u-s-netherlands/. Accessed Dec. 1, 2017.
2. Opinion. How racism and bias criminalized marijuana. *Washington Post* Availabe at: https://www.washingtonpost.com/news/in-theory/wp/2016/04/28/how-racism-and-bias-criminalized-marijuana/. Accessed Dec. 1, 2017.
3. The Road to Prohibition: Why Did America Make Marijuana Illegal in the First Place? - Medical Marijuana, Inc. (OTC: MJNA). Med Marijuana Inc OTC MJNA. February 2016. Available at: http://www.medicalmarijuanainc.com/the-road-to-prohibition-why-did-america-make-marijuana-illegal-in-the-first-place/. Accessed Dec. 1, 2017.
4. Marijuana Timeline. Busted — America's War On Marijuana. FRONTLINE. PBS. Available at: http://www.pbs.org/wgbh/pages/frontline/shows/dope/etc/cron.html. Accessed Aug. 8, 2017.
5. Centers for Disease Control and Prevention. Marijuana and Public Health. Available at: https://www.cdc.gov/marijuana/index.htm. Accessed Aug. 8, 2017.
6. Mead A. The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law. *Epilepsy Behav EB* 2017;70(Pt B):288-291.
7. Leonard K. DEA chief: "Marijuana is not medicine." *Washington Examiner* Available at: http://www.washingtonexaminer.com/dea-chief-marijuana-is-not-medicine/article/2624211. Accessed Dec. 1, 2017.
8. Commissioner O of the. Public Health Focus - FDA and Marijuana. https://www.fda.gov/newsevents/publichealthfocus/ucm421163.htm.
9. Writer RD HelloMD Content. HelloMD and UC Berkeley Release Study on Cannabis Use as a Substitute for Opioid and Non-Opioid Based Pain Medication. https://www.hellomd.com/health-wellness/hellomd-and-uc-berkeley-release-study-on-cannabis-use-as-a-substitute-for-opioid-and-non-opioid-based-pain-medication.
10. Addady M. Court Rules That Medical Marijuana Card Holders Can't Buy Firearms. Fortune. http://fortune.com/2016/09/01/medical-marijuana-gun/. Accessed September 19, 2017.
11. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 2011;163:1344-1364.
12. Smoke Signals: A Social History of Marijuana. PopMatters. Available at: http://www.popmatters.com/feature/174749-smoke-signals-a-social-history-of-marijuana/. Accessed Dec. 1, 2017.
13. Hillig KW. Genetic evidence for speciation in Cannabis (Cannabaceae). *Genet Resour Crop Evol* 2005;52:161-180.
14. The Botany of Cannabis. *Mother Earth Living*. Available at: http://www.motherearthliving.com/Natural-Health/botany-of-cannabis-ze0z1011zdeb. Accessed Dec. 1, 2017.
15. Hemp. In: Wikipedia. ; 2017. Available at: https://en.wikipedia.org/w/index.php?title=Hemp&oldid=793711918. Accessed Aug. 8, 2017.
16. What Is *Cannabis ruderalis*? Leafly. Available at: https://www.leafly.com/news/cannabis-101/what-is-cannabis-ruderalis. Accessed Aug. 8, 2017.
17. Autoflowering cannabis. In: Wikipedia. 2017. Available at: https://en.wikipedia.org/w/index.php?title=Autoflowering_cannabis&oldid=794281707. Accessed Aug. 8, 2017.
18. Turner SE, et al. Molecular pharmacology of phytocannabinoids. *Prog Chem Org Nat Prod* 2017;103:61-101.
19. How Much Marijuana Can One Plant Produce? A Pound! I Love Growing

Marijuana. Available at: http://www.ilovegrowingmarijuana.com/marijuana-cannabis-yield-how-much/. Published January 21, 2014. Accessed Aug. 8, 2017.
20. Medical Marijuana?: Washington State Department of Health. Available at: http://www.doh.wa.gov/YouandYourFamily/Marijuana/MedicalMarijuana. Accessed Sept. 19, 2017.
21. Wyatt K, Press TA. Colorado medical marijuana community concerned with bill that sets much lower plant limit. *The Cannabist* Available at: http://www.thecannabist.co/2017/03/07/colorado-marijuana-plant-limits-home-grows/75068/. Accessed Dec. 1, 2017.
