

Marijuana as Medicine

A Report from the Committee on Medical Marijuana

South Dakota State Medical Association

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Executive Summary

At the time of this writing, the South Dakota State Medical Association (SDSMA) maintains the position that: 1) cannabis is a hazardous drug and as such is a public health concern; 2) sale and possession of marijuana – especially for recreational purposes – should not be legalized; 3) the use of non-Federal Drug Administration (FDA) approved cannabis and/or cannabinoid products for medicinal purposes carries serious risks by circumventing safety and quality testing for efficacy, therapeutic dosing, pharmacokinetics, drug interactions and toxicology. Moreover, use outside of physician oversight or a regulated clinical trial significantly hinders the physician-patient relationship.

The mission of the SDSMA is to promote the art and science of medicine, protect and improve the health of the public, and advocate for the well-being of patients and the best environment for physicians to advance quality health care. We promote:

- Medical knowledge and science and high standards of medical education;
- Medical ethics and competence in the art of healing;
- Laws and regulations that protect and enhance the physician/patient relationship and improve access and delivery of quality medical care; and
- An understanding between the public and the medical profession.

In accordance with our mission, the SDSMA shall remain opposed to a broad-based legalization of cannabis for medical use until adequate and well-controlled studies of marijuana and related cannabinoids have proven their application and efficacy in treatment of disease. Legitimate medications should be able to: 1) have reproducible composition of matter; 2) come in pure and stable forms; 3) be delivered into the body in fixed doses with known pharmacokinetic properties; 4) have dose-response efficacy; and 5) have been safety tested with documented side effects.

Within the last five years, the Drug Enforcement Agency (DEA) has more than doubled the number of individuals and institutions allowed to conduct research on marijuana, as well as increasing the amount of marijuana to study due to public demand – this includes over 90 researchers registered to conduct cannabidiol (CBD) research on humans.

Despite all studies currently taking place, the DEA recently elected to retain marijuana's Schedule I classification. With the exception of Lennox-Gastaut syndrome, and a few other rare, childhood-onset epilepsy disorders, clinical research has failed to identify a medicinal use for the drug. Clinical research

has, however, further proven that marijuana can be highly addictive and has well documented negative consequences with both short- and long-term use. Consequences include impaired short-term memory and decreased concentration, attention span, and problem solving. Alterations in motor control, coordination, judgement, reaction time and tracking ability have also been documented. Negative health effects on lung function associated with smoking cannabis have also been documented, and studies link cannabis use with higher rates of psychosis in patients with a predisposition to schizophrenia. Cannabis use has the potential to cause brain atrophy and permanently change the structure and physiology of the developing brain. Therefore, the use of cannabinoids in children and adolescents needs even more caution and medical oversight.

Non-FDA approved cannabinoids remain in Schedule I classification. Therefore, physicians are prohibited from legally prescribing these compounds. Physicians that do not respect this law risk significant liability. Other states that have legalized cannabinoid use for medicinal purposes must bypass the physician. Unstandardized prescribing, dispensing and documenting practices alongside the inability to rapidly and effectively detect use or overdose of cannabinoids, creates a significant barrier to optimal care of patients. Moreover, non-standardized cannabinoid use may create additional health risk including death due to toxicity, drug interaction or unrecognized adverse effects.

The FDA drug approval process for evaluating potential medicines has worked effectively in this country for more than 50 years – it is a thorough, deliberate, and exacting process grounded in science, and properly so, because the safety of our citizens relies on it. If the scientific understanding of marijuana changes – and it could – then we will reevaluate our position. Meanwhile, we remain tethered to science, and to a patient-physician relationship that assures quality medical care of patients and promotes the overall health of South Dakotans.

History of Cannabis in Medicine

The *Cannabis* plant has a history of medicinal use dating back thousands of years across many cultures.

Ancient China and Taiwan

Cannabis, called *má* (meaning "hemp; cannabis; numbness") or *dàmá* (with "big; great") in Chinese, was used in Taiwan for fiber starting about 10,000 years ago.¹ The botanist Li Hui-Lin wrote that in China, "The use of Cannabis in medicine was probably a very early development. Since ancient humans used hemp seed as food, it was quite natural for them to also discover the medicinal properties of the plant."²

The oldest Chinese pharmacopeia, the (ca. 100 AD) *Shennong Bencaojing* ("Shennong's Materia Medica Classic"), describes *dama* "cannabis."

The flowers when they burst (when the pollen is scattered) are called *mafen* or *mabo*. The best time for gathering is the seventh day of the seventh month. The seeds are gathered in the ninth month. The seeds which have entered the soil are injurious to man. It grows in [Taishan] (in [Shandong] ...). The flowers, the fruit (seed) and the leaves are officinal. The leaves and the fruit are said to be poisonous, but not the flowers and the kernels of the seeds.³

The early Chinese surgeon Hua Tuo (c. 140-208) is credited with being the first recorded person to use cannabis as an anesthetic. He reduced the plant to powder and mixed it with wine for administration prior to conducting surgery.⁴ The Chinese term for "anesthesia" (*mázui*) literally means "cannabis intoxication." Elizabeth Wayland Barber says the Chinese evidence "proves a knowledge of the narcotic properties of *Cannabis* at least from the 1st millennium B.C." when *ma* was already used in a secondary meaning of "numbness; senseless." "Such a strong drug, however, suggests that the Chinese pharmacists had now obtained from far to the southwest not THC-bearing *Cannabis sativa* but *Cannabis indica*, so strong it knocks you out cold."⁵

The Dutch sinologist Frank Dikötter's history of drugs in China says, "The medical uses were highlighted in a pharmacopeia of the Tang, which prescribed the root of the plant to remove a blood clot, while the juice from the leaves could be ingested to combat tapeworm. The seeds of cannabis, reduced to powder and mixed with rice wine, were recommended in various other materia medica against several ailments, ranging from constipation to hair loss." The Ming dynasty *Mingyi bielu* provided detailed instructions about the harvesting of the heads of the cannabis sativa plant (*mafen*, *mabo*), while the few authors who acknowledged hemp in various pharmacopoeias seemed to agree that the resinous female flowering heads were the source of dreams and revelations. After copious consumption, according to the ancient *Shennong bencaojing*, one could see demons and walk like a madman, even becoming 'in touch with the spirits' over time. Other medical writers warned that ghosts could be seen after ingesting a potion based on raw seeds blended with calamus and podophyllum (*guijiu*).⁶

Cannabis is one of the 50 "fundamental" herbs in traditional Chinese medicine⁷ and is prescribed to treat diverse indications. FP Smith writes in *Chinese Materia Medica: Vegetable Kingdom*, "Every part of the hemp plant is used in medicine ... The flowers are recommended in the 120 different forms of (*feng*) disease, in menstrual disorders, and in wounds. The achenia, which are considered to be poisonous,

stimulate the nervous system, and if used in excess, will produce hallucinations and staggering gait. They are prescribed in nervous disorders, especially those marked by local anaesthesia.”

The seeds are considered to be tonic, demulcent, alternative/restorative, laxative, emmenagogue, diuretic, anthelmintic, and corrective, and are prescribed internally in fluxes, post-partum difficulties, aconite poisoning, vermilion poisoning, constipation, and obstinate vomiting. Externally they are used for eruptions, ulcers, favus, wounds, and falling of the hair. The oil is used for falling hair, sulfur poisoning, and dryness of the throat. The leaves are considered to be poisonous, and the freshly expressed juice is used as an anthelmintic, in scorpion stings, to stop the hair from falling out and to prevent it from turning gray. The stalk, or its bark, is considered to be diuretic, and the juice of the root is thought to have a beneficial action in retained placenta and post-partum hemorrhage. An infusion of hemp is used as a demulcent drink for quenching thirst and relieving fluxes.⁸

Ancient Netherlands

In 2007, a late Neolithic grave attributed to the Beaker culture (found near Hattemerbroek (nl), Gelderland; dated 2459-2203 BCE) was found containing an unusually large concentration of pollen. After five years of careful investigation these pollen were concluded to be mostly cannabis along with a smaller amount of meadowsweet. Due to the fever-reducing properties of meadowsweet, the archeologists speculated that the person in the grave had likely been very ill, in which case the cannabis would have served as painkiller.⁹

Ancient Egypt

The Ebers Papyrus (ca. 1550 BC) from Ancient Egypt describes medical cannabis.¹⁰ Other ancient Egyptian papyri that mention medical cannabis are the Ramesseum III Papyrus (1700 BC), the Berlin Papyrus (1300 BC) and the Chester Beatty Medical Papyrus VI (1300 BC).¹¹ The ancient Egyptians even used hemp (cannabis) in suppositories for relieving the pain of hemorrhoids.¹² Around 2000 BCE, the ancient Egyptians used cannabis to treat sore eyes.¹³ The egyptologist Lise Manniche notes the reference to "plant medical cannabis" in several Egyptian texts, one of which dates back to the 18th century BCE.¹⁴

Ancient India

Cannabis was a major component in religious practices in ancient India as well as in medicinal practices. For many centuries, most parts of life in ancient India incorporated cannabis of some form.¹⁵ Surviving texts from ancient India confirm that cannabis' psychoactive properties were recognized, and doctors used it for treating a variety of illnesses and ailments. These included insomnia, headaches, a whole host of

gastrointestinal disorders, and pain: cannabis was frequently used to relieve the pain of childbirth.¹⁶ One Indian philosopher expressed his views on the nature and uses of bhang (a form of cannabis), which combined religious thought with medical practices. "A guardian lives in the bhang leaf... To see in a dream the leaves, plant, or water of bhang is lucky... A longing for bhang foretells happiness. It cures dysentery and sunstroke, clears phlegm, quickens digestion, sharpens appetite, makes the tongue of the lisper plain, freshens the intellect and gives alertness to the body and gaiety to the mind. Such are the useful and needful ends for which in His goodness the Almighty made bhang."¹⁶