22. Dujourdy L, Besacier F. A study of cannabis potency in France over a 25 years period (1992-2016). *Forensic Sci Int* 2017;272:72-80.
23. Mehmedic Z, et al. Potency trends of Delta9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *J Forensic Sci* 2010;55:1209-1217.
24. Male vs Female Cannabis Plants. Grow Weed Easy. Available at: http://www.growweedeasy.com/marijuana-boy-girl. Accessed Aug. 8, 2017.
25. Short D. Cultivating Exceptional Cannabis: An Expert Breeder Shares His Secrets. Ed Rosenthal; 2004.
26. Sharma P, et al. Chemistry, metabolism, and toxicology of cannabis: clinical implications. *Iran J Psychiatry* 2012;7:149-156.
27. White Papers. Available at: http://cannabis-safetyinstitute.org/white-papers/. Accessed Aug. 13, 2017.
28. Plant Secondary Compounds. Available at: http://www2.nau.edu/~gaud/bio300w/secpd.htm. Accessed Aug. 8, 2017.
29. Sirikantaramas S, et al. Tetrahydrocannabinolic acid synthase, the enzyme controlling marijuana psychoactivity, is secreted into the storage cavity of the glandular trichomes. *Plant Cell Physiol* 2005;46:1578-1582.
30. Flores-Sanchez IJ, Verpoorte R. PKS activities and biosynthesis of cannabinoids and flavonoids in *Cannabis sativa* L. plants. *Plant Cell Physiol* 2008;49:1767-1782.
31. Lopez HH. Cannabinoid-hormone interactions in the regulation of motivational processes. *Horm Behav* 2010;58:100-110.
32. Hryhorowicz S, et al. Pharmacogenetics of cannabinoids. *Eur J Drug Metab Pharmacokinet* May 2017; doi:10.1007/s13318-017-0416-z.
33. Erowid Cannabis (Marijuana) Vault?: Effects. Available at: https://erowid.org/plants/cannabis/cannabis_effects.shtml. Accessed Aug. 8, 2017.
34. Bonnet U, Preuss UW. The cannabis withdrawal syndrome: current insights. *Subst Abuse Rehabil* 2017;8:9-37.
35. Zuardi AW. Cannabidiol: From an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr Sao Paulo Braz 1999* 2008;30:271-280.
36. Russo E, Guy GW. A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006;66:234-246.
37. Malfitano AM, et al. What we know and do not know about the cannabinoid receptor 2 (CB2). *Semin Immunol* 2014;26:369-379.
38. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol* 2008;153:199-215.
39. Ryberg E, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol* 2007;152:1092-1101.
40. Cui M, Honore P, Zhong C, et al. TRPV1 receptors in the CNS play a key role in broad-spectrum analgesia of TRPV1 antagonists. *J Neurosci Off J Soc Neurosci* 2006;26:9385-9393.
41. Bisogno T, et al. Molecular targets for cannabidiol and its synthetic analogues: Effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* 2001;134:845-852.
42. Ligresti A, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther* 2006;318:1375-1387.
43. Mishima K, et al. Cannabidiol prevents cerebral infarction via a serotonergic 5-hydroxytryptamine1A receptor-dependent mechanism. *Stroke* 2005;36:1077-1082.
44. Campos AC, Guimaraes FS. Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. *Psychopharmacology* (Berl) 2008;199:223-230.
45. Galli JA, et al. Cannabinoid hyperemesis syndrome. *Curr Drug Abuse Rev* 2011;4:241-249.
46. Rieder SA, et al. Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. *Immunobiology* 2010;215:598-605.
47. Carrier EJ, et al. Inhibition of an equilibrative nucleoside transporter by cannabidiol: A mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci U S A* 2006;103:7895-7900.
48. Strange PG. G-protein coupled receptors: conformations and states. *Biochem Pharmacol* 1999;58:1081-1088.
49. Sugiura T. Physiological roles of 2-arachidonoylglycerol, an endogenous cannabinoid receptor ligand. *BioFactors Oxf Engl* 2009;35:88-97.
50. Sugiura T, Waku K. Cannabinoid receptors and their endogenous ligands. *J Biochem* (Tokyo) 2002;132:7-12.
51. Vinals X, et al. Cognitive impairment induced by delta9-tetrahydrocannabinol occurs through heteromers between cannabinoid CB1 and serotonin 5-HT2A receptors. *PLoS Biol* 2015;13:e1002194.
52. Marijuana. National Multiple Sclerosis Society. Available at: http://www.nationalmssociety.org/Treating-MS/Complementary-Alternative-Medicines/Marijuana. Accessed Dec. 1, 2017.
53. Perez-Reyes M, et al. Intravenous injection in man of 9-tetrahydrocannabinol and 11-OH-9-tetrahydrocannabinol. *Science* 1972;177:633-635.
54. Lemberger L, et al. Clinical studies on the interaction of psychopharmacologic agents with marihuana. *Ann N Y Acad Sci* 1976;281:219-228.
55. Karler R, Turkanis SA. Different cannabinoids exhibit different pharmacological and toxicological properties. *NIDA Res Monogr* 1987;79:96-107.
56. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003;42:327-360.
57. Casajuana C, et al. Psychoactive constituents of cannabis and their clinical implications: a systematic review. *Adicciones* 2017;0:858.
58. Blessing EM, et al. Cannabidiol as a potential treatment for anxiety disorders. *Neurother J Am Soc Exp Neurother* 2015;12:825-836.
59. Guy GW, Flint ME. A single centre, placebo-controlled, four period, crossover, tolerability study assessing pharmacodynamic effects, pharmacokinetic characteristics and cognitive profiles of a single dose of three formulations of cannabis based medicine extracts (CBMEs) (GWPD9901), plus a two period tolerability study comparing pharmacodynamic effects and pharmacokinetic characteristics of a single dose of a cannabis based medicine extract given via two administration routes (GWPD9901 EXT). *J Cannabis Ther* 2004;3:35-77.
60. Englund A, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J Psychopharmacol Oxf Engl* 2013;27:19-27.
61. Karniol IG, Carlini EA. Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. *Psychopharmacologia* 1973;33:53-70.
62. Hollister LE, Gillespie H. Interactions in man of delta-9-tetrahydrocannabinol. II. Cannabinol and cannabidiol. *Clin Pharmacol Ther* 1975;18:80-83.
63. Dalton WS, et al. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. *Clin Pharmacol Ther* 1976;19:300-309.
64. Zuardi AW, et al. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology* (Berl) 1982;76:245-250.
65. Schubart CD, et al. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophr Res* 2011;130:216-221.
66. Borgelt LM, et al. The pharmacologic and clinical effects of medical cannabis. *Pharmacotherapy* 2013;33:195-209.
67. Aggarwal SK, et al. Dosing medical marijuana: Rational guidelines on trial in Washington state. *Medscape Gen Med* 2007;9:52-52.

68. Abrams DI, et al. Vaporization as a smokeless cannabis delivery system: A pilot study. *Clin Pharmacol Ther* 2007;82:572-578.
69. Aggarwal SK. Cannabinergic pain medicine: A concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain* 2013;29:162-171.
70. Mattes RD, et al. Cannabinoids and appetite stimulation. *Pharmacol Biochem Behav* 1994;49:187-195.
71. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers* 2007;4:1770-1804.
72. Schauer GL, et al. Toking, vaping, and eating for health or fun: Marijuana use patterns in adults, U.S., 2014. *Am J Prev Med* 2016;50:1-8.
73. Hess C, et al. Topical application of THC containing products is not able to cause positive cannabinoid finding in blood or urine. *Forensic Sci Int* 2017;272:68-71.
74. Karst M, Wippermann S. Cannabinoids against pain. Efficacy and strategies to reduce psychoactivity: A clinical perspective. *Expert Opin Investig Drugs* 2009;18:125-133.
75. Shahab L, et al. Nicotine, carcinogen, and toxin exposure in long-term E-cigarette and nicotine replacement therapy users: A cross-sectional study. *Ann Intern Med* 2017;166:390-400.