Ancient Greece

The Ancient Greeks used cannabis to dress wounds and sores on their horses.¹⁷ In humans, dried leaves of cannabis were used to treat nose bleeds, and cannabis seeds were used to expel tapeworms.¹⁷ The most frequently described use of cannabis in humans was to steep green seeds of cannabis in either water or wine, later taking the seeds out and using the warm extract to treat inflammation and pain resulting from obstruction of the ear.¹⁷

In the 5th century BC Herodotus, a Greek historian, described how the Scythians of the Middle East used cannabis in steam baths. These baths drove the people to a frenzied state.¹⁷

Medieval Islamic World

In the medieval Islamic world, Arabic physicians made use of the diuretic, antiemetic, antiepileptic, anti-inflammatory, analgesic and antipyretic properties of *Cannabis sativa*, and used it extensively as medication from the 8th to 18th centuries.¹⁸

Modern History

In the mid-19th century, medical interest in the use of cannabis began to grow in the West.²⁰ In the 19th century cannabis was one of the secret ingredients in several so called patent medicines. There were at least 2,000 cannabis medicines prior to 1937, produced by over 280 manufacturers.²¹ The advent of the syringe and injectable medicines contributed to an eventual decline in the popularity of cannabis for therapeutic uses, as did the invention of new drugs such as aspirin.²⁰

An Irish physician, William Brooke O'Shaughnessy, is credited with introducing the therapeutic use of cannabis to Western medicine. He was assistant surgeon and professor of chemistry at the Medical College of Calcutta, and conducted a cannabis experiment in the 1830s, first testing his preparations on animals, then administering them to patients to help treat muscle spasms, stomach cramps or general

pain.²² Modern medical and scientific inquiry began with doctors like O'Shaughnessy and Moreau de Tours, who used it to treat melancholia and migraines, and as a sleeping aid, analgesic and anticonvulsant. At the local level authorities introduced various laws that required the mixtures that contained cannabis, that was not sold on prescription, must be marked with warning labels under the so-called poison laws.²³

In 1905 Samuel Hopkins Adams published an exposé entitled "The Great American Fraud" in *Collier's Weekly* about the patent medicines that led to the passage of the first Pure Food and Drug Act in 1906.²⁴ This statute did not ban the alcohol, narcotics, and stimulants in the medicines; rather, it required medicinal products to be labeled as such and curbed some of the more misleading, overstated, or fraudulent claims that previously appeared on labels.

At the turn of the 20th century the Scandinavian maltose- and cannabis-based drink *Maltos-cannabis* was widely available in Denmark and Norway.^{19,25} Promoted as "an excellent lunch drink, especially for children and young people", the product had won a prize at the Exposition Internationale d'Anvers in 1894.¹⁹ A Swedish encyclopedia from 1912 claim that European hemp, the raw material for Maltos-Sugar, almost lacked the narcotic effect that is typical for Indian hemp and that products from Indian hemp was abandon by modern science for medical use. Maltos-Cannabis was promoted with text about its content of maltose sugar.²⁶

Later in the century, researchers investigating methods of detecting cannabis intoxication discovered that smoking the drug reduced intraocular pressure.²⁷ In 1955 the antibacterial effects were described at the Palacký University of Olomouc. Since 1971 Lumír Ondřej Hanuš was growing cannabis for his scientific research on two large fields in authority of the University. The marijuana extracts were then used at the University hospital as a cure for aphthae and haze.²⁸ In 1973 physician Tod H. Mikuriya reignited the debate concerning cannabis as medicine when he published "Marijuana Medical Papers." High intraocular pressure causes blindness in glaucoma patients, so he hypothesized that using the drug could prevent blindness in patients. Many Vietnam War veterans also found that the drug prevented muscle spasms caused by spinal injuries suffered in battle.²⁹

In 1964, Dr. Albert Lockhart and Manley West began studying the health effects of traditional cannabis use in Jamaican communities. They discovered that Rastafarians had unusually low glaucoma rates and local fishermen were washing their eyes with cannabis extract in the belief that it would improve their sight. Lockhart and West developed, and in 1987 gained permission to market, the pharmaceutical

Canasol: one of the first cannabis extracts. They continued to work with cannabis, developing more pharmaceuticals and eventually receiving the Jamaican Order of Merit for their work.³⁰

Later, in the 1970s, a synthetic version of THC was produced and approved for use in the United States as the drug Marinol. It was delivered as a capsule, to be swallowed. Patients complained that the violent nausea associated with chemotherapy made swallowing capsules difficult. Further, along with ingested cannabis, capsules are harder to dose-titrate accurately than smoked cannabis because their onset of action is so much slower. Smoking has remained the route of choice for many patients because its onset of action provides almost immediate relief from symptoms and because that fast onset greatly simplifies titration. For these reasons, and because of the difficulties arising from the way cannabinoids are metabolized after being ingested, oral dosing is probably the least satisfactory route for cannabis administration.³¹ Relatedly, some studies have indicated that at least some of the beneficial effects that cannabis can provide may derive from synergy among the multiplicity of cannabinoids and other chemicals present in the dried plant material.³²

Medical Cannabis in the United States

Defining Medical Cannabis

Medical cannabis, or *medical marijuana*, can refer to the use of cannabis and its cannabinoids to treat disease or improve symptoms; however, there is no single agreed upon or standardized definition – especially when it comes to a standardized means of production, dosage or method of delivery.

Other common terms when speaking of medical cannabis or marijuana include:

Cannabinoid – A class of chemicals that include the active "ingredients" in marijuana. There are currently three classes of cannabinoids:

1. Phytocannabinoids occur in plants, such as marijuana
2. Endocannabinoids occur naturally in the brain
3. Synthetic cannabinoids are created in laboratories and are not known to exist naturally

The most discussed cannabinoids in the medical marijuana debate are cannabitol (CBN), (CBD) and delta-9-tetrahydrocannabinol (delta 9-THC).

- **Cannabidiol** – One of several cannabinoids in *Cannabis Sativa*. These compounds have some properties of THC, but cause less psychoactive effects – the “high.”

- **THC** – an abbreviation for delta-9-tetrahydrocannabinol, THC is the main component responsible for marijuana’s mind-altering effect. It also may help treat signs and symptoms such as nausea and vomiting that are associated with a number of medical conditions.

Cannabis contains at least 60 different cannabinoid chemicals but that does not mean there are 60 different cannabinoid effects or interactions. Most of the cannabinoids are closely related and many of which only differ by a single chemical moiety and might be the midpoints along biochemical pathways – that is, degradation products, precursors, or byproducts.^{33,34}

The Legality of Prescribing Medical Cannabis

In 1996, the state of California passed Proposition 215, making the Golden State the first in the country to allow for the medical use of marijuana. Since then, 29 more states, the District of Columbia and Guam have enacted similar laws. Of note, for the purpose of this white paper, a “comprehensive” public medical marijuana program is defined as having met the following criteria:

1. Protection from criminal penalties for using marijuana for a medical purpose;
2. Access to marijuana through home cultivation, dispensaries or some other system that is likely to be implemented;
3. Allows for a variety of strains, including those more than “low THC;” and
4. Allows either smoking or vaporization of some kind of marijuana products, plant material or extract.

Since 1996, many states and the District of Columbia have passed laws allowing smoked marijuana to be used for a variety of medical conditions. Although the United States Department of Justice (USDOJ) has limited its enforcement of federal law outlawing the use and possession of marijuana to certain circumstances it deems to be “priorities,” the fact remains that the use, possession, and distribution of marijuana continue to be criminal offenses under federal law. It is also illegal under federal law for a practitioner to prescribe marijuana to a patient. State laws legalizing the use of marijuana for medical or other purposes do not act to change the criteria or process for Food and Drug Administration approval of medications as being safe and effective.

In South Dakota, marijuana is a Schedule I drug and classified as a controlled substance. The possession, use, or distribution of marijuana is illegal in South Dakota, regardless of the intended or proposed use.

Accordingly, in addition to the federal prohibitions, it is and remains illegal under South Dakota law for a practitioner to dispense marijuana or any derivative for medical or any other purposes. Because marijuana is classified as a Schedule I drug and is illegal in South Dakota, a practitioner giving a prescription for marijuana – even to a patient living in a state where it is legal for medical or other purposes – could be subject to disciplinary proceedings before the South Dakota Board of Medical and Osteopathic Examiners (SDBMOE) for committing an act of unprofessional conduct.

In states in which marijuana has been legalized for medical use, patients are often placed on “registries” or to obtain a “certification” from their physician that the use of marijuana is medically necessary or may be appropriate based on the condition/medical ailment in which the patient suffers. Because the use of these registries or certification processes appear, in effect, to be prescriptions, SDSMA recommends that the practitioner not sign off on any such registration or certification. However, the practitioner, using sound medical judgment, may continue to provide diagnoses of conditions that might make the patient eligible for registration or certification in a state where the use of marijuana for medical purposes is legal.

Understanding Drug Schedules

Drugs, substances, and certain chemicals used to make drugs are classified into five 5 distinct categories or schedules depending upon the drug’s acceptable medical use and the drug’s abuse or dependency potential. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs are considered the most dangerous class of drugs with a high potential for abuse and potentially severe psychological and/or physical dependence. As the drug schedule changes - Schedule II, Schedule III, etc., so does the abuse potential. Schedule V drugs represent the least potential for abuse. A listing of drugs and their schedule are located at Controlled Substance Act (CSA) Scheduling or CSA Scheduling by Alphabetical Order. This list describes the basic or parent chemical and does not necessarily describe the salts, isomers and salts of isomers, esters, ethers and derivatives which may also be classified as controlled substances. The list is intended as a general references and is not a comprehensive listings of all controlled substances.