76. Rickner SS, et al. A little "dab" will do ya' in: A case report of neuro-and cardiotoxicity following use of cannabis concentrates. *Clin Toxicol Phila Pa* June 2017:1-3. doi:10.1080/15563650.2017.1334914.
77. Facts For Parents About E-Cigarettes & Electronic Nicotine Delivery Systems. HealthyChildren.org. Available at: http://www.healthychildren.org/English/health-issues/conditions/tobacco/Pages/Facts-For-Parents-About-E-Cigarettes-Electronic-Nicotine-Delivery-Systems.aspx. Accessed Dec. 1, 2017.
78. Ohlsson A, et al. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther 1980;28:409-416.
79. Bland TM, et al. CYP2C-catalyzed delta9-tetrahydrocannabinol metabolism: Kinetics, pharmacogenetics and interaction with phenytoin. *Biochem Pharmacol* 2005;70:1096-1103.
80. Mazur A, et al. Characterization of human hepatic and extrahepatic UDP-glucuronosyltransferase enzymes involved in the metabolism of classic cannabinoids. *Drug Metab Dispos Biol Fate Chem* 2009;37:1496-1504.
81. Watanabe K, et al. Cytochrome P450 enzymes involved in the metabolism of tetrahydrocannabinols and cannabinol by human hepatic microsomes. *Life Sci* 2007;80:1415-1419.
82. Brzozowska NI, et al. The differential binding of antipsychotic drugs to the ABC transporter. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* March 2017; doi:10.1038/npp.2017.50.
83. Jusko WJ. Influence of cigarette smoking on drug metabolism in man. *Drug Metab Rev* 1979;9:221-236.
84. Zullino DF, et al. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *Int Clin Psychopharmacol* 2002;17:141-143.
85. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: A systematic review. *Drug Metab Rev* 2014;46:86-95.
86. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. Accessed Dec. 1, 2017.
87. Hauser N, et al. High on cannabis and calcineurin inhibitors: A word of warning in an era of legalized marijuana. *Case Rep Transplant* 2016;2016:4028492.
88. Sachse-Seeboth C, et al. Interindividual variation in the pharmacokinetics of delta9-tetrahydrocannabinol as related to genetic polymorphisms in CYP2C9. *Clin Pharmacol Ther* 2009;85:273-276.
89. Engels FK, et al. Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. *Oncologist* 2007;12:291-300.
90. Allscripts YouScript Open App Challenge Phase 2.; 2013. Available at: http://www.youtube.com/watch?v=gINFr3rFhO4&feature=youtube_gdata_player. Accessed Sept. 10, 2014.
91. Kosel BW, et al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. *AIDS Lond Engl* 2002;16:543-550.
92. Lake S, et al. High-intensity cannabis use and HIV clinical outcomes among HIV-positive people who use illicit drugs in Vancouver, Canada. *Int J Drug Policy* March 2017. doi:10.1016/j.drugpo.2017.02.009.
93. Parmar JR, et al. Medical marijuana patient counseling points for health care professionals based on trends in the medical uses, efficacy, and adverse effects of cannabis-based pharmaceutical drugs. *Res Soc Adm Pharm RSAP* 2016;12:638-654.
94. Turna J, et al. Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? *Depress Anxiety* June 2017. doi:10.1002/da.22664.
95. Davis MP. Cannabinoids for symptom management and cancer therapy: The evidence. *J Natl Compr Cancer Netw JNCCN* 2016;14:915-922.
96. Todaro B. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. *J Natl Compr Cancer Netw JNCCN* 2012;10:487-492.
97. Mounessa JS, et al. The role of cannabinoids in dermatology. *J Am Acad Dermatol* 2017;77:188-190.
98. Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. *N Engl J Med* 2015;373:1048-1058.
99. Rosenberg EC, et al. Cannabinoids and epilepsy. *Neurother J Am Soc Exp Neurother* 2015;12:747-768.
100. Whiting PF, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 2015;313:2456-2473.
101. Panahi Y, et al. The arguments for and against cannabinoids application in glaucomatous retinopathy. *Biomed Pharmacother Biomedecine Pharmacother* 2017;86:620-627.
102. Hasenoehrl C, et al. Cannabinoids for treating inflammatory bowel diseases: Where are we and where do we go? *Expert Rev Gastroenterol Hepatol* 2017;11:329-337.