Please note that a substance need not be listed as a controlled substance to be treated as a Schedule I substance for criminal prosecution. A controlled substance analogue is a substance which is intended for human consumption and is structurally or pharmacologically substantially similar to or is represented as being similar to a Schedule I or Schedule II substance and is not an approved medication in the United States. (See 21 U.S.C. §802(32)(A) for the definition of a controlled substance analogue and 21 U.S.C. §813 for the schedule.)

Schedule I

Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Schedule I drugs are the most dangerous drugs of all the drug schedules with potentially severe psychological or physical dependence. Some examples of Schedule I drugs are: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote.

Schedule II

Schedule II drugs, substances, or chemicals are defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous. Some examples of Schedule II drugs are: combination products with less than 15 milligrams of hydrocodone per dosage unit (Vicodin), cocaine, methamphetamine, methadone, hydromorphone (Dilaudid), meperidine (Demerol), oxycodone (OxyContin), fentanyl, Dexedrine, Adderall, and Ritalin

Schedule III

Schedule III drugs, substances, or chemicals are defined as drugs with a moderate to low potential for physical and psychological dependence. Schedule III drugs abuse potential is less than Schedule I and Schedule II drugs but more than Schedule IV. Some examples of Schedule III drugs are: products containing less than 90 milligrams of codeine per dosage unit (Tylenol with codeine), ketamine, anabolic steroids, testosterone

Schedule IV

Schedule IV drugs, substances, or chemicals are defined as drugs with a low potential for abuse and low risk of dependence. Some examples of Schedule IV drugs are: Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien, Tramadol

Schedule V

Schedule V drugs, substances, or chemicals are defined as drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes. Some examples of Schedule V drugs are: cough preparations with less than 200 milligrams of codeine or per 100 milliliters (Robitussin AC), Lomotil, Motofen, Lyrica, Parepectolin

At the federal level, marijuana remains classified as a Schedule I substance under the Controlled Substances Act, where Schedule I substances are considered to have a high potential for dependency and no accepted medical use – thus, making distribution of marijuana a federal offense. In October 2009, the Obama Administration sent a memo to federal prosecutors encouraging them not to prosecute people who distribute marijuana for medical purposes in accordance with state law. And in late August 2013, the USDOJ announced an update to their marijuana enforcement policy. The statement reads that while marijuana remains illegal at the federal level, the USDOJ expects states like Colorado and Washington to create “strong, state-based enforcement efforts...and will defer the right to challenge their legalization laws at this time.” The USDOJ also reserves the right to challenge the states at any time they feel it’s necessary.

FDA Drug Requirements

The FDA requires that a drug:

- Is a pure compound;
- Its chemistry, manufacturing, and composition of matter are tightly controlled so that each batch is identical;
- Its production methods are validated;
- Its shelf life is known and can be dated to protect patients from a degraded chemical;
- Its microbiology is known (batches of chemicals contaminated with bacteria are rejected);
- Its pharmacology and toxicology in animals is known;
- Its rate of entry, bioavailability, toxicology are known;
- Its dose response, efficacy, and safety are known;
- Its side effect profile is documented; and
- After approval, requires case reports and safety updates to be submitted to the FDA for ongoing evaluation.

The FDA ruling on marijuana as medicine has not changed. Marijuana is classified as a Schedule I of the Controlled Substances Act, the most restrictive schedule. The DEA, which administers the Controlled Substances Act, continues to support the Schedule I classification of marijuana, and the FDA has concurred, based on marijuana’s meeting of the following criteria:

1. Marijuana has a high potential for abuse and currently has no accepted medical use in treatment in the U.S.;
2. Marijuana lacks accepted safety for use under medical supervision; and

3. There is sound evidence that smoked marijuana is harmful.

A past evaluation by Health & Human Service agencies (FDA, SAMSHA and NIDA) concluded that no sound scientific studies supported medical use of marijuana for treatment in the United States.

Furthermore, no animal or human data supported the safety or efficacy of marijuana for general medical use.

Cannabis Chemistry

Known chemistry of *Marijuana sativa*. The principal cannabinoids in the marijuana plant include THC, CBD, and CBN. THC is the primary psychoactive compound, with CBD, a minimally psychoactive compound, ranking second. THC is found at higher concentrations than CBD, unless the ratio is deliberately altered by genetic selection. The known chemical composition of *Marijuana sativa* is constantly changing. New non-cannabinoid and cannabinoid constituents in the plant are discovered frequently. From 2005 to present, the number of cannabinoids identified in the whole plant increased from 70 to 104, and other known compounds in the plant increased from approximately 400 to approximately 650.^{35,36,37} THC levels are also shifting, as breeding of different strains are yielding plants and resins with dramatic increases in THC content over the past decade, from approximately 3 percent to 12-16 percent or higher.^{38,29,40,41} In some marijuana preparations, THC levels have risen to radically higher levels, by concentrating processes that yield levels approaching 80 percent THC.^{42,43} Special strains have also been developed to raise the ratio of THC to CBD, so as to minimize putative THC antagonism by CBD.⁴⁴ In an unregulated environment, other factors such as soil quality, bacterial and fungal contamination, the use of herbicides, pesticides, insecticides, water, light, soil availability or quality, temperature, bacterial or viral contamination, animal waste, insects, toxic chemicals, active compounds, heavy metals, bear on marijuana quality.⁴⁵ Preclinical research has shown that a number of non-psychoactive phytocannabinoids elicit pharmacological responses of therapeutic interest. For example, CBD has putative therapeutic applications for treating psychosis, affective and seizure disorders, inflammation, and neurodegenerative diseases. CBD has a good safety profile in humans. Other plant cannabinoids, such as delta-9-tetrahydrocannabivarin, may also be prove therapeutic for epilepsy or obesity. Other plant cannabinoids, such as delta-9-tetrahydrocannabivarin, may also be prove therapeutic for epilepsy or obesity.^{46,47,48}

Dose and dose delivery via different routes (smoking, vaporizers, edibles). Marijuana is consumed by various routes, with the most common route smoking,⁴⁹ followed by vaporization, and then by the oral route. Marijuana products may be taken by ingesting edibles, liquids, via sublingual or rectal administration, via transdermal delivery, eye drops, creams and aerosols. Inhalation by smoking or vaporization releases maximal levels of THC into blood within minutes, peaking at 15 to 30 minutes, and decreasing within two to three hours. Even with a fixed dose of THC in a marijuana cigarette, THC pharmacokinetics and effects vary as a function of the weight of a marijuana cigarette, THC potency in the cigarette, its preparation, the concentration of other cannabinoids, the rate of inhalation, depth and duration of puffs, volume inhaled, extent of breath-holding, and dose titration.^{49,50} An extensive comparison of smoke (mainstream and sidestream) generated by igniting marijuana and tobacco cigarettes, showed markedly qualitative similarities in specific compounds (e.g., ammonia, carbon monoxide, among others), and also significant quantitative differences.⁵¹ The presence of known carcinogens and other chemicals in mainstream smoke of marijuana cigarettes and implicated in respiratory diseases, is an important consideration when evaluating the safety and risks associated with marijuana smoking.⁵² Lower temperature vaporization of marijuana has been postulated as safer than smoking, as it may deliver fewer high molecular weight components than smoked marijuana.⁵³ Vaporization reduces the characteristic odor of marijuana smoke, enabling diminished awareness by others. Combined with alcohol, vaporized marijuana yields higher maximum concentrations of blood THC (than without alcohol) possibly explaining why performance is more impaired if marijuana is combined with alcohol.^{54,55} Hashish oil, a solvent-extracted liquid is consumed by smoking or inhalation, vaporization or as a food additive.⁵⁶ Users report more addictive behaviors and withdrawal symptoms with the high THC levels in this preparation.

Oral ingestion from edibles is a slow, absorption process and varies with the ingested matrix, as bioavailability is low (10 to 20 percent). Nevertheless, this route does not result in a loss of pharmacological activity, because the major first-pass metabolite, 11-OH-THC, is also psychoactive. Oral ingestion delays the psychoactive effects to 30 to 90 minutes, with peaks at two to three hours and effects lasting for longer periods of time (four to 12 hours), depending on THC levels. Smoking multiple marijuana cigarettes or chronic long term use leads to higher maximal concentrations, longer duration in blood, and longer biological half-life, compared with smoking a single cigarette or infrequent smoking. Chronic frequent marijuana smokers exhibit extended detection windows for plasma cannabinoids, reflecting a large cannabinoid body burden. Lipophilicity of THC accounts for its accumulation after chronic repeated use.^{57,58,59,60,61} Metabolic elimination of THC is much slower after years of heavy marijuana use and is detectable in blood for 30 days or longer.^{62,63,64}

Cannabinoid Biology, Signaling in Brain and Body

From an evolutionary perspective the cannabinoid signaling system is ancient, and found in invertebrates and advanced vertebrate organisms.^{65,66} The endocannabinoid system has four main components: (1) G protein-coupled cannabinoid CB1 and CB2 receptors, (2) endogenous endocannabinoids that target these receptors, and possibly other receptors, (3) enzymes that catalyze endocannabinoid biosynthesis and metabolism, and (4) mechanisms involved in cell accumulation of specific endocannabinoids.

Cannabinoid receptors: distribution, regulation, function. The CB1 receptor is expressed in the brain and peripheral tissues. In both locales, it has multiple functions.⁶⁷ In the brain, it is the most abundant of the G-protein coupled receptors, and mediates most, if not all the psychoactive effects of THC in marijuana. Its brain distribution is strikingly consistent with the pharmacology of marijuana: CB1 receptors are enriched in the cerebellum (cognition, coordination), hippocampus (learning and memory), cortex (cognitive function, executive function and control, integration of sensory input), basal ganglia (motor control, planning) ventral striatum (prediction and feeling of reward), amygdala (anxiety, emotion, fear), hypothalamus (appetite, hormone levels, sexual behavior), brain stem and spinal cord (vomiting, pain).^{63,64,68,69,70} CB2 receptors are predominant in the periphery, on immune cells, hematopoietic systems and other locales. There is evidence of CB2 receptor expression in brain.^{71,72,73} In the brain, CB2 receptors also modulate the release of chemical signals primarily engaged in immune system functions (cytokines, immune cell migration). CB2 receptors are of considerable interest because THC activation of CB2 does not produce psychoactive effects, as does THC on the CB1 receptor. Accordingly, it is a promising target for therapeutics that may circumvent the adverse effects promulgated by drugs (marijuana or THC) that engender psychoactive effects via CB1 receptors.

Endocannabinoids and signaling. Endocannabinoids play a fundamental role in regulating pleasure, memory, thinking, concentration, body movement, awareness of time, appetite, pain, and sensory processing (taste, touch, smell, hearing, and sight). Endocannabinoids acting at CB1 receptors (and possibly CB2 receptors) modulate and “fine-tune” signaling in most brain regions, to enable the brain to adapt to signals generated by multiple sources.

Function of the endocannabinoid system in the brain. Understanding the multiple functions of endocannabinoid signaling in the brain offers insight into the pharmacological effects of marijuana and

other exogenous cannabinoids, their therapeutic potential and undesirable adverse effects. Brain development, neurogenesis, psychiatric disorders: Endocannabinoid signaling is crucial for brain development, and guides neural stem cell survival and proliferation, cell fate decisions and the motility and differentiation of ensuing neuronal and glial cells.⁷⁴ Developmental endocannabinoid signaling, from fetus to young adult, may be susceptible to marijuana use during pregnancy and adolescence, possibly affecting brain structure and function. Endocannabinoids and marijuana-altered endocannabinoid signaling may contribute to neuropsychiatric diseases of developmental origins and in which modifications to signaling have been observed: autism, schizophrenia, bipolar disorder and depression. The central role of the cannabinoid system in promoting adult neurogenesis in the hippocampus and the lateral ventricles provides insight into the processes underlying post-developmental neurogenesis in the mammalian brain. Both THC⁷⁵ and CBD⁷⁶ inhibit neurogenesis in adolescent or adult rodent brain, a process of potential relevance to a wide range of marijuana-induced adverse events. Cannabinoids and CB1, CB2 receptors display neuroprotective effects in the brain by preventing or decreasing the severity of damage resulting from mechanical, blood flow, or other forms of injury. Genetic ablation of the CB1 receptor exacerbates ischemic stroke,⁷⁷ with CB2 agonists providing anti-inflammatory protection and CB1 activation promoting hypothermia. The use of marijuana for this purpose is compromised by psychoactive effects and the development of tolerance to its neuroprotective effects. The endocannabinoid system contributes to olfactory, auditory and pain sensations. A review of these other functions is beyond the scope of this summary but readers are referred to an excellent overview.⁷⁸ There is extensive anatomical overlap of the opioid and cannabinoid receptor systems, and it appears probable that functional interactions between them occur in the production of analgesia. A number of nuclei in the medulla are involved in the regulation of appetite and nausea. These nuclei coordinate sensory input from the brainstem, vagal complex, vestibular organs, and peripheral organs. Endocannabinoids and CB1 agonists inhibit vagal fibers to promote eating and CB1 antagonists to decrease or inhibit food intake.⁷⁹ Endogenous and exogenous cannabinoids, including marijuana and THC affect sleep patterns and promote sleep. The endocannabinoid system has mood elevating, anti-depressant and anxiolytic effects. The anxiolytic response to marijuana is biphasic, implying that marijuana dosing is a critical factor in minimizing risk of anxiety, depression and maximizing benefit.^{80,81,82} Yet, marijuana at high doses, possibly by down-regulating CB1 receptors, increases the risk for depression or anxiety. The endogenous cannabinoid system inhibits seizure susceptibility. Marijuana has antiseizure activity. However, if the dose of THC is high or marijuana is consumed by susceptible individuals, THC may promote seizures. CBD has therapeutic potential as antiepileptic drug without the psychoactive effects, or potential for pro-seizure activity of whole plant marijuana.^{83,84} The endocannabinoid system plays a complex role in regulating motor pathways, which conceivably are relevant to symptomatic relief, or to addressing the

underlying pathology in a wide range of neurological diseases characterized by motor impairment.⁸⁵ CB1 receptors are abundant in brain regions that regulate motor function and coordination, including the basal ganglia, cerebellum. CB1 receptors are down-regulated in several neurological conditions.⁸⁶ Endocannabinoids apparently facilitate various forms of learning and memory processes in a number of brain regions. The endogenous cannabinoid system is also implicated in extinguishing learning of aversive situations.^{87,88,89} THC and marijuana decrease working memory, apparently by actions in the hippocampus, a brain region critical for learning and memory. The memory decrements induced by THC or marijuana resemble hippocampal lesions. These impairments may result from suppression of glutamate release in the hippocampus, which is responsible for the establishment of synaptic plasticity.

Function of the endocannabinoid system in peripheral tissues. Endocannabinoid signaling systems are found nearly ubiquitously in the peripheral tissues, with their distribution possibly accounting for the myriad of effects and potential medical applications of cannabinoids. This summary is based on a recent review.⁹⁰ Differences in CB1 and CB2 receptor function in the body is a focus of this segment, because THC in the marijuana plant activates both CB1 and CB2 receptors and could have detrimental effects in tissues in which CB1 receptor activity may contribute to pathophysiological states. CB1 and CB2 receptors are highly expressed on enteric nerves and on enteroendocrine cells (CB2) throughout the intestinal mucosa, on immune cells (CB1 and CB2), and enterocytes (CB1 and CB2). Virtually all gut functions are regulated by endocannabinoids, critical for CNS control of its metabolic and homeostatic functions. CB1, CB2, endocannabinoids and their enzymes are present in cardiovascular tissues and may contribute to the development of common cardiovascular disorders. An acute action of marijuana is mild tachycardia, with increases in cardiac output and increased myocardial oxygen requirement. Case reports of cardiovascular side effects of THC/marijuana have been reported and it is essential to proceed cautiously with marijuana and other cannabinoids in susceptible individuals. Cannabinoid receptor expression is normally low in liver, with CB1 and CB2 receptors acting in opposite directions: CB2 receptors mediate several biological functions in various types of liver cells, and CB1 blockade contributes to beneficial metabolic effects. CB1 expression increases in pathological states, promoting fibrogenesis, steatosis, and the cardiovascular complications of liver disease. In contrast, CB2 is protective, reducing these indices of liver dysfunction. Endocannabinoids modulate the functional activities of immune cells, largely through CB2 receptors, providing novel targets for therapeutic manipulation. Endocannabinoid signaling (largely through CB2 receptors) contributes to regulating energy metabolism in muscle and the formation of new muscle fibers. Endocannabinoid signaling, primarily mediated by the CB2 receptor regulates all critical stages of pregnancy and affects pregnancy events. Signaling is also involved in the preservation of normal sperm function, and thus male fertility.

Cannabis Toxicity in Humans

The primary risks of using marijuana have been discovered by investigating users of marijuana for recreational purposes. Few studies have reported on long term consequences of marijuana if used for medical purposes, although there may be few differences in response in the two cohorts as the therapeutic and psychoactive doses overlap extensively. Marijuana engenders acute pharmacological effects, longer term health risks for the brain, body and behavior, and public safety concerns. These effects are summarized in a recent report by the World Health Organization.⁹¹ Topics include acute and persistent effects of marijuana on cognitive function, on recently abstinent marijuana users, on persistent effects one month after last use.^{92,93,94,95,96,97} Other effects, especially relevant to adolescents, include the association of marijuana with psychosis and schizophrenia. Marijuana utilization also effects their developing brain and increases their potential/risk for using other drugs.^{98,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141}

Marijuana impairs driving ability and confers a higher risk for motor vehicle accidents, and workplace disruptions.^{142,143,144,145} Marijuana use is associated with an increased risk for cognitive decline, psychosocial impairment, vehicle crashes, emergency department visits, psychiatric symptoms, poor quality of life, educational and employment achievement, use of other drugs, adverse health effects, and fetal developments.^{146,147,148}

Cannabis (Marijuana) Use Disorder

Marijuana is the most widely used illicit substance in the world.¹⁴⁹ There is strong scientific support for concluding that marijuana has high potential for abuse, is actually abused and is addictive, particularly in youth with other consequences (e.g. psychosis) related to age on onset, marijuana potency and frequency of use.^{150,151,152,153,154,155,156,157}

Marijuana as a Medicine for Treatment

Overview of safety, efficacy standards. Several countries (Canada, Netherlands, Israel) and 24 of 50 states in the U.S. have approved the use of marijuana for medicinal purposes, with or without undergoing

a systematic medicines approval process. In this review of the current status of marijuana as a medicine, a simple question is addressed: are clinical trials that report marijuana-induced therapeutic benefit sufficient to establish “currently accepted medical use?” Globally, the efficacy, safety and quality of the medical products on the market in countries has benefited enormously from a robust scientific and evidence based process. This should continue to be the central organizing principle in evaluating and approving substances for use as medicine. If effective and safe medical applications emerge for phytocannabinoids, synthetic cannabinoids or metabolic modulators, the scientific process is not a barrier to their approval.