103. Babson KA, et al. Cannabis, cannabinoids, and sleep: A review of the literature. *Curr Psychiatry Rep* 2017;19:23.
104. Koppel BS, et al. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014;82:1556-1563.
105. Kim PS, Fishman MA. Cannabis for pain and headaches: Primer. *Curr Pain Headache Rep* 2017;21:19.
106. Mizrachi Zer-Aviv T, et al. Cannabinoids and post-traumatic stress disorder: Clinical and preclinical evidence for treatment and prevention. *Behav Pharmacol* 2016;27:561-569.
107. Steenkamp MM, et al. Marijuana and other cannabinoids as a treatment for post-traumatic stress disorder: A literature review. *Depress Anxiety* 2017;34:207-216.
108. MARINOL (dronabinol). Official Site from AbbVie Inc. Available at: http://www.marinol.com/. Accessed Sept. 19, 2017.
109. Cesamet (nabilone): Treatment Information for Patients and Caregivers. Availabe at: https://www.cesamet.com/patient-home.asp. Accessed Sept. 19, 2017.
110. GW Pharmaceuticals and its U.S. Subsidiary Greenwich Biosciences Announce Publication of Groundbreaking Study of Epidiolex® (cannabidiol) in *The New England Journal of Medicine*. GW Pharmaceuticals, plc. Available at: https://www.gwpharm.com/about-us/news/gw-pharmaceuticals-and-its-us-subsidiary-greenwich-biosciences-announce-publication. Accessed Aug. 8, 2017.
111. Devinsky O, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017;376:2011-2020.
112. Anthony JC, et al. Cannabis epidemiology: A selective review. *Curr Pharm Des* 2017;22:6340-6352.
113. Ellis RJ, et al. Smoked medicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. *Neuropsychopharmacol* 2009;34:672-680.
114. Fiz J, et al. Cannabis use in patients with fibromyalgia: Effect on symptoms relief

and health-related quality of life. *PloS One* 2011;6:e18440.
115. Ware MA, et al. Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ* 2010;182:E694-701.
116. Wilsey B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 2008;9:506-521.
117. Wallace M, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology* 2007;107:785-796.
118. Sullivan GM, Feinn R. Using effect size — or why the P value is not enough. *J Grad Med Educ* 2012;4:279-282.
119. Cohen's D: Definition, Examples, Formulas. http://www.statisticshowto.com/cohens-d/. Accessed Sept. 19, 2017.
120. Carter JA, et al. Cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine to treat opioid use disorder. *J Med Econ* 2017;20:893-901.
121. Piper BJ, et al. Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. *J Psychopharmacol Oxf Engl* 2017;31:569-575.
122. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep* 2016;65.
123. Administration UD of VA Veterans Health. VA and medical marijuana —— What veterans need to know — Public Health. Available at: https://www.publichealth.va.gov/medical-marijuana.asp. Accessed Dec. 1, 2017.
124. Kessler RC, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:593-602.
125. Bandelow B. The medical treatment of obsessive-compulsive disorder and anxiety. *CNS Spectr* 2008;13(9 Suppl 14):37-46.
126. HelloMD_Medical_Marijuana_Patient_Survey.pdf. Availble at: https://s3-us-west-2.amazonaws.com/hellomd-news/HelloMD_Medical_Marijuana_Patient_Survey.pdf. Accessed Aug. 8, 2017.
127. Temple EC, et al. The "grass ceiling": limitations in the literature hinder our understanding of cannabis use and its consequences. Addict Abingdon Engl 2011;106:238-244.
128. Thomas G, et al. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: What cardiologists need to know. *Am J Cardiol* 2014;113:187-190.
129. Zuurman L, et al. Biomarkers for the effects of cannabis and THC in healthy volunteers. *Br J Clin Pharmacol* 2009;67:5-21.
130. Coffman KL. The debate about marijuana usage in transplant candidates: Recent medical evidence on marijuana health effects. *Curr Opin Organ Transplant* 2008;13:189-195.
131. Turcotte C, et al Impact of cannabis, cannabinoids, and endocannabinoids in the lungs. *Front Pharmacol* 2016;7:317.