Marijuana chemistry and route of administration. The two main cannabinoids in marijuana, THC and CBD are instructive. A safe therapeutic window for marijuana has not been established, and clinical trials have used THC from 1 to 23 percent (a 23-fold dose range). If it is ineffective at low doses, how high can THC levels be driven before susceptible users experience intense and severe psychological or neurological symptoms such as anxiety, psychosis and seizures?^{158,159} As stated above, marijuana also contains CBD, and this cannabinoid can oppose the adverse effects of THC.¹⁶⁰ Research indicates that CBD reduces anxiety, and may function as an anti-psychotic and anti-convulsant.^{161,162} Unfortunately, the majority of strains of marijuana that are being grown today have much higher levels of THC than CBD – thus, reducing the likelihood of any reduction in anxiety and increasing the likelihood of adverse mental health consequences among users. The therapeutic potential of CBD, the non-psychoactive constituent of the marijuana plant, is currently under investigation in 20 ongoing or planned clinical trials. These include treatment of psychosis, inflammatory bowel disease, seizure disorders, addiction, and as an immunosuppressant.¹⁶³

Entourage effect.¹⁶⁴ A widely held and user-reported *belief* is that the benefit of whole plant marijuana provides more relief than isolated cannabinoids, the “entourage effect.” This is not a trivial issue, as it is a motivating force for whole plant medicinal marijuana in lieu of isolated compounds. Conceivably, at least four explanations may contribute to these self-reports: (1) as noted above, CBD may ease THC-induced anxiety or psychosis; (2) pharmacokinetics may account for these perceived differences. Side-by-side comparisons with the two preparations can clarify this claim. Yet, a clinical trial comparing the effects of smoked marijuana with dronabinol (THC alone) suggested that, under controlled conditions, marijuana and dronabinol decreased pain, but dronabinol produced longer-lasting decreases in pain sensitivity and lower ratings of abuse-related subjective effects than marijuana.¹⁶⁵ In another pilot study, caloric intake and body weight were measured in HIV-positive marijuana smokers, and compared with placebo or dronabinol. Marijuana and dronabinol effects were comparable, with both dronabinol and marijuana well-tolerated and producing substantial and comparable increases in food intake.¹⁶⁶ All cannabinoid

conditions produced significant intoxication, except for low-dose dronabinol. No other clinical trials have compared smoked marijuana to oral/spray THC or THC/CBD for other medical conditions, leaving the issue of whether smoked marijuana confers an advantage in efficacy and safety unresolved. Randomized clinical trials comparing smoked marijuana with alternative medications are scant. (3) Marijuana users prefer inhalation because swift brain entry conceivably produces rapid euphoria. Yet most medications that provide symptom relief are delivered orally. (4) Cannabinoids are not the only products of the marijuana plant with putative medicinal properties. Marijuana terpenoids share a precursor to cannabinoids, e.g., limonene, myrcene, α -pinene, linalool, and some are under investigation as candidate therapies or as facilitators of cannabinoid efficacy. Evidence is needed to prove the validity of the widely held belief and self-reporting, that whole plant marijuana is superior to isolated compounds because of synergism between various components.

It is generally recognized that smoking can be harmful to health.¹⁶⁷ Standard medicines are not smoked, but enter the body by other routes (pill, injection, topical creams, patches, inhalants, eye drops, liquid drinks, suppositories). Clinical trials measure pharmacokinetic, pharmacodynamic properties of each drug, along with metabolic rates and metabolites. To confound clinical results with marijuana, the percent of THC that enters the body is variable depending on the type of smoking ritual or route of administration.^{168,169,170} Smoking remains a controversial route of delivery, even with a recent report that found no major changes in spirometric measures of lung health of light, but not heavy, recreational marijuana smokers.¹⁷¹ Nearly all cross-sectional and longitudinal studies evaluating marijuana use association with chronic respiratory symptoms (cough, phlegm, wheezing and breathlessness) have found a positive relationship of active smoking with symptoms of chronic bronchitis (mainly cough and phlegm), but not with shortness of breath or lung cancer, but possible cancer risks remaining for heavy smokers.^{172,173} Whether vaping is a safer alternative to smoking marijuana remains uncertain, as health benefits derived from reducing toxic smoke components, (except in persons with chronic lung disease), need to be weighed against hazards of acute intoxication and long term consequences to the brain. Two studies with vaporized marijuana showed modest relief of neuropathic pain in 39 and 8 patients,^{174,175} with one at a very low dose of THC (1.29 percent). In support of this method of delivery, vaporized or smoked marijuana yielded similar maximal, but a *wide range of inter-subject blood levels* of THC. Given similar blood levels from both routes of administration, is it not surprising that CB1 receptor activation was comparable with smoked or vaporized sources of THC.¹⁷⁶

Missing safety data. Isolated cannabinoids have undergone a number of randomized, controlled clinical trials documenting safety, efficacy and side effect profiles, as required in a formalized drug approval

process, whereas few RCT are reported for whole plant marijuana. In the absence of long term clinical trials, most data by necessity is extrapolated from recreational users. Of note, when researching the topic of medical marijuana, we failed to identify clinical trials of long duration that investigate outcomes in people using marijuana long-term for chronic medical conditions, even though marijuana is used primarily by people with chronic medical conditions (e.g., AIDS neuropathy, AIDS wasting, multiple sclerosis, chronic pain, seizures, others). Current estimates are that 25 to 50 percent of daily marijuana users develop an addiction to marijuana. On the basis of current information and especially in view of negative side effects of chronic use (addiction, compromised cognition and executive control), one cannot be assured that marijuana can be safely used under medical supervision, for long term open-ended use. This segment provides guidance on the quality of existing clinical trials and a roadmap for future research. Key information about side-effects and safety would be collected if marijuana went through the normal evaluation process for approval as a medicine. Of randomized controlled trials, the majority of trials do not report a full dose-response evaluation, inclusion criteria generally require subjects to be experienced marijuana users, trials are of short duration (days to weeks, not six to 12 months), the sample populations are low, they do not assess quality of daily life or function when using a psychoactive substance (e.g., driving, work quality, school attentiveness, cognitive impairment) or effects after prolonged use (e.g., addiction, cognition, executive function, motivation, psychosis).

Missing safety data. Cognitive impairment in medical conditions with cognitive decline. Side effects of marijuana have to be viewed in the context of immediate effects and after repeated long term use. In research of subjects under the influence of marijuana, dose-related impairments of immediate and delayed recall of information can be quantified. Various phases of learning and memory can be affected, as well as signs of depersonalization, distorted sensory perception, and altered time perception. Executive function in marijuana users (attention, concentration, decision-making, impulsivity, self-control, reaction time, risk taking, verbal fluency and working memory) is impaired acutely in a dose-dependent manner.¹⁷⁷ Regular marijuana use for medicinal purposes is so recent that its long-term effects on seriously ill people is comparatively unknown, especially among those harboring disease-related cognitive decline (e.g., cancer, HIV-AIDS, multiple sclerosis, Alzheimer's, Parkinson's disease, certain seizure disorders). For example, cancer or chemotherapy promote cognitive decline before, during or after chemotherapy, with memory loss, loss of concentration and attention the most frequent symptoms.^{178,179} Conceivably, the combination of chemotherapy and marijuana reduces cognitive functions in additive or synergistic ways. Yet the impact of marijuana on parameters of cognition has not been tested, although the number of patients using marijuana during chemotherapy is growing. For multiple sclerosis, another disease beleaguered by cognitive impairment, it is now recognized that marijuana worsens cognitive deficits.¹⁸⁰

Reports on marijuana-induced relief of physical symptoms in other neurodegenerative disorders with cognitive impairment (Parkinson's disease, Alzheimer's disease), do not judiciously measure cognition. Marijuana may compromise quality of life for these populations but this parameter remains inadequately explored.

Long-term effects. A significant number of individuals report paranoia, persecutory ideas, or hallucinations while under the influence of marijuana¹⁸¹ and with drug-naïve study subjects, high drop-out rates would compromise the integrity of the clinical trial. Considering the concerted effort during the 20th century to minimize or eliminate psychoactive effects of any medication, clinical trials should include side-by-side comparisons of marijuana with isolated cannabinoids or alternative drugs (e.g., for chemotherapy-induced nausea, pain, or glaucoma). For chronic users, other side effects can include altered brain structure and impaired short-term memory, compromised judgment and decision-making, and mood effects that can range from severe anxiety manifest as paranoia or even psychosis, especially after high doses, as reviewed earlier. Marijuana can reduce motor coordination alone, or combined with alcohol, slow the reaction time of drivers.¹⁸² Marijuana smoking can cause or worsen breathing problems such as bronchitis or chronic cough and evidence is increasing that it may cause serious cardiovascular problems in some users.¹⁸³ The impact of long-term use on young people, whose frequent use for asserted medical reasons is increasing rapidly, cannot be adequately predicted at this time either.

Evidence of marijuana for medicinal use: Use of marijuana by individuals, internationally. A recent international survey of 31 countries investigated self-reported medicinal use of marijuana (and cannabinoids). Respondents (953) from the U.S., Germany, Canada, France, the Netherlands, and Spain were generally male (64 percent), relatively young (mean age 40.7 years) with a smaller cohort using over the age of 51 (24 percent), and far fewer past the age of 60 or 70 (6 percent, 1 percent). Marijuana was used primarily for back pain (11.9 percent), sleeping disorders (6.9 percent), depression (6.7 percent), injury or accident-generated pain (6.2 percent), and multiple sclerosis (4.1 percent).¹⁸⁴ With the exception of multiple sclerosis, and neuropathic pain, randomized controlled trials (RCT) with marijuana use for these symptoms are scant.

It is within reason to acknowledge that certain people report relief and symptom improvement while under the influence of marijuana, as corroborated by surveys, case-based studies, anecdotal self-reports, laboratory-based short-term trials. Nonetheless, rigorous criteria needs to be applied as would be required by the FDA, EMA or World Health Organization (WHO), using the gold standard of RCTs for the drug approval process. Evidence from RCTs is presented, with sources from primary manuscripts an 10 meta-analyses.^{185,186} The psychoactive responses engendered by marijuana confound clinical research, as it is a

significant obstacle to designing randomized, double-blinded clinical trials. Nor are there adequate, well-controlled double-blinded long-term RCTs demonstrating efficacy in drug-naïve populations compared with marijuana-using populations.¹⁸⁷ The majority of RCT trials recruit experienced marijuana using subjects for a number of reasons, including concerns of unacceptably high drop-out rates among marijuana-naïve subjects.¹⁸⁸

Neuropathic pain. Pain can be classified as acute or chronic, or by site of origin, (nociceptive) or nerves (neuropathic). Neuropathic pain occurs in various disease states (e.g., diabetes, HIV-AIDS, post-traumatic pain, cancer, excess alcohol use, rheumatoid arthritis) and can be a persistent, debilitating condition. HIV neuropathic pain affects 30 percent or more of HIV-infected individuals and some antiretroviral therapies can worsen the condition. HIV-infected individuals report improvements in health from smoking marijuana. Of over 200 people with HIV-AIDS, 23 percent used marijuana in the previous month.^{189,190} The association between marijuana use for psychoactive purposes and marijuana used medically for HIV-AIDS is relevant,¹⁹¹ with considerations including both marijuana use and duration of HIV infection may affect cognitive functioning that may impair their ability to follow important treatment guidance.^{192,193} While evidence for an effect of inhaled marijuana on chronic neuropathic pain is promising, trials followed their patients for a maximum of two weeks. Long-term trials, which also examine pragmatic outcomes, are needed to increase confidence that short term trials, conducted largely in experienced marijuana users are relevant to an overall cost-benefit analysis of long term marijuana use to treat chronic neuropathic pain. Six recent manuscripts reporting randomized controlled clinical trials with marijuana smoked or vaporized marijuana. Five were recently summarized positively in a review co-authored by investigators of the primary studies.¹⁹⁴ The pilot studies showed beneficial effects on alleviating pain, and by inhalation, enabled patients to titrate the effects. Yet these six reports did not establish a conclusive dose effect versus adverse events therapeutic window, as doses used varied. Acceptable limits of cognitive impairment were not described and no report addressed cognitive impairment outside a clinical research setting. Others have reviewed the overall evidence for marijuana and cannabinoids for pain.^{195,196} These RCT are currently insufficient and inadequate to recommend use of marijuana (smoked or vaporized) for the treatment of neuropathic pain. No RCT are reported for ingested marijuana, which displays variable onset times, inability to titrate doses, and more side effects.

Cancer, symptom management (nausea, vomiting, appetite, pain): Marijuana has been proposed to alleviate symptoms of cancer, including reduced appetite, chemotherapy-induced nausea and vomiting, cancer pain and even to attenuate the disease process.

Cancer, chemotherapy and anti-emesis. Chemotherapy-induced nausea and vomiting were inadequately controlled in the 1960's and 1970's, motivating investigation of the anti-emetic properties of cannabinoids and leading to FDA approval of nabilone and THC (dronabinol or Marinol). There have been only three small clinical trials on the use of marijuana in cancer patients.¹⁹⁷ All three studies assessed antiemetic activity, with different patient populations and chemotherapy regimens. One study demonstrated no effect, the second study showed a positive effect versus placebo. The report of the third study did not provide enough information to characterize the overall outcome as positive or neutral. Consequently, there is insufficient data to provide an overall level of evidence for the use of marijuana for chemotherapy-induced nausea and vomiting. There is no published data on the use of marijuana for other cancer-related or cancer treatment–related symptoms.¹⁹⁸

Yet some patients prefer smoked marijuana over oral cannabinoids, with rationales that include ability to self-titrate smoked marijuana, the swallowing of pills is difficult while experiencing emesis, onset of relief is faster with smoking, and the whole plant (“entourage”) is more effective.¹⁹⁹ Side-by-side clinical trials with oral cannabinoid compared with smoked marijuana in HIV-AIDS (see above) show scant evidence for therapeutic advantage of smoked marijuana. Furthermore, if the goal is to prevent nausea, factors such as speed of brain entry, challenges of swallowing pills while vomiting, dose titration, are not important factors; an oral cannabinoid can be administered long before chemotherapy to avoid its unpleasant side effects. Inhaled marijuana engenders a higher rate of brain entry and associated undesirable side effects, which can include intoxication, anxiety, acute psychotic reactions, and orthostatic hypotension.²⁰⁰ It is questionable whether the beneficial effects of inhaled marijuana outweigh the risks. Recent drug discovery programs have introduced newer anti-nausea drugs that are superior to cannabinoids in clinical trials. It is also possible that non-psychoactive isolated cannabinoids may prove to be effective for nausea and vomiting.²⁰¹ A significant proportion of older cancer patients with no previous marijuana experience refused to continue its use because they found the psychoactive effects too unpleasant. For such reasons, there is doubt whether smoked marijuana will find widespread clinical application, except among those who have previously used it for nonmedical purposes.²⁰² Paradoxically cannabinoids can be both anti-emetic and pro-emetic. A cannabinoid hyperemesis syndrome has recently been described, in which persistent and regular marijuana use (i.e., daily or weekly use for more than one year) is associated with episodic nausea and vomiting²⁰³ and nonresponse to treatment for cyclic vomiting other than hot showers.²⁰⁴

Marijuana, symptoms and anti-tumor activity. At present, there is insufficient evidence to recommend inhaling marijuana as a treatment for cancer-related symptoms or cancer treatment–related side effects.²⁰⁵

There is no credible evidence that smoked marijuana is an anti-tumor agent.²⁰⁶ In fact data shows contradictory results. The promise of cannabinoids as an anti-tumor agent stems from preclinical research, using either cultured cells derived from human or rodent tumors, or mouse tumor models. These initial steps are insufficient to satisfy stringent criteria for recommending marijuana to treat human cancers. Cell cultures have yielded contradictory results, with THC potentiating or inhibiting tumor proliferation, as a function of tumor type and its pathology. In one small Phase I trial of nine patients with aggressive glioblastoma multiforme treated with direct infusions of THC,²⁰⁷ THC did not extend the life span of these patients.

Post-traumatic stress disorder (PTSD) or sleep disorders. There are no large scale randomized controlled trials with marijuana to alleviate PTSD symptoms. On the contrary, marijuana use may impede the effectiveness of treatment for PTSD, and is associated with poorer clinical outcomes with PTSDs.^{208,209}

Reports from the Experts

U.S. Surgeon General

In 1982, the Surgeon General of the Public Health issued the following warning: Marijuana use is a major public health problem in the United States. In the past 20 years, its' use has increased 30-fold; it is estimated that more than a quarter of the American population has used it. The age at which persons first use marijuana has decreased gradually to the junior high school years. Until recently, nearly 11 percent of high school seniors used it, and although that figure has declined to 7 percent, its daily use still exceeds that of alcohol; more high school seniors use marijuana than smoke cigarettes. In a recent study, 32 percent of those surveyed had used marijuana during the previous 30 days, while 25 percent had smoked tobacco.

On March 24, 1982, the Department of Health and Human Services submitted to Congress a report reviewing the consequences of marijuana use. Marijuana and Health, 1982, ninth in a series, is primarily based on two recently conducted, comprehensive, scientific reviews by the Institute of Medicine of the National Academy of Sciences, the Canadian Addiction Research Foundation, and the WHO. Both independent reviews corroborate the Public Health Service's findings of health hazards associated with marijuana use: Acute intoxication with marijuana interferes with many aspects of mental functioning and has serious, acute effects on perception and skilled performance, such as driving and other complex tasks involving judgement or fine motor skills.

Among the known or suspected chronic effects of marijuana are:

1. Short-term memory impairment and slowness of learning;
2. Impaired lung function similar to that found in cigarette smokers. Indications are that more serious effects, such as cancer and other lung disease, follow extended use;
3. Decreased sperm count and sperm motility;
4. Interference with ovulation and pre-natal development;
5. Impaired immune response;
6. Possible adverse effects on heart function;
7. By-products of marijuana remaining in body fat for several weeks, with unknown consequences. The storage of these by-products increases the possibilities for chronic, as well as residual, effects on performance, even after the acute reaction to the drug has worn off; and
8. Long-term developmental effects in children and adolescents, who are particularly vulnerable to the drug's behavioral and psychological effects. The "amotivational syndrome," characterized by a pattern of energy loss, diminished school performance, harmed parental relationships, and other behavioral disruptions, has been associated with prolonged marijuana use by young persons. Although more research is required, recent national surveys report that 40 percent of heavy users experience some or all of those symptoms.

The Public Health Service concludes that marijuana has a broad range of psychological and biological effects, many of which are dangerous and harmful to health, and it supports the major conclusion of the National Academy of Sciences' Institute of Medicine.