132. Eisenstein TK, Meissler JJ. Effects of cannabinoids on T-cell function and resistance to infection. *J Neuroimmune Pharmacol* 2015;10:204-216.
133. McKernan K, et al. Metagenomic analysis of medicinal Cannabis samples; pathogenic bacteria, toxigenic fungi, and beneficial microbes grow in culture-based yeast and mold tests. *F1000Research*. 2016;5:2471.
134. Gottschalk LA, et al. Effect of marijuana and placebo-marijuana smoking on psychological state and on psychophysiological cardiovascular functioning in anginal patients. *Biol Psychiatry* 1977;12:255-266.
135. Crean RD, et al. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med 2011;5:1-8.
136. Redant S, et al. [Infants poisoned with cannabis]. *Rev Med Brux* 2017;38:158-161.
137. Claudet I, et al. A 10-year review of cannabis exposure in children under 3-years of age: Do we need a more global approach? *Eur J Pediatr* 2017;176:553-556.
138. Wang GS, et al. Unintentional pediatric exposures to marijuana in Colorado, 2009-2015. *JAMA Pediatr* 2016;170:e160971.
139. Yahoo News/Marist Poll. Home of the Marist Poll. Available at: http://maristpoll.marist.edu/yahoo-newsmarist-poll/. Accessed Dec. 1, 2017.
140. Post TW. Marijuana has truly gone mainstream, survey finds. *Denver Post* April 2017. Available at: http://www.denverpost.com/2017/04/19/marijuana-mainstream-study-finds/. Accessed Dec. 1, 2017.
141. sop-001.pdf. Available at: http://www.oregon.gov/oha/ph/LaboratoryServices/EnvironmentalLaboratoryAccreditation/Documents/sop-001.pdf. Accessed Aug. 8, 2017.
142. EMISSIONS: Colo. struggles with marijuana's huge carbon footprint. Available at: https://www.eenews.net/stories/1060036287. Accessed Dec. 1, 2017.
143. Organic Marijuana: The Definitive Guide. Honest Marijuana. Available at: https://honestmarijuana.com/organic-marijuana-guide/. Accessed Sept. 19, 2017.
144. Leafly's State-by-State Guide to Cannabis Testing Regulations. Leafly. Available at: https://www.leafly.com/news/industry/leaflys-state-by-state-guide-to-cannabis-testing-regulations. Published March 4, 2016. Accessed Sept. 19, 2017.
145. News JK. Pot laced with pesticides forces states to act as EPA stays away. *Portland Press Herald* August 2017. Available at: http://www.pressherald.com/2017/08/05/pot-laced-with-pesticides-forces-states-to-act-as-epa-stays-away/. Accessed Dec. 1, 2017.
146. Principles of Biomedical Ethics - Paperback - Tom L. Beauchamp; James F. Childress - Oxford University Press. Available at: https://global.oup.com/ushe/product/principles-of-biomedical-ethics-9780199924585?cc=us&lang=en&. Accessed Sept. 19, 2017.
147. Hall W. Robin Room and cannabis policy: Dangerous comparisons. *Drug Alcohol Rev* 2014;33:612-616.

CME Questions

1. Which is the chemical precursor of both cannabinoids and terpenoids?
   a. Anandamide
   b. 2-Arachindonylglycerol (2 AG)
   c. Geranyl pyrophosphate
   d. Cannabidiol (CBD)
2. Which is *not* a plant terpene found in cannabis?
   a. Limonene
   b. Chlorophene
   c. Linalool
   d. Pinene
3. Reported effects of cannabinoids do *not* include which of the following?
   a. Distorted time perception, palpitations, relaxation
   b. Impairment of short term memory, appetite changes, laughter
   c. Aggression, cirrhosis, renal insufficiency
   d. Euphoria, anxiety, nausea
4. Known routes of delivery for cannabis include all *except*:
   a. rectal/vaginal.
   b. oral.
   c. inhaled.
   d. nasal.
   e. topical.
5. Cannabis has seen use for the treatment of all of the following *except*:
   a. symptoms of multiple sclerosis.
   b. anxiety/post-traumatic stress disorder.
   c. pain.
   d. hypertension.
   e. seizures.

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