National Institutes of Health

In 1997, the National Institutes of Health (NIH) hosted a workshop at which medical experts discussed the potential uses of smoked cannabis. This group reviewed the literature available at the time of the workshop and held hearings to discuss the possible therapeutic uses of cannabis to treat the following conditions: analgesia, neurological and movement disorders, nausea and vomiting associated with chemotherapy, glaucoma, appetite stimulation/cachexia. For a number of these conditions, the workgroup concluded that pursuing further research into the effectiveness of smoked cannabis would be of limited value as effective treatments were already in existence. However, the workgroup did recommend that further research be conducted regarding the effectiveness of smoked cannabis as current research did not provide definitive answers on its risk/benefit profile. Of note, the consensus was that smoked cannabis must meet the same standards as other medications in terms of effectiveness and safety.

Institute of Medicine Report

In 1997, the White House Office of National Drug Control Policy (ONDCP) requested that the Institute of Medicine (IOM) conduct a review of the scientific evidence regarding the potential health benefits and risks of cannabis and its component cannabinoids. In 1999, the IOM issued their report, *Cannabis and Medicine: Assessing the Science Base* that became the foundation of study into medical marijuana. In that report, the IOM made a series of recommendations pertaining to the use of cannabis in medical treatment, much of which revolved around the need for more research and evaluation.

In their report, the IOM made the following recommendations:

- Recommendation 1 – Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.
- Recommendation 2 – Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable and safe delivery systems.
- Recommendation 3 – Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.
- Recommendation 4 – Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which cannabis use is prevalent.
- Recommendation 5 – Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months); should be conducted in patients with conditions for which there is reasonable expectation of efficacy; should be approved by institutional review boards; and should collect data about efficacy.
- Recommendation 6 – Short-term use of smoke marijuana (less than six months) for patients with debilitating symptoms such as intractable pain or vomiting, must meet the following conditions:
 - Failure of all approved medications to provide relief has been documented;
 - The symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs;
 - Such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness; and

- Involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

The IOM clearly stated that the purpose of short-term studies with smoked cannabis would serve, at best, as preliminary support for the development of cannabis-based or cannabinoid modern medications. The goal of clinical trials of smoked cannabis would not be to develop cannabis as a licensed drug but rather to serve as a first step toward the possible development of non-smoked, rapid-onset cannabinoid delivery systems.

While the IOM specifically noted that, “there is little future in smoked marijuana,” there was “no clear alternative” for people suffering from chronic conditions that might be relieved by smoked cannabis until non-smoked, rapid-onset cannabinoid delivery systems become available. IOM suggested that patients be suggested of their status as experimental subjects using a harmful drug delivery system, while their condition be closely monitored and documented under medical supervision – thereby increasing the knowledge base of the risks and benefits of marijuana use.

American Medical Association

In June 2013, the American Medical Association (AMA) released the following policy regarding **Cannabis for Medicinal Use – H-95.952**: (1) Our AMA calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease. (2) Our AMA urges that marijuana's status as a federal Schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines, and alternate delivery methods. This should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product. (3) Our AMA urges the National Institutes of Health (NIH), the DEA, and the FDA to develop a special schedule and implement administrative procedures to facilitate grant applications and the conduct of well-designed clinical research involving cannabis and its potential medical utility. This effort should include: a) disseminating specific information for researchers on the development of safeguards for cannabis clinical research protocols and the development of a model informed consent form for institutional review board evaluation; b) sufficient funding to support such clinical research and access for qualified investigators to adequate supplies of cannabis for clinical research purposes; c) confirming that cannabis of various and consistent strengths and/or placebo will be supplied by the National Institute on

Drug Abuse to investigators registered with the DEA who are conducting bona fide clinical research studies that receive FDA approval, regardless of whether or not the NIH is the primary source of grant support. (4) Our AMA believes that effective patient care requires the free and unfettered exchange of information on treatment alternatives and that discussion of these alternatives between physicians and patients should not subject either party to criminal sanctions.

American Academy of Neurology

In 2014, the American Academy of Neurology (AAN) Guideline Development Subcommittee convened an expert panel to develop an evidence-based systematic review to answer questions regarding the safety and efficacy of cannabinoids in relieving/reducing the following:

1. Spasticity in patients with multiple sclerosis (MS);
2. Central pain and painful spasms in MS (pain could be from any etiology, including spasticity, but excluding neuropathic pain);
3. Bladder dysfunction in MS;
4. Involuntary movements, including tremor, in MS;
5. Dyskinesias of Huntington Disease (HD), levodopa-induced dyskinesias of Parkinson disease, cervical dystonia, and tics of Tourette syndrome; and
6. Seizure frequency in epilepsy.

Of note, non-neurologic pain and other conditions were excluded.

Question – Do cannabinoids relieve spasticity in patients with MS?

Answer – Oral cannabis extract (OCE) is established as effective for reducing patient-reported scores. OCE is probably ineffective for reducing objective measures at 12-15 weeks but possibly effective at one-year. THC is probably effective for reducing patient-reported scores. THC is probably ineffective for reducing objective measures at 12-15 weeks but possibly effective at 1-year. Nabiximols is probably effective for reducing patient-reported symptoms at six weeks but ineffective for reducing objective measures. Smoked marijuana is of uncertain efficacy.

Question – What is the efficacy of using cannabinoids to treat central pain or painful spasms in MS?

Answer – For patients with MS with central pain or painful spasms, OCE is effective for reduction of central pain. THC or nabiximols are probably effective for treating MS-related pain or painful spasms. Smoked marijuana is of unclear efficacy for reducing pain.

Question – Do cannabinoids help treat bladder dysfunction in MS?

Answer – Nabiximols is probably effective for reducing the number of bladder voids per day at 10 weeks. THC and OCE are probably ineffective for reducing bladder complaints. Nabiximols is of unknown efficacy in reducing overall bladder symptoms.

Question – Do cannabinoids help treat tremor in MS?

Answer – THC and OCE are probably ineffective for treating MS-related tremor; nabiximols is probably effective.

Question – Do cannabinoids reduce symptoms in involuntary movement disorders?

Answer – With respect to Huntington disease, the two studies were underpowered and therefore no reliable conclusions could be drawn. OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. For patients with Tourette syndrome, data is insufficient to support or refute efficacy of THC in reducing tic severity. For patients with cervical dystonia, data is insufficient to support or refute the efficacy of dronabinol.

Question – Do cannabinoids decrease seizure frequency?

Answer – For patients with epilepsy, data is insufficient to support or refute the efficacy of cannabinoids for reducing seizure frequency. Of note, neither present review, nor a Cochrane review, which includes abstracts, non-peer reviewed literature, and anecdotal reports of smoked cannabis use by patients with seizure disorders, concluded there is sufficient evidence to prescribe cannabidiols or recommend self-treatment with smoked marijuana.

In looking at marijuana related adverse effects (AEs), data on symptoms that caused medication withdrawal were often incomplete; however, among patients treated with cannabinoids, the following symptoms appeared in at least two studies: nausea, increased weakness, behavioral or mood changes (or both), suicidal ideation or hallucinations (or both), dizziness or vasovagal symptoms (or both), fatigue, feelings of intoxication, and psychosis, dysphoria, and anxiety are associated with higher concentrations of THC.

AEs are a significant concern with marijuana use. Outside the setting of treatment trials, cognitive impairment is more likely to be of concern. One study of patients with MS who smoked cannabis at least once a month showed an increase in cognitive impairment. Another article referenced indicated that patients with MS who used cannabis were twice as likely to be classified as globally cognitively impaired as those who did not use cannabis. And it is especially concerning that a medication may have an AE of

suicide may be prescribed in a population such as patients with MS who already are at increased suicide risk.

The AAN noted that the placebo effect, which has been reported to be as high as 70 percent, interferes with proof of efficacy, although the ability to recognize treatment was mitigated by preparations with less THC and thus less psychoactive effects. Although masking may be lost due to the non-naïve subject's recognition of his or her assigned group (treatment versus control), interviews of subjects also found may who guessed incorrectly which group they were in, especially the first time cannabis was used.

In conclusion, the AAN indicates that cannabinoids should be studied as other drugs are to determine their efficacy, and when evidence is available, should be prescribed as other drugs are.

American Academy of Pediatrics

In September 2015, the American Academy of Pediatrics (AAP) its policy statement regarding, the “Legalization of Marijuana: Potential Impact on Youth.” In doing so, the AAP advised that the adverse effects of marijuana use have been well documented, and studies have demonstrated the negative consequences of short- and long-term recreational use of marijuana in adolescents. These consequences include impaired short-term memory and decreased concentration, attention span, and problem solving – all of which clearly interfere with learning. Alterations in motor control, coordination, judgement, reaction time, and tracking abilities have also been documented. Negative health effects on lung function associated with smoking marijuana have also been documented, as well as studies linking marijuana use with higher rates of psychosis in patients with a predisposition to schizophrenia. New research has also demonstrated that the adolescent brain, particularly the prefrontal cortex areas controlling judgement and decision-making, are not fully developed until the mid-20s, raising questions about how any substance use may affect the developing brain. Research has shown that the younger an adolescent begins using marijuana, the more likely it is that drug dependence or addiction will develop in adulthood. A recent analysis of four large epidemiologic trials found that marijuana use during adolescents is associated with reductions in the odds of high school completion and degree attainment. Marijuana use in adolescents also increases the use of other illicit drugs and suicide attempts in a dose-dependent fashion – which suggests marijuana use is causative.

The AAP published the following recommendations:

1. Given the data supporting negative health and brain development effects of marijuana in children and adolescents, ages 0-21 years, the AAP is opposed to marijuana use in this population;

2. The AAP opposes “medical marijuana” outside the regulatory process of the FDA. Notwithstanding this opposition to use, the AAP recognizes that marijuana may currently be an option for cannabinoid administration for children with life-limiting or severely debilitating conditions and for whom current therapies are inadequate;
3. The AAP opposes legalization of marijuana because of the potential harms to children and adolescents. The AAP supports studying the effects of recent laws legalizing the use of marijuana to better understand the impact and define best policies to reduce adolescent marijuana use;
4. In states that have legalized marijuana for recreational purposes, the AAP strongly recommends strict enforcement of rules and regulations that limit access and marketing and advertising to youth;
5. The AAP strongly supports research and development of pharmaceutical cannabinoids and supports a review of policies promoting research on the medical use of these compounds. The AAP recommends changing marijuana from a DEA Schedule I to a Schedule II to facilitate this research;
6. Although the AAP does not condone state laws that allow the sale of marijuana products, in states where recreational marijuana use is currently legal, pediatricians should advocate that states regulate the product as closely as possible to tobacco and alcohol, with a minimum age of 21 years for purchase. Revenue from this regulation should be used to support research on the health risks and benefits of marijuana use. These regulations should include strict penalties for those who sell marijuana or marijuana products to those younger than 21 years, education and diversion programs for people younger than 21 years who possess marijuana, point-of-sale restrictions, and other marketing restrictions;
7. In states where marijuana is sold legally, either for medical or recreational purposes, regulations should be enacted to ensure that marijuana in all forms is distributed in childproof packaging, to prevent accidental ingestion;
8. The AAP strongly supports the decriminalization of marijuana use for both minors and young adults and encourages pediatricians to advocate for laws that prevent harsh criminal penalties for possession or use of marijuana. A focus on treatment for adolescents with marijuana use problems should be encouraged, and adolescents with marijuana use problems should be referred to treatment;
9. The AAP strongly opposes the use of smoked marijuana because smoking is known to cause lung damage, and the effects of secondhand marijuana smoke are unknown; and

10. The AAP discourages the use of marijuana by adults in the presence of minors because of the important influence of role modeling by adults on child and adolescent behavior.

American Academy of Pain Management

In October 2015, Bob Twillman, PhD, executive director of the American Academy of Pain Management said, “Primary care providers feel increased pressure to treat pain with methods other than opioids, but many don’t know how to do that.”

When asked if there is a role for medical marijuana in pain management, Mr. Twillman said, “We don’t really know the answer to this yet. We certainly have indications that some components of marijuana can be effective in relieving pain, especially neuropathic pain, but we need a good deal more research into which components are most effective and a means of obtaining those positive effects without the unnecessary psychoactive effects from other components. In the best of all possible worlds we would have products that provide standardized doses of a known mix of compounds, supported by research demonstrating effectiveness and safety, but I fear we are a long way from that world. For now that leaves us trying to manage medical marijuana use without really understanding it and feeling pretty unsure every step of the way.”

Concerns Regarding the Impact on Society

Acute effects of marijuana on brain function

Unlike opioids, marijuana is not likely to cause death by overdose but it resides in Schedule I because of its high abuse liability, and no medical indications – essentially because it adversely disturbs brain function and biology. A Saturday night marijuana binge is intoxicating in the short term, but it can also produce residual cognitive deficits (on learning and memory) for several days. Marijuana research protocols generally wait at least five to 30 days for marijuana to clear, before measuring long term residual cognitive effects. These deficits are readily quantified, are exaggerated in schizophrenics, and refute advocacy for marijuana treatment of Alzheimer’s disease.

A 2009 National Highway Traffic Safety Administration (NHTSA) report showed that more people are driving on weekend nights under the influence of marijuana (8.3 percent) than alcohol (2.2 percent). Emergency department mentions of marijuana in the U.S. have increased from 281,619 to 374,435 during 2004-2008, in parallel with linear increases in marijuana potency and marijuana addiction.

Enduring effects: marijuana addiction

Marijuana is addictive in about 9-10 percent of users and progression to addiction reportedly is more rapid than progression to nicotine addiction. Abstinence in the heavily addicted unmasks physical and psychological neuroadaptation, manifest by an unnerving withdrawal syndrome. Nation-wide, more people harbor a medical (DSM-IV) diagnosis of marijuana abuse/addiction than any other illicit drug and more youth are DSM-IV positive for marijuana than for alcohol, as a percentage of users. Extrapolating from national statistics, an average cost for addiction treatment is \$4,000 for ambulatory care and at least four times that amount for residential care. This can add billions of dollars for marijuana treatment needs nationally.

Marijuana and youth

There is no reasonable evidence that marijuana sold for “medical purposes” will prevent diversion to young adolescents. Our ability/failure to prevent youth cigarette smoking or alcohol consumption may serve as our guide. Youthful users of marijuana are at particular risk. The addiction rates of marijuana are 6-fold higher in young adolescents who initiate marijuana use at age 14 or younger. Early onset of marijuana use is also associated with addiction to other drugs in adulthood, including alcohol and heroin.

Some have speculated that genetics, cigarettes smoking, social environment, poverty, child abuse, psychiatric conditions confer this higher risk in the young. But how to explain that adolescent rats exposed to the most active constituent of marijuana, THC, only during adolescence, seek heroin at higher rates after they mature into adults compared with matched controls, and display a fundamental change in brain opioid systems long after their last dose? Social, environmental, poverty, child abuse, psychiatric conditions do not apply to inbred rats – therefore, it appears as though the drug (marijuana) alone alters the trajectory of brain and behavioral development.

Marijuana use and neuropsychiatric disorders

In nine population studies of more than 75,000 people from seven different countries, early marijuana use was found to be associated with an average two-fold higher risk for later-onset psychosis and schizophrenia. The Lancet declared in 1995 that “The smoking of cannabis, even long term, is not harmful to health” changed its conclusion in 2007, by stating that “Research published since 1995, including [the] systematic review in this issue, leads us now to conclude that cannabis use could increase the risk of psychotic illness... governments would do well to invest in sustained and effective education campaigns on the risks to health of taking cannabis.”

A current debate is being waged on whether to revise comparative risk assessment in the Global Burden of Disease (GBD) to include the attribution of psychosis to marijuana use. Degenhardt et al argue that the risk assessment should be included because the evidence is as good as that for many other risk factors in the GBD. Some scientists have estimated that marijuana contributes about 8 percent to new cases of schizophrenia. If this estimate is accurate, unfettered marijuana access in California conceivably would add 25,000+ cases of schizophrenia, with an estimated cost of caring for this cohort for 30 years in excess of \$6 billion (based on a low estimate of \$8,000/per patient/year).

Long term heavy marijuana use

Heavy daily marijuana use across protracted periods can exert harmful effects on brain tissue and mental health. Brain imaging of long-term heavy marijuana users has shown exposure-related structural abnormalities in brain regions critical for learning, memory and emotional responses, with changes associated with impaired verbal memory and other symptoms. Abnormal brain size and brain circuitry of adolescent marijuana users have also been recently documented. Compromised academic performance, school drop-out, and a host of other adverse consequences are elevated in high school or college students who use marijuana. Accurate price tags for these lost educational and employment opportunities don't exist – which is unfortunate as it is also a factor. Peripheral health is also affected, as marijuana use is associated with increased risks for bronchitis, compromised pulmonary function, precancerous lung changes, cardiovascular events, problematic pregnancies, teratogenic and hormonal effects.

Despite this evidence, 2009 was a banner year for marijuana use in our nation. Compared with 2008, 1.5 million more marijuana users were added to the ranks in 2009. The steady decline in marijuana use among youth over the past 6 years was reversed in 2009. Marijuana use among 12-17 year olds increased by over 7 percent, with a 14 percent increase among boys, and a 13 percent increase among college students. Expanding acceptance of medical marijuana and proliferating availability conceivably are driving reduced perception of harm and a pivotal rise in use.

Acceptance is further illustrated by the results of the 2016 election – which not only included presidential and congressional elections but ballot initiatives in 35 states. Voters in Arkansas, Florida, and North Dakota made it legal for doctors to prescribe medical marijuana to their patients, while Montana voted to ease recent restrictions on its decade-old medical marijuana law. As of this publication, smoking marijuana, at least for medical and in some cases recreational purposes, is now legal in 30 states.

Perhaps more concerning, four states voted to pass new laws that make marijuana use equivalent to liquor consumption. In California, Massachusetts, Maine, and Nevada, it is now legal for anyone over 21 years old to smoke pot. Those states join Alaska, Colorado, Oregon, Washington, and the District of Columbia in a loose coalition that is challenging the federal government with regard to the DEA's position on marijuana.

Conclusions

Although there are different schools of thought concerning the efficacy of marijuana to treat certain medical conditions and concerning whether its possession and use ought to be decriminalized altogether, the fact remains that it is a violation of federal law and South Dakota law to possess or distribute it for any purpose. And while many states, including some close to South Dakota, have legalized the use of marijuana for medical purposes, writing a prescription for marijuana, even to a patient living in a state where its use and possession is legal, could result in a disciplinary proceeding brought by the SDBMOE. Accordingly, it is recommended that the practitioner not prescribe (either using a traditional prescription or a certification) marijuana unless and until changes in the law make it clear that doing so is legal, and then only when it is medically-necessary and appropriate.

Resources

American Academy of Neurology
www.aan.com

American Academy of Pain Management
www.aapainmanage.org

American Academy of Pediatrics
www.aap.org

American Medical Association
www.ama-assn.org

Food and Drug Administration (FDA)
www.fda.gov

Institute of Medicine
www.nationalacademies.org

National Institute of Health
www.nih.gov

U.S. Surgeon General
www.surgeongeneral.gov

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